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.

Key words: autonomic nervous system, stress, catecholamine, coronary artery disease, LDH, lactic acid, acidic environment, atherosclerosis.

"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 (1)

Acidity Theory of Atherosclerosis

The Hypothesis

The present hypothesis follows the response to injury concept of atherosclerosis developed by Russel Ross, John Glomset and Laurence Harker in 1977 (2). 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 (3), inspired by the demonstration that normal stretching/relaxing of an artery does not produce atherosclerosis, while stretching/relaxing in different directions simultaneously on every heart beat does. This discovery from scientists in California (4, 5, 6) 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 the mechanism in question
3) To be suitable with the myogenic theory of myocardial infarction, developed by Quintiliano H. de Mesquita in 1972 (7, 8), 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 (9).

We believe the Acidity Theory of Atherosclerosis attend these premises.
The sequence of events according 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 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 (10).

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 (11). Walter Cannon was the first to demonstrate, in 1914, that acute stress results in increased outpouring of adrenaline (12). 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) (13-23).

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 (24). Indeed, the use of sympatholytic agents (55) and stress reduction approaches (25) may lead to a significant reduction in blood pressure levels.

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Related to mental stress and atherosclerosis, studies have showed that:
a) Higher rise in systolic blood pressure during psychological stress results in a more severe and greater progression of carotid atherosclerosis (26, 27, 28);
b) Adrenaline and noradrenaline may act as chemical mediators during atherogenesis in man, thus contributing to the development and subsequent complications of atherosclerosis (29);
c) Mental stress – induced pulse pressure changes may influence the development of early atherosclerosis in the carotid artery of woman (30);
d) Blood pressure changes during psychological stress predict subsequent coronary calcification in young health adults 13 years later (31);
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 (32);
f) Delayed blood pressure recovery after psychological stress is associated with carotid intima-media thickness (IMT) (33);
g) Psychosocial factors are independent significant predictