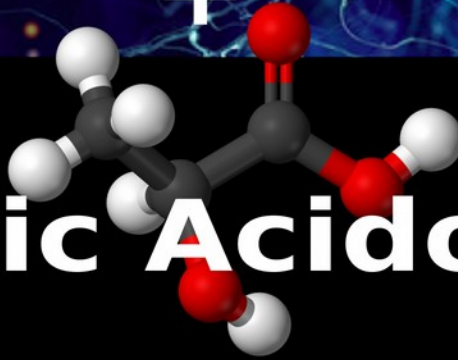


# Autonomic Dysfunction

+



# Lactic Acidosis



Atherosclerosis  
Cancer  
Heart Attacks  
Rheumatoid Arthritis  
Alzheimer's Disease  
Stroke and more ...

**Carlos ETB Monteiro**



**Autonomic Dysfunction  
+ Lactic Acidosis  
= Multiple Diseases**

*Carlos ETB Monteiro*



*“Science is a Method of Investigation  
to Search for Evidences,  
not Beliefs nor Wishes,  
Conveniences or Preferences”,*

## **“Autonomic Dysfunction + Lactic Acidosis = Multiple Diseases”**

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## **A Synopsis**

The present book discusses the causal origin and adequate therapeutics for many diseases, in new hypotheses advocated by the author.

From his point of view, the precursor for many diseases is the autonomic nervous dysfunction that can lead to elevated catecholamine release, accelerating glycolysis metabolism, increasing lactic acid and lactate concentration in blood and tissues.

The book focuses on the following diseases:

Atherosclerosis; coronary artery calcification; coronary thrombosis; ischemic heart disease; acute myocardial infarction; cancer; cerebral stroke, rheumatoid arthritis, Alzheimer's disease, hypertension, diabetes mellitus and covid-19

Other subjects discussed in this book:

- Coronary thrombosis theory of heart attacks: science or creed?
- Digitalis and strophanthin in stable ischemic heart disease and to restrain or reverse heart attacks
- Inflammation is a result of an injury, not the culprit of atherosclerosis and other diseases.

**“The hypotheses described in this book have not been proved to be wrong or false, since their publications”**



## Acknowledgements

To my great mentors in medical science:

- Prof. Dr. Quintiliano H. de Mesquita, Developer of the Myogenic Theory of Myocardial Infarction, 1972. Chief of the Cardiological Institute of Matarazzo Hospital, 1941- 1979, São Paulo - Brazil
- Prof. Dr. Paul J. Rosch, Clinical Professor of Medicine and Psychiatry from the New York College; Chairman of The American Institute of Stress. Author of many medical papers and editor of books like “Bioelectromagnetic and Subtle Energy Medicine” from 2014, “Fat and Cholesterol Don’t Cause Heart Attacks and Statins Are Not The Solution” from 2016 and “Lipid Lunacy, Dietary Delusions - And What Really Causes Coronary Heart Disease” from 2020, aside of several others.
- Dr. Uffe Ravnskov, PhD. Independent researcher; Founder and spokesman for THINCS - The International Network of Cholesterol Skeptics. Author of many medical papers and of the book “The Cholesterol Myth”

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To Sally Fallon Morell, President of the Weston A. Price Foundation. Sally invited me in 2009 to be one of the honorary board members of WAPF. With Sally assistance I have written the article “Stress as Cause of Heart Attacks - The Myogenic Theory” (2014). Its publication took place on their journal Wise Traditions in Food, Farming and the Healing Arts.

To Sandra Goodman, PhD, Editor of the Journal Positive Health Online”, England. There I published many articles since 2015. Most of these articles were new hypotheses about the cause and adequate therapeutics for different diseases. Sandra is an admirable and open mind Editor, with expertise in medical subjects. She is very critical in her analysis on scientific merits, evaluating the logic and evidence, as well the background and references.



*Photo, 2008*

## **About the Author**

Carlos ETB Monteiro, Brazilian researcher, is a disciple and follower in the scientific plan of Dr Quintiliano H. de Mesquita. After the decease of Dr Mesquita in 2000 he assumed the mission to keep the memory of the scientific discoveries from this medical genius, who made great contributions for the advancement in medicine. Carlos Monteiro also sought to bring up to date the myogenic theory of myocardial infarction from 1972, one of the many developments by Dr. Mesquita.

Monteiro is president of Infarct Combat Project ([www.infarctcombat.org](http://www.infarctcombat.org)), an international non-profit organization who fights heart disease through information, research, and education; a non-official member of the International Network of Cholesterol Skeptics ([www.thincs.org](http://www.thincs.org)); Fellow from the American Institute of Stress ([www.stress.org](http://www.stress.org)); and honorary board member of Weston A. Price Foundation, a non-profit organization ([www.westonaprice.org](http://www.westonaprice.org)). The Foundation's quarterly journal, *Wise Traditions in Food, Farming, and the Healing Arts*, is dedicated to exploring the scientific validation of dietary, agricultural, and medical traditions throughout the world.

His first medical scientific hypothesis occurred in 2006 with the development of the acidity theory of atherosclerosis, which gives a new explanation for the pathophysiological process of coronary artery disease. It fits perfectly well to the myogenic theory of myocardial infarction concept. Later he developed other medical hypotheses, all of these inside a spirit of humanitarian contribution.

From the beginning of the new millennium, he devoted most of his time to medical scientific research. His main purpose is the search for the medical truth on the cause and the adequate therapeutics of important human diseases.

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## Introduction: Diseases - Researching the Past, Looking for the Medical Scientific Truth

In 2005, I learned from a 1982 paper by David S. Schade about a study by Carl Ferdinand Cori and Gerty Cori from 1929 which demonstrated the influence of adrenaline on lactic acid production. The couple received a Nobel Prize in 1947 for their discovery of how glycogen - a derivative of glucose - is broken down and resynthesized in the body.

In his paper, Schade supported and expanded on this by supplying the following evidence that catecholamines participate in the development and/or maintenance of lactic acidosis:

1. The common association of stress and lactic acidosis;
2. The rise in plasma lactate concentration during adrenaline infusion;
3. The precipitation of lactic acidosis by adrenaline intoxication and pheochromocytoma;
4. The vasoconstrictor effects of catecholamines leading to tissue anoxia and lactic acid production.



**Carl Ferdinand Cori and Gerty Cori  
Nobel Prize in Medicine, 1947**

For some reason, these findings have not attracted much attention until recently, but I found them stimulating. As a result, I began to investigate the importance of stress and resultant lactic acidosis in order to verify a possible causal role for different diseases. This led to various studies, among these about atherosclerosis, ischemic heart disease, acute myocardial infarction, coronary thrombosis, cancer, stroke, Alzheimer's disease, rheumatoid arthritis, hypertension, diabetes mellitus e Covid-19 .



*"Life is a struggle, not against sin, not against the Money Power, not against malicious animal magnetism, but against hydrogen ions" Mencken H L, 1919*

The first disease I studied was atherosclerosis which the initial data, postulating a new hypothesis for its causal origin, we have presented in 2006. Our paper on the acidity theory of atherosclerosis was published in 2008. An article with updated information happened in 2015.

Recent studies have shown that increased brain lactate production may be a sign for other diseases in this region. For example, panic syndrome, schizophrenia, bipolar disorder and multiple sclerosis.

Further studies involving other diseases need to be carried out in this direction. For instance, there is evidence that a dysregulated autonomic nervous system is common in patients with sepsis which is an early marker of organ dysfunction. Also, elevated serum lactate levels are common in sepsis.

Possibly, there are other determining factors which might influence the formation of a specific disease, in addition to the causal origins advocated here.

In our view one of these influences is genetic predisposition by defining what disease will result in a certain individual affected by autonomic dysfunction and a raised lactate production. That occur at least between cancer and atherosclerosis.

This suggestion was implicit in recent findings from researchers in Germany and in US that found an inverse association between cancer history and autopsy-proven atherosclerotic disease, differing in rates depending on types of cancer. Also, confirming the results of old studies, like the one made by Wansher and colleagues published in 1951. It was based on material from 1835 autopsies showing that atherosclerotic lesions are less pronounced in patients suffering from carcinoma than among non-cancerous persons.

To our knowledge Dr. Benjamin Ward Richardson was the first to found, in 1856, that lactic acidosis might lead to diseases like arthritis and rheumatism. Richardson's said in his paper:

*"The first inference deducible from the experiments, according to my reading of them, is, that lactic acid has the power, when existing in an animal body in excess, of producing a class of symptoms attaching themselves mainly to the fibroserous textures, and which, regarded in all points of view, are essentially the symptoms of acute rheumatic inflammation."*

Experiments from Oswald Loeb, a well-known professor in pharmacology and scientist from the University of Gottingen - Germany, have demonstrated in study from 1913 that feeding rabbits and dogs with lactic acid resulted in atherosclerotic lesions.

The book "Arteriosclerosis and hypertension, with chapters on blood pressure", by Dr. Louis M Warfield, (Johns Hopkins), from 1920, showed the following commentary about the experiments from Oswald Loeb:

*"Oswald Loeb produced changes in the arteries of rabbits by feeding them sodium lactate (lactic acid). His controls fed on other acids became cachectic but showed no arterial changes. He further found that in 100 gm. of human blood there was normally from 15 to 30 mg. of lactic acid. After heavy work, he found as much as 150 gm. He considers that after adrenalin or nicotine injections, the function of the liver is so disturbed that lactic acid is not bound. The arteriosclerosis is actually due to the presence of free lactic acid in the circulation. He succeeded, also, in producing lesions of the intima in a dog fed for a long time on protein poor diet, plus lactic acid and sodium lactate."*

Follows an interesting summary from a book written in 1916 by Dr. George Washington Criles, about acidosis and the human body:

*"The establishment in the body of so powerful a group of organs and mechanisms for the elimination of the acid by-products of energy transformation show how vitally necessary is the maintenance of the normal slight alkaline reaction of the body. This indicates that acidosis is a factor in many diseases - acute and chronic - and that the centers in the medulla are stimulated by acidosis. While the higher centers are depressed; it suggests an explanation of the phenomena of anesthesia, and that the ultimate cause of death is usually acidosis."*

Note: Please read our article "Looking for the Cause and Cure of Diseases" with more info published in Contentment Magazine: Spring 2021 at <https://www.stress.org/contentment-magazine-spring-2021>

### **Suggested Reading**

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## Autonomic Dysfunction and Lactic Acidosis

Follows some basic information that may offer a better understanding why chronic elevated catecholamine release, triggered by the autonomic nervous dysfunction, may accelerate the glycolysis process leading to significant increase in lactate production:

- A. Dysautonomia or autonomic dysfunction is a condition in which the autonomic nervous system does not work properly
- B. Autonomic neuropathies are a collection of syndromes and diseases affecting the autonomic neurons, either parasympathetic or sympathetic, or both;
- C. The vagus nerve is the main component of the parasympathetic nervous system
- D. There are many risk factors leading to dysregulation of the autonomic nervous system, which is related with sympathetic dominance, through sympathetic over-activity or withdrawal of the parasympathetic system. Among these risk factors are stress, smoking, age, high carbohydrate diets, familial dysautonomia, etc.
- E. Lactic acidosis results from increased production of lactate, the final product in the pathway of glucose metabolism. Lactate and lactic acid are not synonymous. Lactic acid is a strong acid which, at physiological pH, is almost completely ionized to lactate. The measurement of lactate concentration can also be made in cerebrospinal fluid, synovial fluid and other fluids and tissues of the body.
- F. Lactate dehydrogenase (LDH) is a cytosolic enzyme involved in reversible transformation of pyruvate to lactate. It participates in anaerobic glycolysis of skeletal muscle and red blood cells, in liver gluconeogenesis and in aerobic metabolism of heart muscle. The determination of its activity helps in the diagnosis of various diseases, because it is increased in the serum of patients suffering from myocardial infarction, acute hepatitis, muscular dystrophy, cancer, and other conditions
- G. Hydrogen ion concentration measured as pH is responsible for the acidic or base nature of the compound. The lower the pH value, the higher concentration of hydrogen ions in the solution.



**Part #1**

**Articles on Ischemic Heart Disease  
and Acute Myocardial Syndromes**



# Chapter 1

## Stress as Cause of Heart Attacks - The Myogenic Theory

*Carlos ETB Monteiro*

The theory that heart attacks begin in the heart itself - the Myogenic Theory - and not in the arteries, was developed by my father-in-law, the Brazilian cardiologist, Quintiliano H de Mesquita, who died in 2000.<sup>[1]</sup> In this article, I propose to describe the history of the myogenic theory for a public that is largely unaware of this alternative theory since its introduction in 1972.<sup>[2,3]</sup>



*Dr Quintiliano H. de Mesquita  
flanked by his daughter Solange and Carlos Monteiro (1982)*

In addition to the myogenic theory, Dr Mesquita developed the concept of ventricular aneurysm surgery. The surgery was first performed by Dr Charles Bailey in 1954 and is still often performed on patients after a heart attack. My father-in-law also made the first diagnosis of right ventricular infarction by the electrocardiogram in 1958. He was the author of more than thirty pioneer contributions to medical literature in the field of cardiology.

The main reasons that led Dr Mesquita to break with the conventional thrombosis theory of heart disease - which states that the heart attack is caused by blocked arteries - are as follows:

- Clinical observations showing the absolute lack of efficacy of anticoagulants in the treatment of unstable angina pectoris. Unstable angina is considered to be a stage leading to myocardial infarction.

- The strong correlation of myocardial infarction with stress or unusual physical activity.
- Frequent coronary angiographies showing no obstructions in the presence of myocardial infarction.

Dr Mesquita's suspicion about the coronary thrombosis theory increased when he found that:

- Many anatomic-pathological studies have demonstrated no relationship between thrombus and infarction, which led many authors since the 1940s to consider coronary thrombosis - the clot in the arteries - as a consequence of acute myocardial infarction, not its cause.
- The development of coronary thrombus after a heart attack, demonstrated experimentally.

Along with these observations, Dr Mesquita also found that since the beginning of the twentieth century, several doctors had used cardiotonics (cardiac glycosides like digoxin, digitoxin, and ouabain / strophanthin), with remarkable results in the treatment of both stable angina pectoris and acute myocardial infarction. Among these were the American Dr James Bryan Herrick (in 1912), even though he was an important supporter of the coronary thrombosis (thrombogenic) theory as the cause of heart attacks. Another was Dr Ernst Edens (1934) from Germany.

In 1975, Dr Mesquita was awarded the Ernst Edens Traditionspreis by the International Society to Fight Infarction (Internationale Gesellschaft für Infarktbekämpfung), located near Stuttgart, Germany. Its president at the time was Dr Berthold Kern, who has used sublingual strophanthin in more than fifteen thousand patients with angina or myocardial infarction.

## Development of Myogenic Theory

Assuming that unstable angina pectoris could be the result of a regional myocardial failure, with episodic, but reversible, manifestations, Dr Mesquita came to the conclusion that only the therapeutic correction by a cardiotonic would be able to reverse the clinical picture and prevent the myocardial infarction. Eventually he came to see heart disease as a three-stage process:

**Stage I:** Stable angina, an intermittent and reversible process indicating regional myocardial ischemia caused by physical exertion or psycho-emotional stress, and loss of regional myocardial contractility;

**Stage II:** Unstable angina, a process that is still reversible, indicating regional myocardial insufficiency, which is episodic, spontaneous, and reversible, with regional myocardial ischemia;

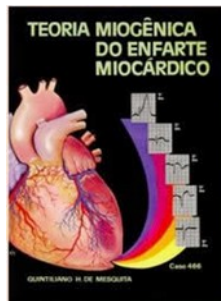
**Stage III:** Acute myocardial infarction, an irreversible process characterized by regional myocardial insufficiency restrained and reversible only by cardiotonics; absolute regional myocardial ischemia; circulatory stagnation followed by myocardial necrosis; satellite coronary artery stasis, with possible fragmentation or displacement of atheromatous plaque due to the heart attack and vascular processes; and, on occasion, secondary coronary thrombosis.

After he formulated the myogenic theory in early 1972, Dr Mesquita sought to start clinical investigations by testing cardiotonics in unstable angina. During his previous thirty-one years of medical practice, he found that all treatments for unstable angina were failures. His many years of clinical experience led him to conclude that intravenous strophanthin (K or G) was the most reliable cardiotoxic in all cases of acute myocardial infarction complicated by heart failure.

Two days after coming up with his theory, Dr Mesquita received in his medical office an engineer of fifty-seven years who had been affected for the previous fifteen days by daily outbreaks of acute coronary insufficiency, unresponsive to treatment, even to rapid-acting nitrates. According to Dr Mesquita, this individual was predestined to provide the therapeutic proof of his new theory. The patient had come to his medical office because he was on the verge of a heart attack and his personal physician passively awaited the event which, he said, could be lethal.

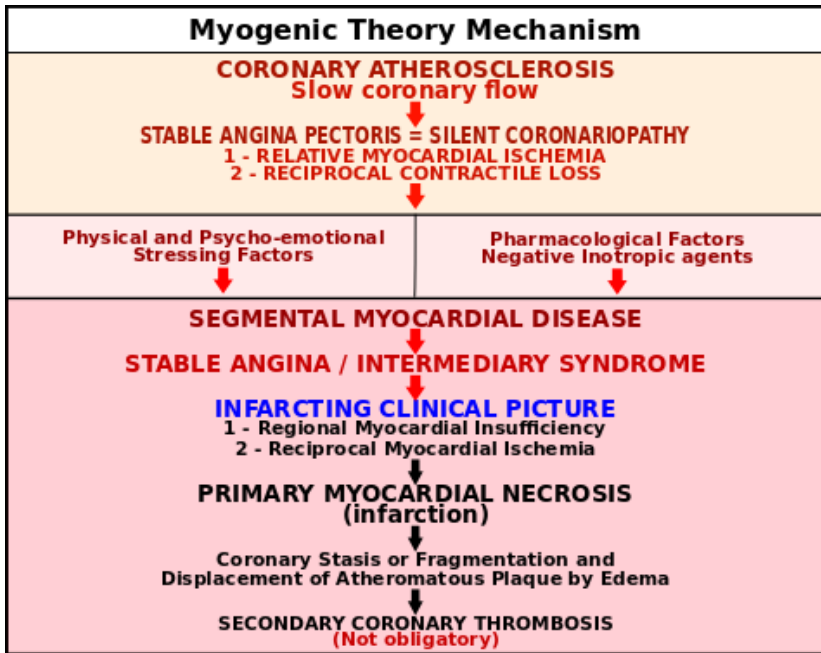
Dr Mesquita gave him an injection of strophanthin-K (1/4 Kombetin mg) plus dipyridamole (Persantine 20mg), plus an oral coronary vasodilator drug, prenylamine (Synadrin 180mg/ day), for ten days, along with bed rest in his home. When he returned to Dr Mesquita's office, the patient was declared cured because the symptoms had ceased after the first injection.

The treatment, confirmed by angiogram and ventriculogram, was so successful that Dr Mesquita felt confident of his theory. At this point, he coined his new concept the myogenic theory of myocardial infarction.



Cover of the book “Myogenic Theory of Myocardial Infarction”

Summary in English at:  
<http://www.infarctcombat.org/LivroTM/parte8.htm>



*Translated chart from the book Myogenic Theory*

## What About Atherosclerosis?

If the heart attack begins in the heart muscle itself, what is the role of atherosclerosis - hardening of the arteries - in heart disease? In his book, *Myogenic Theory of Myocardial Infarction* (1979),<sup>[4]</sup> Dr Mesquita explained that the triggering cause represented by physical exertion or psycho-emotional stress increases the activity of the heart in the face of the fixed or deficient flow in the coronary blood supply, producing the regional ischemia. This lack of blood supply then leads to the loss of contractility within a few seconds, along with reduced ejection phase, increased volume and final diastolic pressure during the ischemia, along with an overload in contractility of normal regions of the heart.

Each episode of myocardial ischemia by stress or emotion affects the cardiac muscle segment dependent on the affected coronary artery, compromising the myocardial structure. Over time the repeated ischemic manifestations in the same regions of the heart will cause pathological structural changes, different from the unaffected surrounding non-ischemic areas of normal structure.

In his book<sup>[4]</sup> Dr. Mesquita says, "Thus, the coronary disease contributes to the deterioration of the ventricular segment, constituting areas of myocardial sclerosis or segmental myocardial disease, the possible future site of the myocardial infarction."



## Stress and the Heart

One point that needs emphasis is the fact that most risk factors for coronary heart disease, including smoking, hypertension and diabetes, are associated with autonomic nervous system dysfunction with overactive sympathetic system, leading to elevation of stress hormones.

Acute stress or chronic stress overload often represents the final blow to a vulnerable segment of the heart muscle, affected by chronic coronary disease, triggering the acute myocardial infarction. However, the impact of acute stress may also trigger an MI in patients with normal coronary arteries.

Several studies have shown a close connection between catecholamine (adrenaline and noradrenaline stress hormones) and myocardial infarction. The hyperactivity of the sympathetic nervous system, with an intense outflow of catecholamine, also occurs in unstable angina, although to a lesser extent and for a shorter period of time than in acute myocardial infarction.

Takotsubo cardiomyopathy, also known as 'broken heart syndrome', is a sudden temporary weakening of the heart muscle, one obviously triggered by acute stress. In broken heart syndrome the patient has an intense outflow of catecholamine, even greater than in patients with acute myocardial infarction.

Takotsubo cardiomyopathy simulates an evolving myocardial infarction clinical picture. It occurs in patients with no signs of coronary heart disease. This is obviously a condition where the etiology is better explained by the myogenic theory of heart disease.

In addition to intense physical activity, particularly in sports competition, or unusual physical efforts that surpass the limits of the individual's heart condition, or the heavy use of stimulant drugs, there are many risk factors for acute myocardial syndromes based on recent severe stress situations or sudden emotional upset. These include marital separation or divorce, retirement or loss of work, loss of revenue or business failure, family conflicts, serious personal injury or illness, death or illness of a close family member, shock of a surprise party, armed robbery or other kinds of violence, heated discussion, threats or acts of war - even earthquakes and other frightening natural disasters.

The most common immediate cause of sudden cardiac death is ventricular fibrillation. Ventricular fibrillation is a condition in which there is uncoordinated contraction of the cardiac muscle of the ventricles in the heart, making them quiver rather than contract properly. Ventricular fibrillation may be triggered by autonomic nervous system disturbance due to acute stress.

## Cardiotonics

The heart is nourished by two main coronary arteries, the right and the left, with branches to supply oxygen and blood throughout the heart muscle, and also by a network of collateral blood vessels.

According to Dr Mesquita, an important role of the cardiotonic remedy is to enhance the effects of collateral coronary circulation and ensure the preservation of the ischemic myocardium. As noted in his book: "The collateral coronary circulation network is not always able to prevent myocardial infarction, because it develops depending on the anatomical features of the obstructive process, and also it is not always sufficient to face the demands of the coronary patient's physical activity."

Indeed, collateral coronary circulation bypasses the blockages in the coronary arteries, supplying enough oxygenated blood to enable the cardiac tissue to survive and recover. A recent meta-analysis confirmed the observation that heart disease patients with a well-developed collateral coronary circulation have an improved survival compared with patients with less developed collaterals.<sup>[5]</sup>

Cardiotonics also act to harmonize the differences in contractility between both the ischemic and non-ischemic regions of the heart and allow for coordinated function among the segments.

Findings showing that cardiotonics such as ouabain/strophanthin and digitalis (digoxin and digitoxin) have a direct relationship between dosage and myocardial contractile force were discussed by Charles C. Wycoff in 1969. Based on these findings, he raised the hypothesis of a possible beneficial effect from digitalis in a dose much lower than that which was considered effective in the past. Noting that in many clinical settings, digitalis showed beneficial effects during surgery and for chronic hypertension, angina, acute myocardial infarction, and healed myocardial infarctions, Wycoff argued for a much wider use of digitalis than the generally accepted indications for this drug.<sup>[6]</sup>

Cardiotonics may offer other possible benefits for ischemic heart disease, independent of their effects on the strengthening of heart muscle contraction, through stress reduction by the improvement of baroreceptor function, reduction of sympathetic nervous system activity, support of the vagus nervous system, and reduction in secretion of catecholamines.<sup>[7,8,9]</sup>

Cardiotonic drugs have been used for over two hundred years to treat patients with heart failure where there is reduced force of muscle contraction, due to overloading of the ventricle.

As predicted by Wycoff, recent studies have indicated that a beneficial effect on morbidity and mortality from digoxin, the most popular cardiotonic drug for heart failure, is seen at lower rather than higher doses.<sup>[10-12]</sup> By the

way, it has been known for more than one hundred years that heart failure is characterized by excessive sympathetic nervous system activity.

## Lactate In The Heart

The heart is an organ of high metabolic activity - it cannot rest as can other body muscles. Chronic or acute elevated catecholamine release may accelerate myocardial glycolysis leading to a significant increase in lactate production. Lactic acidosis results from increased production of lactate, the final product in the pathway of glucose metabolism. Studies show that lactate accumulation predicts ischemic myocardial necrosis.<sup>[13]</sup>

Measurement of arterial blood lactate is considered a consistently useful prognostic indicator of survival or fatality in patients with acute myocardial infarction.<sup>[14]</sup> A recent study has shown a significant association of elevated plasma lactate levels with heart failure and all-cause mortality.<sup>[15]</sup>

Therefore, the reduction of stress due to cardiostimulant use may indirectly lower lactate production by the heart muscle. Bruno Levy and colleagues' postulate that adrenaline increases lactate formation by an increase in the  $\text{Na}^+\text{K}^+$  - ATPase activity,<sup>[16]</sup> which can be inhibited through cardiostimulants that are sodium pump inhibitors. The link between adrenaline and increased  $\text{Na}^+\text{K}^+$  - ATPase activity is well established.

Robert Tennant and Carl J Wiggers hypothesized in 1935 that the accumulation of lactic acid and decrease in pH were linked to myocardial contractile failure after the occlusion of the coronary arteries.<sup>[17]</sup> Tennant also proposed in 1935 that tissue acidosis might account for contractile failure during myocardial ischemia.<sup>[18]</sup>

The first to observe the influence of adrenaline on lactic acid production were the Coris in the early 1920s.<sup>[19]</sup> In 1964, John R. Williamson confirmed the effects of adrenaline infusion on the increased production of lactate in isolated heart tissue, up to five times the normal production.<sup>[20]</sup>

Dr Mesquita reveals in his writings a different source generating excess lactate in the heart muscle leading to the infarction: "The failure of the myocardial ischemic area, losing regional contractility and relaxing the myocardial fiber, would become stagnant and without contractility, thus developing anaerobic metabolism - with the deposit of lactate and catabolites plus depletion of energetic phosphate."<sup>[4]</sup> According to Dr Mesquita, the anaerobic metabolism represents a step toward the myocardial infarction and necrosis in the particular region of the heart.

A seminal paper published in the November 2013 *The Lancet Diabetes & Endocrinology* reviewed recent findings showing that hyperlactatemia is not a consequence of anaerobic metabolism, tissue hypo-perfusion or reduced oxygen to the cells. The authors say in their conclusion that "In all studied settings, lactate production happens under fully aerobic conditions. Such hyperlactatemia is probably indicative of a stress response, with increased

metabolic rate and sympathetic nervous system activation inducing a state of accelerated glycolysis and modified bioenergetic supply.”<sup>[21]</sup>

Increased blood lactate levels are also associated with cigarette smoking,<sup>[22]</sup> diabetes,<sup>[23,24]</sup> hypertension<sup>[25]</sup> and atherosclerosis,<sup>[26]</sup> proven risk factors for heart disease.

## Endogenous Cardiotonics

The recent discovery of endogenous cardiotoxic steroids (also known as digitalis-like compounds and endogenous cardiac glycosides - digoxin, digitoxin, ouabain/ strophanthin, proscillaridine, etc.) - isolated from human tissues and body fluids, may represent a strong new argument for the myogenic theory of myocardial infarction.

Elevated concentrations of endogenous cardiotonics have been found under different clinical conditions such as sodium imbalance, hypertension, cardiac arrhythmias, chronic renal failure, congestive heart failure, and acute myocardial infarction. Vigorous physical exercise as well as physiological stress situations may also elevate the concentration of endogenous cardiotonics in the human body.

We can surmise that the cardiotonics found in nature, like digoxin and ouabain/strophanthin, may compensate for a deficient production of endogenous cardiotoxic steroids by the human body and thus support cardiac metabolism and protect the heart from the infarction, as proposed in the myogenic theory.

## Recent Studies

Sudden emotional stress<sup>[35]</sup> or strenuous exercise<sup>[36]</sup> may precipitate temporary and reversible regional myocardial failure in patients without cardiovascular disease. Moreover, a study published in April 2014 demonstrated that in a large multi-ethnic cohort without symptoms of cardiovascular disease at enrolment, elevated resting heart rate was strongly associated with the development of regional and global left ventricular dysfunction, as well as the incidence of heart failure.<sup>[37]</sup>

In 2006 the same group provided evidence of a direct relationship between subclinical atherosclerosis and reduced regional myocardial function in asymptomatic individuals - with alterations in myocardial contractility - without previous clinical cardiovascular disease.<sup>[38]</sup> Left ventricular dysfunction classification also includes regional myocardial failure, a term coined by Tennant and Wiggers in 1935,<sup>[17]</sup> which was adopted by Mesquita in 1972, but later designated by others as “myocardial stunning.”

These striking findings provide cutting edge evidence to the pathophysiological mechanism of the myogenic theory of myocardial infarction.

## Tribute to Dr Mesquita

In November of 2012, we have made a tribute to Dr Mesquita during the Fourth International Conference of Advanced Cardiac Sciences - the “King of Organs” conference, held in Saudi Arabia, presenting some of Dr Mesquita’s pioneering contributions to medical science, particularly regarding the pathophysiological and therapeutic concepts of the myogenic theory.

The presentation covered the following topics: Coronary Thrombosis: Cause or Consequence of Myocardial Infarction? Introduction and Fundamentals; Mechanism and Sequence of Events; Stress and Acute Myocardial Syndromes; and Benefits of Cardiotoxic Drugs in Patients with Stable Ischemic Heart Disease, Unstable Angina, and Acute Myocardial Infarction.[5]

*(L-R) David Diamond,  
Malcolm Kendrick, Carlos  
Monteiro and  
Paul Rosch during a break in  
proceedings at the  
conference.*



The author is indebted to Dr Paul J Rosch, president of the American Institute of Stress, professor of medicine and psychiatry at New York Medical College, and member from the scientific committee, who suggested him as a speaker for this conference.<sup>[27]</sup>

## Pathologic Q Waves

Pathologic Q waves, as seen on an electrocardiogram, are usually a sign that indicates current or prior myocardial infarction. They show the absence of electrical activity. A myocardial infarction can be thought of as an electrical 'hole', since scar tissue is electrically dead and therefore results in electrocardiographic Q waves. Pathologic Q waves are not an early sign of acute myocardial infarction, but generally take several hours to days to develop. Once pathologic Q waves have developed, they rarely go away.

The use of pathologic Q waves in electrocardiographic diagnosis of acute myocardial infarction has decreased in clinical practice during the last decades.

In 2000, medical boards proposed the first official redefinition of myocardial infarction, followed by others, which were published in 2007 and 2012, with the endorsement of the European Society of Cardiology, the American College of Cardiology Foundation, the American Heart Association, and the World Heart Federation.

These redefinitions of myocardial infarction implied that any signs of necrosis in the setting of myocardial ischemia, regardless of the pathobiology, should be labelled as MI. This favored using the protein troponin as the preferred biomarker for MI. Troponin is considered a highly specific marker for myocardial infarction or heart muscle cell death.

They also spread the use of ST segment elevation in electrocardiographic diagnosis of MI. However, troponin levels may be elevated in other cardiac and non-cardiac disorders, not just in myocardial infarction. Also, both ST segment elevation and ST segment depression may be associated with other ischemic settings, with no infarction. These redefinitions strategy resulted in more cases being diagnosed, adding patients with conditions not so severe and consequently leading to the decrease in statistical indices of global mortality for myocardial infarction.

Despite the significant drop in mortality using this new broadened definition for myocardial infarction, recent studies claim that "Q-waves are a major determinant of in-hospital mortality, and targeted interventions should be directed to these high-risk patients." <sup>[32]</sup>

Incidentally, studies have shown that mental stress <sup>[33]</sup> and exercise <sup>[34]</sup> may induce cardiac troponin elevation, unrelated to myocardial injury, leading many people to unnecessary hospital admissions and invasive procedures.

## Thrombogenic Theory Versus Myogenic Theory of Heart Disease

Let's look at the different philosophies, therapeutics, and outcomes for the three stages of ischemic heart disease.

### **Stage One**

The first stage is represented by symptomatic and myocardial stability, stable angina pectoris, and silent coronary cardiomyopathy, with and without previous infarction. In this stage, the main therapeutic focus of the thrombogenic theory is to maintain the coronary blood flow by correcting or circumventing the obstructions in the coronary arteries caused by atherosclerosis and to avoid coronary thrombosis thought to lead to myocardial infarction. This is accomplished through procedures like angioplasty, stents, and coronary atherectomy; the creation of grafts in the coronary artery; bypass surgery; and by the use of drugs like coronary dilators, adrenergic beta-blockers, cholesterol-lowering agents like statins, anticoagulants and antiplatelet agents. The intention is to ensure the myocardial perfusion by improving the coronary blood flow; however, this strategy leaves the ventricular function to its own fate.

By contrast, the goals of the myogenic theory in the first stage of heart disease are to neutralize the reduced contractility effects of ischemia; to preserve the function of the ventricles; to prevent unstable angina, myocardial infarction, heart failure, and sudden death due to severe arrhythmias; to ensure permanent myocardial stability; to provide a peaceful, comfortable, and predominantly asymptomatic long survival; and to support the natural effects of coronary collateral circulation, when it is already established.

These goals are accomplished by the prophylactic oral use of cardiotonics like low dose digoxin plus coronary dilators and ACE inhibitors - the last one indicated by Dr Mesquita since the 1990s.

An interesting study involved two groups of stable patients using the therapeutics recommended by the myogenic theory in the first stage of ischemic heart disease; these cases were followed by Dr Mesquita and colleagues.<sup>[28,29]</sup>

The first group included 994 patients without prior infarction given cardiotonics, presenting over twenty-eight years the following morbidity and mortality:

- Myocardial infarction: 14 cases (1.4%);
- Heart failure mortality: 32 cases (3.2%);
- Sudden death: 72 cases (7.2%);
- Stroke mortality: 13 cases (1.3%);
- Cancer mortality: 14 cases (1.4%);
- Other causes of mortality: 11 cases (1.1%);

- Total mortality: 142 cases (14.2%) - (0.5% per year!);
- Mean age at death: 76 years.

The second group included 156 patients with prior infarction, also using cardiotonics, presenting over twenty-eight years the following morbidity and mortality:

- Recurrent MI: 8 cases (5.1%);
- Heart failure mortality: 17 cases (10.8%);
- Sudden death: 32 cases (20.5%);
- Stroke mortality: 7 cases (4.4%);
- Cancer mortality: 3 cases (1.9%);
- Other causes of mortality: 5 cases (3.2%);
- Total mortality: 64 cases (40.8%) - (1.45% per year!);
- Mean age at death: 72 years.

As a point of interest, we can compare total, cancer, and stroke mortalities, using the therapy recommended by the myogenic theory, with those found in The Heart Protection Study (HPS),<sup>[30]</sup> which had a follow-up of five years, involving 20,536 patients aged forty to eighty years with coronary heart disease, other vascular diseases, or diabetes. The HPS found a total mortality of 12.9 percent (2.58 percent per year). The specific mortality for cancer was 3.5 percent (0.70 percent per year) in patients taking statins and 3.4 percent (0.68 percent per year) in patients taking a placebo. Regarding the stroke mortality the HPS found a total of 0.9 percent (0.18 percent per year) in patients taking statins and 1.2 percent (0.24 percent per year) in patients taking placebo. Taking digoxin and other cardiotonics administered by Dr Mesquita and colleagues resulted in a much lower mortality rate for cancer (0.06 percent per year) and stroke (0.04 percent - 0.15 percent per year).

## **Stage Two**

Stage two is represented by symptomatic and myocardial instability - unstable angina pectoris, either quiescent or pre-infarction. In this stage the primary focus of the thrombogenic theory of heart disease is to re-establish the coronary blood flow in the coronary arteries, partially or totally obstructed by atherosclerosis, with or without coronary thrombi, and to avoid the imminent myocardial infarction.

The immediate therapeutic is the use of thrombolytics, coronary dilators, beta-blockers, anticoagulants, or antiplatelet drugs - plus coronary angioplasty, stents, coronary artery bypass surgery and coronary atherectomy.

The focus in the myogenic theory is the immediate correction of the regional and primary myocardial insufficiency responsible for the secondary myocardial ischemia and restraining the quiescent angina pectoris episodes; reestablishment of the symptomatic and myocardial stability; and prevention of myocardial infarction.



As with Stage One, the therapeutic action for the unstable angina is the use of cardiotonics plus a coronary dilator. In one hundred ninety-nine patients, Dr Mesquita found that this strategy led to an immediate interruption of the spontaneous episodes, with subsequent myocardial infarction reduced to 0.5 percent and a mortality rate of zero.<sup>[28]</sup>

### **Stage Three**

The third stage is represented by acute myocardial infarction. The main focus in the thrombogenic theory is to re-establish the coronary flow interrupted by vasospasm or intracoronary thrombus. After the detection of complete obstruction of the coronary artery by cardiac catheterization, nitroglycerine is used to control the vasospasms. If the obstruction persists, the patient is submitted to thrombolytic action followed by anticoagulant and antiplatelet agents. The symptomatic treatment is initiated with coronary dilators, beta blockers, and antiplatelets. In cases of partial coronary obstruction, patients undergo bypass surgery, stents, atherectomy or angioplasty. In cases of patients with coronary arteries angiographically normal, the explanation in general is the occurrence of spontaneous fibrinolysis.

The three most common types of electrocardiographic diagnosis for the myocardial infarction are ST-segment elevation myocardial infarction, non-ST-myocardial infarction, and pathological Q waves.

In the Grace multinational observational study, which involved 21,688 cases with acute myocardial syndrome (STsegment elevation MI, non-ST-MI, or unstable angina), 9.1 percent died or experienced a non-fatal myocardial infarction between the hospitalization and the six-month follow-up.<sup>[31]</sup> Many studies have shown a thirty-day mortality for patients with Q-wave MI between 17 and 30 percent (Hutter et al, 1981; Scheinman and Abbott, 1973; Szklo et al, 1978; Cannon et al, 1976; Mahoney et al, 1980; Rigo et al, 1975; Connolly and Elveback, 1985; etc.).

The first goal for Stage Three in the myogenic theory is to correct the regional myocardial insufficiency and reduce myocardial ischemia, halting the infarcting clinical picture immediately as the patient enters the coronary unit, seeking to avoid the infarction or to interrupt its evolution, or at least mitigate the attack.

This includes reducing the size of infarction as well as preventing the secondary coronary thrombosis through the cessation of circulatory stagnation in the satellite artery of the infarction and in the compromised myocardial region. The immediate therapeutic is, again, a cardi tonic, given intravenously, plus coronary dilator.

As for the results of therapy with cardiotonics, without any invasive treatment, Dr Mesquita and his colleagues followed 1109 patients with a heart attack confirmed by Q waves. Mortality in the hospital was 12.2 percent; at thirty days from hospital release, it was an impressive 0.4 percent. Of patients under seventy years old, 9.7 percent died, while in patients over seventy years, 28.1 percent died.<sup>[28]</sup> Results are as follows:

5. Ventricular extrasystoles: 24.1%;
6. Partial AV block: 5.8%;
7. Complete AV block: 4.6%;
8. Atrial tachycardia: 1.7%;
9. Flutter - atrial fibrillation: 4.4%;
10. Tachycardia + ventricular fibrillation: 2.7%;
11. Asystole: 4.5%;
12. Cardiogenic shock: 2%;
13. Acute pulmonary edema: 1.3%;
14. Heart failure: 1%;
15. Overall mortality in-hospital: 12.2%;
16. Mortality in 30 days after the discharge from hospital: 0.4% (5 patients);
17. Mortality by age: 9.7% in patients under 70 years and 28.1% in patients over 70 years.

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Autonomic Dysfunction + Lactic Acidosis = Multiple Diseases

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## Chapter 2

# Digitalis and Strophanthin in Stable Ischemic Heart Disease and to Restrain or Reverse Heart Attacks

An Amazing and Shocking Story

*Carlos ETB Monteiro*

*“Although one can harm or kill even a healthy man with injudicious use of digitalis, in the author's experience with acute myocardial infarction, complications (including the onset of ventricular tachycardia and the occurrence of sudden death) appeared as often in those patients who were not receiving digitalis as in those who were receiving it. In a series of 265 consecutive cases, his first admission mortality rate was 10 percent, compared with that of 16 percent in a similar series of 286 cases.*

*This suggests that the use of digitalis was not strikingly harmful, and may well have been beneficial”,  
Ferdinand R Schemm, 1950 <sup>[1]</sup>*

The first therapeutic use of digitalis with beneficial effects for heart disease was described by William Withering in 1785. Withering did not understand how this drug acted on cardiac dropsy (edema due to congestive heart failure). However, he was aware that digitalis exerted some action on the heart and that it retarded the pulse, for he wrote, “That it has a power over the motion of the heart, to a degree yet unobserved in any other medicine, and that this power may be converted to salutary ends.” <sup>[2]</sup>

It is important to note that during the 19th century the term congestive heart failure was used to designate other diseases of the heart and, in the beginning of the 20th century, digitalis was prescribed for the treatment of organic heart disease, including angina. During this time digitalis was extensively indicated in hypertension cases, especially associated with cardiac enlargement, to prevent heart failure. <sup>[3]</sup>

*Some praises for Digitalis:  
(Digitalis Purpurea)*

*“A God-given remedy”,  
Friedrich Ludwig Kreysig,  
Berlin. 1814 <sup>[4]</sup>*

*“The opium of the heart”,  
Jean Baptiste Bouillaud,  
Paris, 1841<sup>[5]</sup>*



In his classic paper about coronary thrombosis (thrombogenic) theory written in the early 20th century, Dr. James Bryan Herrick (1912), wrote of his therapeutic experience using digitalis and strophanthin for angina pectoris and in the event of coronary thrombosis <sup>[6]</sup>. Herrick said:

*"...If these cases are recognized, the importance of absolute rest in bed for several days is clear. It would seem to be far wiser to use Digitalis, Strophanthus or their congeners than to follow the routine practice of giving Nitroglycerin or allied drugs. The hope for the damaged Myocardium lies in the direction of securing a supply of blood through friendly neighboring vessels, so as to restore so far as possible its functional integrity. Digitalis or Strophanthus, by increasing the force of the heart's beat, would tend to help in this direction more than the Nitrites. The prejudice against Digitalis in cases in which the Myocardium is weak is only partially grounded in fact. Clinical experience shows this remedy to be of great value in Angina, and especially in cases of angina with low blood pressure, and these obstructive cases come under this head. The timely use of this remedy may occasionally in such cases save life. Quick results should also be sought by using it hypodermically or intravenously. Other quickly acting heart remedies would also be of service."*

Herrick's priority in his treatment approach was to preserve the myocardium in the occurrence of coronary thrombosis. Undoubtedly Herrick was the first to raise the importance of coronary collateral circulation using the cardiotonic to restore the functional integrity of the myocardium. This clinical approach was largely ignored by his colleagues; perhaps it didn't sound plausible, possibly due to the absence of experimental support.

Or perhaps Withering was right in his despair:

*"I wish it was easy to write about Digitalis. I despair of pleasing myself or instructing others in a subject so difficult. It is much easier to write about a disease than a remedy. The former is in the hands of nature and a faithful observer with an eye to tolerable judgment cannot fail to delineate a likeness; the latter will ever be subject to the whims, the inaccuracies and the blunders of mankind." William Withering, Letter, Sep 29, 1778.<sup>[7]</sup>*

Regardless, the fact is that Herrick's therapeutic approach isn't taught at medical schools or discussed in scientific papers. As a result, most physicians remain in total medical ignorance about Herrick's clinical practice in the treatment of angina and coronary thrombosis (acute myocardial infarction), also known under the general term 'heart attack'. The Thrombogenic Theory was adopted, but his therapeutic conduct was forgotten. This repeated omission over time has certainly contributed to the formation of the current dogma on how to deal with heart disease.

Louis Hamann in 1926 shared the same idea and enthusiasm of Herrick about the digitalis use in the treatment of coronary thrombosis. He said. "The patient should be promptly and fully digitalized. Not only is the digitalized heart better prepared to withstand the added burden of certain arrhythmias should they come on, but it is also stimulated to put forth its best efforts. How desirable the best efforts may be when a large area of heart muscle is infarcted, needs no further comment. .<sup>[8]</sup>

Doctors in different times and countries have used digitalis or strophanthin in the treatment of acute myocardial infarction and angina. Some doctors also used digitalis or strophanthin as prevention therapy.

*Strophantus Gratus*

**Strophanthins** are extracted from Strophanthus Gratus tree (g-strophanthin), Strophanthus Kombe tree (k-strophanthin) or the Acocanthera ouabaio tree (Ouabain = identical with g-strophanthin).



These drugs were used originally by inhabitants from Africa as arrow poisons. In the USA, due to a few unfavorable experiences during the early years of intravenous strophanthin administration, attributable to individual therapeutic mistakes, there was a general refusal by the American physicians to use intravenous strophanthin for routine treatment.<sup>[9]</sup>

Meanwhile Dr Ernst Edens from Germany, after using for 3 years strophanthin injections - by intravenously route - for angina and infarction, in over 100 patients, referred to it as a divine blessing, saying the strophanthin treatment is the safest treatment for the organic cause of angina pectoris and myocardial infarction.

His idea was that the poor blood supply through the coronaries would be improved by the treatment with strophanthin. He stated that with this recognition nobody would have the right to use strophanthin only for scientific reasons and testing, giving preference to other remedies and thus losing precious time for cure. He also expressed the view that the time will come in which the omission of the use of strophanthin therapy would be seen as a professional malpractice.

Edens, who was Professor at the University of Dusseldorf, presented his initial clinical experience with strophanthin during a medical congress in Wiesbaden held in 1931. On that occasion he stated that he had the myocardial infarction under control. However, he was not apt to explain the exact strophanthin mechanisms in relation to the cardiac muscle, telling that he acted inside the principle:

*"Whether we understand it or not what happens here is that strophanthin works effectively and so we need to use it."*

Few of the doctors participating at the Wiesbaden Congress showed interest in the experiences from Edens regarding the use of strophanthin in the acute myocardial infarction. On the contrary, most of his medical colleagues reacted with hostility, trying to suppress his voice as if it was an intruder. The practical experience of Edens and his pupils H Zimmermann and Wagenfeld, in the treatment of angina and myocardial infarction, by intravenous strophanthin use, gained some followers. <sup>[9,10,11,12,13,14]</sup>

Berthold Kern, cardiologist from Stuttgart, Germany, based on his own theory that the low pH value found in the inner layers of the left ventricle would be the cause of infarction, prescribed oral (sublingual) g-strophanthin for the prevention of myocardial infarction. According to his theory the myocardial infarction occurs due to a formation of lactic acid in excess, destroying the cells and causing a chain reaction such as a fire in a forest which only strophanthin, for its acidity-lowering effect in the heart muscle, would be able to stop the infarction process. He adopted the view that the myocardial infarction was not caused by coronary thrombosis but by myocardial origin.

Berthold Kern prescribed as prophylaxis daily doses of sub-lingual g-strophanthin to 17,000 patients during the period from 1947 to 1971, resulting in a small number of infarctions (150 cases) and near zero deaths related to heart problems. <sup>[15,16,17]</sup>

Berthold Kern and colleagues, defending the use of sub-lingual strophanthin for prevention of the myocardial infarction were literally executed in a symposium held in late 1971 in Heidelberg, at the Molkenkur restaurant. There they met large criticism by the orthodox medicine. The opposing doctors, who attended in considerable numbers to the event, accused their therapy on the grounds that the gastric absorption of strophanthin administered orally, was minimal and insufficient to achieve the desired effect. According to their opponents much larger doses would be needed and that could lead to poisoning. This medical meeting became known as the Heidelberg Tribunal with the attendance of the press, radio and television. Even today, the Heidelberg Tribunal is the starting point for frequently spread obscure conspiracy theories. <sup>[12,18,19,20]</sup>

After this time very few researches, discussions as well as teachings and publications took place in academia about the use of strophanthin for prevention or to fight heart attacks. The use of strophanthin was banned and made taboo by the official medical practice.

However, the opponents of sublingual strophanthin-g were mistaken because it is also absorbed by the adrenal gland, among other findings, showing positive effects for the human body as demonstrated lately. These



findings allowed new opportunities on the use of strophanthin for other medical conditions.

Until the end of the last century about 5,000 doctors from Germany gave prescriptions for oral g-strophanthin to their patients. In a survey published during the eighties 3,645 German doctors made statements on the use of this medicine in their medical practices from 1976 to 1983. This survey showed that nearly 95% of them gave positive testimony, with no reservations.

There was no negative feedback regarding the treatment with oral strophanthin-g, for the remainder of the doctors who participated in the survey.<sup>[21]</sup>

Dr Thomas Cowan, from San Francisco - California USA, is one of those physicians currently using Ouabain (g-strophanthin) for prevention and treatment of infarctions in their patients, with great success.<sup>[22]</sup>

### **The Myogenic Theory**

The Brazilian Dr. Quintiliano H de Mesquita developed in 1972 the myogenic theory of myocardial infarction, where cardiotonics like digitalis and strophanthin are the fundamental and specific drugs for the coronary-myocardial disease, including acute myocardial syndromes.<sup>[23]</sup>

In his view, the anaerobic metabolism, with excessive lactate production, represents a step toward the myocardial infarction and necrosis in the particular region of the heart.<sup>[24]</sup>

Dr Mesquita's prescribed from period 1972-1979 strophanthin or digitalis, intravenously, in 1183 patients with acute myocardial infarction, registering an overall hospital mortality of 12%. In 126 cases of unstable angina, using intravenous strophanthin avoided the infarction and obtained a mortality of 0% during hospital stay.<sup>[25,26,27]</sup>

These patients were treated at the Cardiology Institute at Matarazzo Hospital, headed by Dr Mesquita. His Institute was a centre of medical excellence and school where many doctors came from all over the country for medical internship.

The preference from Dr Mesquita was the use of intravenous strophanthin in patients with unstable angina and acute myocardial infarction.

As I wrote in a recent article about his preference: "His many years of clinical experience led him to conclude that intravenous strophanthin (K or G) was the most reliable cardiotonic in all cases of acute myocardial infarction complicated by heart failure."<sup>[28,29]</sup>

Rolf Dorhman from the Berliner Waldkrankenhauses in Berlin - Germany, achieved for 5 years similar results to the Brazilian professor applying the treatment with intravenous strophanthin to fight the acute myocardial infarction, according to a report by Dr Peter Schmidberger at Bunte Magazine in 1980.<sup>[13, 30]</sup>

Particularly interesting is that besides improving myocardial contractility the drugs Digitalis and Strophanthin have important properties under the view of his myogenic theory like sympatho-inhibitory response and potent inhibition over glycolysis, reducing lactate production.<sup>[31]</sup>

In 1975 Dr Mesquita was awarded the Ernst Edens Traditionspreis by the International Society to Fight Infarction (Internationale Gesellschaft für Infarktbekämpfung), whose president at the time was Dr Berthold Kern.<sup>[32]</sup>

In the treatment of stable ischemic heart disease patients, with or without previous myocardial infarction, Dr Mesquita's preference was the use of oral digitalis at low dosages. During 28 years, using digoxin and other digitalis drugs, he achieved a total annual mortality rate of only 0.5% in patients without infarction (994 pts.) and 1.4% in cases with prior infarction (154 pts.).<sup>[33,34]</sup>

A study published in 1995, by Leor et al, has shown that one-year mortality was significantly higher among patients treated with a full dose [19 of 112 (17%)] than patients treated with a low dose of digoxin [1 of 41 (2%)]. This is comparable to the remarkable results obtained since 1972 by Mesquita and colleagues in patients with previous infarction taking daily digitalis drugs at low concentrations by the oral route.<sup>[35]</sup>

The myogenic theory and its consistent indication for the use of cardiotonics (digitalis, strophanthin, etc.) in the stable ischemic heart disease or in the treatment of acute myocardial infarction had a rather cold reception. There was a continued silence about the subject that lasts to this day.

The skeptical medical elite acted with disinterest regarding the myogenic theory. Dr Mesquita never received external funds for his researches. Neither did he have any intention to give up from the pursuit of the medical truth, even if at his own expenses. Most of his papers about the myogenic theory were rejected in the peer review process from medical journals. However, he never suffered direct attacks by his medical colleagues that recognized his great scientific status and integrity. They were quite satisfied with their apparently well-established theories and medicines.

On the other hand, the public knowledge about the myogenic theory could jeopardize their economic and prestige achievements. So, the myogenic theory was transformed in a taboo inside the medical field.

Dr. Mesquita in the beginning of the forties, participated in the foundation of the Brazilian Cardiology Society being the first treasurer. When he died in October 2000, I paid a posthumous tribute to him which was published in January 2001 in the Brazilian Archives of Cardiology - journal of the Brazilian Cardiology Society. I said in my homage about his many pioneering contributions to the cardiological science, among these:

1. The first case of ventricular aneurysmectomy surgery performed by Charles Bailey, in 1954;

2. The first case of right ventricular infarction with the diagnostic held in a live patient inside new electrocardiographic patterns contradicting Cavity Potential Theory of Q waves and confirming the Vectorial Theory of ECG, in 1960;
3. The Myogenic Theory of Myocardial Infarction, in 1972;
4. The confirmation of the Accelerated Conduction Theory from Myron Prinzmetal, 1999.[36]

Intravenous strophanthin was withdrawn from the pharmaceutical arsenal in Brazil at the end of the seventies, maybe a retaliation from the 'status quo'. Later both intravenous and oral (sublingual) strophanthins were withdrawn from the pharmaceutical arsenal in Germany, certainly due to the same reasons that occurred in Brazil.<sup>[17]</sup> The difficulties to obtain strophanthin in Brazil led Dr. Mesquita to the use of intravenous digitalis in patients having unstable angina or acute myocardial infarction, with good results for digitalis but not as good as strophanthin.

## **Digoxin Removal from the Market: A Possible Scenario?**

Few years ago, a scandalous situation occurred with the lack of digoxin pills from the main pharmacies and drugstores in Brazil, lasting about 4 months (From March until June 2015).<sup>[37]</sup>

The absence of digoxin during this period of time has obliged local physicians to change the prescriptions of patients with heart failure or with atrial fibrillation for drugs without the properties and effectiveness of digoxin. A well-known fact is that the digoxin removal may exacerbate the heart failure, putting the patients in risk of life. Fortunately, the judicial system in Brazil is working satisfactorily. The Prosecutor's Office in their Extrajudicial Civil Division has intervened on the subject that resulted in the normalization of digoxin supply to the Brazilian market. The fact is that digoxin, as well as other drugs derived from digitalis (foxglove) were used for over 200 years in the treatment of heart failure. Digitalis has no patent and a very low cost for the patient. The digoxin therapy was also associated in studies with a significant cost reduction related to hospitalizations for heart failure.

It is unclear if economic factors were the unique reason for the possible tentative to the withdrawal of digoxin from the market, not existing scientific justifications for what has happened in Brazil. It seems like an attempt to probe the terrain that, if successful, might lead the pharmaceutical companies to do the same in other countries (or in a global manner) during the next years.

Coincidentally there was a study published in the European Heart Journal (May 4, 2015), largely promoted in medical news journals and in the media in general, saying that digoxin increases the risk of early death in patients with heart problems. This study, entitled Digoxin associated mortality: a systematic review and meta-analysis of the literature<sup>[38]</sup>, is highly misleading because:

- 1) The authors presented in their study statistical numbers based on increased relative risk instead increased absolute risk, inflating in this

way to 21% what in the real world might be less than 1% increase in mortality, so scaring those people not familiarized with statistical formulas.

- 2) The demonstration from studies that low dose of digoxin (0.125 mg daily) is enough to achieve the serum digoxin concentration (SDC) currently recommended (0.5 to 0.9 ng/mL). Among the benefits of the low dose of digoxin are better hemodynamic effects and improvement of the neurohormonal profile - stress reduction. Obviously, the current recommendation for SDC, that started in 2006, was not followed in many of the papers selected by the authors in the period studied (1993 - 2014).
- 3) The authors made a tremendous cherry picking to find what interested them to present (From a total of 1524 studies initially identified, only 19 matched their search criteria), discarding some important studies and information, not fitting with their plans.
- 4) Also, the authors didn't take into consideration in their analysis that patients taking digoxin are usually older, with more severe pathologies and high mortality risk.
- 5) On the other hand, the authors focused too much in their opinions on the supposed potential mechanisms of digoxin-associated mortality increase, which do not occur with low dose of this drug.

The landmark study made by the Digitalis Investigation Group (DIG) trial from 1997 concluded that digoxin did not reduce overall mortality but reduced the rate of hospitalization both overall and for worsening heart failure.<sup>[39]</sup>

The evidence that the autonomic nervous system dysfunction plays an important role in the pathogenesis of atrial fibrillation was discussed in a recent review.<sup>[40]</sup> It has been known for more than one hundred years that heart failure is also characterized by autonomic dysfunction with excessive sympathetic nervous system activity. The autonomic dysfunction may be improved through the use of digoxin at low dose by restoring the balance between the sympathetic nervous system and the parasympathetic nervous system activity.

Apparently, the paper published in the European Heart Journal wasn't sponsored by the pharmaceutical industry. However, there are declared conflicts of interest from the authors, regarding their relationship with the pharmaceutical industry. Frankly, this paper sounds like a libel in a possible campaign against digoxin.

Incidentally, Dr Melissa Walton Shirley in article entitled "The Demonization of Digitalis: Plain Stupid", published in Medscape, talked about the pressure to doctors from the insurance companies that they stop patient's digitalis and replace it with other cardiac drugs. This represents an unethical and immoral request from those working with insurance companies.<sup>[41]</sup>

## **Groundless Concerns about the Use of Digitalis or Strophanthin in Stable Ischemic Heart Disease or in Acute Myocardial Infarction**

The concern that digitalis and strophanthin might have a detrimental effect on the recent infarcted myocardium have arisen from observations made decades ago in animals, following coronary ligation, which have shown an increased incidence of ventricular arrhythmias and an extension of the area of infarction.

However, these results from experiments in animals have not to date been proved in humans. It should be taken into account that it takes hours and days for a thrombus to develop enough to block a heart artery.

Discussing the use of digitalis in myocardial infarction Arthur Dodek said in 1974:

*“The appropriate use of this drug should be guided by sound scientific studies, not by unsupported opinions, speculations or clinical impressions.”* <sup>[42]</sup>

The reading of the chapter “Cardiotonic in Acute Myocardial Infarction and Chronic Coronaropathy” is strongly recommended, translated to English from the book Myogenic Theory of Myocardial Infarction, 1979..<sup>[43]</sup> It contains the historical use of digitalis (digoxin, digitoxin) and strophanthin /ouabain in the treatment of stable ischemic heart disease and acute myocardial syndromes. In this chapter was presented the view that there are no valid clinical studies proving that digitalis danger exists in human myocardial infarction. In a summary of his book Dr Mesquita, says:

*“Papers on experimental pharmacological studies have been responsible for the absolute contraindication of cardiotonics for acute myocardial infarction, as a result of their possible damaging action, owing to the increase of contractility and of oxygen consumption under conditions of a smaller oxygen supply.*

*Spreading such concepts generated a ban against cardiotonics on acute infarction cases. Nevertheless, clinical papers on the administration of cardiotonics in acute myocardial infarction, despite no experimental support, have been stimulating in their results, with absence of complications and a low mortality rate.*

*These features oppose each other, but they are significant and sound, because the therapeutic results have consecrated these drugs and should awaken the researchers to them”.*

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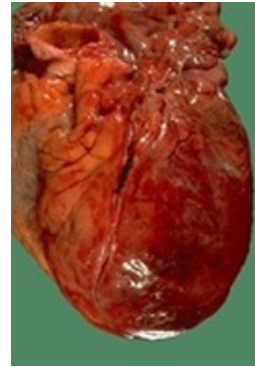
## Chapter 3

# Coronary Thrombosis Theory of Heart Attacks: Science or Creed?

*Carlos ETB Monteiro*

The thrombogenic theory, that advocates the myocardial infarction as consequence of coronary thrombosis, was introduced by the American Dr. James Bryan Herrick in 1912.<sup>[1]</sup> It was entrenched in the medical culture worldwide in spite of important clinical, pathological and cardiac images studies showing discrepancies in their findings, basically conflicting with the conceived pathophysiology for this theory.

*Myocardial Infarction:  
Credit to med.utah.edu*



It is interesting to notice that Herrick in his classic paper have written about his therapeutic experience praising the use of digitalis and strophanthin for angina and in the event of coronary thrombosis, with the hope for the damaged myocardium in the direction of securing a supply of blood through friendly neighboring vessels, so as to restore so far as possible its functional integrity.

He also said that the timely use of this remedy may occasionally in such cases save live and quick results should also be thought by using it hypodermically or intravenously. Herrick's thrombogenic theory was adopted, but his therapeutic conduct was forgotten.<sup>[2]</sup>

### **The Failure of Anticoagulants**

The introduction of anticoagulants - coumadin derivatives and heparin - started in 1944 with the great hope that these specific and logic agents could avoid the myocardial infarction as occurred in the prevention and in the treatment of thrombophlebitis processes.



Allen B Weisse, discussing about the controversies over coronary thrombosis in myocardial infarction, said in his paper from 2006:<sup>[3]</sup>

*“Initial efforts to apply anticoagulant therapy early in the treatment of acute myocardial infarction and then long-term did not serve to further the cause of the coronary thrombosis hypothesis.*

*In addition to some flaws in study design (e.g. failure to achieve true randomization in the selection of treatment and control groups), trials of anticoagulation for acute myocardial infarction were not very encouraging; any improvement in survival statistics were more likely due to prevention of thromboembolic complications (e.g. fatal pulmonary embolism) than in the treatment of the offending coronary artery thrombus itself, and the risk of bleeding sometimes life-threatening, was another consideration.”*

*“In retrospect, such findings could have been expected. The early agents used for anticoagulation, coumadin derivatives, and later heparin, while preventing clot formation, have no effect of dissolving thrombi once formed. However, long-term studies using these agents following an initial myocardial infarction were similar disappointing in preventing recurrences”*

Studies claiming about the failure of the anticoagulant use for the treatment or prevention of acute myocardial infarction were presented in 1969-1970 through the publication of reports in important medical journals like the British Medical Journal, American Medical Association Journal, Lancet, etc. <sup>[4,5,6,7]</sup>

However, some groups still using anticoagulants in acute coronary syndromes. An important study published in 2008 found that compared to placebo, patients treated with heparins had similar risk of mortality, revascularization, recurrent angina, major bleeding and thrombocytopenia.<sup>[8]</sup>

## **The Failure of Thrombolysis**

David K Cundiff, in a review from 2002, said the proof of efficacy of thrombolysis for acute myocardial infarction depends on 9 randomized placebo-controlled trials totaling 58,511 patients. The meta-analysis of these trials showed an overall survival advantage of 2% (11.5% vs 9.6%) in favor of thrombolysis. Iatrogenic deaths from thrombolysis complications occur in about 1% of AMI patients.<sup>[9]</sup>

Incidentally, studies also have shown the failure of thrombolytics in restraining unstable angina pectoris. Bar and colleagues expressed about the matter: “Angiographic but no clinical improvement after thrombolytic treatment with anistreplase was found in patients with unstable angina with an excess of bleeding complications. Therefore, thrombolytic treatment cannot be

recommended in patients diagnosed as having unstable angina until proven otherwise.”<sup>[10 - 15]</sup>

## **Myocardial Reperfusion Injury**

On the other hand, in patients with myocardial infarction (MI), the current treatment of choice for reducing acute myocardial ischemic injury and limiting MI size is the use of myocardial reperfusion either with thrombolytic therapy, primary percutaneous coronary intervention or coronary bypass surgery. However, the process of reperfusion can itself induce cardiomyocyte death (minor infarction/infarctlet), known as myocardial reperfusion injury, for which there is still no effective therapy. <sup>[16]</sup> These myocardial infarctlets may lead to an adverse long-term prognosis, and particularly to an increase in late mortality.<sup>[17]</sup>

## **The Dogmatism on Coronary Thrombosis as the Cause of Myocardial Infarction**

Allen B Weisse also told in his paper <sup>[3]</sup> about the low occurrence of coronary occlusion related with the myocardial infarction, found in many studies. He said:

*“Although the later studies indicated a higher percentage of thrombosis found, the number of studies performed almost contemporaneously by equally respected and competent researchers and showing much lower percentages of coronary thrombi in acute myocardial infarction was disturbing. Also, of importance among some of these researchers was the belief that coronary thrombosis might have occurred as the result of the myocardial infarction and not the other way around.”*

Weisse noticed that in 1973 at the National Heart and Lung Institute of the National Institutes of Health in Bethesda, Maryland, a workshop was convened in which the various investigators who had grappled with the problem discussed their views.<sup>[18]</sup>

About this meeting he said that “attempts were made to reconcile the discordant findings among different groups of investigators, noting the integral relations between the alterations in the artery wall (i.e. atheroma) and thromboses that had been reported in the past. However, the end result, for the most part, consisted of a restatement of positions previously held. Although the joint conclusion emphasized the importance of coronary thrombosis, it also concluded that the idea that coronary thrombosis was a secondary event, following the infarction, was provocative and deserved serious consideration.”

In Weisse’s point of view the role of coronary thrombosis in acute myocardial infarction was resolved, once for all, through a study from Marcus DeWood and colleagues published in 1980.<sup>[19]</sup> This study involved 322 patients, all studied by coronary arteriography. The patients studied within 4 hours of

the event's onset 87 percent demonstrated an occluding coronary artery thrombus on angiography. Among those studied 12 to 24 hours after the onset of symptoms, there was a decline in the frequency of thrombi, 65 percent, evidence according to Weisse showing that soon after formation coronary thrombi begin to undergo lysis. He stated that this supported the contention that among those post-mortem studies previously performed in patients who died several days after their infarction, thrombi would be reduced in size (non-occluding) or absent.

The prevalence of total coronary occlusion during the early hours in patients presenting with transmural infarction by means of coronary arteriography, found by DeWood and colleagues, was accepted peacefully by the large majority of the cardiological community as the definitive clinical evidence about the causal role of thrombosis in acute myocardial infarction (AMI). It also brought some relief in this area by keeping intact the medical options and directions dictated by the mainstream and thus passing over necropsy findings and other pathological studies contradicting the coronary thrombosis concept.

Then, the voice of dissenters advocating coronary thrombosis as consequence of myocardial infarction has been mostly lost since the eighties, due to the mainstream discourse in favor of the coronary thrombosis theory as cause of myocardial infarction.

Even thus the acute myocardial infarction occurring in the absence of obstructive coronary artery disease (CAD), still generating questions as occurred in 2016 through a position of a working group from the European Heart Journal. Some of their questions were: "What is the mechanism of the myocardial damage in these patients?" and "Do these patients differ from those with obstructive CAD?"<sup>[20]</sup>

## **Coronary Thrombosis: Cause or Consequence of Myocardial Infarction?**

Taking in view the controversies already mentioned and the results obtained in the study by Marcus DeWood and colleagues <sup>[19]</sup> we present here old and new pathological studies aside critical reasoning about coronary thrombosis as the cause of myocardial infarction:

a. Friedberg and Horn suggested in 1939 that the term coronary thrombosis should be abandoned in favor of the more generic one of acute myocardial infarction. In their paper they say that "the clinical and electrocardiographic features of coronary thrombosis may be observed in patients in whom a coronary artery thrombus is subsequently not found at necropsy as has been noted by Libman, Obendorfer, Buchner, Hamburger and Saphir, Dietrich, Levy and Bruenn and others";<sup>[21]</sup>

b. Hermann and colleagues published in 1941 their findings that the thrombotic occlusion could occur without infarction when the collateral

circulation appeared adequate and if an infarct has happened, it could be attributed to an occlusive thrombus at a critical location in the coronary tree [22-24]

c. Miller and colleagues in 1951 pointed out that subendocardial infarcts were rarely associated with coronary thrombi;<sup>[25]</sup>

d. Spain and Bradess published in 1960 their findings showing complete coronary obstruction of atherosclerotic nature, representing around of 75% of the cases and recent coronary thrombosis in just 25% of the autopsied cases. Also, they have observed crescent incidence of coronary thrombosis with the crescent duration of survival after the myocardial infarction. Less than an hour with 16% of thrombosis, between 1 and 24 hours with 37% and in more than 24 hours with 52% of coronary thrombosis\*;<sup>[26,27]</sup>

e. Hellstrom in 1970 demonstrated experimentally the coronary thrombosis secondary to acute myocardial infarction caused by ligation of the coronary artery;<sup>[28]</sup>

f. William Roberts suggested in 1972 that the coronary arterial thrombi are consequences rather than causes of acute myocardial infarction. In his study involving 107 patients who were submitted to necropsy he found that only 54% of those with a transmural infarction, and only 10% of those with subendocardial necrosis, had a thrombus in the infarct related artery; <sup>[29]</sup>

g. Quintiliano H. de Mesquita pointed out in 1996 that the interpretation given by DeWood in 1980 <sup>[19]</sup> about the angiographic images, suggestive of intracoronary thrombus, do not correspond to the absolute reality whether it represents a true thrombus or just aggregated platelets that are precocious, unstable or reversible commonly registered in the first hours of unstable angina and in the course of the acute myocardial infarction.<sup>[30]</sup> Platelet aggregation at sites of vascular injury is considered essential for hemostasis and arterial thrombosis. However, most studies on cerebral thrombosis and coronary thrombosis do not discuss that acidosis have effects on platelet function. <sup>[89]</sup>

h. Giorgio Baroldi and colleagues in a study from 2005, discussing the findings from DeWood,<sup>[19]</sup> told that the first main question is how many of the 87% cineangio occlusion are pseudo-occlusion and whether the "layered" thrombus recovered at bypass surgery was a true thrombus or a coagulum which frequently show a layering of blood elements not seen in thrombus formation. Also saying that "Red" thrombus, namely a coagulum, is frequently and erroneously considered as thrombus;<sup>[31]</sup>

i. Giorgio Baroldi and colleagues in a study published in 2005 discussed about the findings that the frequency of an occlusive thrombus is significantly higher in the largest infarcts supporting its secondary formation; <sup>[32,33]</sup>

j. In a study from 2001 Yasunori Ueda and colleagues show that in a significant number of cases angioscopic examination continues to find

thrombus on the presumed culprit lesion, at 6 months after myocardial infarction;<sup>[34]</sup>

k. Murakami in a study published in 1998 using intracoronary catheters to aspirate occlusive tissues, performed during the acute myocardial infarction, have confirmed the pathological findings that intracoronary thrombus is absent in a substantial number of patients indicating it contributes little to the pathogenesis of average acute myocardial infarction;<sup>[35]</sup>

l. Rittersma and colleagues in a study published in 2005 examined retrieved thrombus material aspirated using the percutaneous thrombectomy catheter in 211 patients undergoing primary percutaneous coronary intervention within six hours of symptom onset. They then established, by histological indicators, the age of the aspirated thrombi. The researchers found thrombus in 199 of the 211 patients, of whom fresh thrombus was identified in just under half. By contrast, 51% of patient samples contained thrombus that had lytic or organized changes suggesting that it had originated days or weeks before the occlusive event. They said that “Strikingly, clinical characteristics did not differ between the patients with fresh thrombus and those with ‘older’ thrombus, although men were more likely to have fresh thrombus than were women.”;<sup>[36]</sup>

m. The Post-hoc analysis of the PASSION trial, published in 2012, found that the use of thrombus aspiration in adjunct to primary percutaneous coronary intervention (PPCI) did not affected rates of major adverse cardiac events at 2 years follow-up, as compared with conventional PPCI;<sup>[37]</sup>

n. Bo Lagerqvist and colleagues in a study published in 2014 confirm the findings from the Passion Trial that routine aspiration of thrombus before primary percutaneous coronary intervention in patients with ST segment elevation (STEMI) has not been proved to reduce the rate of death and rehospitalization for myocardial infarction at 1 year after the procedure;<sup>[38]</sup>

o. Myocardial infarction associated with normal coronary arteries is a well-known condition. The overall prevalence rate of myocardial infarction with normal coronary arteries is considered to be low, varying from 1% to 12% depending on the definition of ‘normal’ coronary arteries;<sup>[39,40]</sup>

p. Arbustini and colleagues in a study published in 1993 found in a series of 132 autopsies of hearts from patients who died of noncardiac causes that coronary thrombi were shown to overlay the intima of a coronary vessel independently of plaque type and severity.<sup>[41]</sup>

q. Ambrose and colleagues found in 1988 that the risk of a heart attack or other acute myocardial events is not proportional to the severity of coronary stenosis. Several studies in which more than one angiography was performed in patients who developed acute syndromes showed that most of these syndromes appear to be developed from lesions that on the first angiography caused not significant stenosis. Also saying these less severe stenotic lesions

lead to myocardial infarction because they have not developed a sufficient collateral circulation around that would prevent or limit the extent of myocardial necrosis. This means that a 30% reduction in arterial caliber may have an increased risk for a myocardial infarction than an obstruction of 90%;  
[42-44]

r. Recent papers confirm the finds that non-obstructive coronary artery disease is associated with significantly increased risk of myocardial infarctions, consistent with previous studies indicating most myocardial infarctions are caused by non-significant stenoses. Interesting to mention is that one of these found in patients without obstructive CAD had equivalent rates of all-cause and cardiac rehospitalization as those with obstructive CAD, indicating that the downstream effects of the patients' chest pain, whether truly ischemic or not, were the same in these two groups;<sup>[45-47]</sup>

s. The plaque instability and rupture might start in a considerable time before the AMI, according to some studies.<sup>[36, 48]</sup> Stretching, tearing and perforation, related to cholesterol crystallization and expansion, may play a role in the process.<sup>[49,50]</sup> Also, sympathetic overstimulation and hemodynamic forces like left ventricular muscle mass and elevated heart rate may be associated with the future development of plaque disruption;<sup>[51]</sup>

t. A recent study by Armin Arbab-Zadeh and Valentin Fuster, says: "Despite major advancements in coronary artery imaging and identification of atherosclerotic lesion morphology associated with rupture, there is no conclusive evidence that individual plaque assessment better predicts acute coronary event risk than established risk factors, such as the extent and severity of coronary artery disease. Pathology and clinical studies consistently demonstrate that atherosclerotic plaques rupture without clinical symptoms much more frequently than is widely acknowledged, challenging the notion of a close association between plaque rupture and clinical events. Conversely, the atherosclerotic disease burden is a consistent, strong predictor of adverse cardiovascular events and deserves greater attention. Current data suggest that rather than focusing on individual coronary arterial lesions, we need a comprehensive, integrative approach for identifying and managing patients at risk of adverse cardiovascular events;"<sup>[52]</sup>

u. A "State-of-the-Art" review and commentary by Mario Marzilli and colleagues, published in 2012, have the following conclusion: "A large body of evidence conclusively suggests that coronary artery obstruction is only 1 element in a complex multifactorial pathophysiological process that leads to Ischemic Heart Disease (IHD) and that the presence of obstructive lesions in patients with IHD does not necessarily imply a causative role. A more comprehensive approach seems necessary to refocus preventive and therapeutic strategies and to decrease morbidity and mortality. To this effect, we propose a shift in approach to include the myocardial cell as well as the coronary vessel";<sup>[53]</sup>

v. Erhardt and colleagues in 1973 published findings that radioactive fibrinogen administered to patients with AMI was incorporated into the entire coronary thrombus in non-survivors, supporting the view that myocardial infarction occurs first and thrombus formation is a secondary event. Another study published in 1976 by the same group confirmed the previous findings; [54,55]

w. Giorgio Baroldi, emphasizing the inconsistency of the current myths about the behavior and meaning of components of the human coronary atherosclerotic plaque, told in 2004 that the degree and number of severe coronary plaques do not predict onset, course, complications and death in coronary heart disease (CHD);<sup>[56]</sup>

x. Many other studies have advocated coronary thrombosis as consequence of myocardial infarction; <sup>[57-62]</sup>

y. A study published at JAMA in 2016 found that temporal increases in levels of cardiac troponin T by high-sensitive assay (hs-cTnT), suggestive of myocardial injury or progressive myocardial damage, was independently associated with later risk of death, coronary heart disease, and especially heart failure in apparently healthy middle-aged people. The study which enrolled 8,838 participants (mean age 56) was followed from January 1990 to December 2011, with an analysis of 6-year change in hs-cTnT. In their conclusion the authors say that their results indicated that 2 measurements of hs-cTnT appeared to be better than 1 for characterizing risk and that large increase in hs-cTnT are particularly deleterious. Also, that temporal change in hs-cTnT may help guide the preventive management of asymptomatic persons at risk for coronary artery disease. This study didn't discuss about the etiology of the progressive myocardial injury found. However, one could notice and surmise from it the absence of relationship to the thrombo-centric coronary heart disease universe.<sup>[63]</sup> On the other hand, studies show that mental stress and exercise may induce cardiac troponin T elevation, in apparently healthy individuals; <sup>[64-65]</sup>

z. George E Burch and colleagues raised an important point in 1972 when they said: "The patient with coronary artery disease does not die of coronary artery disease; he dies of myocardial disease. It is the heart muscle that is the pumping element. To accept the term 'heart muscle disease' as the primary factor in coronary artery disease assists the physician in management of the patient." <sup>[66]</sup>

## **Additional studies supporting the idea of coronary thrombosis as consequence of acute myocardial infarction:**

1. Hans Selye, in 1958, has shown experimentally how stress, combined with some agents, may induce myocardial necrosis where the coronary arteries are perfectly normal. He also said in his paper: "It is noteworthy, however, that, under these circumstances, not only cardiac infarction but organic obstruction of the coronary vessels can regularly be produced by humoral means."<sup>[67]</sup>
2. Branwood noticed in 1978 that in one hundred twenty-one patients who had died in a coronary care unit, the incidence of thrombi was only 35.6% (44 cases). No thrombi were detected in any coronary artery in 64.4% (77 cases). The thrombi and infarct were examined microscopically, and the age of each was correlated according to known criteria. This comparison revealed that of the 44 cases in which occlusive thrombi were detected, the infarct and the thrombus were the same age in 14 cases (32%), while the infarct was older than the thrombus in 30 cases (68%). He told that the factors inducing infarction, beyond hypoxia, were stress, altered cell membrane permeability, and increased catecholamines.<sup>[68]</sup>

## **The evidence**

The studies and reasoning listed above provide very strong evidences that can clarify once and for all any doubts about the matter, pointing out that the occasional coronary thrombosis is a consequence of the process and not the real culprit of acute myocardial infarction or death of the patient with coronary-myocardial disease.

On the other hand, there are poor or non-existent benefic results (In absolute risk reduction statistics - Scientific and clinical significance is usually set at 5% level), justifying the use of drugs, coronary bypass surgery, angioplasty and stents, current medical treatments based on the coronary thrombosis theory. These are treating symptoms and/or biomarkers not the disease itself, with the possible risk of harm to the patients. <sup>[69-78]</sup>

Regarding coronary bypass surgery and stents, it is important to mention about the results from the Ischemia Trial, first presented in November 2019. The Ischemia Trial showed that an invasive approach to patients with moderate to severe ischemia did not significantly reduce a composite endpoint of myocardial infarction, cardiovascular death, hospitalization for unstable angina or heart failure, and cardiac arrest compared with a conservative medical strategy—without initial angiography. The hard endpoints of MI, CV death, and all-cause death also did not differ between the treatment arms. <sup>[79-81]</sup>

As can be seen above the coronary thrombosis theory of heart attacks can't be sustained anymore, because it lacks scientific basis.



## The Myogenic Theory of Myocardial Infarction

Our interest on this discussion is related to our position as advocates of the Myogenic Theory of Myocardial Infarction, developed by my father in law, the Brazilian Cardiologist Quintiliano H. de Mesquita, in 1972. In the myogenic theory point of view coronary thrombosis is a consequence of the myocardial infarction being cardiac glycosides (digitalis, strophanthin, etc..) the fundamental and specific therapeutic. <sup>[82-84]</sup>

*Dr Mesquita (1918 - 2000+)*  
*Photo, 1983*



## Anticoagulant Use by Dr Mesquita

One point I would like to emphasize is that Dr Mesquita received the introduction of the anticoagulants in 1944 with large enthusiasm and the hope that finally reached the solution for the prevention of myocardial infarction. Then, he applied anticoagulants, particularly in unstable angina, during a period of 10 years (1944-1954) with records of absolute failure in restraining unstable angina and in prevention of infarction, leading to his abandonment of this therapeutic.

Thenceforth, he started to use only the coronary dilator having published in 1962 a study involving 296 patients with myocardial infarction treated at their home, recording the exceptional mortality of 7.7%, comprising 14 cases of heart failure, 6 cases of sudden death and 3 cases of cardiogenic shock. The low mortality found in his study was later justified due to the habitual conduct from Dr Mesquita to apply intravenous strophanthin in all cases presenting precocious pulmonary stasis in the acute myocardial infarction, ever interpreted as incipient left ventricular insufficiency. <sup>[85]</sup>

## Tributes to Dr. Quintiliano H de Mesquita

In November of 2012 I made a presentation about the myogenic theory in a lecture during the Fourth International Conference of Advanced Cardiac Sciences - the King of Organs Conference, held in Saudi Arabia. <sup>[86]</sup>

In 2014 was published our article Stress as Cause of Heart Attacks: The Myogenic Theory telling the history of its development and making a comparison between the thrombogenic theory versus the myogenic theory in its different philosophies, therapeutics and outcomes for the three stages of ischemic heart disease.<sup>[87]</sup>

The myogenic theory of the myocardial infarction was the template for our acidity theory of atherosclerosis launched in 2006.<sup>[88]</sup> In our view the acidic environment evoked by chronic stress has an important role in the mechanism generating atherosclerotic lesions. It follows the response to injury concept of atherosclerosis.

*“Science is a Method of Investigation to Search for Evidences, not Beliefs nor Wishes, Conveniences or Preferences”*

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## Chapter 4

# Autonomic Dysfunction + Lactic Acidosis: The Causal Factors for Coronary Thrombosis Formation.

*"Not only cardiac infarction but organic obstruction of the coronary vessels can regularly be produced by humoral means",  
Hans Selye, 1958 <sup>[1]</sup>*

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### Abstract

Since more than a century the hypothesis of coronary thrombosis started to be deeply rooted in the medical culture as the cause of acute myocardial infarction. However, it still be just one hypothesis, with many old and recent studies showing conflicting data in relation to its basic concept.

In our present article we raised several findings demonstrating that coronary thrombosis is a consequence of autonomic dysfunction and lactic acidosis, forming the thrombus and platelet aggregation. That represents our new alternative hypothesis for the coronary thrombosis formation.

In this article we also mention many studies confirming the association of a higher production of lactate to atherosclerosis, coronary artery disease, myocardial ischemia, acute myocardial infarction, and brain ischemia.

### Introduction

Arterial thrombosis has been generally accepted as the cause of myocardial infarction (MI) and in ischemic stroke. It is believed that arterial thrombosis results from clot formation in the setting of atherosclerotic plaque rupture, leading to platelet aggregation, thrombus formation and vessel occlusion that might lead to MI.

Atrial fibrillation (AF) is also considered to form blood clots, being associated with stroke and myocardial infarction. The development of thrombosis in the left atrial appendage (LAA), with consequent embolism in the cerebral circulation, is seen as the most important cause of ischemic stroke. It is commonly supposed that in non-valvular AF 90% of clots occur in LAA.

However, a recent study concluded that the frequency of left atrial cavity thrombi is most probably largely overestimated if based on older literature and is mostly confined to cases of rheumatic AF. The very low real frequency of left atrial thrombi out of the left atrial appendage in more modern reports might be an important rationale for LAA occlusion interventions. <sup>[2]</sup>

Otherwise, a study from 2017 says:

*"Despite major advances in elucidating the mechanistic pathways mediating platelet function and thrombosis, challenges in the treatment of vascular occlusive diseases persist. Pharmacological advances have greatly affected thrombotic outcomes, but this has led to the unwanted side effect of bleeding. Detailed assessment of the impact of non-thrombotic diseases on haemostasis and thrombosis is necessary to better evaluate thrombotic risk and establish optimal treatment."* [3]

## **Our postulation**

In the present article we advocate a new mechanism where the autonomic dysfunction and lactic acidosis are the real responsible for the formation of arterial thrombosis and platelets aggregation.

Venous thrombosis may also be caused by autonomic dysfunction [10] and increased lactate production. [15,18,19]

The first to observe the influence of adrenaline on lactic acid production were the Cori's in the early 1920s\*\*. [4] A 1982 article by Schade [5] provided further support for the direct participation of catecholamines in the development and/or maintenance of lactic acidosis as follows:

1. The common association of stress and lactic acidosis
2. The rise in plasma lactate concentration during adrenaline infusion
3. The precipitation of lactic acidosis by adrenaline intoxication and pheochromocytoma
4. The vasoconstrictor effects of catecholamines leading to tissue anoxia and lactic acid production.

Williamson, in 1964, confirmed the effects of adrenaline infusion on the increased production of lactate in isolated heart tissue, up to five times the normal production. [6]

It is important to emphasize that the heart is an organ of high metabolic activity. Therefore, the heart cannot rest as can other body muscles. Chronic or acute elevated catecholamine release may accelerate myocardial glycolysis leading to a significant increase in lactate production.

## **Follows some studies about the effects of the autonomic dysfunction on:**

### **Thrombosis**

- An experimental study with dogs from 1936 has reported about a repeated intravenous injection of a stimulating substance in the blood, simulating parasympathetic activity, namely, acetylcholine. The experiments were carried out on 8 dogs arranged in two groups: The first with young dogs (A) and the second with older dogs (B). These animals were injected daily, seven days in the week, until they died.

Within 10 to 20 seconds after the start of the injection the heart-rate always was greatly accelerated, even to two or three times the resting normal rate

The clinical evidence of progressive myocardial failure with subsequent death was noted in every animal, and pathological examination showed permanent damage to the heart in all but two animals (young).

In those animals which at autopsy showed permanent damage to the heart, which might represent a toxic effect, there was, in the coronary arteries, a hyaline degeneration of the tunica media and a tendency to thrombosis. "Examination of the sections of the heart in old dogs showed areas of hyalinization with developing fibrosis; hyaline degeneration of the media of medium and smaller sized arteries with fibrosis; recent infarcts of myocardium, including papillary muscles; thrombosis of many branches of coronary artery; recanalization of occluding thrombi; fatty degeneration of myocardium about infarcted areas; large areas of fibrosis." [7]

- An article published in 2004 told that historical studies on the physiology of the sympathetic nervous system attributed accelerated blood clotting to the components of the fight-flight response. [8]
- A case report from 2019 suggests an association of thrombotic tendency and catecholamine excess. [9]
- A study from 2015 have demonstrated that both the renal sympathetic nerve system and the oxidative stress contribute to the development of deep venous thrombosis in response to chronic stress. [10]
- Hans Selye, in a study published in 1958, has shown experimentally how stress, combined with some agents, may induce myocardial necrosis where the coronary arteries are perfectly normal. In his study he also told that the possibility of precipitating infarct-like myocardial lesions by sudden exposure to stressors is especially significant, in view of its obvious clinical implications. [1]

### **Platelet activation**

- A study from 2004 found that mean platelet volume (MPV) was significantly higher in patients with acute myocardial infarction. In both groups, MPV showed great daytime and nighttime variation, which can be attributed to alterations in the autonomic nervous system. The authors suggest that the prognostic role of increased MPV in patients with acute MI is closely associated with increased sympathetic activity and decreased HR variability. [11]
- A study from 2012 has shown that activation of the sympathetic nervous system affected blood coagulation, fibrinolysis and platelet activation by several mechanisms. [12]
- A study from 2013 found that MPV was significantly higher in the patients with Vasovagal syncope (VVS), and MPV is also closely associated with increased sympathetic activity in patients with VVS. According the authors their analysis supports the hypothesis that alterations of autonomic status may play a role in the development of platelet size. [13]



## **Follows some studies about the effects of acidosis on:**

### **Thrombosis formation**

- A study from 1970 tried to elucidate the mechanisms triggering disseminated intravascular coagulation in shock. Acidosis was produced in dogs by intravenous infusions of lactic acid over a period of 4 h. They found that a pH value of 7.20 or lower appeared to be a potent trigger of intravascular coagulation. The lower the pH, the more thrombi were found in the tissues. The consumption of clotting factors and thrombus formation thus corresponded to the degree of acidosis. <sup>[14]</sup>
- A study from 2019 found that glycolysis-, purine-, and redox-related metabolites may reflect fresh erythrocyte-rich venous thrombus and altered metabolites may affect venous thrombus formation. An increased level of lactate may reflect active glycolysis of thrombus cellular components, predominantly erythrocytes. <sup>[15]</sup>

### **Platelet aggregation**

- A study from 1974 found that platelet aggregation in response to epinephrine or ADP challenge is inhibited by acidosis and enhanced by alkalosis produced by pH changes while maintaining a constant pCO<sub>2</sub>. <sup>[16]</sup>
- A study from 2012 says: “Our results indicate that extracellular acidosis downregulates most of the haemostatic platelet functions and promotes those involved in amplifying the neutrophil-mediated inflammatory response”. <sup>[17]</sup>

### **Thromboembolism**

- A study from 2011 found that high plasma lactate was associated with increased in-hospital mortality in a sample of patients with acute pulmonary embolism. <sup>[18]</sup>
- A study from 2020 has shown that acute pulmonary embolism, isolated or combined with deep-vein thrombosis, is the major cause of mortality or hospitalization due to venous thromboembolism. It suggests a new mechanism contributing to a negative impact of elevated lactate levels on prognosis in acute pulmonary embolism patients, in particular hypofibrinolysis, associated with enhanced neutrophil extracellular trap formation. <sup>[19]</sup>

### **Coagulation**

- A study from 1997 has shown that the combination of acidosis, hypothermia and coagulopathy is associated with high mortality in polytrauma. <sup>[20]</sup>
- A study from 2006 found that lactic acidosis remarkably impairs the coagulation system. <sup>[21]</sup>

## **Studies demonstrate the association of lactic acidosis with atherosclerosis, coronary artery disease, myocardial ischemia, acute myocardial infarction, and brain ischemia.**

*“It is sobering to recall that many of the important metabolic changes in experimental myocardial infarction have been known for over thirty years. There is rapid glycogen breakdown in the ischaemic area with associated release of lactate” L. H. Opie, 1971 [22]*

### **Atherosclerosis / Coronary Artery Disease / Myocardial Ischemia**

- In advanced plaques the existence of hypoxic areas in the arterial wall – with accumulation of lactic acid in atherosclerotic lesions – seems related to a decreased oxygen diffusion capacity and increased oxygen consumption by the foam cells. [23]
- Macrophages and lymphocytes convert most of their glucose into lactate rather than oxidizing it completely to CO<sub>2</sub>, and macrophages possess a selective transporter in their plasma membranes for lactic acid. This lactic acid may make the extra-cellular space surrounding macrophages acidic in atherosclerotic lesions. [24]
- A pathological study has demonstrated that approximately two-thirds of the atherosclerotic plaques show lactate dehydrogenase isoenzyme shifts significantly above that of the media and intima. [25]
- The association of increased lipid levels with abnormal lactate metabolism may provide a useful screening test for the detection of coronary artery disease. [26]
- The amount of lactate released by the myocardium has been shown to be related to the severity of coronary artery disease. [27]
- Lactate is strongly associated with carotid atherosclerosis and the association is independent of traditional cardiovascular risk factors. [28]
- Elevated blood lactate is associated with increased carotid atherosclerosis. [29]
- Lactate, lowered pH and lactic acid induce endocardial damage. [30]

### **Unstable angina / Acute myocardial infarction**

- Studies have shown that lactate accumulation predicts ischemic myocardial necrosis. [31]
- Tennant found in 1935 that tissue acidosis might account for contractile failure during myocardial ischemia. [32, 33]
- Measurement of arterial blood lactate is considered a consistently useful prognostic indicator of survival or fatality in patients with acute myocardial infarction. [34]
- Fifty patients evaluated because of unstable angina were followed up for a mean period of 63.7 months. Analysis of lactate metabolism thus provides an additional prognostic index in patients presenting with symptoms suggesting unstable angina. Patients in the subgroup demonstrating significant lactate production had a poor prognosis. Risk of an acute coronary event was high in this group in both long- and

short-term follow-up. Conversely patients who demonstrated lactate extraction or had a minimal degree of lactate production had a good prognosis with medical management. <sup>[35]</sup>

### **Heart failure and all-cause mortality**

- A study from 2013 has shown a significant association of elevated plasma lactate levels with heart failure and all-cause mortality in a middle-aged, biethnic general population. <sup>[36]</sup>

### **Cerebral stroke**

- Friede and Van Houten, in 1961, related cellular injury in incubated brain tissue slices to the development of metabolic acidosis. <sup>[37]</sup>
- Lindenberg postulated in 1963 that structural alterations in the hypoxic brain described as "morphotropic necrobiosis" are caused by intracellular acidosis. <sup>[38]</sup>
- Rehnrona, in 1985, have written that severe tissue lactic acidosis limits the possibility for cell survival in brain ischemia. In his article he reviewed data on the relationship between severe tissue acidosis and irreversible brain cell damage. <sup>[39]</sup>
- The measurement of interstitial pH and calculation of intracellular pH during cerebral ischemia indicate that increased acidosis accompanies increased tissue lactate. <sup>[40-42].</sup>
- The accumulation of lactate in ischemic regions has been documented in studies during acute stroke. In 2008, a study involving 187 patients with ischemic stroke or transient ischemic attack has shown that lactate in cerebrospinal fluid was a reliable marker for the metabolic crisis in acute ischemic stroke and a possible cause of secondary neuronal damage in cortical infarction resulting in unfavorable evolution in the sub-acute phase and poor long-term outcome. <sup>[43]</sup>
- Previous studies have already suggested that lactate dehydrogenase levels in the cerebrospinal fluid might be useful for recognizing those patients at high risk of developing severe stroke. <sup>[44]</sup>
- A study from 2012 found that among patients with ischemic stroke, initial hyperlactatemia represents an independent risk factor for poor outcome after controlling for stroke severity, risk factors, initial glucose level, and interval from onset of stroke symptoms to emergency department arrival. <sup>[45]</sup>
- A recent study found that in subarachnoid hemorrhage (the most devastating form of hemorrhagic stroke), elevated serum lactate levels on admission may have a predictive role for mortality and represent a marker of disease severity. <sup>[46]</sup>

## **Conclusion**

The studies described in the present article provide undisputable proof that the autonomic dysfunction and lactic acidosis are the real causal factors for the formation of thrombosis and platelets aggregation. This new concept will give more adequate therapeutics for prevention and in the management of acute myocardial infarction.

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**Part #2**

**Articles on Atherosclerosis  
and Related subjects**



## Chapter 5

# Acidic Environment Evoked by Chronic Stress: A Novel Mechanism to Explain Atherogenesis.

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### Abstract

Here is proposed a new hypothesis where acidity, evoked by stress, has an important role in the generator mechanism of atherosclerotic lesions, giving a new perspective for the understanding of its etiology and pathogenesis. The acidity theory of atherosclerosis is inside the response to injury concept.

It has the following sequence of events:

- I. Sympathetic dominance by continuous stress plus
- II. Deficiency in production of endogenous digitalis-like compounds (DLCs) with alterations of Na(+), K(+)-ATPase activity results in:
- III. Lowered pH (acidity) that increases perfusion pressure and provokes effects on contractility of coronary arteries leading to changes in hemodynamic shear stress and atherosclerosis as consequence.

The heart is an organ of high metabolic activity, susceptible to drops in pH during ischemia and hypoxia. Chronic elevated sympathetic bias may accelerate the myocardial anaerobic glycolysis with a significant increase in lactate production. In hypertension the concentration of lactic acid in both venous and arterial blood may be significantly elevated. Lactic acid in blood plasma is also significantly elevated during stress situations and indicative of stress levels. Psychosocial factors are independent significant predictors of carotid intima-media thickness (IMT) progression. Stress reduction through behavioral changes or use of sympatho-inhibitory drugs like Beta-blockers slow the progression of carotid IMT. Cardiac glycosides at lower daily doses also blocks excessive catecholamine release, resulting in very low mortality rate in prevention of acute coronary syndromes in patients with heart disease, as treated under the myogenic theory of myocardial infarction, a complementary hypothesis. Cardiac glycoside drugs show additional therapeutic possibilities, like re-elevation of lowered pH, appearing to attend the demand in insufficient production of endogenous DLCs, in some clinical conditions.

*"Certainly all tissues change with age. There is anatomic and chemical aging. The acidity of tissues increases with age; this favors the precipitation of cholesterol", O. J. Pollak, 1952 <sup>[1]</sup>*



## The Hypothesis

The present hypothesis follows the response to injury concept of atherosclerosis developed by Russel Ross, John Glomset and Laurence Harker in 1977 <sup>[2]</sup>. According to this concept, physiologically active substances are released in response to injury of the arterial endothelium, and these substances induce pathologic reactions by the cells constituting the vascular wall.

Our hypothesis was developed in the mid 2006 <sup>[3]</sup>, inspired by the demonstration that normal stretching/relaxing of an artery does not produce atherosclerosis, while stretching/relaxing in different directions simultaneously on every heartbeat does. This discovery from scientists in California <sup>[4, 5, 6]</sup> prompted us to search for other potential mechanisms beyond the simplistic idea of cholesterol as the culprit, and could offer:

1. An alternative understanding for the etiology and pathogenesis of atherosclerosis
2. A compatible and efficient therapy according to the mechanism in question
3. To be suitable with the myogenic theory of myocardial infarction, developed by Quintiliano H. de Mesquita in 1972 <sup>[7, 8]</sup>, which we support since that time. The myogenic theory accepts atherosclerosis as responsible for the reduced regional myocardial function, relationship recognized by participants of the MESA study in a paper published in 2006. <sup>[9]</sup>

We believe the Acidity Theory of Atherosclerosis attend these premises.

The sequence of events according to our proposition:

- I. Sympathetic dominance by continuous stress plus
- II. Deficiency in production of endogenous digitalis-like compounds with alterations of Na(+), K(+)-ATPase activity results in
- III. Lowered pH (acidity) that increases perfusion pressure and provokes effects on contractility of coronary arteries, leading to changes in hemodynamic shear stress and atherosclerosis as consequence.

The acidity theory of atherosclerosis does not underestimate the importance of other key factors for atherosclerosis like ageing, improper diet, environmental pollution, lifestyle, physical inactivity, tobacco smoking and genetic predisposition. However, most of these risk factors might result in altered autonomic nervous system, sympathetic bias, increased lactic acid and acidic environment thus propitiating atherogenesis. Our proposal may extend to any respiratory or metabolic disturbances resulting in acidosis.

Note: We prefer to use the term coronary-myocardial disease rather coronary artery disease or coronary heart disease, to make clear the dual pathologies involved, according to the theories we defend.

## Evidence and Fundamentals

Coincidentally, a very recent paper attempted to explain the mechanism behind the association of many disparate risk factors like diet, age, gender, family history, stress, lifestyle, smoking, diabetes, dyslipidemias, hypertension and HIV, believing these could encourage the development of atherosclerosis by inducing adventitial autonomic dysfunction and sympathetic bias. Accordingly, the authors have proposed that atherosclerosis is caused by stress dysfunction particularly of neurogenic origin. <sup>[10]</sup>

Studies linking stress to atherosclerosis are not new. We should remember that Hans Selye proposed in 1950 that stress could induce hormonal autonomic responses and, overtime, these hormonal changes lead to atherosclerosis and other diseases. <sup>[11]</sup> Walter Cannon was the first to demonstrate, in 1914, that acute stress results in increased outpouring of adrenaline. <sup>[12]</sup>

Many cardiovascular disease processes, including myocardial ischemia, congestive heart failure, unstable angina pectoris, acute myocardial infarction, heart broken syndrome, arrhythmias and ischemic stroke are precipitated or worsened by perturbations in the autonomic nervous system, with sympathetic activation and excessive secretion of catecholamine (adrenaline and noradrenaline). <sup>[13-23]</sup>

Even hypertension, traditionally considered as originated from kidneys, now is regarded as triggered primarily through the nervous system and later exacerbated by non-neural factors. <sup>[24]</sup>

Indeed, the use of sympatholytic agents <sup>[55]</sup> and stress reduction approaches <sup>[25]</sup> may lead to a significant reduction in blood pressure levels.

Related to mental stress and atherosclerosis, studies have showed that:

1. Higher rise in systolic blood pressure during psychological stress results in a more severe and greater progression of carotid atherosclerosis <sup>[26, 27, 28]</sup>
2. Adrenaline and noradrenaline may act as chemical mediators during atherogenesis in man, thus contributing to the development and subsequent complications of atherosclerosis <sup>[29]</sup>
3. Mental stress - induced pulse pressure changes may influence the development of early atherosclerosis in the carotid artery of woman <sup>[30]</sup>
4. d) Blood pressure changes during psychological stress predict subsequent coronary calcification in young health adults 13 years later <sup>[31]</sup>
5. e) Brief episodes of mental stress, similar to those encountered in everyday life may cause transient (up to 4 hours) endothelial dysfunction in healthy young individuals <sup>[32]</sup>
6. f) Delayed blood pressure recovery after psychological stress is associated with carotid intima media thickness (IMT) <sup>[33]</sup>

7. g) Psychosocial factors are independent significant predictors of IMT progression <sup>[34]</sup>
8. h) Depressive symptoms are associated with the development of atherosclerosis <sup>[35]</sup>

## **Deficiency of endogenous digitalis-like compounds, the sodium potassium pump and cardiac glycosides**

Endogenous digitalis-like compounds (DLCs) of the cardenolide (digoxin and ouabain /strophanthin) and bufadienolide (Proscillaridin-A and Marinobufagenin) types, recently isolated from human tissues and body fluids, have similar molecular structure of cardiac glycosides extracted from plants and toad venom <sup>[36, 37]</sup>. Endogenous DLCs are steroidal hormones that are synthesized in, and released from the adrenal gland, whose regulation may be directed by the hypothalamic-pituitary-adrenal (HPA) axis <sup>[38, 39]</sup>. Cholesterol, a vital substance produced by the human body, is the major precursor of endogenous digitalis-like compounds. <sup>[40]</sup>

Many hormones, including aldosterone, insulin, thyroid hormone and catecholamines regulate not only the expression but also the insertion of Na<sup>+</sup>, K<sup>+</sup>-ATPase into the plasma membrane, according to specific physiological needs. The Na<sup>+</sup>, K<sup>+</sup>-ATPase which was considered the ion transporting pump now appears to have many other unrelated functions, some of which may be regulated by DLC. In fact, DLCs have already been implicated in the regulation of several major physiological parameters including water and salt homeostasis. <sup>[37]</sup> In many cases, perturbation of the DLC system has been implied in pathological conditions including cardiac arrhythmias, hypertension, cancer and depressive disorders. <sup>[37, 41]</sup>

Stress situations may affect the release of endogenous digitalis-like compounds by the adrenal gland. <sup>[39]</sup> Also, the extracellular acidification may affect the signaling and transport of endogenous DLCs. <sup>[42, 43]</sup> This raises the possibility that an insufficient production of endogenous DLCs to attend the demand in some medical conditions, like coronary-myocardial disease, hypothetically can be resolved through the use of cardiac glycosides at low concentration, as a supplement. This postulation is confirmed by clinical studies using cardiac glycosides with largely positive effects in prevention of acute coronary syndromes. <sup>[44, 45, 46]</sup>

Cardiac glycosides, that in higher concentrations inhibit the Na/K pump, in low therapeutic doses <sup>[147]</sup>, including at nanomolar range concentration <sup>[47]</sup>, can stimulate it. Also, cardiac glycosides have specific sympathoinhibitory response by blocking the overproduction of catecholamine. This property is unrelated to the positive inotropic action of cardiac glycosides. <sup>[48, 49]</sup> We hypothesize that endogenous digitalis-like compounds may have similar action on neurohormonal levels.

It has been shown that cardiac glycosides can re-elevate lowered pH by stopping the over production of lactic acid by the heart and in some other

clinical and experimental conditions. <sup>[50, 51, 52, 53]</sup> It is interesting to note that studies have suggested a causal relationship between noradrenaline/adrenaline and concentrations of lactic acid. <sup>[54]</sup>

We should also notice the cardiac glycosides digoxin and digitoxin may lower blood pressure in hypertensive patients. <sup>[55]</sup> Paradoxically, some studies have shown that infusion of ouabain over several weeks produces hypertension in rats <sup>[56]</sup>, situation in which digoxin and digitoxin can also lower the blood pressure. <sup>[57]</sup> There was no evidence of ventricular hypertrophy in animals receiving ouabain in this study, despite the documented hypertension, with the authors considering that ouabain may actually be cardioprotective. <sup>[56]</sup>

It was recently demonstrated that cardiac glycoside drugs potently block activation of NF- $\kappa$ B signaling pathway, providing a feasible therapeutic use for the treatment of inflammatory diseases, like in atherosclerosis. <sup>[58]</sup> The activation of Nuclear factor-kappa B (NF- $\kappa$ B), that has been called a “smoke sensor” of the body, is induced by a variety of agents including stress, cigarette smoke, viruses, bacteria, inflammatory stimuli, cytokines, free radicals, carcinogens, tumor promoters, and endotoxins.

We think a deficient production of DLCs may result in a dysfunctional HPA axis response associated with increased susceptibility to inflammatory disease. <sup>[59]</sup>

A recent study has identified phagocytes (macrophages and neutrophils) as a new source of catecholamine, which may enhance the inflammatory response. <sup>[146]</sup>

## **Acidic environment and cardiovascular diseases**

The heart is an organ of high metabolic activity – that cannot rest as other body muscles, being susceptible to drops in pH during ischemia and hypoxia. <sup>[13]</sup> The chronic or acute elevated catecholamine release, mainly from sympathetic nerve terminals in cardiac tissue <sup>[60]</sup>, with alterations in Na(+), K(+)-ATPase activity, may accelerate the myocardial anaerobic glycolysis leading to significant increase in lactate production.

Studies have shown that:

a) Either in essential or renal hypertension the concentration of lactic acid in both venous and arterial blood may be significantly elevated. <sup>[61]</sup>

b) Lactic acid in the blood plasma is significantly elevated during stress situations and serving as indicative of stress levels. <sup>[62, 33]</sup>

c) Catecholamine may be important determinants for the development of ketoacidosis and/or lactic acid. <sup>[54]</sup>

d) Lowered pH increases perfusion pressure. <sup>[64, 6]</sup> Also, pH changes have profound effects on contractility of coronary arteries <sup>[65, 66]</sup>, that may happen through the sodium/potassium pump and K induced relaxation channels. <sup>[67]</sup>

e) Lactate, lowered pH and lactic acid induce endocardial damage. <sup>[68]</sup>

f) A decreased pH may be associated with an increased blood-pressure response to salt loading. <sup>[69]</sup>

g) Ingestion of glucose, fructose and other sugars may have the effect to raise blood lactic acid with this increase being most marked and lasting longest after fructose, that is largely used as sweetener in soft drinks, fruit punches, pastries and processed foods. Dietary fructose has also resulted in increases in blood pressure. <sup>[70, 71]</sup>

h) High carbohydrate diet may increase significantly the activity of serum lactate dehydrogenase. <sup>[149, 150]</sup>

i) Lactic acid produced by anaerobic metabolism during cardiac ischemia is among several compounds suggested to trigger anginal chest pain <sup>[13]</sup>, though the raise in lactate production has also been recorded in myocardial ischemia without angina pectoris with the distinction between symptomatic and asymptomatic cases attributed to an individual defect of the stimuli receptor system and its transformation in painful nervous reflexes in front of equal grade of ischemia. <sup>[72]</sup>

j) Lactate, acting through extracellular divalent ions, dramatically increases activity of an acid sensing ion channel that is highly expressed on sensory neurons that innervate the heart, being ASIC-3 the most specific to detect ischemic pain. <sup>[73]</sup>

k) Lactate accumulation predicts and determines the development and expansion of ischemic myocardial necrosis <sup>[7, 50, 74]</sup>, albeit cardiotoxic catecholamines may induce myocardial necrosis -- acute contraction band lesions. <sup>[75]</sup>

l) Measurement of arterial blood lactate is considered as a consistently useful prognostic indicator of survival or fatality in patients with acute myocardial infarction (AMI) and myocardial failure. <sup>[76]</sup>

m) In sudden cardiac death, a histochemical study of enzymatic activity in the myocardium found that lactate dehydrogenase was 22.6% higher than in trauma and brain hemorrhage that served as control, seeming to be connected as a response to the catecholamine excess. <sup>[77]</sup>

n) In ischemic stroke acidosis-mediated activation of acid-sensing ion channels may play a role to ischemic damage of brain tissue. <sup>[78]</sup>

o) Tissue acidosis has been proposed to account for contractile failure during myocardial ischemia <sup>[79, 80]</sup> and to contribute for the genesis of cardiac dysrhythmias. <sup>[81]</sup>

It has been demonstrated that pH is lowered intracellularly and extracellularly in ischemic heart models and clinically in patients with coronary artery disease. In dogs, lowered pH stimulates afferent cardiac sympathetic

nerve fibers. In another organ system, rat skin, acid plays a dominant role in exciting sensory neurons when compared with other potential chemical mediators of inflammation. <sup>[13]</sup> In cats, the occlusion of the coronary artery for 5 min decreased epicardial tissue pH from 7.35 to 6.98. <sup>[82]</sup>

## **Acidic environment and atherosclerosis**

In advanced plaques the existence of hypoxic areas in the arterial wall - with accumulation of lactic acid in atherosclerotic lesions - seems related to a decreased oxygen diffusion capacity and increased oxygen consumption by the foam cells. <sup>[144]</sup>

Macrophages and lymphocytes convert most of their glucose into lactate rather than oxidizing it completely to CO<sub>2</sub>, and macrophages possess a selective transporter in their plasma membranes for lactic acid. This lactic acid may make the extracellular space surrounding macrophages acidic in atherosclerotic lesions. <sup>[83]</sup>

A pathological study has demonstrated that approximately two-thirds of the atherosclerotic plaques show lactate dehydrogenase isoenzyme shifts significantly above that of the media and intima. <sup>[84]</sup>

It has been reported that lowering pH augments the oxidation of low-density lipoprotein (LDL) by releasing Fe and Cu radicals and decreasing antioxidant defense capacity. <sup>[83, 85, 86]</sup>

Recent evidence showed that LDL oxidation occurs not within the interstitial fluid of atherosclerotic lesions but within lysosomes in macrophages in atherosclerotic lesions. Most important, the study found that this oxidative modification was inhibited by the drug chloroquine, which increases the pH of lysosomes, as oxidation can be promoted by acidic pH. <sup>[148]</sup>

It has been shown that atherosclerotic plaques have pH heterogeneity, suggesting a possible role for detecting low pH in the identification of plaque vulnerability. pH heterogeneity can affect numerous plaque functions. <sup>[87, 88]</sup>

Recent in-vitro findings suggest that in areas of atherosclerotic arterial intima, where the extracellular pH is decreased, binding of apolipoprotein B100 containing lipoproteins to proteoglycans and modification of the lipoproteins by acidic enzymes are enhanced. The pH induced amplification of these processes would lead to enhanced extracellular accumulation of lipoproteins and accelerated progression of the disease. <sup>[89, 90]</sup>

It was suggested that uric acid has antioxidant and prooxidant activities towards the oxidation of native and mildly oxidized LDL, respectively. <sup>[91]</sup> In the atherosclerotic process this antioxidant-prooxidant urate redox shuttle appeared to some investigators to rely heavily on its surrounding environment such as timing (early or late in the disease process), location of the tissue and substrate, acidity, the surrounding oxidant milieu, depletion of other local antioxidants, the supply and duration of oxidant substrate and its oxidant

enzyme.<sup>[92]</sup> However, an elevated concentration of lactic acid in blood may inhibit renal excretion of uric acid, leading to its accumulation in the body.<sup>[145]</sup>

Also important is the value of homocysteine and its acidic derivatives as contributors to the corrosive environment that may lead to the generation of atherosclerosis. Homocysteine, a sulphur amino acid, is discussed as a cause of atherosclerosis since 1969.<sup>[93]</sup> It has been demonstrated that plasma homocysteine levels also increase during psychological stress.<sup>[94, 95, 96]</sup>

It was found that low-density lipoprotein modification is affected by myeloperoxidase (MPO). MPO's major product is hypochlorous acid (a weak acid) which appears to be important in the development process of atherosclerosis. The study has shown that acidic environment play an important role of hypochlorous acid on LDL modification. A positive correlation was found between the maximal rate of low-density lipoprotein modification and the acidity of the medium.<sup>[97, 98, 99]</sup> A new study has shown that elevated MPO levels predict future risk of coronary artery disease in apparently healthy individuals. It suggests that inflammatory activation precedes the onset of overt coronary artery disease by many years.<sup>[100]</sup>

It is interesting to notice the evidence that, apart from its occurrence in atherosclerosis, acidity of the environment is also increased in inflammatory sites.<sup>[83, 101]</sup> This raises a potential importance of acidity for inflammation results in formation of atheroma's.

The timing of crystallization depends on several local physical factors, including cholesterol concentration, pH, temperature, and pressure.<sup>[102]</sup> We believe that the grade in pH of the acidic environment may play a role in the cholesterol crystallization, as it occurs in the formation of uric acid crystals in the development of gout.

## **Hemodynamic shear stress and atherosclerosis**

As the final step in this process the changes in pH may lead to mechanical forces<sup>[64, 65, 66, 67]</sup> over the acidic coronary blood flow resulted from stress intensifying the damaging action in the development of atherosclerotic lesions.

Atherosclerosis preferentially affects the outer edges of vessel bifurcations. In these predisposed areas, hemodynamic shear stress, the frictional force acting on the endothelial cell surface as a result of blood flow is weaker than in protected regions. Studies have identified hemodynamic shear stress as an important determinant of endothelial function and phenotype.<sup>[103]</sup>

The pulsatile nature of blood pressure and flow creates hemodynamic stimuli in the forms of cyclic stretch and shear stress.<sup>[6]</sup> The changes in flow patterns can produce potentially deleterious effects on vascular biology. Lowered shear stress and oscillatory shear stress are essential conditions in atherosclerotic lesion size and vulnerability.<sup>[104, 105]</sup> The first paper to mention about the importance of forces such as those derived from changes in

hemodynamic shear stress could cause atherosclerosis, was wrote by Meyer Texon in 1957. <sup>[106, 107]</sup>

## **The plaque rupture**

The plaque instability and rupture may start a considerable time before the AMI, according to some studies. <sup>[108, 109]</sup> Stretching, tearing and perforation, related to cholesterol crystallization and expansion, may play a role in the process. <sup>[102]</sup> Also, sympathetic overstimulation and hemodynamic forces like left ventricular muscle mass and elevated heart rate may be associated with the future development of plaque disruption. <sup>[110]</sup>

The release and displacement of thrombi may occur during the acute myocardial infarction <sup>[8, 111]</sup>, being the lactate accumulation <sup>[7, 50, 74]</sup>, regional myocardial insufficiency and stasis of the related artery <sup>[7, 111, 112]</sup>, a plausible mechanism to explain this secondary instability phenomenon, which may have pan-coronary repercussion. <sup>[113]</sup>

### **Some facts supporting the secondary release of coronary thrombus:**

a) Increased frequency of thrombi with increasing intervals between onset of the acute myocardial infarction and death. <sup>[112]</sup>

b) In a significant number of cases angioscopic examination continues to find thrombus on the presumed culprit lesion, at 6 months after myocardial infarction. <sup>[114]</sup>

c) The frequency of an occlusive thrombus is significantly higher in the larger infarcts. <sup>[115]</sup> Anyway, the bottom-line is that coronary thrombus is absent in a substantial number of patients as shown in recent studies using intracoronary catheters to aspirate occlusive tissues performed during myocardial infarction. <sup>[108, 116]</sup> These findings confirm previous autopsy studies, which came to the conclusion that thrombus is a consequence not a cause of AMI. <sup>[8, 111, 112]</sup>

## **Stress reduction, sympatholytic agents and regression or lower progression of Atherosclerosis**

As a recent paper has shown, coronary atherosclerosis regressed in women who were free of stress through the use of serial quantitative angiography. <sup>[117]</sup> Its data confirm the results of other papers. One study reports a decrease in carotid IMT in African Americans with hypertension submitted to stress reduction through Transcendental Meditation. <sup>[118]</sup> A second study indicates that a decrease in carotid IMT was related with older persons with multiple factors for coronary heart disease submitted to the Maharishi Vedic Medicine treatment, which also includes stress reduction through Transcendental Meditation program. <sup>[119]</sup> A third study has shown that yoga intervention retards progression and increases regression of coronary atherosclerosis in patients with severe coronary artery disease. <sup>[120]</sup> Another study has demonstrated that aerobic physical exercise resulted in statistically significant



attenuation in the progression of carotid IMT in middle-aged white men who were not taking statins. <sup>[121]</sup> Carotid intima-media thickness (IMT) is a valid surrogate measure for coronary atherosclerosis.

Also, studies have shown that rhesus monkeys submitted to sympatholytic agents like betablockers or bilateral surgical thoracic sympathectomy have had a marked reduction in the progression of atherosclerosis. <sup>[122]</sup> The first randomized trial showing that betablockers can reduce the rate of progression of carotid IMT in clinically healthy symptom-free subjects with carotid plaque was published in 2001 <sup>[123]</sup> and evidenced later by other studies. <sup>[124]</sup> A recent pooled analysis data from 4 intravascular ultrasonography trials involving 1,515 patients has confirmed that betablocker therapy is associated with reduced atheroma progression. <sup>[125]</sup>

To our knowledge only one angiographic study assessed data on regression (15%), inalterability (62%) or progression (23%) of atherosclerosis in patients treated with cardiac glycosides [126], that also have sympatholytic properties by blocking excessive release of catecholamine. <sup>[48, 49]</sup>

Years later the same group of researchers from Brazil presented a case study involving 1,150 patients with coronary-myocardial disease taking daily lower oral doses of cardiac glycosides - most of times digoxin and digitoxin, showing in a long run (28 years), a very low mortality rate for cardiac causes, cerebral stroke, cancer or all causes. The global mortality for patients without previous myocardial infarction was 14,2% (0,5% per year) while for patients with previous myocardial infarction was 41,0% (1,4% per year). <sup>[44, 45]</sup> Another study, this one made in Germany by Berthold Kern, has achieved similar results. It showed a very low mortality rate in prevention of acute myocardial infarction using sub-lingual cardiac glycoside strophanthin, in about 15,000 patients with heart disease, for 23 years. <sup>[46]</sup>

## Implications and Perspectives

A decade ago, the treatment of hypercholesterolemia and hypertension was expected to eliminate coronary artery disease by the end of the 20th century. Lately, however, that optimistic prediction has needed revision. Cardiovascular diseases are expected to be the main cause of death globally within the next 15 years owing to a rapidly increasing prevalence in developing countries and Eastern Europe and the rising incidence of obesity and diabetes in the Western world. <sup>[127]</sup> This information is contrary to the popular belief that the widespread use of lowering cholesterol drugs like statins could have the potential to become a major effect on the global burden of cardiovascular disease. According to some researchers, statins have been overhyped and consequently over-used, but not providing significant overall health benefits. Also, that statins have many more side effects than is generally accepted, despite the huge and rising costs. <sup>[128]</sup>

On the other side studies are showing that long term psychological stress is associated with progression from prehypertension to hypertension or coronary heart disease. <sup>[129]</sup> There are indications that sympathetic predominance might favour the development of sustained hypertension and hypercholesterolemia early in life, and lead to increased susceptibility to vascular complications. <sup>[130]</sup> Also, studies have shown that several components of the metabolic syndrome, such as obesity and insulin resistance states, are associated with indirect or direct markers of adrenergic overdrive. <sup>[131]</sup> Yet the elevation of plasma lactate levels may induce insulin resistance by suppressing glycolysis. <sup>[132]</sup> Moreover, the autonomic nervous system is influenced by high-carbohydrate dietary, with greater sympathetic nervous activity. <sup>[133, 134]</sup>

Dietary carbohydrate is the major determinant of postprandial glucose levels. Post-prandial hyperglycemia is recognized as a significant risk factor for cardiovascular disease not only in diabetic patients, but also among the general population.

The acidity theory represents a new paradigm, offering a sea-change in alternatives for the treatment of atherosclerosis, by stress management alone or in adjunct to other pharmaceutical or technological medical approaches. It prioritizes lifestyle modifications like diet, physical exercises, yoga, Transcendental Meditation and through biofeedback stress reduction devices or by other behavioral approaches aimed to reduce chronic stress through relaxation response, consequently decreasing sympathetic bias and its harmful effects.

Accumulated evidence indicates that fish intake and fish oil supplementation reduce morbidity/mortality associated with cardiovascular disease. In fact, studies are showing that the habitual intake of omega-3 fatty acid may reduce the progression of coronary atherosclerosis. <sup>[135]</sup> Among the possible mechanisms underlying these effects is its capability to reduce the elevated blood lactic acid. <sup>[136]</sup>

Quercetin, the most abundant of the flavonoids, found in high concentration in red wine and in fruits and vegetables used in Mediterranean diet, may also decrease lactic acid production <sup>[137]</sup>

This may give an additional explanation on how flavonoids can help to reduce the risk of atherosclerosis and offer protection against coronary-myocardial disease. Other polyphenols like resveratrol and curcumin may also reduce lactic acid production in blood. <sup>[138, 139]</sup> Some phytochemicals with proved therapeutic benefit for the treatment of cardiovascular disease, like crataegus oxyacantha, have demonstrated in studies a decrease in lactic acid production. <sup>[140]</sup>

Interventions through pharmacological management for atherosclerosis should be used in our view only in established disease – or in old vulnerable patients, for the restoration of Sympatho-vagal balance, to slow the progression or in regression of atherosclerosis.

Cardiac glycosides, which are compatible with the acidity theory, should be the drug of choice for the treatment of atherosclerosis and in prevention of acute coronary syndromes – unstable angina, myocardial infarction and sudden cardiac death, experienced with success in many patients with coronary-myocardial disease <sup>[44, 45]</sup> treated inside the myogenic theory of myocardial infarction, a complementary hypothesis, where psycho-emotional and physical stresses are considered to be the main triggers. <sup>[7, 8]</sup>

It was demonstrated in patients taking cardiac glycosides when recovering from myocardial infarction <sup>[141]</sup>, treated for congestive heart failure [142] or prophylactic in the heart not in failure <sup>[143]</sup>, that a beneficial effect on morbidity and mortality is seen at lower doses but not at higher doses, which are traditionally considered to be therapeutic.

Cardiac glycosides sympatho-inhibitory properties as well other of their important therapeutic possibilities were confirmed in recent studies. Like re-elevation of lowered pH and to attend the demand on insufficient production of endogenous DLCs in some clinical conditions.

Due to all these reasons, we believe that the usage of cardiac glycosides may relate to coronary-myocardial disease the same way as insulin relates to diabetes.

It seems that in digitalis therapy, “less is more!” Remembering Paracelsus, 16th century:

*“All substances are poisonous; there is none which is not a poison.  
The right dose differentiates a poison from a remedy”*

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## Chapter 6

# Acidity Theory of Atherosclerosis: History, Pathophysiology, Therapeutics and Risk Factors

*Carlos ETB Monteiro*

### **Abstract**

The link between stress and atherosclerosis is well-known with many studies and postulations in this regard. However, there is a general unawareness that stress can induce hyperlactatemia and lactic acidosis because this relationship has been little discussed in medical science.

The influence of adrenaline on lactic acid production was first noticed by Carl Ferdinand Cory in 1925. The heart is an organ of high metabolic activity – that cannot rest as other body muscles, being susceptible to drops in pH during ischemia and hypoxia.

The chronic elevated catecholamine release, triggered by sympathetic dominance, may accelerate the myocardial glycolysis leading to significant increase in lactate production. Risk factors for atherosclerosis like hypertension, diabetes, cigarette smoking, stress conditions and high carbohydrate diets are linked to autonomic dysfunction.

These risk factors present an increased concentration of lactate in plasma. Blood lactate is also associated with carotid atherosclerosis. Plasma lipid abnormalities and myocardial lactate production were significantly associated with subsequent arteriographic progression.

The amount of lactate released by the myocardium has been shown to be related to the severity of coronary artery disease. Reduced pH increases the oxidation of low-density lipoprotein that is considered to have a significant role in atherogenesis.

According to the acidity theory of atherosclerosis the acidosis evoked by sympathetic dominance or continuous stress leads to changes in shear stress, the final stage in the development of atherosclerotic lesions.

The importance of mechanical forces such as those derived from changes in hemodynamic shear stress, as a decisive factor for atherosclerosis, was advocated by Meyer Texon since 1957

## Introduction

During the nineties, in a conversation with Quintiliano H de Mesquita – my father-in-law and a brilliant cardiologist and professor – I asked to him to express his thoughts about cholesterol (The Lipid Hypothesis), whether it was the culprit or not for coronary artery disease. Dr Mesquita was my mentor in medical science who has developed, among other pioneer advances in medicine, the myogenic theory of myocardial infarction in 1972, about which I have had the great honor and gratification to make a recent review. It was entitled Stress as Cause of Heart Attacks - The Myogenic Theory.<sup>[1]</sup>

In reality, the question I made to Dr Mesquita had origin in my knowledge that some important researchers like Drs Uffe Ravnskov and George Mann pointed many flaws to the whole cholesterol idea.

The approximate answer from Dr Mesquita was: “Carlos, I don’t believe the cholesterol is the enemy. In my view, it represents just a healing agent to repair the injury suffered by the arterial endothelium. In reality, I think the cholesterol theory reasoning is very simplistic, limited and superficial.” Then I went back to ask: What causes atherosclerosis in your opinion? His response to this question was: “Carlos, I do not have any alternative explanation, so I prefer to say I do not know.” This has shaped my mind that atherosclerosis could be a response to injury, and the lipid hypothesis a delusion.

*“Let us now try to look at some of the facts about cholesterol in light of the idea that cholesterol is part of an attempted tissue repair. Its accumulation in the arteriosclerotic lesion may be viewed as a protective mechanism”. Hans Kaunits, 1978 <sup>[146]</sup>*

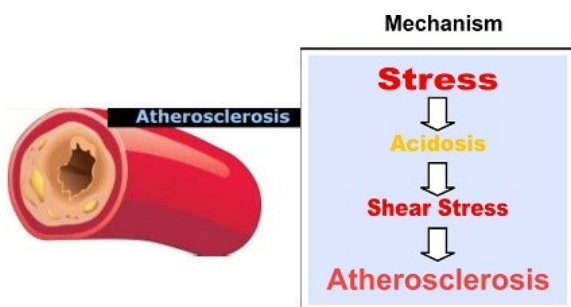
We could not fail to quote the following excerpt from the chapter ‘How evolves coronary disease’ from the book “How to escape coronary bypass surgery and myocardial infarction only with a remedy”, originally published in the Portuguese language, written in 1991 by Dr Quintiliano H de Mesquita.

*“The natural tendency of the too little-known atherosclerotic process is evolutionary, gradual and inexorable, in which the arterial walls are transformed, becoming hardened without elasticity and reduced vascular caliber throughout its course. When coincides with sharp deviations from the metabolism of fat (total lipids, triglycerides, cholesterol, etc.) and carbohydrates, that require therapeutics and dietary control, sets up an apparent relation of cause and effect. However, often we observe atherosclerotic coronaries without any deviations from those elements measured in blood, which seems to complicate and undermine the traditional concepts as cause of atherosclerosis.”*

On July 29, 2006, I participated, as a recent member, in a discussion inside the internal forum at internet of the International Network of Cholesterol Skeptics (THINCS), regarding the role of mechanical forces in atherosclerosis.

Melchior Meijer, a journalist specialized in medical areas, noticed the demonstration by scientists from California that normal stretching/relaxing of an artery does not produce atherosclerosis, while stretching/relaxing in different directions simultaneously on every heartbeat does. [2, 3, 4].

Dr Paul Rosch, participating in the discussion about these findings, told that in relation of the contribution of psychological stress his friend Meyer Texon, the developer of the hemodynamic theory of atherosclerosis, conceded to him in a conversation that stress might accelerate the development of atherosclerotic lesions by aggravating the basic mechanism of shear stress, which he felt was responsible.



A few days after, inspired by the findings from the researchers in California and by the information brought by Dr Paul Rosch, I came to the draft about the acidity theory of atherosclerosis presenting my proposal for its pathophysiological mechanism and sequence of events at the THINCS forum, on August 2, 2006.

The acidity theory of atherosclerosis was in line with some scientific medical matters that I was researching at the time. After 16 months, a period during which we gathered several studies giving scientific support to the pathophysiological mechanism proposed in the Acidity Theory of Atherosclerosis, I wrote the manuscript "Acidic Environment Evoked by Chronic Stress: A Novel Mechanism to Explain Atherogenesis". [5]

In 2009 I launched the blog New Evidences: Acidity Theory of Atherosclerosis [6] which became the basis for my book Acidity Theory of Atherosclerosis - New Evidences, launched in early 2012.[7] A few months later I was invited by Professor Dr Paul Rosch, the president of the American Institute of Stress, as one of speakers for the IV International Conference of Advanced Cardiac Sciences - The King of Organs Conference, November 2012[8], in Saudi Arabia.

Dr Paul Rosch, who also is a remarkable researcher, well-known and respected for his scientific integrity, started to fight for stress as the main risk factor for coronary heart disease more than 3 decades ago. Meanwhile he was a strong opponent to the Lipid Hypothesis.

Dr Paul Rosch belonged to the scientific committee of this event. In his letter to Dr Abdullah Alabdulgader, the President of The King of Organs Conference, he said:

*"Carlos Monteiro, another of our fellows who is based in Brazil just published Acidity Theory of Atherosclerosis. It is a fascinating book that extends Dr De Mesquita's myogenic theory of myocardial infarction and its focus on the crucial role of the sympathetic nervous system and stress in the pathogenesis of atherosclerotic heart disease. I feel confident that he could give one or more presentations that would be cutting edge and informative to this audience"*

During the King of Organs Conference, I delivered to Dr Paul Rosch my book with the following inscription:

*"To my friend Dr Paul Rosch, one of the greatest medical teachers I have known, and who gave us the initial inspiration for the development of the acidity theory of atherosclerosis. Paul, I have to thank you greatly about this and for your decisive support about our proposal to be effectively recorded and discussed within the medical community, as is happening in King of Organs Conference. Please accept our book with the compliments from your friend who much admires you."*

I have given two lectures at The King of Organs Conference. The first speech was about the Myogenic Theory of Myocardial Infarction (Powerpoint presentation and video) and the second about the Acidity Theory of Atherosclerosis (Powerpoint presentation and video).

*Members from the International Network of Cholesterol Skeptics - THINCS*

*at the Fourth International Conference of Advanced Cardiac Sciences (The King of Organs Conference), November 2012.*

*L-R: David Diamond, Malcolm Kendrick, Carlos Monteiro, Paul Rosch.*



Some topics presented by our group:

- 1 The demise of lipid hypothesis.
- 2 Why stress is more important than cholesterol.
- 3 Stress, atherosclerosis and coronary heart disease.
- 4 Why statins are not solution to coronary heart disease - or anything else.

One of the subjects I have presented in “The King of Organs Conference” was “What causes the elevation of cholesterol levels in blood?” In it I have pointed to studies showing that some risk factors for coronary artery disease, like stress (anxiety, hostility, extreme physical exertion, etc.), high carbohydrate diets, smoke and exposition to some chemicals like perfluorooctanoic acid might lead to a raise in total cholesterol and low-density lipoproteins levels.<sup>[6, 7]</sup> It should also be noticed that in stress conditions, high carbohydrate diets and cigarette smoking there is a significant elevation in blood lactate levels.

Particularly interesting was the declaration from Dr Malcolm Kendrick in one of his speeches at “The King of Organs Conference, 2012”:

“Do cigarettes contain fat? No, not at all. So, how can smoking a cigarette, containing no fat or cholesterol, end up depositing fat and cholesterol in the artery walls. What is the mechanism for that? “

## **Our Hypothesis**

The myogenic theory, developed by Dr Mesquita, became the template for the acidity theory of atherosclerosis. In his point of view the heart disease process involves two distinct pathologies, one for coronary artery disease/atherosclerosis, the other for the myocardial disease, what led to his adoption of the terms ‘coronary-cardiomyopathy’ or ‘coronary-myocardial disease’, instead of “coronary heart disease” and the term ‘acute myocardial syndromes’ instead of ‘acute coronary syndromes’. His reasoning was contrary to the currently accepted thinking which has its cause-and-effect relationship based in the thrombo-centric coronary heart disease model.

Noteworthy is the citation from Dr George E Burch, a shaper of modern cardiology, which goes strikingly to the point:

*“The coronary patient does not die from coronary disease he dies from myocardial disease.” (1972)<sup>[9]</sup>*

Indeed, our acidity theory of atherosclerosis fits perfectly with the myogenic theory of myocardial infarction concept. The myogenic theory accepts that stress or emotion affects the cardiac muscle dependent on the affected coronary artery, compromising the myocardial structure. In his book about the myogenic theory (1979) he says:

*“Thus, the coronary disease contributes to the deterioration of the ventricular segment, constituting areas of myocardial sclerosis or segmental myocardial disease, the possible future site of the myocardial infarction”.<sup>[10]</sup>*

**Here is the sequence of events to explain atherogenesis, inside the acidity theory of atherosclerosis concept:**

1. Sympathetic dominance by continuous stress plus;
2. Deficiency in production of endogenous digitalis-like compounds (DLCs) with alterations of Na(+), K(+)-ATPase activity results in;
3. Lowered pH (acidosis) that increases perfusion pressure and provokes effects on contractility of coronary arteries leading to changes in hemodynamic shear stress and atherosclerosis as consequence.

**Some Fundamentals about the Acidity Theory of Atherosclerosis:**

The heart is an organ of high metabolic activity - that cannot rest as other body muscles, being susceptible to drops in pH during ischemia and hypoxia. The chronic elevated catecholamine release, triggered by sympathetic dominance, may accelerate the myocardial glycolysis leading to significant increase in lactate production.

The association of increased lipid levels with abnormal lactate metabolism may provide a useful screening test for the detection of coronary artery disease. It was demonstrated that plasma lipid abnormalities and myocardial lactate production were significantly associated with subsequent arteriographic progression. The amount of lactate released by the myocardium has been shown to be related to the severity of coronary artery disease. <sup>[11,12,13]</sup>

In our opinion the raise in plasma lipids presented in these studies might be a response to injury of the arterial endothelium due to an increased release of lactate triggered by sympathetic activation resulting in changes on hemodynamic shear stress.

**Notes:**

- Findings from studies in human beings and animals have shown that epinephrine increases lactate formation by an increase in the Na+K+ ATPase activity.<sup>[14]</sup>
- This can be inhibited through digitalis or strophanthin/ouabain that are sodium pump inhibitors.<sup>[15]</sup>
- Perturbation of the endogenous digitalis-like compounds (DLCs) system has been implied in pathological conditions including cardiac arrhythmias, hypertension, cancer and depressive disorders.<sup>[16, 17]</sup>
- Stress situations may affect the release of endogenous DLCs by the adrenal gland.<sup>[18]</sup> Also, the extracellular acidification may affect the signaling and transport of endogenous DLCs.<sup>[19, 20]</sup> This raises the possibility that an insufficient production of endogenous DLCs to attend the demand in some medical conditions, like coronary-myocardial disease, hypothetically can be resolved through the use of cardiac glycosides at low concentration, as a supplement.

- This is confirmed by clinical studies using digitalis and strophanthin / ouabain, with largely positive effects in prevention of acute coronary syndromes. <sup>[1, 21]</sup>
- Low therapeutic doses of digitalis or strophanthin/ouabain have specific sympatho-inhibitory response by blocking the overproduction of catecholamine. This property is unrelated to the positive inotropic action of cardiac glycosides. <sup>[1]</sup>
- We hypothesize that endogenous digitalis-like compounds may have similar action on neurohormonal levels. <sup>[5]</sup>

## **The Link Between Sympathetic Dominance and Changes in Hemodynamic Shear Stress**

The sympathetic activation with elevation of circulating catecholamine (epinephrine, etc.), causes coronary vasoconstriction and consequent reduction in blood flow.

On the other hand, the increased lactate (or decreased blood pH) may evoke vascular smooth muscle relaxation and increase of blood flow.

These opposite forces working in sequence - with the sympathetic overdrive leading to metabolic acidosis, in our view, may be reconciled to represent one of the explanations for the occurrence of the resulting abnormal stretching/relaxing of coronary arteries, in different directions, simultaneously, demonstrated by scientists from California , producing changes in hemodynamic shear stress and ultimately leading to atherosclerotic disease. <sup>[7]</sup>

## **The Most Important Scientific Advances by Researchers that Paved the Way for our Acidity Theory of Atherosclerosis**

1. Walter Holbrook Gaskell demonstrated in 1880 that acid solutions have effects on the contractility of heart tissues and vascular smooth muscle, representing an important mechanism for the local regulation of blood flow during increased metabolic activity. <sup>[22]</sup>
2. Rudolph Virchow in 1856 described atherosclerosis as “endarteritis deformans” meaning that the atheroma was a product of vascular injury inducing inflammation within the intima of the artery wall. <sup>[23]</sup>
3. The first to observe the influence of adrenaline on lactic acid production were the Coris in the early 1920s. <sup>[24]</sup>
4. Meyer Texon in 1957 postulated that forces such as those derived from changes in hemodynamic shear stress might cause atherosclerosis. <sup>[25]</sup>
5. Zsotér et al have demonstrated in 1961 that reduction of blood pH increases blood flow. <sup>[26]</sup>
6. James P. Henry and Patricia M. Stephens, in 1977, postulated that chronic stress or the constantly heightened sympathetic-adrenomedullary activity might lead to atherosclerosis and cardiovascular disease\*. <sup>[27]</sup>
7. Redford B. Williams, in 1978, postulated that recurrent physiologic actions involving exaggerated heart rate and pressor responses to



behavioral stimuli might promote arterial injury via hemodynamic forces such as turbulence and shear stress.<sup>[28]</sup>

## **Risk Factors for Atherosclerosis /Coronary Artery Disease**

Most risk factors for atherosclerosis have as common denominator the dysregulation of the autonomic nervous system, related with sympathetic dominance, through sympathetic over-activity or withdrawal of the parasympathetic system.

1. Psychosocial factors: The 5 specific psychosocial domains that contribute significantly to the pathogenesis and expression of coronary artery disease are: Depression; Anxiety; Personality factors and character traits; Social isolation and Chronic life stress.<sup>[29,30]</sup>
2. Age: Atherosclerosis and age are intimately linked, being the best example of an age-related disease. It is generally accepted that sympathetic nervous activity increases progressively with age. Also, that plasma noradrenaline levels increase may be mediated by the age-related impairment of baroreflex sensitivity.<sup>[31,32,33]</sup>
3. Hypercholesterolemia: Sympathetic dominance may favor hypertension and hypercholesterolemia early in life, and lead to increased susceptibility to vascular complications.<sup>[34]</sup>
4. Hypertriglyceridemia: Elevated levels of triglycerides are associated with atherosclerosis. Recent studies found that the sympathetic nervous system play an important role in control of triglyceride metabolism.<sup>[35,36]</sup>
5. Hypertension: is considered as an important risk factor for the development of atherosclerosis, with these processes sharing some common mechanisms. The endothelium is usually placed as the probable central focus for the effects in both diseases, with evidences leading to the postulation that hypertension predispose and accelerate atherosclerosis. The sympathetic activation plays an important role in the regulation of the blood pressure.<sup>[37,38,39]</sup>
6. Chronic kidney disease: Patients with chronic kidney disease are at increased risk of atherosclerotic cardiovascular disease. A marked increase in sympathetic neural discharge, as accessed via the microneurographic technique, has been shown to occur in the predialytic stage of chronic renal failure. Recent evidence, however, indicates that also in the earlier clinical phases of kidney disease, sympathetic activation is detectable. Further data show that sympathetic neural mechanisms participate in renal and/or hypertensive disease progression, favoring the development of target organ damage.<sup>[40]</sup>
7. Diabetes: Patients with diabetes are at increased risk for atherosclerosis. It has long been recognized that cardiac autonomic neuropathy increases morbidity and mortality in diabetes and may have greater predictive power than traditional risk factors for cardiovascular events. Significant morbidity and mortality in diabetes can now be attributable to autonomic imbalance between the sympathetic and parasympathetic nervous system regulation of cardiovascular function.<sup>[41,42]</sup>

8. Cigarette smoking: Cigarette smoking increases efferent sympathetic nerve traffic acutely, as well norepinephrine and epinephrine release. The acute sympatho-excitatory effects of smoking on the cardiovascular system are partially mediated by catecholamine release, muscle sympathetic nerve excitation and peripheral chemoreceptor sensitivity increase, consecutive to nicotinic receptor stimulation in the autonomic nervous system. Both active smoking and exposure to environmental tobacco smoke are associated with the progression of atherosclerosis as indexed by intimal-medial thickness of the carotid artery assessed by ultrasound. Carotid intima-media thickness is a valid surrogate measure for coronary atherosclerosis. Blood lactate levels are increased after passive smoking. <sup>[43-46]</sup>
9. Air pollution: Studies in humans have confirmed the association of the exposure to ambient air pollution and atherosclerosis, through the progression of carotid artery intima-media thickness. It was demonstrated that particulate air pollutants continuous exposition decreases the heart rate variability and may lead to an impaired autonomic control with potential acceleration in the progression of atherosclerosis. <sup>[47-50]</sup>
10. Noise: Living near main roads and aircraft noise near airports causes stress reactions similar to other stressors in the occupational and ambient environment. In these situations of sympathetic and endocrine arousal, concentrations of stress hormones in blood are increased. Laboratory and epidemiological studies have demonstrated a link between noise and cardiovascular disease. A large study recently published found that long-term exposure to fine particulate matter and night-time traffic noise are both independently associated with subclinical atherosclerosis. <sup>[51-55]</sup>
11. High carbohydrate diets: It is well established that the sympathetic nervous system activity is also influenced by food ingestion, and that diet composition plays an important role. High carbohydrate diets, particularly in the form of high-glycemic carbohydrate, have the ability to directly induce endothelial dysfunction, vascular inflammation and subsequent development of atherosclerosis. A study from 2009 advocates that the widespread use of starchy food and sugars has brought a new metabolic problem: a chronically increased sympathetic nervous system activity, where the high glycaemic index nutrition has been suggested to play a key role in the pathogenesis of hypertension and atherosclerosis. On the other side protein or fat ingestion have no significant sympatho-excitatory effect. <sup>[56-59]</sup>
12. Obstructive sleep apnea: The prevalence of coronary artery disease is 3 to 5 times higher in patients with obstructive sleep apnea (OSA) compared with control populations. Increased carotid intima-media thickness and plaque occurrence was reported in OSA patients without any other significant co-morbidity compared to matched controls. OSA patients experience intermittent hypoxemia and CO<sub>2</sub> retention that modify the autonomic and hemodynamic responses to sleep. Chronic intermittent hypoxia may lead to sympathetic over-activity. <sup>[60-63]</sup>
13. Erectile dysfunction: Recent studies have demonstrated that coronary atherosclerosis is more severe in patients with vascular erectile dysfunction (ED), with indications that ED may be an additional, early

warning sign of coronary atherosclerosis. One of these studies has shown that men with idiopathic ED have evidence of endothelial dysfunction in forearm resistance vessels, increased pulse pressure and impaired heart rate variability. The authors of this study say that this supports the concept that erectile dysfunction is a predictor of cardiovascular dysfunction and a precursor of clinical cardiovascular disease. Another recent study has demonstrated that patients with ED exhibited different heart rate variability compared with normal controls, confirming the results of other findings showing that patients with ED may have excessive sympathetic activity. <sup>[64-66]</sup>

14. **Metabolic syndrome:** The metabolic syndrome is associated with increased risk for development of both cardiovascular disease and type-2 diabetes in humans. Central obesity and insulin resistance are thought to represent common underlying factors of the syndrome, which features a chronic low-grade inflammatory state. Several markers of adrenergic drive, such as plasma norepinephrine, norepinephrine spillover from adrenergic nerve terminals, heart rate and others, with sympathetic activation, have all shown an increase in the different conditions clustering in metabolic syndrome like obesity, hypertension and insulin resistance state. <sup>[67-69]</sup>
15. **Infection through bacteremia:** Periodontal disease, one the most common chronic bacterial infection, may represent a favorable scenario to verify the connection of infection and atherosclerosis/cardiovascular disease. Several studies are suggesting an oral source for atherosclerotic plaque - associated bacteria with demonstration about the presence of viable periodontal pathogens in atherosclerotic plaques. In this regard an interesting hypothesis was proposed in 2004 that periodontal infection may lead to brief episodes of bacteremia with inoculation of atherosclerotic plaque by periodontal pathogens. However, important information is left aside by most investigators studying the connection between oral infection and atherosclerosis / coronary myocardial disease. These investigators don't take in consideration that the sympathetic nervous system is intensely activated during bacteremia. <sup>[70-72]</sup>
16. **Salt:** There is an intense discussion on the benefits and potential harm of reducing salt intake in the general population. In our view, both restriction and high salt intake may result in coronary artery disease\*. The reason is that in both cases exist an increased sympathetic nerve activity. <sup>[7, 73-75]</sup>
17. **Insomnia:** Insomnia is characterized by a constant sympathetic hyperactivation. In 1999 it was hypothesized that insomnia may be related to continual stressors, reduced slow-wave sleep, and autonomic dysfunction, which increase the risk of heart problems. <sup>[76-77]</sup>
18. **Extreme physical exertion:** Studies have shown that long-term marathon runners may have increased coronary calcium and calcified plaque volume. Other findings support an increased awareness of atherosclerosis prevalence and cardiovascular risk factors in marathon runners. In our view the sympathetic activation and the resulted increase in blood lactate levels may represent the biological mechanism leading to atherosclerosis in marathon runners. <sup>[78-80]</sup>

19. Vitamin D deficiency: Vitamin D deficiency is a risk factor for atherosclerosis. It has been shown that vitamin D deficiency alters activity of the cardiovascular system and related pressor responses and may lead to dysfunction of the cardiac autonomic nervous system. <sup>[81-82]</sup>
20. Preeclampsia: A history of preeclampsia has a higher risk of cardiovascular disease and mortality later in life. Studies have shown that women with preeclampsia had significantly more atherosclerotic plaques than parous controls. The carotid intima-media thickness in these women with preeclampsia also tended to be higher than in other groups. The autonomic nervous system appears to play an important role in the etiology of preeclampsia where there is increased sympathetic and decreased parasympathetic control of heart rate. The lactate dehydrogenase levels are also significantly elevated in women with preeclampsia. <sup>[83-88]</sup>
21. Chemical and Organic Pollutants: The studies associating cardiovascular disease with the exposition to certain chemicals like perfluorooctanoic acid, arsenic, lead and cadmium, besides some persistent organic pollutants, reminds me the experiments from the beginning of the last century showing that acid-fed rabbits and dogs develop atherosclerotic lesions. In our opinion the effects generating atherosclerotic lesions in these experiments were caused not only by chronic hyperacidity in rabbits and dogs but also related to an intense activation of the sympathetic system provoked by acid ingestion. Studies also suggest that chemotherapy may be a risk factor for the development of atherosclerosis. <sup>[7, 89-97]</sup>
22. Radiation: Radiation may also induce atherosclerosis. Recent epidemiological studies provided evidence that an excess risk of cardiovascular disease can be associated with moderate and low dose radiation. It is recognized for more than 50 years the effects of radiation over the nervous system. This may also include radiation from wireless technology. <sup>[98-99]</sup>
23. Myocardial infarction (A paradoxical risk factor?): Recent studies show that acute myocardial infarction leads to acceleration of atherosclerosis. In our view this happens because the acute sympathetic activity in AMI results in lactic acidosis and lactate accumulation leading to increased perfusion pressure and effects on contractility of coronary arteries, with changes in hemodynamic shear stress ending in atherosclerosis as consequence. <sup>[100-101]</sup>
24. Associated Diseases with Elevated Lactic Acid or Lactate: In addition of diabetes and hypertension there are various diseases associated with atherosclerosis/coronary artery disease where the common denominator is the elevation of lactic acid or lactate, for example: psoriasis, rheumatoid arthritis and migraine. Certainly, the raise in lactic acid/lactate levels might also be related to an altered autonomic nervous system with sympathetic predominance. Incidentally, blood lactate was also found recently to be associated with carotid atherosclerosis. <sup>[102-113]</sup>

## Individuals with Lower Degree or Absence of Atherosclerosis

1. Why atherosclerosis is milder or non-existent in individuals with Down syndrome? Different necropsy studies have shown that the occurrence of atherosclerosis is milder or non-existent in subjects with Down syndrome. A reasonable explanation for the reduced incidence of atherosclerosis is the altered autonomic regulation in individuals with DS, with effects of smaller changes in baroreflex sensitivity and in sympatho-excitation response. The reduced sympathetic response to stress in DS is supported by the low circulating catecholamine levels in response to incremental cycle ergometer exercise in individuals with DS. <sup>[114-118]</sup>
2. Why atherosclerosis has a lower degree in individuals suffering from alcoholism? Necropsy studies have shown that individuals suffering from alcoholism have a significantly lower degree of atherosclerosis in the coronary arteries. A paper published in 2002 may have the answer to this question. William Lovallo, one of the authors of this paper, told in interview to EurekAlert: "Before testing alcoholics for their responses to a public-speaking task, researchers first needed to establish if their sympathetic nervous system was able to respond at all." This would tell us if their blunting was specific to psychological stressors like public speaking," said Lovallo, "or due to a generalized autonomic deficit." The patients reacted as if the social challenge of public speaking had no special meaning for them. So, the sympathetic nervous system in the patients looked normal, but their response to a psychological stressor was almost absent. When faced with a socially meaningful stressor, neither part of their fight-flight mechanism was working." <sup>[119-121]</sup>

## Reversion or Lower Progression of Atherosclerosis

### **#1 - Beta blockers and sympathectomy may reduce progression of atherosclerosis**

Studies have shown that rhesus monkeys submitted to sympatholytic agents like betablockers or bilateral surgical thoracic sympathectomy have had a marked reduction in the progression of atherosclerosis. The first randomized trial showing that betablockers can reduce the rate of progression of carotid IMT in clinically healthy symptom-free subjects with carotid plaque was published in 2001. A pooled analysis data from 4 intravascular ultrasonography trials involving 1,515 patients has confirmed that betablocker therapy is associated with reduced atheroma progression. A study by Strawn and colleagues in 1991 have indicated that social disruption is associated with both sympathetic nervous system arousal and indexes of endothelial dysfunction, effects that may be prevented by treatment with B-adrenergic blocking agent. Also interesting is the study showing a decrease in glycogenolytic rate, blood lactate concentration and lactate clearance after B-Adrenergic blockade with propranolol, probable an indirect effect of its sympatholytic properties. <sup>[122-125]</sup>

**#2 - Cardiac glycosides like digoxin, digitoxin, etc.... may reduce progression of atherosclerosis**

To our knowledge only one angiographic study assessed data on regression (15%), inalterability (62%) or progression (23%) of atherosclerosis in patients treated with cardiac glycosides. Indeed, cardiac glycosides at low concentration may lead to stress reduction by the improvement of baroreceptor function, sympatho-inhibitory effects, vagomimetic effects and decrease in heightened secretion of catecholamines. There are studies showing the existence of potential positive effects of cardiac glycosides (digoxin, digitoxin, etc.) for the treatment of atherosclerosis. <sup>[127-130]</sup>

**#3 -Stress reduction shows reversion or lower progression of atherosclerosis**

Regression of coronary atherosclerosis in women who were free of stress demonstrated through the use of serial quantitative angiography; Decrease of carotid intima media thickness in African Americans with hypertension submitted to stress reduction through Transcendental Meditation; Decrease in carotid intima media thickness in older persons with multiple factors for coronary heart disease submitted to the Maharishi Vedic Medicine treatment -- which also includes stress reduction through Transcendental Meditation program; Yoga intervention retards progression and increases regression of coronary atherosclerosis in patients with severe coronary artery disease; Aerobic physical exercise did not attenuate progression of atherosclerosis, except in a subgroup of men not taking statins. <sup>[131-135]</sup>

**#4 - The baroreflex function and the autonomic nervous system**

It is interesting to notice about the impairment or decrease of baroreflex sensitivity in front of some key factors for atherosclerosis, coronary myocardial disease and stroke, like in ageing, ingestion of sugars, in special high-fructose diets, and smoking. Indeed, there are some studies showing that in bilateral carotid atherosclerosis and in greater intima-media thickness the baroreflex sensitivity is reduced or impaired. On the other hand, the result of the baroreceptor improvement is the inhibition of the sympathetic nervous system and activation of the parasympathetic nervous system. <sup>[136-139]</sup>

## External Risk Markers for Atherosclerosis

### **Baldness**

Severe vertex pattern of androgenetic alopecia is considered to have an increased risk of subclinical atherosclerosis. There is a postulation made in 1997 by Marino Salin, from Italy, telling if there is excess adrenergic tone in the metabolic system, then there is also vasoconstriction, ischemia and hypoxia and if there is hypoxia, glycolysis leads to lactic acid that causes caustic damage to the inner sheath and this sheath seems to be raised above the hair cuticle.<sup>[140-142]</sup>

### **Earlobe Crease**

Diagonal earlobe crease is another external marker for coronary artery disease. Interesting is that the earlobe is one local to determine blood lactate concentration which, when elevated, may be the culprit for the earlobe wrinkle. A recent study confirmed that diagonal bilateral Earlobe crease is independently associated with cardiovascular events in the hospitalized population. An independent association with ischemic stroke has also been demonstrated for the first time.<sup>[143-144]</sup>

## Final Considerations

This article presents the main points and arguments in favor of the Acidity Theory of Atherosclerosis. However, there are additional information that you may find useful in our short (100 pages) and low-cost book from 2012,<sup>[7]</sup> that includes our manuscript from 2008.<sup>[5]</sup>

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# Chapter 7

## Does Lactic Acidosis Cause Coronary Artery Calcification?

*Carlos ETB Monteiro*

### Abstract

Coronary artery calcification is highly prevalent in patients with coronary heart disease and is associated with an increase in major adverse cardiovascular events. It may also have prognostic significance for individuals with no evidence of coronary disease. Various studies have shown that the process of arterial calcification shares some features with skeletal bone formation, including chondrocyte and osteoblast differentiation, mineralization, as well as bone matrix deposition and resorption. It had been suggested over five decades ago that the body draws minerals from the bones to neutralize the effects of an acid ash diet.

We propose that an increase in lactic acid/lactate production is a more important and unappreciated cause of atherosclerosis and coronary artery calcification. We will also discuss the risk factors that influence both bone loss and atherosclerosis that leads to coronary calcification, such as age, diabetes, hypertension, tobacco smoking, chronic kidney disease, rheumatoid arthritis and air pollution. In addition, warfarin, statins, metformin and other drugs can influence lactic acidosis that then leads to osteoporosis and coronary calcification. There is also good evidence that acidosis may be responsible for calcification in the aortic valve, brain and other tissues.

### Introduction

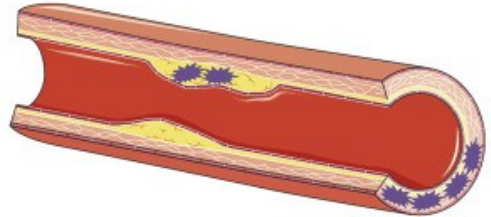
Coronary artery calcification (CAC) is widespread in patients with coronary heart disease (CHD), and although previously considered a benign, asymptomatic, and age-related trait, it is now believed to be an active process that can result in atherosclerosis. Calcification forms within the intimal layer of the arterial wall and begins with spotty minuscule deposits that coalesce to form larger sheet-like accumulations that are readily visible on radiography, computed tomography and intravascular imaging. <sup>[1]</sup>

Because there is a strong correlation between the extent of calcification and the degree of atherosclerosis, it has now been proposed that CAC may be the most accurate way to predict future cardiac events, especially in asymptomatic individuals. <sup>[2-4]</sup> The prevalence of CAC is age and gender related, since it occurs in more than 90% of men and 67% of women over the age of 70 years.

[4]

Vascular calcifications can be classified into 2 separate types depending on whether they are located within the intimal or medial layer. Medial arterial calcification primarily affects the legs and is prevalent in patients with peripheral vascular disease. Intimal calcification predominates in coronary vessels, and both types can be found in the carotid arteries. <sup>[5,6]</sup>

- Intimal calcification**
- age (OR 1.89 per 10 years)
  - pulse pressure (OR 1.12 per 10 mmHg)
  - smoking (OR 2.09)
  - hypertension (OR 2.09)
  - positive family history (OR 1.80)



- Medial calcification**
- age (OR 2.84 per 10 years)
  - pulse pressure (OR 1.12 per 10 mmHg)
  - diabetes mellitus (OR 2.39)
  - previous vascular disease (OR 2.21)
  - positive family history (OR 1.75)

Figure 1 - From Vos A et al <sup>[6]</sup>

The progression of medial arterial calcification is associated with renal failure, hypercalcemia, hyperphosphatemia, and parathyroid hormone. These abnormalities are not seen with intimal coronary calcification although both types of calcification share some risk factors, most of which are age related, as shown in Figure 1.

**Risk Factors For Coronary Calcification**

	Intimal Calcification	Medial Calcification
Advanced age	Yes	Yes
Diabetes mellitus	Yes	Yes
Dyslipidemia	Yes	No
Hypertension	Yes	No
Male	Yes	No
Cigarette smoking	Yes	No
Renal Dysfunction	No	Yes
Hypercalcemia	No	Yes
Hyperphosphatemia	Yes	Yes
PTH abnormalities	No	No

Table 1: Modified from Goodman et al. <sup>[7]</sup>

There is no treatment to prevent arterial calcification or its progression, which is not surprising, since the cause is not clear. There are no satisfactory animal models, because in contrast to humans, rodents, rabbits and dogs do not spontaneously develop atherosclerosis with age.

Patients with end stage renal disease or uremia also have increased coronary artery calcification <sup>[8]</sup> Calciphylaxis is a rare disorder that causes subcutaneous vascular calcification and cutaneous necrosis. It is sometimes called calcific uremic arteriopathy, since it also usually occurs in patients

with severe kidney disease. Little is known about its etiology and pathogenesis other than more than 50 percent of those affected die within 12 months after the diagnosis is made. It was first described in 1898 by Bryant and White,<sup>[9]</sup> but it was not until 1962 that the term “calciophylaxis” was coined by Hans Selye. He defined it as a hypersensitivity disorder, since in his experimental animal model, it was necessary to administration both a “sensitizer” and a “challenger” to produce calcification in various structures.<sup>[10,11]</sup>

Arterial calcification has been induced in rabbits and other herbivores with extremely elevated cholesterol levels due to a very high fat diet because cholesterol is a foreign substance for them and can elicit an inflammatory response. However, these lesions are mainly in the aorta and large arteries rather than the coronaries, differ under the microscope from atherosclerotic plaque in humans, and the identical high fat diet produces no lesions in carnivorous animals.

Severe fat restriction and intensive statin therapy to lower cholesterol or LDL did not prevent or diminish coronary calcification in one study,<sup>[12]</sup> and in another review of over 1,000 patients with high calcium artery calcification scores who were randomized to receive a statin or a placebo, LDL was lowered in the treatment group but there was no reduction in coronary calcification progression.<sup>[13]</sup>

The severity of coronary artery calcification is usually assessed by ultrafast computerized tomography that measures the degree of density multiplied by the area of the coronary calcification to provide a calcium artery calcification (CAC) or Agatston score, after its originator.<sup>[14]</sup> The CAC score is an independent risk marker for cardiac events, cardiac mortality, all-cause mortality, provides prognostic information and helps to identify diabetics and others at greatest risk who could benefit from screening for silent ischemia and may require more aggressive treatment.<sup>[15]</sup>

It has been suggested that the process of arterial intimal calcification shares some features with skeletal bone formation, including chondrocyte and osteoblast differentiation, as well as bone matrix deposition and resorption. In addition, a variety of bone related proteins have been identified in calcified arteries,<sup>[16,17]</sup> and calcium is in the form of calcium phosphate in both bone and arteries.<sup>[18]</sup> The extent of coronary artery calcification is a better indication of the degree of atherosclerotic plaque than a reduction in lumen,<sup>[19]</sup> and is also associated with an increase in all-cause mortality.<sup>[20]</sup> It is believed that spotty and incomplete calcification is more likely to cause major adverse cardiac events because of unstable and vulnerable plaque, whereas extensive calcification is more stable.<sup>[21]</sup>

Since statins increase calcification,<sup>[22,23]</sup> it has been proposed they would benefit patients by making plaque more stable via some pleiotropic effect, since it is not related to lowering cholesterol or LDL.<sup>[24]</sup> This creates a conundrum for clinicians, since high calcium artery scores are associated with

an increased risk of heart attacks and deaths, and no benefits have been found with statins or other cholesterol lowering drugs.

The first clue that calcification might be due to acidosis came in 2006, during the development of the Acidity Theory of Atherosclerosis. Numerous articles that had been retrieved led to the hypothesis there was a link between osteoporosis and atherosclerosis, as explained in my 2012 book *Acidity Theory of Atherosclerosis: New Evidences* <sup>[25]</sup> as follows:

Although the prevalence of both atherosclerosis and osteoporosis increase with age, evidence that has accumulated since these initial studies <sup>[26,27]</sup> suggest a more direct relationship between these two disorders. This is supported by other studies that show an increase in carotid intima-media thickness, a marker for atherosclerosis in women who develop osteoporosis. <sup>[28,29]</sup>

Hip fracture, a frequent complication of osteoporosis, is two to five times more common in patients with heart disease than in those with no history of cardiovascular problems. <sup>[30]</sup> Other studies have shown that bisphosphonates not only decreased the progression of osteoporosis, but also inhibited the development of atherosclerosis, in addition to reducing total mortality. <sup>[31]</sup>

In that regard, it is important to note that bisphosphonates also reduce the production of lactic acid, <sup>[32]</sup> which further supports the hypothesis that lactic acidosis may be involved in the etiology and pathogenesis of coronary heart disease. <sup>[33]</sup> This also substantiates the role of stress in coronary atherosclerosis, since chronic stress increases lactate. <sup>[34]</sup>

## Studies Linking Acidosis to Bone Loss

*"Life is a struggle, not against sin, not against the Money Power, not against malicious animal magnetism, but against hydrogen ions" - H.L. Mencken <sup>[35]</sup>*

In commenting on Mencken's statement 75 years later, Kraut and Coburn wrote, "These words, about the meaning of life and death, may also apply to the struggle of the healthy skeleton against the deleterious effects of retained acid." <sup>[36]</sup>

It had been known since the early 20th century, that systemic acidosis causes depletion of the skeleton, an effect assumed to result from physico-chemical dissolution of bone mineral. And, as noted previously, coronary calcification is no longer viewed as a benign, asymptomatic, age-related trait, but an active process that can predict risk of coronary atherosclerosis and calcification. <sup>[37]</sup>

In 1918, Kingo Goto, at the Rockefeller Institute for Medical Research, showed that feeding acid to rabbits resulted in depletion of skeleton minerals <sup>[38]</sup> This paper also includes an excellent review of pertinent 19th century publications.



More recent reports over the last two decades suggest that even subtle chronic acidosis can cause appreciable bone loss if prolonged. <sup>[39]</sup> In 1968, Wachman and Bernstein postulated that bone mineral functioned as a mechanism to buffer the fixed acid load imposed by the digestion of an “acid ash” diet in man. <sup>[40]</sup>

## **Lactic Acidosis Is Associated With Coronary Disease And Atherosclerosis**

However, not everyone agrees, <sup>[41]</sup> and our alternative hypothesis is that autonomic dysfunction results in an increased secretion of catecholamines that accelerates glycolysis and raises lactic acid and lactate concentration in blood and tissues for the following reasons.

- a) In advanced plaques the existence of hypoxic areas in the arterial wall – with accumulation of lactic acid in atherosclerotic lesions – appears to be related to a decreased oxygen diffusion capacity and increased oxygen consumption by foam cells. <sup>[42]</sup>
- b) Macrophages and lymphocytes convert most of their glucose into lactate rather than oxidizing it completely to CO<sub>2</sub>, and macrophages possess a selective transporter in their plasma membranes for lactic acid. This lactic acid may make the extracellular space surrounding macrophages acidic in atherosclerotic lesions. <sup>[43]</sup>
- c) It has been demonstrated that approximately two-thirds of atherosclerotic plaques show lactate dehydrogenase isoenzyme shifts significantly above that of the media and intima. <sup>[44]</sup>
- d) The association of increased lipid levels with abnormal lactate metabolism might provide a useful screening test for the detection of coronary artery disease. <sup>[45]</sup>
- e) Plasma lipid abnormalities and myocardial lactate production were significantly associated with subsequent arteriographic progression of coronary artery disease. <sup>[46]</sup>
- f) The amount of lactate released by the myocardium has been shown to be related to the severity of coronary artery disease. <sup>[47]</sup>
- g) Lactate levels are strongly associated with increased carotid atherosclerosis and the association is independent of traditional cardiovascular risk factors. <sup>[48]</sup>

## **Risk Factors For Atherosclerosis That Are Associated With Lactic Acidosis, Bone Loss And Coronary Artery Calcification**

### **Age**

1. Lactic acidosis <sup>[49,50]</sup>
2. Bone loss <sup>[51]</sup>
3. Coronary artery calcification <sup>[52]</sup>

Increased brain lactate is the hallmark of aging, which is associated with an elevation of brain lactate due to effects on lactate dehydrogenase. <sup>[49]</sup> In that

regard, a 1989 study designed to obtain normal blood chemistry references in elderly subjects, reviewed pertinent laboratory data from 1822 male and 1870 females.

The values for most analyses except inorganic phosphorus and total protein were significantly higher in males than female when compared to subjects aged 21 to 50, The values for lactic dehydrogenase, albumin, sodium, and calcium were higher in females older than 50 years of age than in their counterpart. When males and females were combined, the normal reference ranges for lactic dehydrogenase, alkaline phosphatase, uric acid, blood urea nitrogen, creatinine and potassium tended to be elevated, while those for total protein, albumin and calcium declined with aging.<sup>[50]</sup> In the aging skeleton, bone volume and mass declines in both sexes and in people of all ethnic backgrounds, and is often associated with osteoporosis and an increased risk of fracture.<sup>[51]</sup>

As Leopold noted, “Vascular calcification, once considered a passive consequence of aging, is now recognized to be a highly regulated process akin to bone formation. Vascular calcification is prevalent across ethnicities and age groups and observational studies show an interaction with aging in asymptomatic adults and in individuals with established coronary artery disease.”<sup>[52]</sup>

### **Diabetes**

1. Lactic acidosis<sup>[53-55]</sup>
2. Bone loss<sup>[56-58]</sup>
3. Coronary artery calcification<sup>[59]</sup>

As noted in a 2016 study, “Elevated circulating lactate is a common occurrence in diabetes patients and this finding suggest it may contribute to the increased prevalence of vascular calcification in this population.”<sup>[53]</sup>

### **Hypertension**

1. Lactic acidosis<sup>[60]</sup>
2. Bone loss<sup>[61]</sup>
3. Coronary artery calcification<sup>[62,63]</sup>

### **Smoking**

1. Lactic acidosis<sup>[64,65]</sup>
2. Bone loss<sup>[66]</sup>
3. Coronary artery calcification<sup>[67]</sup>

### **Chronic Kidney Disease**

1. Lactic acidosis<sup>[68,69]</sup>
2. Bone loss<sup>[70]</sup>
3. Coronary artery calcification<sup>[71,72]</sup>

### **High Carbohydrate Diets**

1. Lactic acidosis <sup>[73-75]</sup>
2. Bone loss <sup>[76]</sup>
3. Coronary artery calcification <sup>[77,78]</sup>

“High levels of sugar-sweetened carbonated beverage consumption may be associated with a higher prevalence and degree of CAC in asymptomatic adults without a history of cardiovascular disease, cancer, or diabetes.” <sup>[77]</sup>

“Diets low in carbohydrate and high in fat and/or protein, regardless of the sources of protein and fat, were not associated with higher levels of CAC, a validated predictor of cardiovascular events, in this large multi-ethnic cohort.” <sup>[78]</sup>

### **Rheumatoid Arthritis**

1. Lactic acidosis <sup>[79]</sup>
2. Bone loss <sup>[80,81]</sup>
3. Coronary artery calcification <sup>[82,83]</sup>

### **Air Pollution**

1. Lactic acidosis <sup>[84]</sup>
2. Bone loss <sup>[85]</sup>
3. Coronary artery calcification <sup>[86]</sup>

## **Drugs that are associated with lactic acidosis, bone loss and coronary artery calcification**

### **Warfarin**

1. Lactic acidosis <sup>[87]</sup>
2. Bone loss <sup>[88]</sup>
3. Coronary artery calcification <sup>[88,90]</sup>

### **Metformin**

1. Lactic acidosis <sup>[91-93]</sup>
2. Bone loss <sup>[94]</sup>
3. Coronary artery calcification <sup>[95]</sup>

Several older studies showed that metformin was osteogenic in vitro. In contrast, recent research found no effect of metformin on the osteogenic differentiation of bone marrow-derived mesenchymal stem cells. And a 2015 report on forty postmenopausal diabetic women found that metformin is neither osteogenic nor did it have anti-osteoporotic effects. <sup>[94]</sup>

A more recent report found that there were no CAC differences between lifestyle and placebo intervention groups in either sex. CAC severity and presence were significantly lower among men in the metformin versus the placebo group (age-adjusted mean CAC severity. <sup>[95]</sup>

However, according to the authors, there are several limitations in their study, since “Interpretation of the effect of the interventions was based on the assumption that there were no differences in baseline CAC given the randomization of subjects into intervention groups at baseline.” In addition, “We found no differences in cardiometabolic risk factors at baseline between treatment groups except for slightly lower HDL-C and higher smoking rates in women in the placebo group only”, and concluded that “Whether these findings translate into beneficial effects on CVD events will require follow-up” [95]

### **Statins**

1. Lactic acidosis [96-98]
2. Bone loss [99, 117]
3. Coronary artery calcification [100]

The 2015 JUPITER Trial in men and women with evidence of inflammation concluded that randomization to rosuvastatin did not reduce the risk of fracture and that, higher baseline hs C-Reactive Protein was not associated with an increased risk of fracture.<sup>[99]</sup> This is consistent with other statin trial results. The authors also state, “Baseline use of thiazide diuretics, bisphosphonates, calcium, vitamin D, and inhaled or oral steroids did not result in a change in effect estimates and thus were omitted from the multivariate model.”<sup>[99]</sup> However, it is important to emphasize that bisphosphonates reduce the increased production of lactic acid caused by statins, therefore offsetting their negative effects, which could have influenced the JUPITER statistics and conclusions.

A study published in 2019 concluded that the diagnosis of osteoporosis in statin-treated patients is dose-dependent [117]

A 2016 study [100] found that statin intake in subjects with an LDL cholesterol equal or greater than 115 milligrams per deciliter, was associated with lower CAC progression than statin intake in subjects with LDL cholesterol levels below 115 mg/dL. But guidelines suggest that individuals with an optimal LDL-C at or below 100 mg/dL have lower rates of heart disease and stroke, and some claim that LDL-C should be lowered as much as possible. This could pose a perplexing problem for physicians when prescribing statins.

The acidity theory of atherosclerosis theory may be helpful in this regard, because of the following findings.

- a) Lowering pH augments the oxidation of low-density lipoprotein (LDL) by releasing iron and copper radicals, and decreasing anti-oxidant defenses. [101,102]
- b) LDL oxidation occurs within lysosomes in macrophages of atherosclerotic lesions rather than the surrounding interstitial fluid. Most importantly, studies have shown that this oxidative process can be promoted by an acidic pH, and is inhibited by chloroquine, which increases lysosome pH. [103]

## **Cardiac events, Acidosis and Coronary Artery Calcification**

Coronary artery calcium is associated with an increase in major adverse cardiovascular events over the next 3 months.

A study presented at the American College of Cardiology Scientific Session on March 16, 2019, reported that patients whose scans revealed significant CAC scores were at higher risk of a cardiac event within 90 days compared with controls whose scans showed no CAC. The study involved 5,547 symptomatic patients without a history of coronary artery disease or elevated troponin, who underwent Rb-82 cardiac PET/CT scans from April 2013 to July 2016. CAC was associated with a statistically significant higher risk of 90-day coronary angiography, high-grade obstructive CAD, revascularization and long-term major adverse coronary events ( $p < 0.0001$ ).<sup>[104]</sup>

It is important to recognize that the heart is an organ that is always active and never rests, in contrast to other muscles in the body. Chronic or acute elevations of catecholamines can accelerate myocardial glycolysis and result in a significant increase in lactate production during coronary events.<sup>[105]</sup>

## **Stroke, Acidosis and Coronary Artery Calcification**

Acidosis is also a hallmark of stroke<sup>[106]</sup> and the presence and severity of coronary artery calcification is an independent predictor of future stroke events in the general population.<sup>[107,108]</sup>

## **Cancer, Acidosis and Coronary Artery Calcification**

Acidosis is another hallmark of cancer,<sup>[109]</sup> and the 2015 Multi-Ethnic Study of Atherosclerosis trial demonstrated an increase in the incidence of coronary artery calcification over time in individuals with cancer compared with non-cancer controls.<sup>[110]</sup>

This relationship persisted even when other risk factors for atherosclerosis were excluded. A subsequent 2018 study revealed that cancer chemotherapy can also worsen CAC.<sup>[111]</sup> In that regard, it is important to note that Cisplatin, a popular chemotherapy drug in use for over four decades has recently been shown to cause acidosis.<sup>[112]</sup>

## **Conclusion**

We have tried to demonstrate and explain how lactic acidosis increases coronary artery calcification and why various drugs and other factors also influence this process. Long-term and high dose statin therapy increase coronary artery calcification, which poses a problem for practitioners.<sup>[113]</sup> Statin proponents claim that spotty and incomplete calcification is more likely to cause major adverse events and that statins stabilize vulnerable plaque.<sup>[114]</sup> They also propose that PCSK9 inhibitors suppress coronary artery calcification by regulation of inflammation.<sup>[115]</sup>

However, we concur with A. Arbeb-Zadah and V. Fuster's conclusion that:

*Despite major advancements in coronary artery imaging and identification of atherosclerotic lesion morphology associated with rupture, there is no conclusive evidence that individual plaque assessment better predicts acute coronary event risk than established risk factors, such as the extent and severity of coronary artery disease. Pathology and clinical studies consistently demonstrate that atherosclerotic plaques rupture without clinical symptoms much more frequently than is widely acknowledged, challenging the notion of a close association between plaque rupture and clinical events.<sup>[116]</sup>*

In addition to coronary artery calcification, lactic acidosis may also cause calcification in the aortic valve, brain, and other tissues.

Regarding to treatment, a study from 2016 has shown that pharmacological inhibition with digoxin can efficiently inhibit calcification and enhance tenogenesis in vitro and in the Achilles's tendinopathy model. <sup>[118]</sup> This is obtained, in our view, because digoxin and other cardiac glycosides, may induce a potent inhibition of glycolysis (glucose consumption and lactate). <sup>[119]</sup>

**Notes:**

1. The introduction of this article was developed by Prof. Dr. Paul J. Rosch, Chairman from The American Institute of Stress, to whom I dedicate our present postulation on lactic acidosis as cause of coronary artery calcification, noting that this is not the first time I have been inspired by this brilliant teacher and researcher.
2. The postulation contained in the present article was first introduced during my lecture on March 27 at the "Fifth International Congress for Advanced Cardiac Sciences. King Of Organs, 2019", occurred in Saudi Arabia (Schedule at <https://bit.ly/2G5U3xe>)

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Autonomic Dysfunction + Lactic Acidosis = Multiple Diseases

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## Chapter 8

# Inflammation Does Not Cause Coronary Atherosclerosis

*Carlos ETB Monteiro and Paul J. Rosch, MD*

### Abstract

It has been proposed that inflammation, as defined by an elevated hs-CRP, causes coronary atherosclerosis and contributes to numerous other diseases. However, this inflammation is a response to injury to the endothelial layer of the coronary arteries, which can be due to infections and other irritants. In addition, if inflammation caused coronary heart disease, then why did powerful nonsteroidal anti-inflammatory drugs increase heart attacks in low-risk patients? In addition, this inflammatory process cannot be felt or seen, in contrast to the heat, swelling, pain and redness of inflammation as it was defined by Celsus, so perhaps it should be called something else to avoid confusion.

This presentation will discuss various influences that affect inflammation, such as the pivotal role of sympathetic nervous system stimulation and humoral influences that also regulate heart rate and other vital functions. In that regard, studies show that inflammation is associated with an increase in heart rate as well as reduced heart rate variability, a powerful predictor of risk for coronary heart disease and sudden cardiac death.

Inflammation is also associated with an increased acid environment due to metabolic acidosis, which affects the function of monocytes and macrophages that modulate immune system responses. Stimulation of the sympathetic nervous system also promotes glycolysis and increases lactic acid and lactate production that further lower pH. In contrast, stimulation of the vagus nerve and parasympathetic activities have anti-inflammatory effects that provide significant benefits in patients with rheumatoid arthritis, depression and other diseases that are unresponsive to conventional therapies.

We will discuss the role of canakinumab in heart disease patients with an elevated hs-CRP signifying increased inflammation, as revealed in the CANTOS trial. Canakinumab is a monoclonal antibody that lowers hs-CRP and inhibits interleukin-1 $\beta$ , another marker of inflammation. Although both were lowered, the treated group had more deaths from infection and the FDA rejected the request for the treatment of heart disease. We will also discuss Omega-3 fatty acids, the surprising anti-inflammatory effects of cardiac glycosides, and the role of lactate and acidosis.

## Atherosclerosis And Inflammation

There have been increasing claims that coronary atherosclerosis is due to a silent “low-grade chronic inflammation “. This is associated with an increase in hs-CRP (high sensitivity C-reactive protein), which measures levels much lower than the traditional CRP test used for more than 8 decades to assess the degree of acute inflammation. Over 2000 years ago, Celsus defined inflammation as heat, swelling, redness and pain. But all of these can be seen or felt, whereas this subtle chronic inflammation produces no signs or symptoms. Nor does it respond to anti-inflammatory drugs or antibiotics.

It has also been proposed that hs-CRP actually causes inflammation and coronary atherosclerosis, rather than being a mere marker like high LDL and low HDL. The JUPITER rosuvastatin trial contradicted this, since although LDL-C was reduced by 50%, the largest drop in any statin trial, and hs-CRP was lowered by 37%, there were more fatal heart attacks in the statin treatment group. Moreover, as noted above, reducing inflammation does not reduce heart disease. Vioxx, a powerful non-steroidal anti-inflammatory drug, was taken off the market because it caused heart attacks, and other anti-inflammatory drugs have similar effects.<sup>[1]</sup>

Rudolph Virchow, who first noted the presence of cholesterol in atheroma, described what would later be called atherosclerosis as “endarteritis deformans”<sup>[2]</sup> The “itis” signified inflammation, because he did not believe that atherosclerosis was due to the deposition of cholesterol, since this came later.

Van Haller used the Greek word “atheroma” to refer to a gruel-like material in 1775, but “atherosclerosis” did not appear until 1904, when Marchand coined it to indicate a hardening of this material in the walls of arteries. A few years earlier, Lobstein had introduced arteriosclerosis to depict a calcification of these arterial lesions as they aged.

Vascular calcifications can be classified into 2 separate types depending on whether they are located within the intimal or medial layer. Medial arterial calcification primarily affects the legs, and is prevalent in patients with peripheral vascular disease. Intimal calcification predominates in coronary vessels. While both types can be found in the carotid arteries and they share some features, they have different causes and consequences.

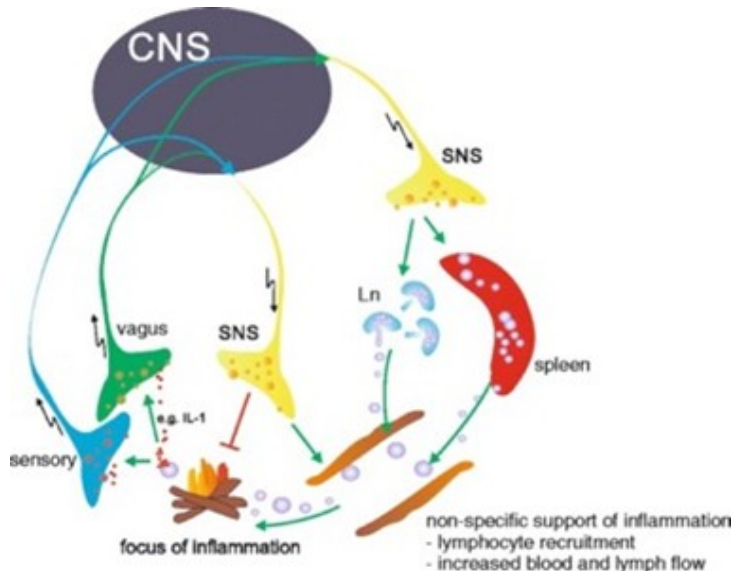
Although atherosclerosis and arteriosclerosis are relatively recent terms, these disorders are not new. CT analyses of Egyptian mummies and other ancient cultures where corpses were well preserved due to very dry or cold conditions, such as the Peruvian Incas, the Aleutian Island Unangans and the Ancestral Puebloans of southwest America, reveal that they were not uncommon 3500 to 4000 years ago, especially in the elderly and elite. Atherosclerosis was regarded as definite if a calcified plaque was seen in the wall of an artery, and probable if it was seen along the expected course of an artery.

Most of this calcification occurs in large vessels like the aorta, iliac and carotid arteries. It is primarily medial arteriosclerosis since the deposits are found in the muscular middle layer of the arterial wall, and is often called Mönckeberg's sclerosis, after Johann Georg Mönckeberg, who first described it in 1903. Although it differs from coronary atherosclerosis, it is likely that was also prevalent in individuals who lived longer.

## The Autonomic Nervous System And Inflammation

The involuntary nervous system maintains stability in the body whenever homeostasis is threatened via its complementary but antagonistic sympathetic and parasympathetic constituents. The sympathetic nervous system and its neurotransmitters are stimulated during acute stress, which results in an increase in heart rate and blood pressure and a host of other activities throughout the body to facilitate “fight or flight”.

As follows, local inflammation is detected by vagal and sensory nerve fibers that have receptors for inflammatory mediators like interleukin and a signal sent to the brain's central nervous system (CNS) that leads to activation of the sympathetic nervous system (SNS) and the release of neurotransmitters like noradrenaline at the site, which has an anti-inflammatory effect that is transient response to a local threat.



*Sympathetic Nervous System Responses To Inflammation*

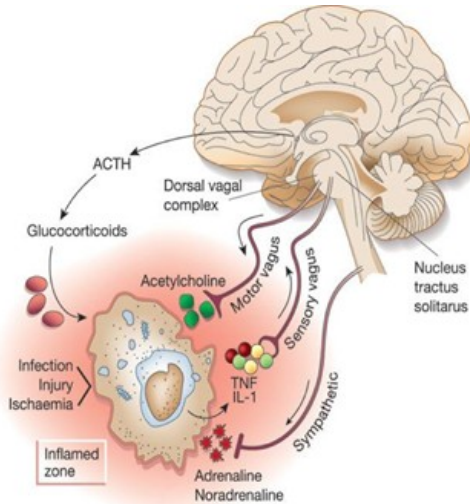
There is a marked increase in neutrophils, white cells that inactivate bacteria and their toxic products and promote tissue repair. Stimulation of the hypothalamic-pituitary-adrenal axis causes a rise in the secretion of cortisol that initially reduces inflammation, but this only lasts for a day or two. This contrasts with chronic systemic inflammation, which can evoke a cascade of

non-specific responses such as recruitment of lymphocytes, white cells that can recognize and respond to antigens by producing antibodies.

There is also increased lymph and blood flow to the affected areas. When inflammation persists and becomes chronic, the sympathetic nervous system and hypothalamic-pituitary-adrenal responses continue to be activated, but the anti-inflammatory effects of cortisol and other glucocorticoids dwindle, which ultimately results in tissue damage and organ dysfunction. Macrophages, fibroblasts, mast cells, monocytes and other immune system cells and cytokines can also contribute to this.

The parasympathetic nervous system also modulates chronic inflammation by vagal stimulation through the cholinergic anti-inflammatory pathway.

As follows, inflammatory products and debris produced by damaged tissues activates afferent signals that are transmitted to the nucleus tractus solitarius, Subsequent stimulation of vagus efferent activity inhibits cytokine synthesis via the anti-inflammatory cholinergic pathway. Information can also be relayed to the hypothalamus as well as the dorsal vagal complex to stimulate the production of ACTH by the anterior pituitary. This results in an increased secretion of glucocorticoid hormones like cortisol that decrease inflammation.



*Autonomic Nervous System responses to Inflammation*

These observations have led to the development of new approaches to treating inflammation, such as modulating vagus nerve activity, or targeting specific components of this complex pathway. Meditation, biofeedback and other stress reduction measures, as well as hypnosis or acupuncture also have the potential to modulate vagal output. A variety of non-steroidal anti-inflammatory and psychoactive drugs could be designed to stimulate macrophage cholinergic receptors in the periphery or to increase vagal output comparable to a pharmacological vagus nerve stimulator.



Vagal nerve stimulation has resulted in spectacular results in rheumatoid arthritis that is resistant to all other therapies and has none of their adverse side effects or addictive tendencies. It may also be effective in Crohn's disease and other inflammatory bowel disorders, as well as drug resistant depression. This non-invasive treatment is administered by the patient at home, and the dosage, frequency and duration of stimulation can easily be changed as needed.

Support for the protective effect of the parasympathetic nervous system in preventing or reducing inflammation and atherosclerosis can be found in numerous articles, and excerpts or synopses from some, are appended below:

2007 - "Based on converging evidence, we propose a neuroimmunomodulation approach to atherogenesis. In this model, the vagus nerve "informs" the brain about coronary artery disease related cytokines; in turn, activation of the vagus (via vagus nerve stimulation, vagomimetic drugs or relaxation) induces an anti-inflammatory response that can slow down the chronic process of atherogenesis."<sup>[3]</sup>

2011- "It is also likely that in the future, the currently available treatment regimens for coronary heart disease, cardiac arrhythmias and atherosclerosis could be combined with vagus nerve stimulation and nicotinic acetylcholine receptor  $\alpha 7$  subunit agonists."<sup>[4]</sup>

2012 - "The inflammatory reflex mediated by the vagus nerve has been successfully exploited therapeutically in preclinical models of diseases with aetiologies characterized by excessive inflammatory responses", and that "Insufficient efferent vagus nerve cholinergic output might have a causative role in the dysfunctional immune and metabolic regulation observed in obesity, as selective activation of the efferent cholinergic arm of the inflammatory reflex attenuates both inflammation and metabolic derangements."<sup>[5]</sup>

2014 - "Central cholinergic activation of a vagus nerve-to spleen circuit controls alleviates intestinal inflammation."<sup>[6]</sup>

2016 - Vagus nerve stimulation inhibits cytokine production and attenuates disease severity in rheumatoid arthritis.<sup>[7]</sup>

## **Regulation Of Inflammation By The Sympathetic Nervous System And Acidosis**

2012 - "Extracellular acidosis downregulates most of the hemostatic platelet functions and promotes those involved in amplifying the neutrophil-mediated inflammatory response." (Platelet aggregation at sites of vascular injury is considered essential for hemostasis and arterial thrombosis.)<sup>[8]</sup>

2012 - "The discovery that cholinergic neurons inhibit acute inflammation has qualitatively expanded our understanding of how the nervous system modulates immune responses. The nervous system reflexively regulates the

inflammatory response in real time, just as it controls heart rate and other vital functions.”<sup>[9]</sup>

2013 - Data is provided suggesting that an acidic environment represents a novel endogenous danger signal alerting the innate immunity. “Low pH may thus contribute to inflammation in acidosis-associated pathologies, such as atherosclerosis and post-ischemic inflammatory responses.”<sup>[10]</sup>

2014 - “Over the past decades evidence has accumulated clearly demonstrating a pivotal role for the sympathetic nervous system (SNS) and its neurotransmitters in regulating inflammation.” The authors concluded “However, if a ‘chronic inflammatory configuration’ persists, as in autoimmunity, the effects are detrimental because of the persistently increased SNS activity, HPA activity, and the resultant chronic catabolic state. This leads to known comorbidities in chronic inflammatory disease, like cachexia, high blood pressure, insulin resistance, and increased cardiovascular mortality. The challenge is now to translate this conceptual knowledge into clinical benefit.”<sup>[11]</sup>

2016 - Study demonstrating that moderate extracellular acidosis, which is a common finding in different pathological conditions such as inflammation, ischemia or in solid growing tumors, affects the functional behavior of monocytes and macrophages, and can therefore modulate the immune response<sup>[12]</sup>

## **Canakinumab Anti-inflammatory Therapy And Atherosclerosis**

One of the highlights of the August 2017 European Society of Cardiology Congress was the landmark CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcome Study) showing that decreasing inflammation, even in the absence of any lipid lowering, significantly reduced recurrent cardiovascular events in patients with a history of myocardial infarction and an hs C-reactive protein of 2 mg or more per liter.<sup>[13]</sup>

It also reduced cancer incidence and mortality. Canakinumab is currently indicated for the treatment of interleukin-1 $\beta$  associated inflammatory diseases, and this study allegedly provided strong support for the belief that inflammation caused recurrent coronary events because it increased atherosclerosis. In fact, the title of the paper that was published in the September 21, 2017 New England Journal of Medicine was ‘Anti-inflammatory Therapy with Canakinumab for Atherosclerotic Disease.’<sup>[14]</sup>

However, the reduction in recurrent cardiovascular event rates showed only a 2% absolute risk reduction study over median follow-up of 3.7 years, Canakinumab was associated with a higher incidence of fatal infections compared to placebo and there was no significant difference in all-cause mortality. In addition, the \$16,000-per-dose price tag meant that treatment would cost approximately \$200,000 per year, and many doctors also expressed

concerns about the future of this drug based on the study results. Some argued that the same results might have been obtained with existing and much less expensive drugs.<sup>[15]</sup> In October 2018 the FDA declined to approve Canakinumab for cardiovascular risk reduction based on the CANTOS results.<sup>[16]</sup>

Not mentioned was the fact that numerous studies have shown that C-Reactive Protein is elevated with chronic stress as well inflammation. Danish researchers also found that higher hs-CRP blood levels were associated with a greater risk of psychological stress and especially clinical depression. As the lead author noted, “Irrespective of other factors, we found that basically healthy people with hs-CRP levels above 3 milligrams per liter had a two- to threefold increased risk of depression. Dampening inflammation may be one way of treating depression.” It is not clear what explains this association, but the authors suggest that elevated CRP levels may indicate elevated levels of certain cytokines that can increase feelings of stress, or that depression itself may lead to increased inflammation.<sup>[17]</sup>

Myocardial ischemia provoked in the laboratory during acute mental stress in patients with stable coronary artery disease predicts subsequent clinical events, much like exercise induced ischemia with treadmill stress tests, but the mechanisms responsible for this are different. While sympathetic nervous system activation may play a role, little is known about how mental stress increases risk for coronary events. Since an elevated hs-C-reactive protein is also a risk marker for future coronary events in patients with heart disease, perhaps increased inflammation was responsible.

To evaluate this, 83 patients with stable heart disease underwent simultaneous single-photon emission computed tomography (SPECT) and transthoracic echocardiography (TTE) at rest, and during laboratory induced mental stress. Serum hs-CRP levels were measured before and 24 hours after mental stress. Of the 83 patients, 30 (36%) showed ischemic changes due to mental stress.

There was no difference in gender, sex, BMI, histories of diabetes, hypertension, smoking, lipid profile, medications used (including statins,  $\beta$ -blockers, ACE inhibitors, and aspirin), or hemodynamic responses during mental stress between this group and those who had no evidence of ischemia. However, they did show a greater increase in hs-CRP, and each 1 mg/L increase in this level was associated with a 20% higher risk of mental stress induced ischemia.<sup>[18]</sup> However, this does not prove that either hs-CRP or inflammation cause heart disease, since association never proves causation. Other studies have found that emotional stress can provoke ischemia in 30%-50% of patients with chronic, stable coronary disease.<sup>[19,20]</sup>

Chronic stress, especially job stress,<sup>[21]</sup> socioeconomic status,<sup>[22]</sup> as well as social and personality factors have also been associated with increased risk of

coronary heart disease as well as atherosclerotic progression.<sup>[23]</sup> Acute stress, whether provoked by national emergencies<sup>[24,25]</sup> or severe anger<sup>[26-29]</sup> have been associated with triggering cardiac events and heart failure.<sup>[30]</sup> While mental stress-induced ischemic episodes are good indicators of 5-year rates of cardiac events,<sup>[31]</sup> stress-induced ischemia without angina occurs much more frequently than appreciated.<sup>[32-33]</sup>

There is also evidence that acute stress events such as public speaking and anger-provoking situations can disrupt cardiac electrical signaling and lead to arrhythmias and other acute cardiac events, including myocardial infarction.<sup>[34]</sup>

## **Cardiac Glycosides, Omega-3 Fatty Acids And Acidosis**

The anti-inflammatory and beneficial effects of digoxin and other cardiac glycosides have been known for decades.<sup>[35-42]</sup> A 2009 study concluded "Digitoxin elicits anti-inflammatory and vasoprotective properties.

These observations indicate a potential therapeutic application of digitoxin in the treatment of cardiovascular diseases, such as atherosclerosis."<sup>[36]</sup> Another review that discussed this and other cardiac glycosides and their mechanisms of action by providing "an overview of the in vivo and in vitro actions of cardiac glycosides on inflammatory processes and of the signaling mechanisms responsible for these effects: cardiac glycosides have been found to decrease inflammatory responses in different animal models of acute and chronic inflammation. Regarding the underlying mechanisms most research has focused on leukocytes. In these cells, cardiac glycosides primarily inhibit cell proliferation and the secretion of proinflammatory cytokines"<sup>[35]</sup>

It is not generally appreciated that glycosides like digoxin,<sup>[43]</sup> digitoxin,<sup>[44]</sup> and ouabain<sup>[45]</sup> inhibit the sympathetic nervous system when administered in low dosages. A study done over 50 years ago showed that they inhibited epinephrine induced glycolysis and glycogenesis in skeletal muscle.<sup>[46]</sup>

A more recent one demonstrated that they also inhibited lactate production and glycolysis in lung cancer cells, which require glucose, and increase the cytotoxicity of platinum compounds that are frequently used to treat lung cancer.<sup>[47]</sup>

Other drugs or factors might provide similar benefits. Omega-3 fatty acids inhibit atherosclerosis without lowering cholesterol or triglycerides,<sup>[48]</sup> and some, like docosahexaenoic acid, can improve heart rate variability and baroreflex sensitivity via effects on the autonomic nervous system.<sup>[49]</sup> However, their ability to lower elevated blood lactic acid levels,<sup>[50,51]</sup> may be even more important with respect to inhibiting coronary atherosclerosis.

## **Lactic Acidosis, Inflammation And Coronary Atherosclerosis**

It has been known since 1934 that “Acidity of the environment is increased in inflammatory sites.”<sup>[52]</sup> Over a half century ago, it was proposed that osteoporosis was due to an “acid ash” diet, and that this was buffered by bone minerals.<sup>[53]</sup> A review of this issue in 2018 confirmed that that even subtle chronic acidosis can cause appreciable bone loss if prolonged.<sup>[54]</sup>

In another chapter in this book, it was demonstrated that lactic acidosis is associated with coronary disease and atherosclerosis explaining why it increases coronary artery calcification. This is consistent with the acidity theory of atherosclerosis<sup>[55,56]</sup> that also explains how stress can cause coronary atherosclerosis.<sup>[57]</sup> It proposes autonomic dysfunction as a precursor, and particularly stimulation of the sympathetic nervous system. This increases the secretion of adrenaline and noradrenaline, which accelerates glycolysis, and results in higher concentrations of lactic acid and lactate in blood, other body fluids and tissues. Conversely, stimulation of the parasympathetic system has anti-inflammatory effects. Other factors such as age, genes, gender, lifestyle and various drugs can also influence the positive or negative effects of autonomic activities.

Association never proves causation, and as others have warned, “Correlation implies association, but not causation. Conversely, causation implies association, but not correlation.”<sup>[58]</sup> Association should not be confused with causality unless it is clear that A always causes B and there is no other cause. Tuberculosis is one example, since it can only be caused by the tubercle bacillus, so this is not a theory but a fact. However, A and B could also be associated but not interdependent, because they are both caused by something else.

An elevated cholesterol and hypertension are associated with coronary atherosclerosis, but are not always present, since this is a multifaceted disorder that can have many associated risk markers. Unlike tuberculosis, there is no vera causa or solitary true cause so that all other explanations are merely theories.

As the famous philosopher Karl Popper stated, “A medical hypothesis cannot be proved, but it can be falsified. If it cannot be falsified, it is not a scientific hypothesis.”<sup>[59]</sup> The prevailing hypothesis that cholesterol causes coronary atherosclerosis has been refuted so many times, that it is no longer tenable. It has been replaced by a process that has been labelled inflammation, but bears no resemblance to its definition by Celsus, since it has no signs or symptoms. It can only be detected by elevations of hs-CRP, certain interleukins or other risk markers for inflammation, although these are not always consistent or correlative.

This is hardly a new concept, since, as previously indicated, the renowned pathologist Rudolph Virchow, who first demonstrated the presence of cholesterol in atheroma, described atherosclerosis as *endarteritis chronica deformans sive nodosa* (chronic arterial inflammation with a deforming or knotty appearance), since this is what he saw under the microscope.<sup>[2]</sup>

The suffix “itis” signified that it resembled or was reminiscent of inflammation, but he was very careful to avoid calling it inflammation, since it had none of the tumor, rubor, calor or dolor (swelling, redness, heat, pain) components that Celsus listed, to which Virchow added *functio laesa* (loss of function.) What Virchow wrote was:

*We cannot help regarding the process as one which has arisen out of irritation of the parts stimulating them to new, formative actions; so far therefore it comes under our ideas of inflammation, or at least of those processes which are extremely nearly allied to inflammation.....We can distinguish a stage of irritation preceding the fatty metamorphosis, comparable to the stage of swelling, cloudiness, and enlargement which we see in other inflamed parts.<sup>[2]</sup>*

In other words, inflammation was a response to injury of the “inner arterial coat” (endothelial layer) by some irritant, and the “so-called atheromatous degeneration” (cholesterol deposits) came later. Calling this asymptomatic prothrombotic disorder inflammation is confusing, and hopefully, future advances will lead to a more meaningful definition. As the Nobel Laureate Richard Feynman said, “I learned a long time ago the difference between knowing something and the name of something.”

Virchow is still cited to support claims that inflammation rather than cholesterol causes atherosclerosis. Carl von Rokitansky, an eminent contemporary Austrian pathologist who also described inflammatory cells in atheroma, rejected inflammation as the cause of atherosclerosis, and proposed a thrombogenic origin due to the deposition of fibrinogen and other debris from repeated clot formation.<sup>[60]</sup>

It is interesting to notice that Hans Selye, in 1958, has shown experimentally how stress, combined with some agents, may induce myocardial necrosis where the coronary arteries are perfectly normal. He also said in his paper: “It is noteworthy, however, that, under these circumstances, not only cardiac infarction but organic obstruction of the coronary vessels can regularly be produced by humoral means.”<sup>[61]</sup>

There are several hundred risk factors for coronary heart disease and atherosclerosis, but the vast majority are simply risk markers that show some statistical association but have no causal relationship.

Coronary heart disease is a multifactorial disorder that can have many causes, some of which, like stress, homocysteine, infections, and free radical

damage may be interrelated. Numerous contributing factors that influence susceptibility range from family history, age, genetics, gender, diabetes, hypertension and smoking, to sex hormones, obesity, physical activity, and alcohol consumption. It would be inane to believe that levels of CRP, interleukins or other inflammation markers can provide an accurate assessment of all the varied negative and positive activities of these diverse agencies.

It would be equally foolish to assume that lowering CRP will safely and effectively reduce coronary mortality in healthy people. Treating an elevated CRP would simply repeat the same mistake that is still being made with LDL. As Albert Einstein warned, "Not everything that counts can be counted, and not everything that can be counted counts."

The first part of this statement applies to CRP and LDL, which are easy to measure, but have no causal relationships. Association never proves causation. The second part pertains to our inability to define, much less measure, something that we call "inflammation", but may include several different processes that have yet to be elucidated.

We have tried to explain how acidosis, and especially lactate and lactic acidosis can contribute to inflammation and atherosclerosis. We also agree with Virchow's contention that a process resembling inflammation represents a response to endothelial irritation or injury. In addition, the latter is not due to lipid deposits, since these occurred subsequent to the "swelling and cloudiness" Virchow had observed.

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## Autonomic Dysfunction + Lactic Acidosis = Multiple Diseases

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**Part #3**

**Articles on Cancer**



# Chapter 9

## Stress - Inductive Factor for Increased Lactate Production - Evolutionary Path to Carcinogenesis

Carlos ETB Monteiro

*"The concept that cancer might in some way be related to stress or other emotional factors is probably as old as the history of recorded medicine itself" by Professor Doctor Paul J. Rosch, 1979.<sup>[1]</sup>*

### Abstract

In the present paper is discussed the recent evolution in the understanding of the role of lactate formation in promoting cancer.

On it is postulated the hypothesis that chronic stress is the major risk factor and inductor of the increased lactate production which might lead to the carcinogenic process. It also explains how stress develops lactate formation, which was discovered in 1925.

The current hypothesis supports ketogenic diets for prevention and therapy for cancer. This follows the reasoning that while fats do not have appreciable effects on the sympathetic nervous system (SNS) or in lactate formation, high carbohydrate diets have significantly effects on both SNS and lactate formation.

At the end of the paper is a short explanation and link to a parallel article where is discussed cardiac glycosides as the fundamental drugs for prevention and treatment of cancer.

### Introduction

The Recent Evolution of the Role of Lactate in Promoting Cancer

A paper by Thomas N Seyfried and Laura M Shelton has presented in 2010 a hypothesis that genomic instability and essentially all hallmarks of cancer, including aerobic glycolysis (Warburg effect), can be linked to impaired mitochondrial function and energy metabolism.

This paper raised the point that emerging evidence questions the genetic origin of cancer and suggests that cancer is primarily a metabolic disease.<sup>[2]</sup>

This study from Seyfried and Shelton also stirred a great and new interest about the concept of Otto Warburg, developed in the early twenties of the past century. Warburg observed that cancer cells were characterized by accelerated glycolysis and excessive lactate formation even under fully

oxygenated conditions. According to Warburg, many tumors depend heavily on glucose for their metabolic demands and ferment it to lactate. His concept was later called the Warburg effect



Otto Heinrich Warburg

Advocating that energy restricted diets combined with drugs targeting glucose and glutamine can provide a rational strategy for the longer-term management and prevention of most cancers, these authors say that fats and especially ketone bodies can replace glucose as a primary metabolic fuel under calorie restriction.<sup>[2]</sup>

Mercedes Garcia-Alvarez and colleagues, in a study from 2013<sup>[3]</sup> expressed their point of view that “In almost all severe disease-related physiological stress, a raised blood lactate concentration is an independent predictor of mortality. However, the source, biochemistry, pathophysiology, and metabolic function of lactate remain unclear. Whether such stress hyperlactataemia represents a maladaptive or protective response is also unknown”.

Fortunately, Iñigo San-Millán and George A. Brooks, through a study published in 2017<sup>[4]</sup> arrived, in my opinion, to a clear and straightforward explanation of the Warburg effect. They introduced a proposal in which the augmented lactate formation, initiated by gene mutations, is the reason and purpose of the Warburg effect and that dysregulated lactate metabolism and signaling are the key elements in carcinogenesis. According to their proposition, therapies to limit lactate exchanging and signaling within and among cancer cells should be priorities for discover.

We see the proposition made by San-Millán and Brooks<sup>[4]</sup> as a breakthrough in the research for the cure of cancer. We also agree with their view that lactate is necessary for all the major steps in carcinogenesis.

However, I beg to differ from these authors in relation to the initiation of the process. Instead of gene mutation we postulate that chronic stress is the major risk factor and the initial inductor to the whole process of cancer.

## Stress as the Major Risk Factor for Cancer

For a better understanding, in conformity with our postulation, stress is defined here as any risk factor leading to dysregulation of the autonomic nervous system. This may be related to chronic sympathetic dominance through sympathetic over-activity or withdrawal of the parasympathetic system.

Some examples of risk factors for cancer linked to altered autonomic function: Psychological stress; Age; Tobacco; Radiation; Infection; Exposure to some chemicals and persistent organic pollutants; and Genetic predisposition (e.g.: Familial dysautonomia).



Moreover, recent studies have confirmed the important role of the autonomic nervous system in cancer by demonstrating that the denervation of the primary tumor suppresses cancer growth and metastasis.<sup>[5, 6]</sup>

This evidence is supported by the longstanding hypothesis that chronic stress can influence tumor growth and progression.<sup>[1, 7]</sup> It has been shown that sympathetic nervous neurotransmitters can affect both cancer cell growth and tumor vascularization.<sup>[8]</sup> Recent reviews have discussed the role of the nervous system in cancer and metastasis.<sup>[9, 10]</sup>

Related to the subject, a recent meta-analysis involving a total of 46 studies with more than a million patients confirms that high resting heart rate is independently associated with increased risk of all-cause mortality in the general population. Its results suggest the risk is increased by 9% and 8% for every 10 beats/min increment of resting heart rate. Higher resting heart rate is a marker of an imbalance between the vagal and the sympathetic tone, and dysfunctional autonomic nervous system, playing a central role in the pathogenesis of numerous adverse health conditions.<sup>[11]</sup>

## Stress and the Development of Lactate / Lactic Acid

The sympathetic dominance leads to a raised catecholamine (adrenaline/epinephrine and noradrenaline) release accelerating glycolysis metabolism, therefore increasing lactic acid and lactate concentration in blood and tissues.

The higher lactate concentration in blood the greater is the risk of death.<sup>[12]</sup>

The first to observe the influence of adrenaline on lactic acid production were the Coris in the early 1920s.<sup>[13]</sup>

John R. Williamson confirmed in 1964 the effects of adrenaline infusion on the increased production of lactate in isolated heart tissue, up to five times the normal production.<sup>[14]</sup>

According to an article published in 1982<sup>[15]</sup> the support for a direct participation of catecholamines in the development and/or maintenance of lactic acidosis includes:

1. The common association of stress and lactic acidosis.
2. The rise in plasma lactate concentration during adrenaline infusion.
3. The precipitation of lactic acidosis by adrenaline intoxication and pheochromocytoma.
4. The vasoconstrictor effects of catecholamines leading to tissue anoxia and lactic acid production.

However, according to new findings, hyperlactatemia is not a consequence of anaerobic glycolysis, tissue hypo-perfusion, or cellular hypoxia, as believed in the past. Such hyperlactatemia is probably indicative of a stress response, with increased metabolic rate and sympathetic nervous system activity.<sup>[3]</sup>

The relationship between stress and increased lactic acid/lactate concentration was recently discussed by us as having a causal role for atherosclerosis<sup>[16, 17]</sup> and for acute myocardial infarction.<sup>[18]</sup>

### **Notes**

1. Hyperlactatemia is defined as a mild to moderate persistent increase in blood lactate concentration (2-4 mmol/L) without metabolic acidosis, whereas lactic acidosis is characterized by persistently increased blood lactate levels (usually >4-5 mmol/L) in association with metabolic acidosis;
2. Lactic acidosis results from increased production of lactate, the final product in the pathway of glucose metabolism. Lactate and lactic acid are not synonymous. Lactic acid is a strong acid which, at physiological pH, is almost completely ionized to lactate.

## **Acidic Environment and Lactic Acid**

The extracellular pH of tumor tissue is often acidic, and acidic metabolites, e.g., lactic acid seems to be its main cause.<sup>[19]</sup>

Thus, hindering the outflow of catecholamine may consequently decrease the lactate production with effects on the acidic environment, basifying the extracellular pH in tumor tissues.

## **Ketogenic Diets for Cancer**

The use of Ketogenic diets (high fats/low carbs), in prevention or in treatment of cancer is supported by our present hypothesis due to the following reasons:

1. High carbohydrate diets cause greater sympathetic nervous system activation while fat ingestion does not result in any appreciable changes;<sup>[20]</sup>
2. High carbohydrate diets may increase significantly the activity of serum lactate;<sup>[21]</sup>

3. The Ingestion of monosaccharides (simple sugars like glucose, fructose and galactose) may have the effect to raise blood lactic acid with this increase being most marked and lasting longest after fructose, that is largely used today as sweetener in soft drinks, fruit punches, pastries and processed foods.<sup>[22,23]</sup>

Melanie Schmidt and colleagues, in their clinical study about ketogenic diet from 2011,<sup>[24]</sup> share with us some old but important information about carbohydrates and cancer:

*"Since 1885, when E Freund observed that patients with malignant disease can develop spontaneous hyperglycaemia, there has been episodic interest in the association of the altered glucose metabolism with the path of nutrition and neoplasia in man. As early as 1924, Händel and Tadeuma summarized the findings in those days as: 'a diet rich in carbohydrates has a pronounced stimulating impact on tumour growth'."*

Therefore, according our hypothesis, high carbohydrate diets and simple sugars may represent potential risk factors for cancer.

## **Cardiac Glycosides: The Fundamental Drugs Against Cancer**

Studies using cardiac glycosides like digitalis, an old heart drug, have shown properties of induction of apoptosis and inhibition of proliferation of cancer cells. The use of cardiac glycosides also resulted in a large reduction in mortality of cancer in patients taking these drugs when given at low concentration doses.

In our view the beneficial use of cardiac glycosides in prevention or in therapy of cancer is derived from their neuro-hormonal effects through the inhibition of the sympathetic nervous system and by strengthening the parasympathetic system, avoiding in this way a raise in catecholamine release and acceleration of glycolysis metabolism, therefore, reducing lactate production.<sup>[25]</sup>

### **Inscription**

I dedicate this paper to my friend Prof Dr Paul J. Rosch. Paul brought knowledge, advices and inspiration to our researches on the link stress and lactate leading to cancer.

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## Chapter 10

# Cardiac Glycosides at Low Concentration Providing Neurohormonal Effects:

*Carlos ETB Monteiro*

The Final Solution Against Cancer?

*“Although there is not total agreement on the nature and clinical significance of the effects of digitalis on the autonomic nervous system, the following points seem well established and generally accepted:*

- 1) the actions of digitalis on the autonomic nervous system are very important clinically and play a major role in determining the clinical pharmacodynamic effects of the drug;*
  - 2) with therapeutic concentrations of the drug, the predominant effect is activation of vagal tone; and*
  - 3) with toxic concentrations of the drug there may be activation of sympathetic tone.”*
- August M. Watanabe, 1985 <sup>[1]</sup>*

### Abstract

In a central article published in the present edition of this journal was introduced a new hypothesis postulating stress (chronic sympathetic dominance) as the inductive factor for the increased lactate production found in cancer patients. In it has shown the important role of stress as the major risk factor for cancer, also discussing on how it develops lactate formation. <sup>[2]</sup>

In the present article is postulated that cardiac glycosides at low concentration doses fit perfectly well with the hypothesis of stress as the primary risk factor for cancer being these fundamental drugs for its prevention and therapeutic.

The article also discusses laboratory experimentation and clinical studies using cardiac glycosides. These have shown properties of induction of apoptosis and inhibition of proliferation of cancer cells. This apart of a large reduction in mortality of cancer, in patients taking these drugs at low concentration doses.

It also tells that some cardiac glycosides have shown sympathetic and glycolysis (glucose consumption and lactate) inhibitory effects.

Finally, this article explores the role of endogenous digitalis-like compounds in cancer and in other diseases.

## Introduction

Our research on cancer started about 15 years ago. Follows an extract of the article “Digitalis: the Insulin for Cancer?” published at the News Bulletin of Infarct Combat Project from April 20, 2006, that is self-explanatory about my interest on the matter: <sup>[3]</sup>

### ***“Digitalis: the Insulin for Cancer?”***

Coronary heart disease is the prime motivation of Infarct Combat Project (ICP). However, there are paramount cases in other medical conditions which ICP can't neglect its participation and contribution. The present news is related with the use of an effective and inexpensive heart drug, for the treatment of cancer.

In a paper published in 2002 at *Ars Cvrandi*, a Brazilian medical journal, we have noticed an exceptional low mortality by cancer in cardiac patients treated with digitalis or other cardiac glycosides, when used in prevention of cardiac failure, unstable angina, acute myocardial infarction and sudden death. <sup>[4]</sup>

This case study involved 1150 patients with stable coronary heart disease. The follow-up period was 28 years. The cardiac glycosides employed were: Digitoxin, Digoxin, Acetyldigoxin, Betamethyldigoxin, Proscillaridin-A or Lanatoside-C at daily therapeutic oral doses - non-toxic, preferably lower.

It was shown in this study that the global mortality for the patients without previous myocardial infarction was 14.2% (0.5% per year) while the global mortality for the patients with previous myocardial infarction was 41.0% (1.4% per year). Surprisingly, the cancer mortality in these patients treated with digitalis or other cardiac glycosides was just 1.7% in total.

This curious information prompted us to verify the cancer mortality rate for patients in similar medical condition and age, presented in other studies. Also, we have made a search at Medline, finding out many studies showing digitalis as anticancer drug, with properties of inducing apoptosis (cell death) and inhibiting proliferation of cancer cells.

For the cancer mortality comparison, the data was taken from a large study which had a follow-up of 5 years, involving 20.536 patients aged 40-80 years with coronary heart disease, other vascular diseases or diabetes. <sup>[5]</sup>

The bench-mark study found a cancer mortality of 3.3% (0.7% per year), in patients taking statin or placebo (inactive substance), while the study using digitalis or other cardiac glycosides, found a much lower mortality rate for cancer (0.06% per year).

Unfortunately, the astonishing finding of extremely low cancer mortality in the cardiac patients taking digitalis couldn't be explored in the study signed by Quintiliano de Mesquita and Claudio Baptista. Cancer was not its main focus and a control group for this purpose was lacking.

Studies pointing to a reduction in mortality by cancer in patients taking digitalis are not new. In fact, there are some writings stating that in the beginning of the past century the first study about this relationship was happened. Anyway, just in recent years the scientific confirmation came, suggesting digitalis as a potential anticancer agent”.

Before presenting an update on the previous information published in 2006 at the News Bulletin from ICP, it is important to show the daily maintenance doses, for the cardiac glycosides used by Quintiliano de Mesquita and Claudio Baptista in their study. <sup>[4]</sup> It follows:

Daily Maintenance Doses <sup>[6]</sup>

- Proscillaridin A: 0,75 - 1.50 mg
- Acetyldigoxin: 0,50 mg
- Lanatoside C: 0,50 mg
- Digitoxin: 0,1 mg
- Digoxin: 0,125 - 0,25 mg
- Betamethyldigoxin: 0,10 - 0,20 mg

**Note:**

- Digoxin, since its insertion, is still the cardiac glycoside most used in Brazil. Therefore, it represented a large proportion of the prescriptions from these authors to their patients. <sup>[6]</sup>

## Cardiac Glycosides Tested for Cancer

Over the last decade it was augmented the range of cardiac glycosides used both as antitumor agents as in cancer prevention. Among the cardiac glycosides tested in studies for many cancer types, are included: digitoxin, digoxin, oleandrin, ouabain, lanatosid C, proscillaridin A, and bufalin. <sup>[7]</sup>

### **The Catalyst on the Research of Cardiac Glycosides for Cancer Therapy**

Johan Haux and colleagues, in their seminal paper from 1999, <sup>[8]</sup> examined the effects of digitoxin and digoxin on some malignant cell lines with newly developed methods for estimating apoptosis. They found, for both of these cells' lines, there was a dose response pattern and digitoxin in therapeutic concentration was more effective than digoxin in inhibiting these cell lines.

Haux, in a subsequent study, <sup>[9]</sup> pointed out that “Glycosides are common substances in herbal and plant extracts and the aglycone is usually poisonous. However, in lower concentrations, many of them exhibit antiproliferative effects on cancer cells. Interestingly, digitalis-like factors are also found in plasma from healthy individuals”.

Haux also told in his article <sup>[9]</sup>: “Until now, focus has been on the Na<sup>+</sup>/K<sup>+</sup>ATPase as the primary target for the effects of the digitalis compounds, also when it comes to explaining the anticancer effect. That is logical in view of the fact that halt of proliferation has been regarded as the

main mechanism for explaining the inhibiting activities. However, now when we know that apoptosis induction is a major effect of digitalis on several types of tumor cells it seems fruitful to explore mechanisms other than just the Na<sup>+</sup>/K<sup>+</sup>ATPase inhibition”.

## **Digitoxin X Digoxin in the Treatment of Heart Failure**

Up to the 1950s, digitoxin was the most commonly used glycoside in Germany; thereafter, Anglo-American prescription habits were quite closely followed, and digoxin became more popular. However, France and Norway continued using digitoxin as their standard glycoside.

Digoxin's are less lipophilic, show lower protein binding and shorter half-life, are mainly eliminated via the kidney and accumulate quite rapidly in cases of insufficient kidney function. The incidence of toxic side effects seems to be higher with digoxin than with digitoxin treatment.

In contrast, digitoxin is highly lipophilic and extensively bound to plasma proteins, has a longer half-life, is mainly eliminated in the metabolized state via urine and feces, and does not accumulate under kidney dysfunction.

The daily oral maintenance dosages of digitoxin traditionally recommended are 0,05 mg, 0,07 mg or 0,1 mg in the objective of achieving a therapeutic serum concentration of digitoxin in the range of 10 to 30 ng/ml, depending on the assay used. <sup>[10]</sup>

The daily oral maintenance dosages of digoxin traditionally recommended by guidelines, until 2010, were 0,125 mg, 0,250 mg and 0,375 mg in the objective of achieving a therapeutic serum digoxin concentration (SDC) in the range of 0.5 to 2.0 ng/ml. <sup>[12, 15]</sup>

### **Note:**

In vitro and ex vivo experiments have revealed that some cardiac glycosides (e.g, digitoxin) induce potent and selective anticancer effects, at concentrations commonly found in the plasma of patients treated with these drugs. <sup>[11]</sup>

## **Digoxin: Lowering the Dosage for Better Outcomes**

Rathore et al, in a study published in 2003 <sup>[12]</sup>, on a post hoc analysis of data from The Digitalis Investigation Trial (DIG) of 1997 <sup>[13]</sup>, dividing the men treated into three groups according to their serum digoxin concentration after one month of treatment: 0.5-0.8 ng/ml, 0.9-1.1 ng/ml and > 1.2 ng/ml, found that mortality in men in the lowest level group was 6.3% lower than that of men in the placebo group. In contrast, mortality in men in the intermediate and highest-level groups was 2.6% and 11.8% higher respectively than that of the placebo group.

Adams et al, in a study published in 2005, <sup>[14]</sup> presenting another retrospective analysis of data from the DIG trial <sup>[13]</sup>, have indicated a beneficial

effect of digoxin on morbidity and no excess mortality in women at serum concentrations from 0.5 to 0.9 ng/ml, whereas serum concentrations  $\geq 1.2$  ng/ml seemed harmful.

The result of the studies from Rathore et al [12] and Adams et al [14] led to changes on the Heart Failure Guidelines issued by the Heart Failure Society of America in 2010. [15] Follows some extracts of the Session 7 of these guidelines related to the use of Digoxin recommendations from the chapter 'Heart Failure in Patients with Reduced Ejection Fraction':

1. Recent data suggest that the target dose (and serum concentration) of digoxin therapy should be lower than traditionally assumed. Although higher doses may be necessary for maximal hemodynamic effects, beneficial neurohormonal and functional effects appear to be achieved at relatively low serum digoxin concentrations (SDC) typically associated with daily doses of 0.125 to 0.25 mg. A retrospective analysis of the relationship of SDC to outcomes in the DIG trial demonstrated a strong direct relationship between the risk of death and SDC, with concentrations  $\geq 1.2$  ng/mL being associated with harm, whereas concentrations  $\leq 1.0$  ng/mL were associated with favorable outcomes.
2. The efficacy of digoxin in HF with reduced LVEF has traditionally been attributed to its relatively weak positive inotropic action arising from inhibition of sodium potassium ATPase and the resulting increase in cardiac myocyte intracellular calcium. However, digitalis has additional actions that may contribute significantly to its beneficial effects in patients with HF. Digoxin has important neuro-hormonal modulating effects that cannot be ascribed to its inotropic action, and it ameliorates autonomic dysfunction as shown by studies of heart rate variability, which indicate increased parasympathetic and baroreceptor sensitivity during therapy.

**Notes:**

- Studies have shown an increased risk of breast and uterus cancer occurring in woman taking digoxin, with suggestion that these results were due to estrogen like effects, because digoxin and digitoxin drugs are phyto-estrogens, and that both breast and uterus cancers are often estrogen sensitive. [16]  
The possible association with estrogen brought some suspicion to the use of cardiac glycosides, particularly digoxin, in the treatment of cancers. This despite many studies indicating little evidence of an increased risk by digoxin in many cancer types like in lung, colon and prostate cancers.  
The digoxin exposure in studies, which found raised risk for breast and uterus cancers, was obtained through the national prescription database from Denmark, initiated in 1995 [15].
- In view there was no knowledge in 1995 about better outcomes using digoxin at low concentration, it is extremely necessarily to make a retrospective analysis of data in these studies. This in order to verify the serum digoxin concentration, separating by groups of patients as done

in the studies by Rathore et al <sup>[12]</sup> and Adams et al <sup>[14]</sup>, in their analysis of The Digitalis Investigation Trial (DIG), from 1997. <sup>[13]</sup>

We think that reviewing the results in this manner will lead to a closure on the case of cardiac glycosides, oestrogen and cancer.

## **Cardiac Glycosides and Sympatho-Inhibitory Effects**

Studies have shown that the following cardiac glycosides drugs have a sympatho-inhibitory response:

- Cedilanid\* <sup>[17]</sup>
- Digoxin <sup>[18, 19]</sup>
- Digitoxin <sup>[20]</sup>
- Ouabain <sup>[21]</sup>

\* *Cedilanid is the trade name. The active ingredient is Lanatoside C*

## **Cardiac Glycosides in Reduction of Lactate Production**

A recent paper has demonstrated that inhibiting the overproduction of catecholamine by digoxin, digitoxin and ouabain may induce a potent inhibition of glycolysis (glucose consumption and lactate) in cancer. <sup>[22]</sup> It confirms the results of old studies on this matter. <sup>[23]</sup>

## **Endogenous digitalis-like compounds (DLCs)**

Endogenous DLCs like digoxin, ouabain/strophanthin, proscillaridin-A and marinobufagenin were isolated from human tissues and body fluids having similar molecular structure of cardiac glycosides extracted from plants and toad venom. <sup>[24,25]</sup>

Perturbation of the endogenous digitalis-like compounds system has been implied in many pathological conditions including cardiac arrhythmias, hypertension, heart failure, cancer and depressive disorders. <sup>[25, 26]</sup>

An example about this perturbation is the study which found that a majority (73.6%) of breast cancer patients (n = 84) expressed lower DLC plasma concentrations (<50 pmol/L) than a control group (150 ± 30 pmol/L), but about 10.8% of the patients revealed extremely high (>2000 pmol/L) DLC plasma concentrations. <sup>[27]</sup> Endogenous digitalis-like compounds may have similar action on neuro-hormonal levels.

The insufficient production of endogenous DLCs by the human body, to attend the demand in some medical conditions, like in cancer, hypothetically might be resolved using cardiac glycosides at low concentration dosages as a supplement. We consider this view as an important direction in research of cancer what investigators should pursue in the future. <sup>[28]</sup>

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## Autonomic Dysfunction + Lactic Acidosis = Multiple Diseases

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# Chapter 11

## Cancer, Atherosclerosis and Sympathetic Dominance

*Carlos ETB Monteiro*

I have read with interest the article Hypothesis: Cancer causes and mechanisms by John Spottiswoode <sup>[1]</sup> where he proposes the imbalance of the autonomic nervous system (ANS) as cause of cancer.

From his article I have learned about a study presented at the Third World Congress on Cancer held in 1997, showing an extremely high correlation to cancer developed in individuals having a high sympathetic nervous system activity.<sup>[2]</sup> He also has cited in his article, aside other studies whose authors had the same line of thought, a paper showing that major ANS dysfunction is extremely common in advanced cancer.<sup>[3]</sup>

Well, I think that John Spottiswoode is right in his assumption. Moreover taking in account the discovery that drugs with sympatholytic properties - directly by reduction of sympathetic nervous system activity or indirectly through the improvement of baroreceptor function or by strengthening the vagus nervous system, like digitalis (digoxin, digitoxin, etc..., at low dosages)<sup>[4]</sup> and Beta blockers,<sup>[5]</sup> are now considered as potential anticancer agents. Recently, a study found that intravenous Vitamin C Boosts Chemo's Cancer-Fighting Power.[6] Certainly the benefit of Vitamin C for cancer is resulted from its property by improvement of baroreceptor function or reducing the sympathetic activity.<sup>[7,8,9]</sup>

On the other hand, it is well-known that cancer and atherosclerosis share many common risk factors, most of them leading to sympathetic dominance over the parasympathetic system.<sup>[10]</sup> Besides, it was long recognized the value of stress reduction programs like relaxation techniques for cancer and atherosclerotic disease.

Digitalis, Beta Blockers and vitamin C are also potential anti-atherosclerotic agents which are advocated through our acidity theory of atherosclerosis <sup>[11,12,13]</sup> where sympathetic dominance is the primary step in the cascade of events leading to the atherogenic process.

It is particularly interesting to notice about the recent findings by researchers from Germany <sup>[14]</sup> and from US <sup>[15]</sup> showing there is an inverse association between cancer history and autopsy-proven atherosclerotic disease, differing in rates depending on types of cancer.

These papers confirm the results of old studies like the one made by Wansher and colleagues in 1951 which, based on material from 1835

autopsies, have demonstrated that atherosclerotic lesions are less pronounced in patients suffering from carcinoma than among non-cancerous persons.<sup>[16]</sup> The solution of the puzzle represented by the inverse relationship between cancer and atherosclerotic disease may take some time. In our view the autonomic nervous dysfunction and metabolic pathways are potential ways to solve the matter and should be prioritized by the investigators for this task. Meanwhile, millions and millions of people with cancer or atherosclerosis deserve immediate solution for their illnesses. Sympatholytic drugs and vitamin C, aside of stress reduction management, are very good alternative ways for that.

**Note:**

- The chronic sympathetic dominance leads to raised catecholamine (stress hormones like adrenaline and noradrenaline) release, accelerating glycolysis metabolism, therefore increasing lactic acid/lactate concentration in blood and tissues worsening cancer and atherosclerotic disease among other clinical conditions <sup>[17]</sup>.

Finally, it is important to mention a study published in 2013 at Science Journal, where the authors say in their conclusion:<sup>[18]</sup>

*"These results suggest that the formation of new nerve fibers within and around prostate tumors can alter their behavior. The autonomic nervous system appears to exert dual functions in prostate cancer: Sympathetic neo-nerves promote early stages of tumorigenesis, whereas parasympathetic nerve fibers promote cancer dissemination. Conceivably, drugs targeting both branches of the autonomic nervous system could provide therapeutic benefit."*

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**Part #4**

**Articles on Other Diseases**



# Chapter 12

## The Fundamental Role of Autonomic Dysfunction and Lactic Acidosis in Alzheimer's Disease

*Carlos ETB Monteiro and Paul J. Rosch, MD*

*"Acidosis may stimulate an extracellular deposition of amyloid and contribute to the pathogenesis of Alzheimer disease",  
Gregory J. Brewer, 1997<sup>[1]</sup>*

### Abstract

This article discusses recent findings that amyloid-beta peptide is a consequence of acidosis, rather than the initial cause of Alzheimer's Disease (AD). It postulates that autonomic dysfunction is a precursor of AD because it increases plasma lactate concentrations.

This is consistent with the acidity theory of atherosclerosis proposed in 2006, which supports the vascular hypothesis as well as the role of brain lactate production in the progression of AD.

Other influences such as digoxin, ketogenic or high fat-- low carb diets, choline intake and supplements like Vitamin C, Vitamin D, Vitamin E, Quercetin and Omega-3 are also important, since they may prevent or improve cognitive deficits in AD.

The article also present studies showing that some drugs like beta-blockers and statins as much as diseases like diabetes and coronary artery calcification, may induce cognitive decline.

### Introduction

A study published in 2019 on AD drug development <sup>[2]</sup> reviewed the clinicaltrials.gov website to evaluate all pharmacological agents currently being developed for the treatment of AD. It concluded that:

- The lack of success in AD drug development has given rise to nihilism with regard to the ability of the field to develop agents that meaningfully modify the progression of AD. Suggestions to abandon the amyloid hypothesis, focus exclusively to combination therapies, place more emphasis on lifestyle interventions to prevent AD or reassess our assumptions and build new models to drive drug development are all voiced, and each of these perspectives have merit.

Other recent studies have also discussed the failure of drugs to treat AD.

[3,4,5,6]

With respect to the effect of acidosis on amyloid-beta, a recent study<sup>[7]</sup> noted:

- The accumulation of toxic A $\beta$  and p-tau may not be the initial cause of neural degeneration and may instead be consequences of other causative factors. . . . Neurons don't ordinarily make adaptive and compensatory shifts to glycolysis, including under stress conditions. Instead, they have a high demand for other oxidative substrates and, in particular, lactate, which is largely provided by proliferating astrocytes through their high glycolytic capacity.

### **Lactate Levels In AD**

- a) A 2014 study showed that patients with early AD have higher glucose concentration in an area susceptible to AD pathology compared to controls. In addition, lactate concentration is higher, suggesting greater regional metabolic reliance on glycolysis. These results motivated a longitudinal study of MRS glucose and lactate as novel AD biomarkers<sup>[8]</sup>
- b) A 2015 study suggests a dynamic relationship between neuronal energy metabolism, tau proteins and cognitive decline in AD and proposes the clinical potential of assessing CSF lactate levels in patients with AD to better define damage to neuronal brain communication.<sup>[9]</sup>
- c) A 2016 study suggests that during progression of AD, aerobic glycolysis and lactate production may in fact be detrimental and contribute to cognitive decline.<sup>[10]</sup>

## **The Vascular Hypothesis Of Alzheimer's Disease**

Evidence from pathological, clinical and epidemiological studies indicates an association between AD and atherosclerotic disease due to a progressive reduction of blood flow to the brain.<sup>[11]</sup>

Other studies have shown that a severe increase in carotid intimal medial thickness may be considered as a marker for progression of the cognitive decline in AD, and that interventions to reduce atherosclerosis may help to prevent the onset of vascular dementia and AD<sup>[12, 13,14]</sup>

Jack C. de la Torre, one of the authors of the vascular hypothesis as a cause of Alzheimer's Disease that was developed in 1993<sup>[15]</sup>, recently noted:<sup>[16]</sup>

- There is growing evidence that chronic brain hypoperfusion plays a central role in the development of Alzheimer's disease long before dyscognitive symptoms or amyloid- $\beta$  accumulation in the brain appear.

De la Torre, has also implicated many other cardiovascular risk factors in the development of cognitive impairment preceding AD, including atrial fibrillation, thrombotic events, hypertension, hypotension, heart failure, low cardiac index and valvular pathology.<sup>[17]</sup> Additional risk factors for AD such as: aging, family history, gender, lifestyle, diabetes mellitus, stroke and genetic influences have also been mentioned in other studies.

What sparked our interest regarding Alzheimer's disease and its possible association with atherosclerosis was a Medscape report<sup>[18]</sup> of a study showing

that beta-blockers used to treat hypertension resulted in fewer Alzheimer's type brain lesions than other antihypertensive drugs.

The study, which was published in September 2013 <sup>[19]</sup>, involved 774 elderly male Japanese Americans who participated in the Honolulu-Asia Aging Study <sup>[20]</sup>. Of these, 610 had high blood pressure or were being treated with medication for hypertension. Among those who had been treated (about 350 patients), 15 percent received only a beta blocker, 18 percent received a beta blocker plus one or more other medications, and the rest of the participants received other antihypertensive drugs.

It found that all types of treatment to lower elevated blood pressure were clearly better than no treatment. Autopsies were performed on all participants, and men who had received beta blockers as their only blood pressure medication had fewer abnormalities in their brains compared to those who had not been treated for their hypertension, or who had received other blood pressure medications. The brains of participants who had received beta blockers plus other medications showed an intermediate reduction in numbers of brain abnormalities.

These included two distinct types of brain lesion: those indicating Alzheimer's disease, and lesions called microinfarcts, usually attributed to tiny, multiple, unrecognized strokes. Study participants who had taken beta blockers alone or in combination with another blood pressure medication also had significantly less brain pathology. The association between beta blocker use and cognitive impairment was stronger among men with diabetes aged >75 years and those with a pulse pressure  $\geq 70$  mm Hg. <sup>[19]</sup>

Dr. Lon R. White, one of the authors of the study, speculated on the mechanisms of action in a Medscape interview <sup>[18]</sup> in which he noted that beta blockers reduce pulse rate, which might have an effect on small-vessel microinfarcts in the brain, as follows:

*"Lifelong exposure of the pulse pressure in the brain might cause some damage," - he said. "While we thought beta-blockers may reduce brain microinfarcts, which they did, we actually saw a larger reduction in the Alzheimer's-type lesions, which we had not expected. This is somewhat of a mystery at present and may be a chance finding. But if it is a real effect, I would think it was something to do with autonomic function."*

White suggested that a reasonable next step could be to test this hypothesis in mice genetically engineered to produce these Alzheimer's lesions.

*"If we treat these mice with beta-blockers and they develop fewer lesions, then we will know that it is an effect of the drugs."*



## **The Acidity Theory of Atherosclerosis And The Vascular Hypothesis Of AD**

We see some concordance between White's interpretations and the concept that the autonomic nervous system dysfunction, with sympathetic dominance representing the primary factor in the cascade of events leading to atherosclerosis.

The acidity theory of atherosclerosis developed in 2006 <sup>[21]</sup> pointed out that beta blockers, through their sympatholytic effects, have been shown to reduce the progression of atherosclerotic plaques in many studies. It emphasizes that cardiac glycosides like digoxin can also reduce progression of atherosclerosis <sup>[22]</sup>, which suggests that sympatholytic drugs might also offer some benefits to patients with AD or cognitive deficits.

### **Do Beta Blockers Cause Cognitive Decline?**

Despite studies supporting the beneficial results of beta blockers in AD and dementia, other research suggests these drugs may cause a decline in cognition. For example, a 2007 study investigated the influence of  $\beta$ -blockers on delayed memory function in cognitively impaired patients. The authors concluded that there was a trend for worsened or delayed memory retrieval in patients who were on CNS-active  $\beta$ -blockers. They believe this supports the notion that common medications used in cognitively impaired elderly patients can worsen cognition, and that careful selection of medications may help to prevent this and improve retrieval of newly formed memories. <sup>[23]</sup>

A 2012 letter commenting on this in J Neuropsychiatry in 2012 <sup>[24]</sup> concluded:

There is insufficient evidence for this assertion currently, but further studies should investigate the effects of beta-blockers in patients with cognitive impairment or dementia."

More recently, a 2016 JAMA study showed that the use of beta-blockers resulted in worsened functional outcomes among nursing home residents with substantial cognitive or functional deficits.

The initial cohort of 15,720 patients (11,140 women [70.9%] and 4,580 men [29.1%]; mean age, 83 years) included 8,953 new beta-blocker users and 6,767 nonusers. The propensity-matched cohort included 5,496 new users of beta-blockers and an equal number of nonusers for a total cohort of 10,992 participants.

The authors concluded that the use of beta-blockers after acute myocardial infarction is associated with functional decline in older nursing home residents with substantial cognitive or functional impairment, but not in those with relatively preserved mental and functional abilities. <sup>[25]</sup>

## Is Beta-blocker Therapy For Hypertension Dangerous?

1. A 2005 Lancet paper <sup>[26]</sup> concluded:  
In comparison with other antihypertensive drugs, the effect of beta blockers is less than optimum, with a raised risk of stroke. Hence, we believe that beta blockers should not remain first choice in the treatment of primary hypertension and should not be used as reference drugs in future randomised controlled trials of hypertension.
2. A 2008 study <sup>[27]</sup> also found that:  
Beta-blocker associated reduction in heart rate increased the risk of cardiovascular events and deaths of hypertensive patients in a meta-analysis of more than 60,000 patients in 9 large beta blocker trials. In subsequent correspondence <sup>[28]</sup>, the authors suggested that drug-induced bradycardia is less beneficial than spontaneously occurring bradycardia. and may be related to the “dyssynchrony of the reflected pulse wave and the outgoing pressure wave.”
3. A 2017 Cochrane Database paper <sup>[29]</sup>. concluded that:  
Most outcome RCTs on beta-blockers as initial therapy for hypertension have high risk of bias. Atenolol was the beta-blocker most used. Current evidence suggests that initiating treatment of hypertension with beta-blockers leads to modest cardiovascular disease reductions and little or no effects on mortality.

## Coronary Artery Calcification and Cognitive decline

1. Studies from 2013 and 2014 have reported the reduced pineal volume and have found calcification in AD. <sup>[30, 31]</sup>
2. A study from 2015 found that larger calcification volume in all vessels, except in the coronaries, was associated with a higher risk of dementia. Additional analyses for Alzheimer's disease showed similar results. These larger calcification volumes were also associated with cognitive decline. <sup>[32]</sup>
3. A study published in 2017 confirmed that higher baseline coronary artery calcification was significantly associated with increased risk of dementia. <sup>[33]</sup>
4. A study published in 2019 has observed reduced pineal gland volume and pineal calcification, accompanied by cognitive decline and sleep disturbances in AD patients. <sup>[34]</sup>
5. A recent study postulated that increased lactate production is the responsible for coronary artery calcification. <sup>[35]</sup>

## Diabetes and cognitive decline

1. Data from a large veteran's registry in the USA from 2011 has shown that, among people with diabetes, the prevalence of dementia and cognitive impairment combined was 13.1% for those aged 65-74 years and 24.2% for those aged 75 years and older. <sup>[36]</sup>
2. A study from 2018 provided evidence to support the association of diabetes with subsequent cognitive decline. Their findings show a linear correlation between circulating HbA1c levels and cognitive decline, regardless of diabetic status. The study comprised 5189 participants and the mean follow-up duration was  $8.1 \pm 2.8$  years and the mean

number of cognitive assessments was  $4.9 \pm 1.5$ . According the authors their findings suggest that interventions that delay diabetes onset as well as management strategies for glucose control, might help to alleviate the progression of subsequent cognitive decline over the long term. <sup>[37]</sup>

3. Autonomic dysfunction and raised lactate production are common in Diabetes. <sup>[38-40]</sup>

## Statins and Cognitive decline

A paper from 2019 analyzed relevant studies of the relationship between cognitive performance and statin and usage. It included articles published between 2018 and 1992.

It was identified three randomized trials, one observational study and 66 case reports that provided credible evidence of statin induced cognitive impairment. It also identified seven randomized trials and two observational studies reporting no significant evidence of statin-induced cognitive impairment.

This study found methodological differences that may have contributed to the divergence of these results. Evaluation of all these studies indicated that statin-associated cognitive decline is a real entity.

### Likely mechanisms to explain the adverse effects include

1. Reduction of synthesis of coenzyme Q10 with consequent increasing oxidative stress and reduction of cerebral energy production;
2. Depletion of central nervous system myelin by inhibition of cholesterol synthesis.

The authors concluded that statin-induced cognitive decline does exist, needs to be better recognized and requires more studies of prevention and treatment.” <sup>[41]</sup>

**Note:** Statin therapy may induce acidosis. <sup>[42,43]</sup>

## Vitamin D Improvement Of Cognitive Function

The neuroprotective effect of vitamin D is likely an important contributor to memory development and preservation of normal cognitive function. <sup>[44]</sup> Moreover, compared with healthy people of the same age, the plasma 25-D level of AD patients seems to be markedly lower. This suggests that vitamin D may have potential benefits on cognitive function. <sup>[45]</sup> A recent 2019 study found that oral vitamin D supplementation (800 IU/day) for 12 months may improve cognitive function and decrease amyloid beta-related biomarkers in elderly patients with AD. <sup>[46]</sup>

## **Omega-3 Improvement Of Cognitive Function**

A 2017 study found that quantitative omega-3 EPA+DHA erythrocyte concentrations are independently correlated with brain perfusion on SPECT imaging and neurocognitive tests. These results have implications for the role of omega-3 fatty acids toward contributing to cognitive reserve. <sup>[47]</sup>

The effects of omega-3 fatty acids supplementation in mild AD corroborate epidemiological observational studies showing that omega-3 fatty acids may be beneficial in disease onset, when there is slight impairment of brain function.

This systematic review published in 2017 says that although some studies have shown changes in scales of cognitive function in more severe cases, more studies are necessary to confirm the benefit of omega-3 fatty acid supplementation in the treatment of AD. <sup>[48]</sup>

## **Improvement Of Cognitive Function With Digoxin**

In a NEURO2019 presentation, the authors discussed their observation that digoxin significantly prevented the ICV-STZ (intracerebroventricular-streptozotocin) induced memory deficit by attenuating hippocampal neuronal loss, neuroinflammation and cholinergic deficit in rats.

These findings suggest that digoxin might be beneficial for treating AD. <sup>[49]</sup> A study from 2009 has shown that treatment with digoxin may selectively improve cognitive function in older patients with heart failure. <sup>[50]</sup>

## **Increased Choline And Egg Intake Improve Cognitive Function**

A recent study found that higher phosphatidylcholine intake was associated with lower risk of incident dementia and better cognitive performance in men in eastern Finland <sup>[51]</sup>. According to the authors, choline is an essential nutrient that is needed as a precursor for the neurotransmitter acetylcholine, and for phosphatidylcholine, a membrane constituent.

They also suggested that choline has a role in the prevention of cognitive decline and Alzheimer disease. In addition, it is an ingredient in a multi-nutrient medical food developed for treating mild AD. These authors previously reported that higher egg intake was associated with better performance in certain cognitive tests and tended to lower risk of dementia <sup>[52]</sup>.

Other studies have also observed a beneficial association between egg intake and cognitive performance. In addition to meat and other animal products, egg yolk is a major dietary source of choline and especially phosphatidylcholine. Consumers of eggs had almost double the usual intake of choline as compared to non-consumers. <sup>[53]</sup>

Another animal study, also published in 2019, demonstrated that lifelong choline supplementation produces profound benefits, suggesting that simply

modifying diet throughout life may reduce AD pathology. <sup>[54]</sup> Acetylcholine is the chief neurotransmitter of the parasympathetic nervous system an important component of the autonomic nervous system.

## **Quercetin Improvement of Cognitive Function**

Several studies have reported on the neuroprotective effects of the flavonoid quercetin, both in vitro and in vivo models of neurodegenerative disorders, such as cognitive impairment. <sup>[55]</sup>

Some recent studies:

1. A study from 2015 <sup>[56]</sup> evaluated the neuroprotective effect of quercetin (25 mg/kg) administration via Intraperitoneal injection every 48 hours for 3 months on aged (21–24 months old) triple transgenic triple transgenic AD model (3xTg-AD) mice. Its data has shown that quercetin decreases extracellular  $\beta$ -amyloidosis, tauopathy, astrogliosis and microgliosis in the hippocampus and the amygdala suggesting it reverses histological hallmarks of AD and protects cognitive and emotional function.
2. In a study published in 2019 <sup>[57]</sup>, the same group of researchers <sup>[56]</sup> suggested that preventive and chronic administration of quercetin might help to delay the development of histopathological hallmarks and cognitive function deficits in AD.

## **Vitamin E and C Improvement of Cognitive Function**

A study from 1998 <sup>[58]</sup> examined the relation between use of vitamin E and vitamin C and incident Alzheimer disease in a prospective study of 633 persons 65 years and older. After an average follow-up period of 4.3 years, 91 of the sample participants with vitamin information met accepted criteria for the clinical diagnosis of Alzheimer disease. None of the 27 vitamin E supplement users had Alzheimer disease compared with 3.9 predicted based on the crude observed incidence among nonusers ( $p = 0.04$ ) and 2.5 predicted based on age, sex, years of education, and length of follow-up interval ( $p = 0.23$ ). None of the 23 vitamin C supplement users had Alzheimer disease compared with 3.3 predicted based on the crude observed incidence among nonusers ( $p = 0.10$ ) and 3.2 predicted adjusted for age, sex, education, and follow-up interval ( $p = 0.04$ ). There was no relation between Alzheimer disease and use of multivitamins. These data suggest that use of the higher-dose vitamin E and vitamin C supplements may lower the risk of Alzheimer disease.

A study from 2004 <sup>[59]</sup> found that using both prevalence and incidence data from the large, population-based Cache County study suggest that antioxidant vitamins, specifically the combination of vitamin E and C supplements, may prevent AD. As is widely appreciated, formal proof of such an effect can come only from randomized prevention trials. If proven efficacious in such trials, antioxidant vitamins (believed to offer other health benefits) would offer an attractive prevention strategy for AD. Formal demonstration of their efficacy

would therefore have significant public health implications, and we suggest that prevention trials are warranted.

A study from 2017 <sup>[60]</sup> says: “Ascorbic acid can be considered vital for neuronal repair and offers new molecular mechanisms to understand the true neuroprotective role of AA in brain aging and neurodegeneration”

A study from 2019 <sup>[61]</sup> found there was a significant association between vitamin-C plasma concentrations and performance on tasks involving attention, focus, working memory, decision speed, delayed and total recall, and recognition. Plasma vitamin C concentrations obtained through vitamin C supplementation did not affect cognitive performance differently to adequate concentrations obtained through dietary intake.

A study published in 2014 told that the relative safety of vitamin E combined with the low cost and the absence of valid alternative treatments for AD, suggest vitamin E as a nutritional compound to promote healthy brain ageing and to delay AD-related functional decline.<sup>[62]</sup> On the other hand a recent study says vitamin E clinical safety remains controversial and warrants further investigation. <sup>[63]</sup>

## **Autonomic Dysfunction As A Precursor Of AD**

Our present postulate supports both the vascular hypothesis as well brain lactate production in the development of AD. There are numerous studies linking autonomic dysfunction to AD that suggest increased sympathetic and/or decreased parasympathetic activity in AD patients <sup>[64-73]</sup>.

A 2010 study proposed that elevated endogenous brain norepinephrine might be an etiological factor in some patients, and could also accelerate progression of the disease. <sup>[74]</sup>

Another study found that baroreflex function, which influences sympathetic and parasympathetic activity, is reduced in Alzheimer’s disease. <sup>[75]</sup>

## **Risk Factors For Atherosclerosis Consistent With The Acidity Theory**

In parallel, it is important to notice the lengthy list of risk factors for atherosclerosis that have dysregulation of the autonomic nervous system as a common denominator. These risk factors were cited in a 2015 paper on the acidity theory of atherosclerosis that included psychosocial factors, diabetes, smoking, air pollution, noise, high carbohydrate diets, vitamin D deficiency, radiation, etc. <sup>[22]</sup>

With respect to high carbohydrate diets, the article states:

- It is well established that the sympathetic nervous system activity is also influenced by food ingestion, and that diet composition plays an important role. High carbohydrate diets, particularly in the form of high-

glycemic carbohydrate, can directly induce endothelial dysfunction, vascular inflammation and subsequent development of atherosclerosis.

A study from 2009 advocates that the widespread use of starchy food and sugars has brought a new metabolic problem: a chronically increased sympathetic nervous system activity, where the high glycemic index nutrition has been suggested to play a key role in the pathogenesis of hypertension and atherosclerosis.

On the other hand, protein or fat ingestion have no significant sympatho-excitatory effect.

### **Trans fatty acid (TFA) -- An additional risk factor for AD?**

TFA consumption is associated with increased risk of cardiovascular disease as well as a decrease in heart rate variability that reflects the autonomic dysfunction. <sup>[76]</sup>

A recent study found that higher serum elaidic acid (an objective biomarker for industrial trans fatty acids) is a possible risk factor for the development of all-cause dementia and AD in later life. <sup>[77]</sup>

### **High Carbohydrate Versus High-Fat And ketogenic Diets In AD**

The literature linking high-fat/low-carbohydrate diet, metabolic ketosis, and cognitive function in the elderly is increasing at a rapid rate. A 2012 paper studied the effects of a high carbohydrate or a very low carbohydrate diet on cognition and mood in mild cognitive impairment (MCI) patients.

Only those in the low-carbohydrate group had improved scores on a memory test after 6 weeks; this effect correlated significantly with ketone levels. <sup>[78]</sup> A 2016 paper reported the effects of diet on risk for dementia in nearly 1,000 older Americans.

Senior citizens who normally consumed a high carbohydrate diet had an elevated risk of MCI and dementia, whereas controls with high fat and protein diets had reduced risks. <sup>[79]</sup>

A small 2017 study enrolled 15 AD patients in a non-controlled trial of a ketogenic diet plus a medium-chain-triglyceride fat supplement. Among the 10 who completed the 3-month trial, there was a modest improvement in the Alzheimer's Assessment Scale-Cognitive subscale. <sup>[80]</sup>

Another study the following year suggested that the protective effect induced by a high fat diet on AD-like mice, resulted from mechanisms that involve better blood-brain barrier properties and brain morphology (normal ventricle volume, consistent with less brain atrophy). <sup>[81]</sup>

A more recent paper reported that 14 elderly individuals with mild cognitive impairment consistent with early Alzheimer's disease, had improved memory and brain function on a high-fat, low-carbohydrate diet.<sup>[82]</sup>

## **How Autonomic Dysfunction Leads To Lactic Acidosis**

The chronic elevated release of catecholamine release triggered by the sympathetic nervous system can accelerate myocardial glycolysis, which results in a significant increase in lactate production.

The first to observe the influence of adrenaline on lactic acid production were the Coris in the early 1920s.<sup>[83]</sup> A 1982 article by Schade provided further support for the direct participation of catecholamines in the development and/or maintenance of lactic acidosis as follows:<sup>[84]</sup>

1. The common association of stress and lactic acidosis.
2. The rise in plasma lactate concentration during adrenaline infusion.
3. The precipitation of lactic acidosis by adrenaline intoxication and pheochromocytoma.
4. The vasoconstrictor effects of catecholamines leading to tissue anoxia and lactic acid production.

## **Risk Factors For Atherosclerosis With Increased Concentration Of Lactate In Plasma That Support The Acidity Theory Of Atherosclerosis.**

Elevated blood lactate is associated with increased carotid atherosclerosis.<sup>[85]</sup> A 1961 study found that that reduction of blood pH increases blood flow.<sup>[86]</sup> Lowered pH increases perfusion pressure.<sup>[87,88]</sup> pH changes also have profound effects on the contractility of coronary arteries,<sup>[88,89]</sup> that may be due to sodium/potassium pump and potassium induced relaxation activities.<sup>[90]</sup> Lactate, lowered pH and lactic acid induce endocardial damage.<sup>[91]</sup>

The association of increased lipid levels with abnormal lactate metabolism may provide a useful screening test for the detection of coronary artery disease.

Plasma lipid abnormalities and myocardial lactate production are significantly associated with subsequent progression of atherosclerosis on arteriography. In addition, the amount of lactate released by the myocardium has been shown to be related to the severity of coronary artery disease.<sup>[92-94]</sup>



## Drugs And Supplements That Inhibit Sympathetic Or Enhance Parasympathetic Effects

- Digoxin <sup>[95]</sup>
- Omega 3 <sup>[96]</sup>
- Vitamin C <sup>[97-99]</sup>
- Vitamin E <sup>[100,101]</sup>
- Vitamin D <sup>[102]</sup>

## Diet, Drugs And Supplements That Reduce Lactate/Lactic Acid Production

- Dichloroacetate <sup>[103,104]</sup>
- Digoxin <sup>[105,106]</sup>
- Ketogenic diet <sup>[107]</sup>
- Omega 3 <sup>[108]</sup>
- Quecertin <sup>[109,110]</sup>

## What we can expect on Dementia and Alzheimer's disease in the future\*

\*The viewpoint from the Blue Cross Blue Shield Association <sup>[111]</sup>

### Follows the BCBSA report <sup>[112]</sup>

The number of commercially insured Americans age 30 to 64 diagnosed with early-onset dementia or Alzheimer's disease increased by 200% from 2013 to 2017. The average age of a person living with either form of dementia is 49.

These conditions are more common in women, who make up 58% of those diagnosed. Additional findings from the study include:

- The number diagnosed with these conditions increased 373% among 30- to 44-year-olds, 311% among 45- to 54-year-olds and 143% among 55- to 64-year-olds from 2013 to 2017.
- Rates of diagnosis were higher in the East, the South, and parts of the Midwest, while western states showed lower rates of diagnosis.

*"The increase in early-onset dementia and Alzheimer's diagnoses among a generation who typically wouldn't expect to encounter these conditions for several decades is concerning, especially since there is no cure for Alzheimer's disease," said Dr. Vincent Nelson, vice president of medical affairs for BCBSA.*

*"Further education and research is needed to learn more about early-onset dementia and Alzheimer's, how to treat these conditions and what can be done to better prevent diagnoses."*

**Our perspective:**

We hope, through our postulation and data contained in the present article, to contribute positively in order to avoid that the terrible expectations expressed above by BCBSA do not turn in reality.

**Conclusion**

The present article shows a large number of evidences giving support to our postulation about the autonomic dysfunction as the precursor of the process leading to lactic acidosis, the ultimate causal factor for the development of Alzheimer's disease.

Adequate to this new hypothesis are provided solutions for the prevention and possible recovery of the patients affected by this neurodegenerative disease, through specific drugs, diets, vitamins and other supplements which were discussed in this article.

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## **Chapter 13**

# **Intense Stress Leading to Raised Production and Accumulation of Lactate in Brain Ischemia: The Ultimate Cause of Acute Stroke**

### **- Mechanism, Risk Factors and Therapeutics**

*Carlos ETB Monteiro*

*"In severe ischemia (and tissue hypoxia) oxygen delivery to brain cells is insufficient for normal energy production, and acid-base homeostasis is threatened by the accumulation of acid equivalents (metabolic acidosis)".*

*Stig Rehncrona MD PhD - Lund, Sweden, 1985<sup>[1]</sup>*



**Stig Rehncrona (Photo 2013)**

### **Abstract**

The present paper introduces a new hypothesis postulating that acute stress, chronic stress overload and other risk factors with intense sympathetic nervous system activity may induce a raised lactate production and accumulation in brain ischemia. This represents, in our view, the ultimate cause for the triggering of acute stroke, resulting in the cerebral infarction. It explains how stress (sympathetic dominance) may lead to a raised lactate production.



The fundamental therapeutic for prevention and management of acute stroke, according to this proposed concept, are old drugs called cardiac glycosides (CGs). Studies using cardiac glycosides have demonstrated neuroprotective effects in experimental brain ischemia, on the protection against vasospasm in subarachnoid hemorrhage, sympatho-inhibitory effects and a potent inhibition of glycolysis (glucose consumption and lactate). The use of CGs has also shown a very low total mortality (including for stroke) in cardiac patients taking low doses of these drugs.

Cardiac glycosides like digoxin and Lanatoside C are drugs approved by the US Federal Drugs Administration (FDA), and by other similar organizations around the world, with some of these having also approval for the use of digitoxin and other CGs . Therefore, these drugs can be prescribed for prevention and in the management of acute stroke, with no major obstacles, by a well-informed physician.

The paper also discusses on the limitations and failures in the concept of thrombus as the cornerstone of acute ischemic stroke (AIS)

## Introduction

Friede and Van Houten in 1961<sup>[2]</sup> related cellular injury in incubated brain tissue slices to the development of metabolic acidosis. Lindenberg postulated in 1963<sup>[3]</sup> that structural alterations in the hypoxic brain described as "morphotropic necrobiosis" are caused by intracellular acidosis. Rehncrona, in 1985<sup>[1]</sup> declared that severe tissue lactic acidosis limits the possibility for cell survival in brain ischemia. In his article, he reviewed data on the relationship between severe tissue acidosis and irreversible brain cell damage.

The measurement of interstitial pH and calculation of intracellular pH during cerebral ischemia indicate that increased acidosis accompanies increased tissue lactate <sup>[4, 5, 6]</sup> The accumulation of lactate in ischemic regions has been documented in studies during acute stroke.<sup>[7]</sup>

In 2008, a study involving 187 patients with ischemic stroke or transient ischemic attack has shown that lactate in cerebrospinal fluid (CSF) was a reliable marker for the metabolic crisis in acute ischemic stroke and a possible cause of secondary neuronal damage in cortical infarction resulting in unfavorable evolution in the sub-acute phase and poor long-term outcome.<sup>[7]</sup> Previous studies have already suggested that lactate dehydrogenase levels in the cerebrospinal fluid might be useful for recognizing those patients at high risk of developing severe stroke.<sup>[8]</sup>

A study from 2012 found that among patients with ischemic stroke, initial hyperlactatemia [a pathological state in which resting blood lactate concentration is abnormally high (>1.5 mmol/L) represents an independent risk factor for poor outcome after controlling for stroke severity, risk factors, initial glucose level, and interval from onset of stroke symptoms to emergency department arrival.<sup>[9]</sup>

A recent study found that in subarachnoid hemorrhage (the most devastating form of hemorrhagic stroke), elevated serum lactate levels on admission may have a predictive role for mortality and represent a marker of disease severity.<sup>[10]</sup>

## **The Blood Clot as Cause of Acute Ischemic Stroke**

Before presenting the basis for our hypothesis I would like to point out my disagreement about the current thinking that acute ischemic stroke occurs due to a sudden blood clot (thrombus) of an artery inside or leading to the brain, which may become completely blocked.

In our point of view, the blood clot doesn't have a fundamental role in the triggering of AIS. That also applies to the relationship between the thrombus and acute myocardial infarction.<sup>[11]</sup> The collateral circulation may protect the brain against ischemic injury and can potentially bypass the effect of a blocked artery, thereby influencing ischemic lesion and growth.<sup>[12]</sup>

Some data on limitations and failures in the concept of thrombus as the cornerstone of AIS.

### **1. Cerebral Thrombi**

An analysis of thrombi in acute ischemic stroke, published in 2017,<sup>[13]</sup> raise some questions like complexities, varieties, etc.... The authors say these points make difficult the improvement for the acute ischemic stroke therapy.

- a) 'The age of the thrombus may provide additional useful information on, for example, etiology. Current age descriptors of thrombi in the literature include old, mature, young, fresh (less than five days old), lytic (1-5 days old) and organized (greater than five days old)'.
- b) 'Since the thrombus itself is the primary target of current acute stroke treatments, its composition will most likely determine the most effective treatment modality. Thrombus composition is a key factor in determining susceptibility to mechanical and pharmacological thrombus disruption and thus the degree of successful recanalization. Yet such information is currently unknown prior to treatment and thus all thrombi are approached in the same manner. Several studies have investigated the histopathological composition of cerebral thrombi from stroke patients and revealed a wide variety. Correlations between thrombus components (red block clots, fibrin, platelets, white blood cells) and parameters such as stroke etiology, imaging parameters and treatment outcome have been reported but remain inconsistent, potentially due to the small sample sizes. One challenge is that the most treatment-resistant thrombi, which lead to failure of the procedure, are not available for analysis'.
- c) Current imaging techniques can provide some information about the thrombus, but there remains much to learn about what relationships exist between thrombus composition, various occlusion characteristics and treatment outcomes.

## **2. Trombolysis**

Clot properties have a number of potential implications for clinical treatment. Modest rates of early recanalization with IV rtPA [Recombinant Tissue Plasminogen Activator] therapy is associated with specific thrombus properties (short thrombus length, RBC-rich composition, and perviousness/residual forward flow). If a combination of these or more sophisticated features could predict successful intravenous thrombolysis prior to treatment, then transport and procedural costs of endovascular therapy could be saved. However, only those thrombi that did not dissolve spontaneously or after rtPA administration and that can be successfully retrieved via thrombectomy are available for study, which impedes the assessment of rtPA susceptible and thrombectomy-resistant thrombi.<sup>[13]</sup>

Despite of the spreading use of rtPA in different countries and continents, there are still a number of burdens and failures in the optimal accomplishment of thrombolytic treatment.<sup>[14]</sup> The low number of victims with AIS typically eligible for rtPA treatment occurs in part because of the varying etiologies of stroke and the very brief window of time for reperfusion therapy.

A study from Cochrane Database, published in 2014<sup>[15]</sup> states in its conclusion:

*“Thrombolytic therapy given up to six hours after stroke reduces the proportion of dead or dependent people. Those treated within the first three hours derive substantially more benefit than with later treatment. This overall benefit was apparent despite an increase in symptomatic intracranial hemorrhage, deaths at seven to 10 days, and deaths at final follow-up (except for trials testing rt-PA, which had no effect on death at final follow-up).*

*Further trials are needed to identify the latest time window, whether people with mild stroke benefit from thrombolysis, to find ways of reducing symptomatic intracranial hemorrhage and deaths, and to identify the environment in which thrombolysis may best be given in routine practice.*

*Deaths from all causes during follow-up: Data were available for all 27 trials (10,187 participants). There was a modest but significant increase in deaths within scheduled follow-up, from 18.0% in controls to 19.4% in the participants allocated to thrombolysis. In absolute terms, this represented an extra 15 deaths at the end of follow-up per 1000 participants treated with thrombolysis”*

That means an increased absolute risk in mortality of 1.5%, in the group treated with thrombolysis [15]

Intravenous administration of rtPA (alteplase) is the only U.S. Food and Drug Administration (FDA) - approved medical therapy for treatment of patients with acute ischemic stroke.

### **3. Mechanical Thrombectomy Devices to Remove the Thrombus**

The history of endovascular therapy for acute ischemic stroke has been controversial. In 2013, three trials of first generation mechanical thrombectomy devices for acute ischemic stroke were published showing no benefit of endovascular therapy on functional or clinical outcomes. These trials caused a noticeable increase in clinical skepticism regarding the utility of endovascular therapy for acute ischemic stroke.

The skepticism was enhanced by subsequent meta-analyses emphasizing the lack of efficacy of endovascular treatment in acute ischemic stroke patients.

A meta-analysis of five prospective randomized controlled trials comparing endovascular therapy using predominantly second-generation mechanical thrombectomy devices as an adjunct to medical management versus medical management alone in acute ischemic stroke was published in 2016. In one hand it has demonstrated superior functional outcomes in subjects receiving endovascular therapy. On the other hand, however, it found no significant differences in symptomatic intracerebral hemorrhage or 90-day all-cause mortality between endovascular therapy and medical management of stroke patients.<sup>[16]</sup>

### **4. Anticoagulants**

A review from the Cochrane Database found that immediate anticoagulant therapy in patients with acute ischemic stroke is not associated with net short- or long-term benefit. The authors say that their review data do not support the routine use of any type of anticoagulant in acute ischemic stroke. People treated with anticoagulants had less chance of developing deep vein thrombosis and pulmonary embolism following their stroke, but these sorts of blood clots are not very common and may be prevented in other ways.<sup>[17]</sup>

## **Our Current Hypothesis**

In 2006 we have postulated <sup>[18]</sup> that most risk factors for atherosclerosis have as a common denominator the dysregulation of the autonomic nervous system, related with sympathetic dominance, through sympathetic over-activity or withdrawal of the parasympathetic system.

In the present article, we introduce the hypothesis that acute stress, chronic stress overload and other risk factors with intense sympathetic nervous system activity may lead to a raised lactate production and accumulation in the brain what may eventually trigger the acute stroke, resulting in the cerebral infarction,

Thus, reducing the incidence of risk factors for atherosclerosis (related to autonomic dysfunction) <sup>[18]</sup>, by avoiding elevated levels of lactate in ischemic regions may, greatly lower acute stroke occurrence.

Autonomic dysfunction has been associated with worse functional outcome and increased mortality for ischemic stroke. However, a recent and extensive review says that autonomic dysfunction is not yet considered a specific therapeutic target, mainly because researchers do not fully understand its mechanisms and role. Such review deals with methods to measure autonomic dysfunction, clinical manifestations that have been associated with autonomic dysfunction and poor outcome in AIS, the role of brain infarct location, as well as therapeutic implications.<sup>[19]</sup>

## **The Increase of Heart Rate over Time May Predict Cardiovascular Events, Including Stroke**

A paper published in 2018 at JAMA Cardiology, presented a retrospective analysis of ARIC (Atherosclerosis Risk in Communities Study), assessing data from 15,680 patients in over 28 years of follow-up. It has shown that for each 5 beats per minute (bpm) increase of heart rate overtime, with a median of 3 years between measurements, was associated with 12% for all-cause mortality, 13% for incident heart failure, 9% for myocardial infarction, and 6% for stroke.<sup>[20]</sup>

Earlier, a meta-analysis published in 2015 involving a total of 46 studies with more than a million patients found that high resting heart rate is independently associated with increased risk of all-cause and cardiovascular mortality in the general population. Its results suggested the risk is increased by 9% and 8% for every 10-bpm increment of resting heart rate. Higher resting heart rate is a marker of an imbalance between the vagal and the sympathetic tone, and dysfunctional autonomic nervous system, playing a central role in the pathogenesis of numerous adverse health conditions.<sup>[21]</sup>

## **Some risk factors for acute stroke, based on our present concept:**

(Autonomic dysfunction leading to significant elevation in plasma lactate levels)

- Stress, depression, anger, hostility, panic disorder <sup>[22-25]</sup>
- Age <sup>[26-29]</sup>
- High carbohydrate diets <sup>[30-33]</sup>
- Rheumatoid arthritis <sup>[34-37]</sup>
- Migraine <sup>[38-41]</sup>
- Hypertension <sup>[42-47]</sup>
- Diabetes <sup>[48-52]</sup>
- Infection through bacteremia <sup>[53-55]</sup>
- Smoking <sup>[56-59]</sup>
- Atrial fibrillation <sup>[60-62]</sup>
- Heart Failure <sup>[63-65]</sup>

## **Stress (Sympathetic Dominance) and the Development of Lactate / Lactic Acid**

The sympathetic dominance leads to a raised catecholamine (adrenaline/epinephrine and noradrenaline) release, accelerating glycolysis metabolism, therefore increasing lactic acid and lactate concentration in blood and tissues.

The first to observe the influence of adrenaline on lactic acid production were the Coris in the early 1920s.<sup>[66]</sup> Carl Ferdinand Cori together his wife Gerty Cori, received a Nobel Prize in 1947 for their discovery of how glycogen - a derivative of glucose - is broken down and resynthesized in the body.<sup>[67]</sup>

John R Williamson confirmed in 1964 the effects of adrenaline infusion on the increased production of lactate in isolated heart tissue, up to five times the normal production.<sup>[68]</sup> An article published in 1982<sup>[69]</sup> supported the following points for a direct participation of catecholamines in the development and/or maintenance of lactic acidosis:

1. The common association of stress and lactic acidosis.
2. The rise in plasma lactate concentration during adrenaline infusion.
3. The precipitation of lactic acidosis by adrenaline intoxication and phaeochromocytoma.
4. The vasoconstrictor effects of catecholamines leading to tissue anoxia and lactic acid production.

However, according to new findings, hyperlactatemia is not a consequence of anaerobic glycolysis, tissue hypo-perfusion, or cellular hypoxia, as believed in the past. Such hyperlactatemia is probably indicative of a stress response, with increased metabolic rate and sympathetic nervous system activity.<sup>[70]</sup>

Nevertheless, an important point to take in consideration is that the heart is an organ of high metabolic activity - being susceptible to drops in pH during ischemia and hypoxia.<sup>[71]</sup> According to Rehnrcrona<sup>[1]</sup> the evidence for a deleterious effect of increased lactic acid accumulation during ischemia in vivo was first presented by Myers and associates, who found that glucose pre-treatment of animals worsened the outcome of reversible ischemic-hypoxic insults.<sup>[72]</sup>

Recent studies confirmed that increased lactate in the brain may be a signal of cerebral harm in other medical conditions. For example, it was shown that patients with panic disorder consistently build up excess lactate. The authors of this study have suggested that one of the triggers for "spontaneous" panic attacks in patients with panic disorder might be lactic acid accumulating in acid-sensitive fear circuits.<sup>[73]</sup>

Also, a study published in 2017, suggested that lower pH associated with increased lactate levels is not a mere artefact, but rather implicated in the underlying pathophysiology of schizophrenia and bipolar disorder.<sup>[74]</sup>

An older study by Shimoda et al. published in 1989, have reported that the increase of cerebrospinal fluid lactate concentration reflected not only glycolysis of shed blood cells but also brain tissue hypoxia caused by primary subarachnoid hemorrhage. It was demonstrated that the delayed increase of CSF lactate occurred concurrently with the onset of cerebral vasospasm. These authors attributed this result to brain hypoxia due to the vasospasm.<sup>[75]</sup>

On the other side studies have shown that acute exposure to hypoxia may cause chemo-reflex activation of the sympathetic nervous system, including in cerebral vasculature.<sup>[76, 77]</sup>

The relationship between sympathetic dominance and increased lactic acid/lactate concentration was recently discussed by us as having a causal role for atherosclerosis,<sup>[18, 78]</sup> acute myocardial infarction<sup>[79]</sup> and cancer.<sup>[80]</sup>

**Note:**

- Hyperlactatemia is defined as a mild to moderate persistent increase in blood lactate concentration (2-4 mmol/L) without metabolic acidosis, whereas lactic acidosis is characterized by persistently increased blood lactate levels (usually >4-5 mmol/L) in association with metabolic acidosis.

## **Cardiac Glycosides, the Fundamental Drugs for Prevention of Stroke**

*“Although there is not total agreement on the nature and clinical significance of the effects of digitalis on the autonomic nervous system, the following points seem well established and generally accepted:*

- 1) the actions of digitalis on the autonomic nervous system are very important clinically and play a major role in determining the clinical pharmacodynamic effects of the drug;*
- 2) with therapeutic concentrations of the drug, the predominant effect is activation of vagal tone; and*
- 3) with toxic concentrations of the drug there may be activation of sympathetic tone.”,*  
*August M. Watanabe, 1985<sup>[81]</sup>*

## **The Reason of our Interest in Relation to Stroke (Cerebrovascular Accident)**

The following extract of our article published at the News Bulletin of Infarct Combat Project from July 2006<sup>[82]</sup> is self-explanatory:

## Cardiac Glycosides in Prevention of Stroke

Brazilian study confirms the findings of Duke University Medical Center researchers that, cardiac glycosides, provide neuroprotection in stroke occurrence. It was a study of 28 years that showed a low mortality for stroke in 1150 cardiac patients taking these drugs.

ICP, July 10, 2006: Using a novel screening technology, Duke University Medical Center researchers have shown that drugs called cardiac glycosides can protect brain cells from death after stroke in laboratory models, and that the drugs are effective even if delivered six hours or more after the onset of stroke conditions. <sup>[83]</sup>

*"This discovery is exciting because it may lead to interventions to prevent or lessen the amount of brain damage suffered after stroke,"*

*... said Donald C. Lo, PhD, Director of the Center for Drug Discovery and associate professor of neurobiology at Duke, and primary investigator on the study.*

Currently, only one drug has been approved by the Food and Drug Administration to treat stroke -- and it faces serious limitations, Lo said. Called recombinant tissue plasminogen activator, the drug must be given within a three-hour window after the onset of stroke. Also, because the drug is delivered intravenously and acts by breaking blood clots, it is ineffective against "hemorrhagic" strokes that happen when an artery bursts.

Lo speculates that cardiac glycosides may exert their beneficial effect during stroke in an analogous manner that in heart disease, by restoring calcium to healthy levels in brain cells and thereby preventing cell death. Calcium plays a key role in regulating normal cell function, and any changes in its cellular concentration -- such as those caused by stroke -- can be toxic. <sup>[84]</sup>

Another recent study with statin drugs concluded that its use is associated with a reduced risk of stroke but not severity or mortality. <sup>[85]</sup>

Related to the Duke University Medical Center research, a case study from Brazil confirms the very low mortality for stroke in 1150 patients with stable heart disease taking cardiac glycosides, for 28 years. The study was authored by Quintiliano H. de Mesquita and Claudio A. S. Baptista and published in *Ars Cvrandi*, a Brazilian medical journal, in 2002. <sup>[86]</sup>

The stroke (ischemic + hemorrhagic) mortality in 28 years for the cardiac patients taking cardiac glycosides was:

1. 994 patients w/out prior infarction - Stroke mortality: 13 cases (1.3%) = 0.04% per year.
2. 156 patients with prior infarction - Stroke mortality: 7 cases (4.4%) = 0.15% per year.



For a better comparison in stroke mortality, with those taking cardiac glycosides, we can take the data from the HPS study, which had a follow-up of 5 years, involving 20.536 patients aged 40-80 years with coronary heart disease, other vascular diseases or diabetes. The HPS found a total stroke mortality of 0.9% (0.18% per year) in patients taking statins and 1.2% (0.24% per year) in patients taking placebo.<sup>[87]</sup>

The permanent use of cardiac glycosides (Digitoxin, Digoxin, Acetildigoxin, Lanatoside-C, Betametildigoxin, or Proscillaridin-A) in low, daily therapeutic (non-toxic), doses from the Brazilian study was based on the Myogenic Theory of Myocardial Infarction and had as its objective the prevention of acute coronary syndromes.<sup>[79]</sup>

The global mortality for the patients without previous myocardial infarction was 14.2% (0.5% per year), while the global mortality for the patients with previous myocardial infarction was 41.0% (1.4% per year)."

Before presenting an update on the previous information published in 2006 at the News Bulletin from ICP, it is important to inform the daily maintenance doses, for the cardiac glycosides used by Quintiliano de Mesquita and Claudio Baptista in their study.<sup>[86]</sup> It follows:

#### Daily Maintenance Doses <sup>[88]</sup>

- Proscillaridin A: 0,75 - 1.50 mg
- Acetyldigoxin: 0,50 mg
- Lanatoside C: 0,50 mg
- Digitoxin: 0,1 mg
- Digoxin: 0,125 - 0,25 mg
- Betamethyldigoxin: 0,10 - 0,20 mg

#### **Note:**

- Digoxin, since its insertion, still is the cardiac glycoside most used in Brazil. Therefore, it represented a large proportion of the prescriptions from these authors to their patients.

## **Neuroprotective Effects of Digoxin and other cardiac glycosides in Brain Ischemia**

A study from 2009 <sup>[89]</sup> investigated the possible neuroprotective effect of digoxin-induced pharmacological preconditioning and its probable mechanism in ischemia and reperfusion in cerebral injury in male Swiss albino mice. Digoxin treatment produced a significant decrease in cerebral infarct size and reversal of ischemia and reperfusion-induced impairment of memory and motor incoordination. These findings indicated to the authors that digoxin preconditioning exerts a marked neuroprotective effect on the ischemic brain.

A study published in 2010 <sup>[90]</sup> has discussed findings showing the effects of cardiac glycosides drugs (digoxin, ouabain and marinobufagenin), when given

at low dosages, on the increase (stimulation) of the sodium-potassium ATPase activity. Then, they examined whether digoxin, ouabain and marinobufagenin increased the Na<sup>+</sup>/K<sup>+</sup>ATPase in hippocampal slice cultures and whether this increased Na<sup>+</sup>/K<sup>+</sup>ATPase protected against experimental ischemia. They made tests in vitro in hippocampal slice cultures as well in the hippocampus in vivo. The increased Na<sup>+</sup>/K<sup>+</sup>ATPase activity protected slice culture neurons from hypoxia-hypoglycemia. These data suggested to the authors that the protective effect of these drugs was due to increased Na<sup>+</sup>/K<sup>+</sup>ATPase activity. Also, this demonstrated that the neuroprotective effect of these drugs could protect against in vitro experimental ischemia, representing a potential treatment strategy for their use in the management of stroke.

A study from 2016<sup>[91]</sup> had the aim to investigate the possible neuroprotective effect of digoxin-induced pharmacological preconditioning after hypoxia-ischemia and underlying mechanisms. Neonatal rats were assigned randomly to control, hypoxic-ischemic brain damage (HIBD), or HIBD+digoxin groups. Pharmacological preconditioning was induced by administration of digoxin 72 h before inducing HIBD by carotid occlusion+hypoxia. Behavioural assays and neuropathological and apoptotic assessments were performed to examine the effects; the expression of Na<sup>+</sup>/K<sup>+</sup>ATPase was also assessed. Rats in the HIBD group showed deficiencies on the T-maze, radial water maze, and postural reflex tests, whereas the HIBD+digoxin group showed significant improvements on all behavioral tests.

The rats treated with digoxin showed recovery of pathological conditions, increased number of neural cells and proliferative cells, and decreased number of apoptotic cells. Meanwhile, an increased expression level of Na<sup>+</sup>/K<sup>+</sup>ATPase was observed after digoxin preconditioning treatment. The preconditioning treatment of digoxin contributed toward an improved functional recovery and exerted a marked neuroprotective effect including promotion of cell proliferation and reduction of apoptosis after HIBD, and the neuroprotective action was likely associated with increased expression of Na<sup>+</sup>/K<sup>+</sup>ATPase.

Incidentally, cardiac glycosides like digoxin and Lanatoside C are drugs approved by the U.S. Federal Drugs Administration (FDA), and by other similar organizations around the world, with some having also approval for the use of digitoxin and other CGs. Therefore, these drugs can be prescribed for prevention and in the management of acute ischemic stroke, with no major obstacles, by a well-informed physician.

## **Digoxin Use in Some Risk Factors for Stroke**

### **Heart Failure**

Digitalis was used for more than 200 years in the treatment of heart failure. Digoxin and digitoxin are some of the cardiac glycosides derived from digitalis (foxglove plant).

The daily oral maintenance dosages of digoxin recommended for heart failure, until recently, were 0,125 mg, 0,250 mg and 0,375. These dosages had the objective of achieving a therapeutic serum digoxin concentration (SDC) in the range of 0.5 to 2.0 ng/ml.

The DIG (Digitalis Investigated Group) trial, published in 1997<sup>[92]</sup> indicated that digoxin had no effect on overall mortality in heart failure compared to patients taking placebo, but reduced the rate of hospitalization both overall and for worsening heart failure.

The results from the DIG trial were interpreted with disappointment being the use of digitalis subsequently declined. Although digoxin received approval from the FDA in 1997, the major guideline-issuing professional societies currently offer a secondary recommendation for digoxin in patients with HF with reduced ejection fraction (EF) in normal sinus rhythm experiencing persistent symptoms despite optimal medical therapy.<sup>[93]</sup>

### **Digoxin: Lowering the Dosage for Better Outcomes in Heart Failure**

*"However, there is available clear clinical experimental proof of the beneficial action of very small doses (of digitalis), and, as I have said repeatedly, this puts us under the obligation of not omitting this safe clinical experiment in suitable cases",  
Wenckebach K. F., 1930<sup>[94]</sup>*

Rathore et al, in a study published in 2003<sup>[95]</sup>, on a post hoc analysis of data from the DIG Trial,<sup>[92]</sup> dividing the man treated into three groups according to their serum digoxin concentration after one month of treatment: 0.5-0.8 ng/ml, 0.9-1.1 ng/ml and > 1.2 ng/ml, found that mortality in men in the lowest level group was 6.3% lower than that of men in the placebo group. In contrast, mortality in men in the intermediate and highest-level groups was 2.6% and 11.8% higher respectively than that of the placebo group.

Adams et al, in a study published in 2005,<sup>[96]</sup> presenting another retrospective analysis of data from the DIG trial,<sup>[88]</sup> have indicated a beneficial effect of digoxin on morbidity and no excess mortality in women at serum concentrations from 0.5 to 0.9 ng/ml, whereas serum concentrations > or =1.2 ng/ml seemed harmful.

The result of the studies from Rathore et al<sup>[95]</sup> and Adams et al<sup>[96]</sup> led to changes on the Heart Failure Guidelines issued by the Heart Failure Society of America in 2010.<sup>[97]</sup> Following are some extracts of the Session 7 of these guidelines related to the use of Digoxin recommendations from the chapter 'Heart Failure in Patients with Reduced Ejection Fraction':

1. Recent data suggest that the target dose (and serum concentration) of digoxin therapy should be lower than traditionally assumed. Although higher doses may be necessary for maximal hemodynamic effects, beneficial neurohormonal and functional effects appear to be achieved at relatively low serum digoxin concentrations (SDC) typically associated with daily doses of 0.125 to 0.25 mg. A retrospective

analysis of the relationship of SDC to outcomes in the DIG trial demonstrated a strong direct relationship between the risk of death and SDC, with concentrations  $\geq 1.2$  ng/mL being associated with harm, whereas concentrations  $\leq 1.0$  ng/mL were associated with favorable outcomes.

2. The efficacy of digoxin in HF with reduced LVEF [left ventricular ejection fraction] has traditionally been attributed to its relatively weak positive inotropic action arising from inhibition of sodium potassium ATPase and the resulting increase in cardiac myocyte intracellular calcium. However, digitalis has additional actions that may contribute significantly to its beneficial effects in patients with HF. Digoxin has important neuro-hormonal modulating effects that cannot be ascribed to its inotropic action, and it ameliorates autonomic dysfunction as shown by studies of heart rate variability, which indicate increased parasympathetic and baroreceptor sensitivity during therapy.

### **Atrial Fibrillation**

*“Digitalis itself, which in large doses may be the cause of regular extra-systoles, may in very small doses abolish this phenomenon and be very helpful in combating auricular (atrial) fibrillation.”,  
Wenckebach K. F., 1930 [94]*

Digitalis is indicated for patients with atrial fibrillation, with or without heart failure, since the beginning of the last century.

Observational studies have associated digoxin use with excess mortality in atrial fibrillation patients, but this association is likely due to selection and prescription biases rather than harm caused by digoxin, particularly as digoxin is commonly prescribed to sicker patients.<sup>[98]</sup>

Lower doses of digoxin (< 0,25 mg once daily) corresponding to serum digoxin levels of 0.5 - 0.9 ng/mL, may be associated with better prognosis for the management of atrial fibrillation, according to the European Society of Cardiology guidelines which is endorsed by the European Stroke Organization<sup>[98]</sup>.

### **Digoxin and Vasospasm in Subarachnoid Hemorrhage**

Vasospasm is a significant reason for poor clinical outcome in subarachnoid hemorrhage (SAH). A study from 2009<sup>[99]</sup> investigated the effect of digoxin on an experimental vasospasm after SAH in rats.

It has shown that increased wall thickness and reduced vessel luminal area were conspicuously significant in the SAH groups which did not receive digoxin. In SAH groups after digoxin administration, the vessel wall thickness decreased, and no significant change was found in vessel wall thickness when compared with the normal and saline groups. The vessel luminal area was not reduced in SAH after digoxin administration.

According to the authors their results suggest that digoxin administration in experimental SAH may have a beneficial effect on the protection against

vasospasm. Also saying that “if further investigations support our results, the present study may offer a new insight into the treatment of SAH.” [99]

### **Cardiac Glycosides and Sympatho-Inhibitory Effects**

Evidences that the following cardiac glycosides have a sympatho-inhibitory response:

- Cedilanid\* [100]
- Digoxin [101-102]
- Digitoxin [103]
- Ouabain [104]

\* *Cedilanid is the trade name. The active ingredient is Lanatoside C*

### **Cardiac Glycosides in Reduction of Lactate Production**

A recent paper has demonstrated that inhibiting the overproduction of catecholamine by digoxin, digitoxin and ouabain may induce a potent inhibition of glycolysis (glucose consumption and lactate). [105] It confirms the results of old studies on this matter. [106]

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# Chapter 14

## Autonomic Dysfunction and Increased Lactate Production with Accumulation in the Body: - Key Factors for the Development of Rheumatoid Arthritis

Carlos ETB Monteiro

*"The first inference deducible from the experiments, according to my reading of them, is, that lactic acid has the power, when existing in an animal body in excess, of producing a class of symptoms attaching themselves mainly to the fibroserous textures, and which, regarded in all points of view, are essentially the symptoms of acute rheumatic inflammation."*

*Benjamin Ward Richardson --*

*'The Effect of Lactic Acid on Animal Bodies' (P. 389), 1856 <sup>[1,2]</sup>*



Benjamin Ward Richardson

### Abstract

The major focus of the present article is Rheumatoid Arthritis (RA). It tells about:

- The history of discovery of the autonomic dysfunction as the precursor of Rheumatoid Arthritis.
- The forgotten theory of the accumulation of lactic acid as the cause of arthritis and rheumatism, and its renaissance in the case of RA.
- A new hypothesis for the cause of RA that links autonomic dysfunction to the development of increased lactic acid production with its accumulation in the body.
- The risk factors for RA based in this new hypothesis, covering almost all of those already know and in use.
- An old and inexpensive drug comply with the new perspectives above mentioned, representing an adequate and potential solution for prevention and treatment of RA.

## Introduction

Aretaeus, who lived in Cappadocia in Asia Minor during the first century AD and was ranked by some next to Hippocrates as a clinician, described a polyarthritis in phrases reminiscent of features of rheumatoid arthritis: “a general pain of all the joints-the disease lies concealed for a long time, when the pain and the disease are kindled up by any slight cause-it is incredible how far the mischief spreads.”<sup>[3]</sup>

Sir Alfred Baring Garrod, physician to the West London Hospital, coined the name Rheumatoid Arthritis (RA), in 1859, wishing, as he stated,

*“To imply an inflammatory affection of the joints, not unlike rheumatism in some of its characters, but differing materially from it.”*

At that time rheumatism was the common designation for rheumatic fever: the term rheumatoid arthritis thus may be freely translated as joint inflammation resembling that seen in rheumatic fever.”<sup>[3]</sup>

RA is considered today as a chronic autoimmune disorder, estimated to affect approximately 1% of the world’s population. It may affect more than the joints, damaging other parts of the body, like the lungs, heart and blood vessels.

Some of the etiological theories presented for RA, through the ages, were neurogenic, vascular, infectious, hypersensitivity, metabolic, endocrine, psychogenic<sup>[4]</sup> and Selye’s disease of adaptation.<sup>[5]</sup> More recently other etiological theories for RA were developed as of genetic origin and environment triggers (including smoking).<sup>[6]</sup> Although, some of the etiologies above mentioned for RA are not really causes, but rather risk factors for RA.

Elapsed many centuries from its initial description by Aretaeus <sup>[3]</sup>, the causative factor of rheumatoid arthritis remains unknown, On the other hand, the cure for RA was not found until today. Existing treatments may only improve symptoms and slow the progress of the disease.

## A New Hypothesis

In this paper we postulate a new hypothesis for the cause of RA which has autonomic dysfunction as precursor, by stimulating an increased lactate/lactic acid production and its accumulation in the body.

Also, we present a compatible and fundamental drug, according this hypothesis, for the prevention or in management of RA, eventually with a cure, of some patients.

**Notes:**

- A) There are many risk factors leading to dysregulation of the autonomic nervous system, which is related with sympathetic dominance, through sympathetic over-activity or withdrawal of the parasympathetic system. Among these risk factors are stress, smoking, age, high carbohydrate diets and genetic predisposition (ex: familial dysautonomia);
- B) Dysautonomia or autonomic dysfunction is a condition in which the autonomic nervous system (ANS) does not work properly.
- C) Autonomic neuropathies are a collection of syndromes and diseases affecting the autonomic neurons, either parasympathetic or sympathetic, or both.
- D) The vagus nerve is the main component of the parasympathetic nervous system.
- E) Hyperlactatemia is defined here as a mild to moderate persistent increase in blood lactate concentration (2-4 mmol/L) without metabolic acidosis, whereas lactic acidosis is characterized by persistently increased blood lactate levels (usually >4-5 mmol/L) in association with metabolic acidosis; Lactic acidosis results from increased production of lactate, the final product in the pathway of glucose metabolism. Lactate and lactic acid are not synonymous. Lactic acid is a strong acid which, at physiological pH, is almost completely ionized to lactate. The measurement of lactate concentration can also be made in cerebrospinal fluid, synovial fluid and other fluids and tissues of the body.

**The Autonomic Dysfunction in RA**

Related to this topic a fundamental theory is the Selye's diseases of adaptation, developed in 1936, when he coined the term stress.<sup>[5]</sup> This theory from Hans Selye involves a complex neurohormonal model of stress that implicates pituitary and adrenal function in the etiology of many chronic diseases, including rheumatism.<sup>[6]</sup>



Paul Rosch and Hans Selye  
Inauguration of the  
American Institute of Stress  
(1978)

L. J. Michotte, in a presentation occurred in 1953 at the 7th International Congress at Geneva, has linked the autonomic nervous system to RA. He found

that the spleen of patients with rheumatoid arthritis does not contract under the action of adrenaline injected intravenously, This led to his proposition of the hypothesis that RA may be a perturbation of the autonomous nervous system bearing on the chemical transmitters noradrenaline and adrenaline. [7, 8]

Edmonds and colleagues have written in 1979<sup>[9]</sup>:

*“Peripheral neuropathy is a well-described complication of rheumatoid arthritis, but few reports on autonomic neuropathy exist.*

*In 1963 Kalliomaki et al showed a deficient sweating response to an intradermal injection of nicotine in patients with RA.*

*In 1965 Bennett and Scott found areas of deficient sweating corresponding to cutaneous sensory disease in patients with seropositive RA with peripheral neuropathy but did not examine seronegative patients.*

*In three of their patients a deficient sweating response was found in the absence of peripheral neuropathy, suggesting the presence of a lone autonomic neuropathy.”*

In the same paper from 1979, Edmonds and colleagues have written about their investigation involving 68 subjects which were divided into four groups: patients with classical and definite RA, both seropositive and seronegative (mean age 54-6 (range 22-67) years); patients with osteoarthritis (mean age 54-2 (range 42-65) years); old controls (mean age 51-0 (range 41-67) years); and young controls (mean age 24-6 (range 20-28) years).

The summary on their investigation<sup>[9]</sup> presented the following results:

*“Significantly more patients with RA had abnormal autonomic function, suggesting that autonomic neuropathy occurs more commonly in RA than hitherto suspected.*

*The existence of an autonomic neuropathy may be an important complicating factor in rheumatoid disease and may lead to increased morbidity and mortality.”*

A study published in 2004 found that cardiac sympathetic nervous system activity is elevated in RA, whereas cardiac parasympathetic activity remains at a normal level.<sup>[10]</sup>

A study by Koopman et al, published in 2016, made the postulation that autonomic dysfunction precedes the development of RA, which would suggest that it plays a role in its etiopathogenesis.<sup>[11]</sup>

## **Lactic Acid Accumulation in the Body and RA**

In 1856, Benjamin Ward Richardson, a famous British physician, published the results of extensive experiment on dogs in which the injection of large quantities of lactic acid, intraperitoneally, was followed by severe joint involvement.

The condition of the joints showed in his studies were similar to that seen in acute arthritis. These results led Richardson to suggest that the acute arthritis was due to an accumulation of lactic acid in the body (pages 371 - 396).<sup>[1, 2]</sup>

In 1874, Balthazar Foster found that the administration of lactic acid by the mouth to two diabetic patients resulted in painful and swollen joints. These manifestations persisted so long as the lactic acid was continued and disappeared when it was discontinued<sup>[12]</sup>. This discovery by Foster gave some support to the Richardson's theory at that time.<sup>[1]</sup>

In 1922, the theory that arthritis is characterized by an excessive accumulation of lactic acid in the body was revived by Percy Wilde, mainly on the clinical area.<sup>[13]</sup>

In 1924, a study by Cajori and colleagues<sup>[14]</sup> presented findings that conflicted with the idea that arthritis and rheumatism are caused or characterized by abnormal production or disposal of lactic acid. According to their study the lactic acid contents of the blood, urine and sweat of patients suffering from arthritis and rheumatic disabilities has been determined and the results have been compared with the respective lactic acid contents from nonarthritic persons. The lactic acid was determined also in the synovial fluid from a case of joint effusion. In no case have they observed abnormal quantities of lactic acid in the arthritic patients. Therefore, to the authors, their findings lend no support to the idea that arthritis, at least of the types studied, is caused or characterized by abnormal production or disposal of lactic acid.

However, the study by Cajori and colleagues was based in insufficient measurements of lactic acid in synovial fluid (just one case), for their judgement on the Richardson's medical theory.<sup>[1]</sup>

This is because, years later, starting in the seventies, many studies have shown accumulation of lactic acid in synovial fluid of patients with rheumatoid arthritis, These later studies demonstrated that the measurement of lactic acid or lactate in synovial fluid is the correct place for analysis and determination of cases with RA.

So, in practice, the precipitated conclusion of the study from Cajori et al<sup>[14]</sup> led the lactic acid theory, as cause of arthritis and rheumatism, to be erroneously abandoned and almost forgotten until the present day.

For example, a study from 1971 by Lindy and colleagues measured total lactate dehydrogenase activity in the synovial tissue from 19 patients with rheumatoid arthritis and from 13 control subjects. It found that total enzyme activity in synovium was increased about two-fold in rheumatoid arthritis when compared to controls. It suggested an increased glycolytic metabolism in the RA synovial joints.<sup>[15]</sup>

Also, in a study by Gobelet et al, published in 1984, lactate concentration was measured in 383 synovial fluid specimens from patients with various

arthritis. The highest concentrations of lactate occurred in nongonococcal septic synovial fluids. High values were recorded in seropositive rheumatoid arthritis and crystal induced arthritis, medium values in synovial fluids from seronegative rheumatoid arthritis, seronegative spondylarthritides, gonococcal arthritis and haemarthrosis, and the lowest values in aspirates from osteoarthritic joints. There was a positive correlation between synovial pH and lactic acid concentration with the finding of high values of lactate in seropositive RA and crystal-induced arthritis.<sup>[16]</sup>

In their paper from 2011 Chang and Wei said in conclusion: “Studies to date regarding the roles of glucose metabolism in RA have confirmed the increased glycolytic activity and autoimmune responses to some enzymes involved in glycolysis, which provides new perspectives to understand the pathogenesis of RA. In view of the important roles of glycolysis in RA pathogenesis, we suggest inhibiting the activity of glycolysis as a means of treating RA.”<sup>[17]</sup>

### **Some risk factors for RA, based in our hypothesis:**

- Stress<sup>[18, 19]</sup>;
- Age<sup>[20, 21, 22]</sup>;
- High carbohydrate diets<sup>[23-30]</sup>,\*
- Smoking<sup>[31-34]</sup>;
- Obesity<sup>[35-37]</sup>;
- Air pollution<sup>[38,39]</sup>;
- Vitamin D deficiency<sup>[40, 41]</sup>.

### **\* Important Facts about High Carbohydrate Diets as Risk Factors for RA:**

1. Old studies have already show that patients with chronic arthritis do best when their intake of vitamins is increased, and their intake of carbohydrate reduced<sup>[23]</sup>;
2. After the intake of refined sugar and sweets there is an aggravation of symptoms in RA, what may be explained by metabolic changes, such as an increased concentration of blood glucose;<sup>[24]</sup>
3. Evidence of high carbohydrate diets in the stool of patients with RA compared to controls. Starch in stools is prone to occur in patients with chronic arthritis, and adds further evidence that diets low in starch are of use in this disease;<sup>[25]</sup>
4. High carbohydrate diets cause greater sympathetic nervous system activation while fat ingestion does not result in any appreciable changes;<sup>[26]</sup>
5. High carbohydrate diets may increase significantly the activity of serum lactate;<sup>[27]</sup>
6. The Ingestion of monosaccharides (simple sugars like glucose, fructose and galactose) may have the effect to raise blood lactic acid with this increase being most marked and lasting longest after fructose, that is largely used today as sweetener in soft drinks, fruit punches, pastries and processed foods;<sup>[28,29]</sup>

7. Sweetened soda has been associated with an increased risk of RA. When compared to no consumption of sugar sweetened soda or <1 soda per month, consumption of  $\geq 1$  sugar-sweetened soda per day has 63% increased risk of developing seropositive RA <sup>[30]</sup>.

## **Autonomic Dysfunction and the Development of Lactate / Lactic Acid**

The sympathetic dominance leads to a raised catecholamine (adrenaline/epinephrine and noradrenaline) release, accelerating glycolysis metabolism, therefore increasing lactic acid and lactate concentration in blood and tissues.

We hypothesize that a raised catecholamine release may equally produce the same effects of lactic acid measurements in cerebrospinal and synovial fluids

The first to observe the influence of adrenaline on lactic acid production were the Coris in the early 1920s. Carl Ferdinand Cori together with his wife Gerty Cori, received a Nobel Prize in 1947 for their discovery of how glycogen - a derivative of glucose - is broken down and resynthesized in the body. <sup>[42, 43]</sup>

John R Williamson confirmed in 1964 the effects of adrenaline infusion on the increased production of lactate in isolated heart tissue, up to five times the normal production. <sup>[44]</sup>

An article published in 1982 by Schade <sup>[45]</sup> supported the following points for a direct participation of catecholamines in the development and/or maintenance of lactic acidosis:

1. The common association of stress and lactic acidosis.
2. The rise in plasma lactate concentration during adrenaline infusion.
3. The precipitation of lactic acidosis by adrenaline intoxication and pheochromocytoma.
4. The vasoconstrictor effects of catecholamines leading to tissue anoxia and lactic acid production.

However, according to new findings, hyperlactatemia is not a consequence of anaerobic glycolysis, tissue hypoperfusion, or cellular hypoxia, as believed in the past. Such hyperlactatemia is probably indicative of a stress response, with increased metabolic rate and sympathetic nervous system activity. <sup>[46]</sup>

The relationship between the autonomic dysfunction and increased lactic acid/lactate concentration was recently discussed by us as having a causal role for atherosclerosis, <sup>[47, 48]</sup> acute myocardial infarction, <sup>[49]</sup> cancer <sup>[50, 51]</sup> and stroke <sup>[52]</sup>.



## Cardiac Glycosides, the Fundamental Drugs for RA

The fundamental therapeutic for prevention and management of RA, according to our hypothesis, are old drugs called cardiac glycosides. The cardiac glycosides family include digitalis (foxglove plants) from which are derived the drugs digitoxin and digoxin.

Digitalis was used for more than 200 years in the treatment of heart failure and more than 100 years in the treatment of atrial fibrillation.

Recent studies have confirmed that low doses of digoxin (< 0.25 mg daily, by oral route) are associated with better outcomes for both heart failure and atrial fibrillation.

### **Remembering the words of August M. Watanabe, from 1985 [53]:**

*“Although there is not total agreement on the nature and clinical significance of the effects of digitalis on the autonomic nervous system, the following points seem well established and generally accepted:*

- 1) The actions of digitalis on the autonomic nervous system are very important clinically and play a major role in determining the clinical pharmacodynamic effects of the drug;*
- 2) With therapeutic concentrations of the drug, the predominant effect is activation of vagal tone; and;*
- 3) With toxic concentrations of the drug there may be activation of sympathetic tone.”*

In recent articles, where we have presented an equivalent hypothesis for the cause of other diseases, was shown the information that cardiac glycosides at low concentration doses may also be beneficial in the prevention and in the treatment of atherosclerosis/ischemic heart disease <sup>[47, 49]</sup>, cancer <sup>[51]</sup> and stroke <sup>[52]</sup>.

Cardiac glycosides like digoxin and Lanatoside C are drugs approved by the US Federal Drugs Administration (FDA), and by other similar organizations around the world, with some of these having also approval for the use of digitoxin and other CGs . Therefore, these drugs can be prescribed for prevention and in the management of rheumatoid arthritis, with no major obstacles, by a well-informed physician.

## Cardiac Glycosides and Sympatho-Inhibitory Effects

Evidences that the following cardiac glycosides have a sympatho-inhibitory response:

- .....Cedilanid\* <sup>[54]</sup>;
- .....Digoxin <sup>[55-56]</sup>;
- .....Digitoxin <sup>[57]</sup>;
- .....Ouabain <sup>[58]</sup>.

\* *Cedilanid is the trade name. The active ingredient is Lanatoside C*

## Cardiac Glycosides in Reduction of Lactate Production

A recent paper has demonstrated that inhibiting the overproduction of catecholamine by digoxin, digitoxin and ouabain may induce a potent inhibition of glycolysis (glucose consumption and lactate).<sup>[59]</sup> It confirms the results of old studies on this matter. <sup>[60]</sup>

## Cardiac Glycosides in RA

A recent study has investigated whether digoxin would suppress pathogenic Th17 and consequently ameliorate arthritis and joint damage in the collagen-induced arthritis (CIA) model, a prototype animal of RA. As result, digoxin regulated pathogenic Th17 differentiation and suppressed autoimmune arthritis in mice, appearing to be able to prevent the incidence and ameliorate the severity of CIA. <sup>[61]</sup>

## Acidosis and Bone Loss in RA

Finally, studies have shown a strong evidence that osteoclasts may be the primary effectors of the bone erosions that are typical in RA. So, to prevent the progression of the erosive damage of bones seems to be an important initiative in RA. <sup>[62,63]</sup>

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# Chapter 15

## The Causal Role of Autonomic Dysfunction and Lactic Acidosis in the Development of Hypertension

*Carlos ETB Monteiro*

### **Abstract**

In the present article is postulated a new hypothesis that may explain the basic causes of hypertension.

It presents a list of common risk factors for hypertension which are associated to overactive sympathetic nervous system what may lead to autonomic dysfunction.

Also, it discusses recent findings showing that hypertension is associated with increased lactate production getting worse the disease process.

The autonomic dysfunction may accelerate glycolysis, which results in increased lactate production in hypertension.

Finally, it shows the potential use of digoxin (*Digitalis Lanata*), at daily low concentration dosages, for the management of hypertension. This by restoring the balance of the autonomic nervous system and reduction of lactate production in the body.

*Digitalis* was used for the treatment of hypertension until the middle of the past century. Drew Luten have written in his book from 1936: "By many physicians, hypertension, especially when associated with cardiac enlargement, is now regarded as an indication for the continuous use of *digitalis*"

### **Introduction**

The fundamental cause of hypertension remains in discussion. What is known are some risk factors associated with this condition.

The autonomic nervous system (ANS) is responsible for controlling many physiological functions like inducing the force of contraction of the heart, peripheral resistance of blood vessels and the heart rate. The ANS has both sympathetic and parasympathetic divisions that work together to maintain balance. Cardiovascular diseases, such as hypertension, acute myocardial infarction and heart failure, are diseases of the autonomic nervous system

We support the concept that autonomic dysfunction is the primary inductor for the development of the hypertensive process.

## Autonomic dysfunction in hypertension

The autonomic nervous system plays an important role in the regulation of arterial pressure and, increased sympathetic nervous system (SNS) activity has been implicated as a primary precursor of hypertension in both humans and animal models of the disease. <sup>[1-3]</sup>

Essential hypertension is significantly associated with higher mean fasting insulin levels and insulin resistance. Hyperinsulinemia plays a possible role in the pathophysiology of essential hypertension, with insulin resistance being the likely predominant mechanism. <sup>[4]</sup>

Some studies advocate that insulin resistance might contribute to enhance the SNS activity. <sup>[5]</sup> However, other studies advocate that the SNS may increase insulin resistance. <sup>[6,7]</sup>

We should emphasize that many risk factors leading to insulin resistance <sup>[8]</sup>, like obesity <sup>[9]</sup> and physical inactivity, <sup>[10]</sup> are associated with sympathetic activation.

A study published in 2019 <sup>[11]</sup> demonstrated the evidence that an important factor driving at least some of the obesity-associated end-organ damage is overactivity of the sympathetic nervous system (SNS), an observation that suggests that targeting SNS in obesity may help to reduce the cardiovascular risk associated with obesity. In their review, the authors highlighted the current knowledge of the potential role of SNS function in obesity-induced organ damage and examine whether interventions aimed at reducing cardiovascular risk in obesity may be mediated via alterations in SNS activity. While not discounting the important and prolific preclinical data on this subject, the authors pointed out their review is primarily focused on recent observations from human trials.

The results of a study from 2010 suggest that high fructose intake, in the form of added sugar, independently associates with higher blood pressure levels among US adults without a history of hypertension. <sup>[12]</sup> Excess fructose has been found to activate vasoconstrictors, inactivate vasodilators, and over-stimulate the SNS. <sup>[13]</sup> Other carbohydrate diets may also stimulate the SNS. <sup>[14]</sup>

Hypertension is common among patients with diabetes, with the prevalence depending on type and duration of diabetes, age, sex, race/ethnicity, BMI, history of glycemic control, and the presence of kidney disease, among other factors. <sup>[15]</sup>

On the causal role and triggers of diabetes mellitus, involving the autonomic dysfunction and increased lactate production, we have written an article which will be published soon. <sup>[16]</sup>

### **Other risk factors for hypertension**

There are many other risk factors leading to dysregulation of the autonomic nervous system in hypertension.

Some examples:

- Age <sup>[17,18]</sup>
- Tobacco consumption <sup>[19]</sup>
- High salt intake <sup>[20-22]</sup>
- Restricted salt intake <sup>[23,24]</sup>
- Depression <sup>[25,26]</sup>

According to our present postulation the autonomic dysfunction may lead to increased lactate production, which get worse the hypertensive process.

### **Increased lactate production in hypertension**

Two cross-sectional studies published in 1998 <sup>[27, 28]</sup> have shown that lactate is associated with blood pressure.

In 2008 the 'Atherosclerosis Risk in Communities - Carotid MRI Study' <sup>[29]</sup> found that high plasma lactate was independently associated with the odds of hypertension. The authors suggested that the decreased oxidative capacity may play an important role in hypertension prevalence.

Also, a study from 2008 <sup>[30]</sup> demonstrated that lactate is associated with obesity and that change in lactate is associated with change in diastolic and mean arterial pressure after adjustment for weight loss and other factors. The authors told that although the cause of this association cannot be identified in the study, their results are consistent with the notion that insufficient oxidative capacity in muscle may be an important mechanism in obesity-related hypertension. They also said that several lines of evidence suggest that lactate is also associated with other downstream complications of obesity including insulin resistance and type 2 diabetes

In 2014 researchers from the 'Atherosclerosis Risk in Communities Study' <sup>[31]</sup> hypothesized that lactate would be positively associated with incident hypertension even after accounting for traditional hypertension risk factors.

A study published in 2016 <sup>[32]</sup> concluded that plasma lactate level in non-dipping hypertension is significantly higher than dipping hypertension, and this difference may be the potential mechanism non-dipping hypertension contributes to greater targeted organ damage.

On the other hand, a study from 2016 <sup>[33]</sup> found that plasma lactate is independently associated with incident atrial fibrillation, and its contribution to AF may be, at least in part, mediated by diabetes and/or hypertension.

Sugars in excess may raise lactic acid production in the body. <sup>[34,35]</sup>



### **How autonomic dysfunction leads to lactic acidosis**

The chronic elevated release of catecholamine, precipitated by the sympathetic nervous system, may accelerate glycolysis, which results in a significant increase in lactate production.

The influence of adrenaline on lactic acid production was observed in the early 1920s by the Cori's. They have discussed about these findings in a study published in 1929. <sup>[36]</sup> Carl Ferdinand Cori and his wife Gerty Cori received a Nobel Prize in 1947 for their discovery of how glycogen - a derivative of glucose - is broken down and resynthesized in the body.

A 1982 article by David S. Schade <sup>[37]</sup> provided further support for the direct participation of catecholamines in the development and/or maintenance of lactic acidosis as follows:

1. The common association of stress and lactic acidosis
2. The rise in plasma lactate concentration during adrenaline infusion
3. The precipitation of lactic acidosis by adrenaline intoxication and pheochromocytoma
4. The vasoconstrictor effects of catecholamines leading to tissue anoxia and lactic acid production.

A study from John R. Williamson confirmed in 1964 the effects of adrenaline infusion on the increased production of lactate in isolated heart tissue, up to five times the normal production. <sup>[38]</sup>

### **Digitalis for hypertension**

Drew Luten have written about digitalis on hypertension in his book 'The Clinical Use of Digitalis', from 1936: <sup>[39]</sup>

*"It is well known that hypertension is associated with heart strain, and that perhaps its chief danger is ultimate heart failure. By many physicians, hypertension, especially when associated with cardiac enlargement, is now regarded as an indication for the continuous use of digitalis. There is much to comment this conception of the value of what might be called the prophylactic use of digitalis. It appears to be based on sound theory. It is applied in practice by physicians of authority. Its reasonableness is further augmented by the fact that the cases to which it applies merge almost imperceptibly with cases in which digitalis is used with known benefit..... The evidence so far available indicates that the drug in proper dosage may be of considerable value in some cases"*

Charles C. Wycoff cited the following studies about the beneficial effects of digitalis on hypertension, in his paper from 1969 <sup>[40]</sup>:

- a) In 1908 and 1929 Cloetta found that digitalis prevented the chronically stressed rabbit heart from enlarging as much as the undigitalized stressed heart. He avulsed a single aortic valve in the animals and maintained half of the group on digitalis. At the end of one year, the untreated animals had an increase of heart size 80 percent above the normal unstressed rabbit heart and the digitalis-treated animals had only a 38 percent increase of heart size above normal. In addition, acute performance tests of the hearts were made, and the results were summarized: ". . . one finds that the crippled digitalis treated heart is almost equal to the normal while the defective heart without digitalis treatment is much more rapidly exhausted. The capacity of the former is nearly double that of the latter, a fact of great importance in practice. This should be sufficient to induce prophylactic treatment with digitalis in all early cases of endocarditis which are apt to terminate in valvular lesions." Williams and Braunwald in 1965, studied chronic heart strain in rats by constricting the abdominal aorta, which resulted in hypertension. Some of the rats were maintained on digitalis. Their results were similar to those of Cloetta. Fewer of the digitalized rats died from heart failure and the weight gain of the digitalized hearts was less than the undigitalized hearts.
- b) Reindell and Konig in 1967, reported on studies of several hundred volunteers and patients during which, they determined the myocardial reserve by doing exercise tests. During the exercise tests, they measured the heart rate, the heart size and the oxygen uptake. They found that patients who were not in failure but who had fixed hypertension, coronary insufficiency, or branch blocks, or who had had myocardial infarction, showed performance tests that were well below the normal for their ages. In other words, a "loading insufficiency" developed. These patients were shifted to the normal or near normal status by digitalization.
- c) Mason in 1968, told in his article: "Digitalis may be of potential clinical value in preventing the development of ventricular hypertrophy in patients with aortic valvular disease or hypertension without heart failure, since the drug reduces the degree of mortality from heart failure and the degree of ventricular hypertrophy resulting from a chronic pressure load in experimental animals, further, the belief that the administration of digitalis in special situations may be helpful in certain cardiac patients without failure is gaining in prevalence".

Several investigators have reported that digitalis administration reduces cardiac hypertrophy in rats with experimental hypertension. A study from 1990 found that the comparison of hypertensive rats receiving to those not receiving digoxin revealed no differences in arterial pressure or aortic water content, but aortic growth was significantly attenuated (-41%,  $P = 0.02$ ) in the hypertensive rats receiving digoxin. These results provide evidence that digoxin reduces hypertensive arterial growth by a mechanism that does not affect normal growth. <sup>[41]</sup>

Although, even with the support of many studies, the use of digitalis (like digoxin), for the treatment of hypertension, was abandoned and forgotten.

A study from 2015 <sup>[42]</sup> found that in hypertensive patients with ECG left ventricular hypertrophy with existing or new atrial fibrillation, digoxin use was not associated with a significantly increased risk of all-cause mortality after adjusting for other independent predictors of death and for the factors associated with the propensity to use digoxin in this population. These findings suggested to the authors that factors other than digoxin use may account for the increased mortality found with digoxin use in some studies.

Most probable, the increased mortality using digoxin in studies related to hypertension, or other diseases, were due to inadequate dosages of this drug.

As Wycoff told in his paper from 1969 <sup>[40]</sup>: “It is now recognized that even small doses of digitalis have a positive inotropic effect on the heart and produce an increase in the contractile force. Therefore, it is possible to get a beneficial effect from digitalis in a dose much lower than that which was considered a digitalizing dose in the past.”

The retrospective analysis of data from Rathore and colleagues in 2003 <sup>[43]</sup> and Adams and colleagues in 2005 <sup>[44]</sup> on the DIG (Digitalis Investigation Group) trial, published in 1997 <sup>[45]</sup>, confirms Wycoff’s prediction. <sup>[40]</sup> Their retrospective analysis has indicated a beneficial effect of digoxin on morbidity and no excess mortality at serum concentrations from 0.5 to 0.9 ng/ml, whereas serum concentrations > or =1.2 ng/ml seemed harmful.

Moreover, taking in view that digoxin and other cardiac glycosides, at daily low concentration dosages, can restore the balance of the autonomic nervous system and reduce the production of lactic acid in the body.

*“Although there is not total agreement on the nature and clinical significance of the effects of digitalis on the autonomic nervous system, the following points seem well established and generally accepted:  
1) the actions of digitalis on the autonomic nervous system are very important clinically and play a major role in determining the clinical pharmacodynamic effects of the drug;  
2) with therapeutic concentrations of the drug, the predominant effect is activation of vagal tone; and  
3) with toxic concentrations of the drug there may be activation of sympathetic tone.”  
August M. Watanabe, 1985 <sup>[46]</sup>*

**Cardiac glycoside drugs that inhibit the sympathetic or enhance parasympathetic Effects:**

- Cedilanid\* <sup>[47]</sup>
- Digoxin <sup>[48,49]</sup>
- Digitoxin <sup>[50]</sup>
- Ouabain <sup>[51]</sup>

\* *Cedilanid is the trade name. The active ingredient is Lanatoside C*

**Cardiac glycosides and reduction of lactate production**

A paper from 2013 has demonstrated that inhibiting the overproduction of catecholamine by digoxin, digitoxin and ouabain may induce a potent inhibition of glycolysis (glucose consumption and lactate). <sup>[52]</sup> It confirm the results of old studies on this matter. <sup>[53]</sup>

**Blood pressure (BP), atrial fibrillation (AF), ANS and Digoxin**

A recent study <sup>[54]</sup> found an association between increased BP levels and the risk of atrial fibrillation is likely causal and applies for different BP indices independently from other risk factors. Also, that optimal BP control might represent an important therapeutic target for AF prevention in the general population.

The autonomic nervous system plays an important role in the regulation of blood pressure. Their role in the short-term regulation of blood pressure, especially in responses to transient changes in arterial pressure, via baroreflex mechanisms, is well known. <sup>[55]</sup>

In a significant portion of patients with atrial fibrillation, the autonomic nervous system activity is likely a composite of reflex excitation due to atrial fibrillation itself and contribution of concomitant risk factors such as hypertension, obesity and sleep-disordered breathing. <sup>[56]</sup>

According to the European Society of Cardiology guidelines <sup>[57]</sup>, which is endorsed by the European Stroke Organization, lower doses of digoxin (< 0,25 mg once daily) corresponding to serum digoxin levels of 0.5 – 0.9 ng/mL, may be associated with better prognosis for the management of atrial fibrillation.

**Covid-19**

Finally, it is important to mention the clinical perspective from a recent study showing that patients with cardiometabolic conditions, in particular obesity, hypertension, diabetes mellitus, and heart failure, have a high risk of poor outcomes from coronavirus disease 2019 infection. Among >900 000 US coronavirus disease 2019 hospitalizations through November 18, 2020, nearly two thirds (63.5%) were estimated to be attributable to these cardiometabolic conditions, that is, preventable if these conditions had not been present. The top risks were obesity (30.2%), hypertension (26.2%), and diabetes mellitus (20.5%). <sup>[58]</sup>

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# Chapter 16

## The Causal Role of Autonomic Dysfunction and Lactic Acidosis in the Development of Diabetes Mellitus

*Carlos ETB Monteiro*

*“With adrenalin a marked rise can occur, and instead of a fall in lactic acid we observed an actual rise amounting often to 100 percent. The results suggest that there is some factor common to the action both of insulin and adrenalin, which increases the lactic acid in spite of the divergent effects on the blood sugar”  
Tolstoi E, Loebel RO, Levine SZ and Richardson HB. 1924 <sup>[1]</sup>*

### Abstract

In the present article is postulated a new hypothesis that may explain the underlying causes of diabetes mellitus.

Some highlights:

- a. Diabetes is associated with overactive sympathetic nervous system what may lead to autonomic dysfunction.
- b. The autonomic dysfunction may accelerate glycolysis, what results in increased lactate production.
- c. Diabetes is associated with increased lactate production which gets worse the diabetic process.
- d. Obesity, an important risk factor for type 2 diabetes, is associated with autonomic dysfunction and high plasma lactate concentration.
- e. Type 2 diabetes is associated with increased cardiovascular mortality.
- f. The article shows potential drugs to fight diabetes by restoring the balance of the autonomic nervous system and reducing the production of lactic acid in the body.

### Introduction

According to the World Health Organization (WHO) neither the cause of type 1 diabetes nor the means to prevent it are known <sup>[2]</sup> Also, the sequence of events from the causal factors for both diabetes type 2 and gestational diabetes remain under discussion. As well it is unknown how to cure diabetes. Most people with diabetes have type 2.

#### **The pandemic of diabetes**

The number of people with diabetes rose from 108 million in 1980 to 422 million in 2014. About 8.5% of adults aged 18 years and older had diabetes in



2014. In 2019, diabetes was the direct cause of 1.5 million deaths. (WHO, 13 April 2021)

### **Autonomic nervous system**

The autonomic nervous system (ANS) is responsible for controlling many physiological functions: inducing the force of contraction of the heart, peripheral resistance of blood vessels and the heart rate. The ANS has both sympathetic and parasympathetic divisions that work together to maintain balance.

We support the concept that autonomic dysfunction is the precursor for the development of the diabetic mellitus process.

### **Autonomic dysfunction in diabetes**

ANS also influences many of the functions of the body, including the pancreas. The parasympathetic nervous system (PNS) and the sympathetic nervous system (SNS) have opposing effects on insulin secretion from islet beta cells; feeding-induced parasympathetic neural activity to the pancreas stimulates insulin secretion, whereas stress-induced sympathetic neural activity to the pancreas inhibits insulin secretion. <sup>[3]</sup>

It has long been recognized that cardiac autonomic neuropathy (CAN) increases morbidity and mortality in diabetes and may have greater predictive power than traditional risk factors for cardiovascular events. This is attributable to the autonomic imbalance between the sympathetic and the parasympathetic nervous system regulation of cardiovascular function that is associated with both type 1 and type 2 diabetes. <sup>[4-7]</sup>

A study from 2001 have predicted: “As the world faces an obesity ‘epidemic, the mechanisms by which overweight is translated into insulin resistance, hypertension, and diabetes need to be better understood. Although the processes of transition remain uncertain, overactivity of the sympathetic nervous system appears pivotal”. <sup>[8]</sup>

A study from 2014 <sup>[9]</sup> aimed to investigate the development of severe hypoglycemia (SH) in the presence of cardiovascular autonomic neuropathy (CAN) in patients with type 2 diabetes. A total of 894 patients with type 2 diabetes were enrolled. The authors found that in the long-term of the study (10 years), prospective, observational cohort study, was demonstrated a significant relationship between diabetic cardiovascular autonomic dysfunction and the development of SH in patients with type 2 diabetes during the follow-up period. They showed that a higher cardiovascular autonomic function test (AFT) score, especially a score indicating definite CAN, had a tendency to increase the risk of SH in patients with type 2 diabetes.

A study from 2019 <sup>[10]</sup> aimed to determine clinical factors related to CAN recovery. It concluded that younger age is the most important factor in CAN recovery in subjects with type 2 diabetes, including recovery from the definite

or severe stage. Glycated hemoglobin (HbA1c) reduction, body weight reduction, no concurrent micro/macroalbuminuria, and shorter duration of diabetes were also significantly associated with CAN recovery. Another study, this one from 2021, <sup>[11]</sup> said that the poorer the glycemic control and the longer the duration of the disease, the higher the incidence of CAN in T2DM and age, duration of disease, waist-hip ratio, and HbA1c, are well correlated with the severity of CAN.

The autonomic imbalance is also associated with gestational diabetes. <sup>[12]</sup>

## **The association of Cardiovascular disease (CVD) with Diabetes**

Hypertension is common among patients with diabetes, with the prevalence depending on type and duration of diabetes, age, sex, race/ethnicity, BMI, history of glycemic control, and the presence of kidney disease, among other factors <sup>[13]</sup>

A study from 2018 demonstrated that globally, overall cardiovascular disease affects approximately 32.2% of all persons with type 2 diabetes. CVD is a major cause of mortality among people with type 2 diabetes, accounting for approximately half of all deaths over the study period. <sup>[14]</sup>

### **Risk factors for diabetes Mellitus**

Excess body weight and physical inactivity are foreseen as the most important factors for the development of type 2 diabetes. Obesity is believed to account for 80-85% of the risk of developing type 2 diabetes, while recent research suggests that obese people are up to 80 times more likely to develop type 2 diabetes than those with a BMI of less than 22. <sup>[15]</sup> Both obesity <sup>[16]</sup> and physical inactivity <sup>[17]</sup> are affected by autonomic dysfunction.

Recent studies have argued that added sugars increase the risk of obesity and diabetes. <sup>[18-21]</sup> The stimulatory effect of dietary carbohydrate on SNS activity was first recognized in 1977, during sucrose feeding. <sup>[22]</sup> Oral fructose has been shown to be as potent as glucose in stimulating the SNS in animals or human subjects. <sup>[23-25]</sup> Many studies have shown that high carbohydrate diets consumption may activate the sympathetic system. <sup>[26-29]</sup>

Exceptional glycemic control of type 1 diabetes with low rates of adverse events was reported in 2018 by a community of children and adults who consume a very low-carbohydrate diet. <sup>[30]</sup> The authors have highlighted in their paper:

*"Before the discovery of insulin, the lives of children with type 1 diabetes mellitus were extended, sometimes for years, by severe carbohydrate restriction. After the advent of insulin treatment, the recommended carbohydrate intake was increased without clinical trial proof of superiority. By the 1980s, a low-fat diet containing up to 60% of energy from*

*carbohydrates became the standard of care.  
More recently, the American Diabetes Association has emphasized  
the individualization of diet rather than focusing on  
macronutrients."*

Follows some additional risk factors that may dysregulate the autonomic nervous system in diabetes type 2:

- Age <sup>[31,32]</sup>
- Tobacco <sup>[33]</sup>

A recent study demonstrated that elevated heart rate is independently, in interaction with a higher body mass index, associated with a higher incidence of type 2 diabetes mellitus. <sup>[34]</sup>

Resting electrocardiogram abnormalities are common in all people with type 2 diabetes, including those without a history of CVD and their prevalence is related to traditional cardiovascular risk factors such as older age, male sex, hypertension, lower HDL cholesterol, higher BMI, and smoking behavior. <sup>[35]</sup>

According to our present postulation the autonomic dysfunction leads to increased lactate production, which gets worse the diabetic disease process.

## **Increased lactate production in diabetes**

Diabetes can cause changes in the musculoskeletal system, which is the term for our muscles, bones, joints, ligaments, and tendons. <sup>[36]</sup> It is interesting to notice that, in 1874, Balthazar Foster found the administration of lactic acid by the mouth to diabetic patients resulted in painful and swollen joints. These manifestations persisted so long as the lactic acid was continued and disappeared when it was discontinued. <sup>[37]</sup>

Oswald Loeb, in a study from 1913, <sup>[38]</sup> was the first to link lactic acidosis to atherosclerosis. He has demonstrated in his experiments that injecting lactic acid to rabbits and dogs, resulted in atherosclerotic lesions in these animals. In his study he also mentioned about a similar hypothesis for diabetes, that follows:

*"Let us remember that when we inject adrenaline and nicotine causes the most serious disturbances on the part of the animals blood pressure and breathing show, even temporarily, reactions with convulsions, so the assumption is not of that hard to indicate that it is a production or a less destruction of lactic acid.*

*It is well known that rabbits react to adrenaline intake with glycosuria, it would not be impossible that with, simultaneous hyperglycemia, the build-up to sugar is disturbed and a greater build-up of lactic acid and thereby aldehyde formation would be given.*

*We can also make a similar hypothesis for diabetes, in which is well known, arteriosclerosis occurs frequently.*

*Remarkable is still that even those researchers who investigate arterial changes seen occurring with abnormal diet, report glycosuria and severe metabolic disorders."*

*(Diabetes is also a risk factor for atherosclerosis under our acidity theory point of view. This theory was developed in 2006)*

A study from 1924 <sup>[1]</sup> involved four patients with uncomplicated diabetes. They varied from extremely mild to moderately severe. In each case the effect of a single intravenous dose varying from 8 to 33 units of insulin (Iletin, Lilly) was observed. The blood was taken before, and between 1 and 2 hours after, the injection, and analyzed for sugar, lactic acid, and inorganic phosphates. The study has highlighted that "With adrenalin a marked rise can occur, and instead of a fall in lactic acid we observed an actual rise amounting often to 100 percent. The results suggest that there is some factor common to the action both of insulin and adrenalin, which increases the lactic acid in spite of the divergent effects on the blood sugar."

A comparison of the effects of insulin and adrenaline, led the authors to the following conclusions:

- a Both extracts lower the inorganic phosphate of the blood.
- b Extreme drops in blood sugar may occur with no change in the lactic acid concentration. With our patients increases in lactic acid were observed only when an insulin hypoglycemia was produced, and this may turn out to be the general rule.
- c Lactic acid increases with an adrenaline hyperglycemia.
- d Insulin causes an increase in the respiratory quotient over and above that which can be accounted for by the production of lactic acid. This is evidence of the stimulating action exerted by the extract on the oxidation of carbohydrate.

The above study was discussed in the same year by Carl Ferdinand Cori <sup>[39]</sup> who made experiences in animals in this direction, saying that his results and conclusions looked like to be in harmony with Tolstoi and colleagues' findings.  
<sup>[1]</sup>

Follows the results and conclusions from Cori:

1. Insulin hypoglycemia produces no definite change in the lactic acid content of the blood of either fasting rabbits or cats, nor does insulin have an effect on the blood lactic acid of phlorhizinized rabbits or depancreatized cats.
2. Insulin convulsions lead to a strong increase in the lactic acid concentration of the blood.
3. Epinephrine causes a rise in the blood lactic acid of rabbits and cats. The effect is more marked in the former animals than in the latter.
4. The lactic acid concentration in the liver and in the muscles of mice remained uninfluenced by insulin hypoglycemia, by insulin convulsions or coma plus convulsions, and by epinephrine. The free sugar content of

the liver was strongly lowered by insulin and remained low in spite of insulin convulsions.

5. It was concluded that insulin has no effect on the reaction  $\text{glucose} \rightleftharpoons \text{lactic acid}$  in the direction to the right.

A study from 1988 <sup>[40]</sup> found that disturbed liver function and increased levels of lactate are early risk factors for diabetes.

The results of a study from 1990 <sup>[41]</sup> suggested that even prior to frank carbohydrate intolerance, progressive changes in basal levels of glucose, insulin, and lactate, as well as sum of glucose, accompany the expansion of adipose mass in obesity. Two different aspects of lactate metabolism have been examined in obesity. First, the association of increased basal lactate levels with increased obesity may reflect increased lactate production from enlarged adipocytes and an increased fat mass. Secondly, the inverse association between acute lactate generation following glucose ingestion and obesity, despite the increased sum of glucose in obese subjects, may reflect a decreased ability of adipose and/or extra-adipose tissues to convert glucose to lactate due to insulin resistance.

A study from 1992 found that lactate is correlated with insulin resistance, independent of obesity. <sup>[42]</sup>

A study published in 1993 <sup>[43]</sup> demonstrated that plasma lactate concentration was lowest in the non-obese group with normal glucose tolerance (0.81 +/- 0.07 mmol/L), highest in the obese subjects with type 2 diabetes (1.46 +/- 0.14 mmol/L), and intermediate in obese individuals with normal glucose tolerance (1.17 +/- 0.13 mmol/L).

A study from 2002 provided evidence that the elevation of plasma lactate suppressed glycolysis before its effect on insulin-stimulated glucose uptake, consistent with the hypothesis that suppression of glucose metabolism could precede and cause insulin resistance. In addition, lactate-induced insulin resistance was associated with impaired insulin signaling and decreased insulin-stimulated glucose transport in skeletal muscle. <sup>[44]</sup>

A study from 2007 <sup>[45]</sup> concluded that adipose tissue (AT) and skeletal muscle (SM) are both significant sources of lactate release post-absorptivity, and AT is at least as responsive to insulin as SM. It was assumed by the authors that the ability to increase lactate release in response to insulin is impaired in AT and SM in insulin-resistant obese women, involving defective insulin regulation of both tissue lactate metabolism and local blood flow.

A study from 2010 <sup>[46]</sup> confirmed that plasma lactate was strongly associated with type 2 diabetes in older adults. The authors said that plasma lactate deserves greater attention in studies of oxidative capacity and diabetes risk.

A study from 2015 <sup>[47]</sup> suggested that an increase in lactate could herald the early stages of insulin resistance long time before patients are diagnosed with diabetes mellitus.

Another study from 2015 <sup>[48]</sup> postulated that elevated plasma lactate levels are part of the clinical spectrum of glycogenic hepatopathy in patients with poorly controlled type 1 diabetes.

A study from 2016 <sup>[49]</sup> found that plasma lactate is independently associated with incident atrial fibrillation, and its contribution to AF may be, at least in part, mediated by diabetes and/or hypertension.

Sugars in excess may raise lactic acid production in the body. <sup>[50, 51]</sup>

Increased blood lactate concentration is also associated with gestational diabetes. <sup>[52]</sup>

## How autonomic dysfunction leads to lactic acidosis

The chronic elevated release of catecholamine precipitated by the sympathetic nervous system can accelerate glycolysis, which results in a significant increase in lactate production.

The influence of adrenaline on lactic acid production have been observed in the early 1920s by the Cori's. They have discussed about this subject in 1929. <sup>[53]</sup> Carl Ferdinand Cori and his wife Gerty Cori received a Nobel Prize in 1947 for their discovery of how glycogen - a derivative of glucose - is broken down and resynthesized in the body.



Carl Ferdinand Cori and Gerty Cori  
Nobel Prize in Medicine, 1947

A 1982 article by David S. Schade <sup>[54]</sup> provided further support for the direct participation of catecholamines in the development and/or maintenance of lactic acidosis as follows:

1. The common association of stress and lactic acidosis
2. The rise in plasma lactate concentration during adrenaline infusion
3. The precipitation of lactic acidosis by adrenaline intoxication and pheochromocytoma
4. The vasoconstrictor effects of catecholamines leading to tissue anoxia and lactic acid production.

A study from John R. Williamson confirmed in 1964 the effects of adrenaline infusion on the increased production of lactate in isolated heart tissue, up to five times the normal production. <sup>[55]</sup>

**The controversial use of Digitalis and Digitoxin in diabetes mellitus**

In 1999, <sup>[56]</sup> a study reported three patients with type 2 diabetes mellitus who after digoxin, coincidentally discontinued, experienced better antidiabetic control with decreases in their blood glucose levels, making significant reductions in the antidiabetic treatment necessary.

Madsen in 2012, commented on a case report showing that patient's levels of HbA1c and glucose rose significantly after commencement of digitoxin therapy. In his article <sup>[57]</sup> he told that "One thing that was learned was that the serum concentration should be lower than had been usual earlier". Mentioning the study from 1999 <sup>[56]</sup> Madsen said that if there really is a connection between digitalis and exacerbated diabetes, it was very strange that this was not discovered earlier. He said that possible explanations are that the effects in most patients are less pronounced than in the present case, or that diabetes is so common among persons who take digitalis that exacerbation or a few extra cases are not noticed. He also told that, perhaps, more could be learned from looking at patients from the major blood pressure and heart failure studies who were given digitalis. He reasoned that in order to do this, access to original data would probably be necessary. Madsen also recommended that the HbA1c and glucose levels of patients with known diabetes be closely monitored after they start taking digitalis.

A study from 2016 <sup>[58]</sup> found that digoxin reduced heart failure hospitalization in low ejection fraction patients with and without diabetes having no substantial risk of toxicity. It examined the efficacy and safety of digoxin in HF-REF patients with and without diabetes in the Digitalis Investigation Group trial (DIG). Mortality from all-cause, cardiovascular causes and heart failure (HF), along with HF hospitalization and suspected digoxin toxicity were analyzed according to diabetes status and randomized treatment assignment.

Of the 6800 patients, those with diabetes (n = 1933) were older, more often women, had worse clinical status and more co-morbidity than those without diabetes. All-cause and cardiovascular mortality were higher in patients with diabetes than in those without and digoxin did not reduce mortality in either sub-group. The rate of HF hospitalization (per 100 person-years) in patients with diabetes was higher than in those without and was reduced by digoxin in both patient groups: diabetes - placebo 20.5 and digoxin 16.0 (HR 0.79, 95% CI: 0.68-0.91); no diabetes - placebo 12.7 and digoxin 8.7 (HR 0.69, 0.62-0.77); interaction p = 0.14. Suspected digoxin toxicity in patients randomized to digoxin was more common among patients with diabetes than without (6.5% versus 5.8%), as was hospitalization for digoxin toxicity (1.4% versus 0.8%).

The patients were randomly assigned to receive digoxin or placebo. The initial dose of study drug was determined using an algorithm which took account of patient age, sex, weight, and renal function. The Investigators were permitted to modify dose of study drug based on other factors, such as use of concomitant drugs that might alter digoxin pharmacokinetics.

Overall, the daily dose of digoxin taken by the patients in this study was 0.125 mg in 17.5%, 0.250 mg in 70.6%, 0.375 mg in 10.3% and 0.500 mg in 1.1% of patients (median daily dose 0.250 mg). In patients with diabetes, the daily dose of digoxin taken was 0.125 mg in 17.5%, 0.250 mg in 69.1%, 0.375 mg in 12.7% and 0.500 mg in 0.8%. In patient without diabetes, the daily dose of digoxin taken was 0.125 mg in 20.3%, 0.250 mg in 69.5%, 0.375 mg in 9.0% and 0.500 mg in 1.1%. The median daily dose for patients with diabetes and those without was the same (0.250 mg).

According to this study<sup>[58]</sup> serum concentrations of digoxin were available only for a part of the study cohort. So, losing a great opportunity to compare patients, particularly diabetics, with the use of lower digoxin concentration dosages versus those given higher concentration doses of this drug. This taking in consideration the retrospective analysis of data by Rathore and col. in 2003<sup>[59]</sup> and Adams and col. in 2005<sup>[60]</sup>, of the DIG trial from 1997.<sup>[61]</sup> Their retrospective analysis has indicated a beneficial effect of digoxin on morbidity and no excess mortality at serum concentrations from 0.5 to 0.9 ng/ml, whereas serum concentrations  $>$  or  $=$  1.2 ng/ml seemed harmful.

These retrospective analyses of the DIG trial led the Heart Failure Society of America to issue new Heart Failure Guidelines in 2010.<sup>[62]</sup> Follow extracts of the Session 7 of these guidelines that are related to the use of Digoxin recommendations from the chapter Heart Failure in Patients with Reduced Ejection Fraction:

1. Recent data suggest that the target dose (and serum concentration) of digoxin therapy should be lower than traditionally assumed. Although higher doses may be necessary for maximal hemodynamic effects, beneficial neurohormonal and functional effects appear to be achieved at relatively low serum digoxin concentrations (SDC) typically associated with daily doses of 0.125 to 0.25 mg. A retrospective analysis of the relationship of SDC to outcomes in the DIG trial demonstrated a strong direct relationship between the risk of death and SDC, with concentrations  $\geq$  1.2 ng/mL being associated with harm, whereas concentrations  $\leq$  1.0 ng/mL were associated with favorable outcomes.
2. The efficacy of digoxin in HF with reduced LVEF has traditionally been attributed to its relatively weak positive inotropic action arising from inhibition of sodium potassium ATPase and the resulting increase in cardiac myocyte intracellular calcium. However, digitalis has additional actions that may contribute significantly to its beneficial effects in patients with HF. Digoxin has important neuro-hormonal modulating effects that cannot be ascribed to its inotropic action, and it ameliorates autonomic dysfunction as shown by studies of heart rate variability, which



indicate increased parasympathetic and baroreceptor sensitivity during therapy.

*“Although there is not total agreement on the nature and clinical significance of the effects of digitalis on the autonomic nervous system, the following points seem well established and generally accepted:*

- 1) the actions of digitalis on the autonomic nervous system are very important clinically and play a major role in determining the clinical pharmacodynamic effects of the drug;*
- 2) with therapeutic concentrations of the drug, the predominant effect is activation of vagal tone; and*
- 3) with toxic concentrations of the drug there may be activation of sympathetic tone.” August M. Watanabe, 1985 [63]*

## **Digoxin at daily low concentration dosages: The magic bullet to fight diabetes?**

Digoxin and other cardiac glycosides, at low concentration dosages, can restore the balance of the autonomic nervous system and reduce the production of lactic acid in the body.

### **The following cardiac glycosides inhibit sympathetic overactivity:**

- Cedilanid\* [64]
- Digoxin [65,66]
- Digitoxin [67]
- Ouabain [68]

\* Cedilanid is the trade name. The active ingredient is Lanatoside C

### **Cardiac glycosides reduce lactate production**

A recent paper has demonstrated that inhibiting the overproduction of catecholamine by digoxin, digitoxin and ouabain may induce a potent inhibition of glycolysis (glucose consumption and lactate) [69] It confirms the results of old studies on this matter. [70]

### **ANS, Cardiac Glycosides, Hyperglycemia in Diabetes, and the Immune System**

The results of many studies have established a critical role for the ANS in mediating interactions between the nervous and immune systems, two important adaptive systems that were originally considered to function independently of each other [71]

Recently, a study has suggested that some cardiac glycosides activate immune responses. [72]

Hyperglycemia in diabetes may cause dysfunction of the immune response, which fails to control the spread of invading pathogens in diabetic subjects. Therefore, diabetic subjects are thought to be more susceptible to infections. The increased prevalence of type 2 diabetes will increase the incidence of infectious diseases and related comorbidities. [73]

## Covid-19

It is important to cite the clinical perspective from a recent study showing that patients with cardiometabolic conditions, in particular obesity, hypertension, diabetes mellitus, and heart failure, have a high risk of poor outcomes from coronavirus disease 2019 infection. Among >900 000 US coronavirus disease 2019 hospitalizations through November 18, 2020, nearly two thirds (63.5%) were estimated to be attributable to these cardiometabolic conditions, that is, preventable if these conditions had not been present. The top risks were obesity (30.2%), hypertension (26.2%), and diabetes mellitus (20.5%).<sup>[74]</sup>

## Conclusion

The studies and concepts described in our present hypothesis provide strong evidence that autonomic dysfunction, as a precursor to the development of diabetes mellitus, being accompanied by increased lactic acid production, are important causal factors for this disease. The adoption of the directions proposed in the present article would open new horizons in the prevention of diabetes and in the search for new drugs, or the use of old drugs like cardiac glycosides. Therefore, offering the right solution in the prevention or in the treatment of diabetic patients.

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# Chapter 17

## Covid-19: Treating Cause and Effects - “Autonomic Dysfunction, the Immune System and Lactic Acidosis”

*Carlos ETB Monteiro*

### **Covid-19 and the central nervous system**

- Presentation of a global portrait of some of the most prevalent or emerging human respiratory viruses that have been associated with possible pathogenic processes in Central Nervous System infection, with a special emphasis on human coronaviruses. <sup>[1]</sup>
- Review about the research into neurological complications in Cov infections and the possible mechanisms of damage to the nervous system. <sup>[2]</sup>
- Patients with COVID-19 commonly have neurologic manifestations. Compared with patients with non-severe infection, patients with severe infection were older, and had more underlying disorders. <sup>[3]</sup>
- Increasing evidence shows that coronaviruses are not always confined to the respiratory tract and that they may also invade the central nervous system inducing neurological diseases. <sup>[4]</sup>

### **Covid-19 and the Autonomic Nervous System**

- Svetlana Blitshteyn, MD, said in article from 2020:  
“While there is no data on how COVID-19 affects individuals with autoimmune and/or autonomic disorders, we can hypothesize how they would respond to COVID-19 based on their response to the flu. My personal opinion is that patients with these disorders should be viewed as high-risk population....” <sup>[5]</sup>
- During the 2020 Congress from the European Academy of Neurology the Scientific Panel for Autonomic Nervous System (ANS) Disorders, stated:  
“Autonomic disorders, or their treatment, may place the patient at a greater risk of contracting infections or of a more severe course.” <sup>[6]</sup>
- Autonomic dysfunction has been reported in retrovirus (human immunodeficiency virus (HIV), human T-lymphotropic virus), herpes viruses, flavivirus, enterovirus 71 and lyssavirus infections. Autonomic dysfunction may be responsible for additional morbidity in some infectious diseases <sup>[7]</sup>
- A recent study has shown that autonomic dysfunction is associated with Covid-19, being the heart rate variability (HRV) associated with the severity of the disease. The changing trend of HRV was related to the prognosis, indicating that HRV measurements can be used as a non-invasive predictor for clinical outcome of Covid-19 <sup>[8]</sup>

## **Autonomic Nervous System and the Immune System**

- Both sympathetic and parasympathetic arms of the autonomic nervous system are instrumental in orchestrating the neuroimmune processes. <sup>[9]</sup>

## **Covid-19 and the Immune System**

- The immune response is essential to control and eliminate CoV infections, however, maladjusted immune responses may result in immunopathology and impaired pulmonary gas exchange. <sup>[10]</sup>

## **Lactic acidosis and Immune System**

Lactate has been shown to regulate immune responses during infections. Its reduction may start the immune response <sup>[11,12]</sup>

## **Lactic acidosis and Coagulation in Covid-19**

- It was observed that the most common laboratory abnormalities were depressed total lymphocytes, prolonged prothrombin time, and elevated lactate dehydrogenase. <sup>[13]</sup>
- The coagulation function in patients with SARS-CoV-2 is significantly deranged compared with healthy people <sup>[14]</sup>. However, lactic acidosis remarkably impairs the coagulation system. <sup>[15]</sup>

## **Lactic acidosis and Covid-19**

- The coronavirus disease Covid-19 may further highlight lactic acidosis as one of many markers that may indicate intensive care admission or prognosis in disease. To date (Dec 09, 2020), however, no COVID-19 morbidity or mortality data has been published specific to lactic acidosis or lactate clearance <sup>[34]</sup>
- Recent study has shown that elevated lactate levels were associated with poor prognosis in patients with Covid-19. <sup>[16]</sup>

## **Fighting Covid-19**

### **Our view**

- Old people and patients with chronic diseases pose a large risk for Covid-19.
- However, in all patients infected with Covid-19, we should fight both the virus as well to prevent or solve the autonomic nervous dysfunction, the weakened immune system, and to reduce the production of lactic acid in the body.

## **The solution:**

### **Cardiac glycosides: For autonomic dysfunction, lactic acidosis, and the immune system**

- The right drugs to fight the autonomic nervous dysfunction and lactic acidosis are digoxin, digitoxin and other cardiac glycosides, at daily low concentration doses, because these attends both situations. <sup>[17-19]</sup>
- Cardiac glycosides may also strengthen the innate immune system. <sup>[20]</sup>

### **Cardiac Glycosides: Potential drugs to fight Covid-19**

- Studies demonstrated potential positive effects from digoxin and other cardiac glycosides as antivirals, including for Covid-19. <sup>[21-26]</sup>
- Also, it has been shown that viruses that target lung epithelial cells are severely impaired by cardiac glycosides". <sup>[27]</sup>

### **Vitamin C and D are also helpful for Covid-19**

- Acute administration of Vitamin C at high doses improves baroreflex sensitivity and vagal sinus modulation. Consequently, it influences the stabilization of the autonomic function. <sup>[28,29]</sup> Vitamin C may also contribute to immune defense by supporting various cellular functions of both the innate and adaptive immune system. <sup>[30]</sup>
- A recent study elucidates the potential therapeutic role of Vitamin D for autonomic dysfunction. According to this study Vitamin D is a neuroactive hormone that modulates autonomic balance, regulating the sympathetic and parasympathetic nervous systems, and has multisystem benefits. <sup>[31]</sup> Vitamin D can also modulate the innate and adaptive immune responses. <sup>[32]</sup>

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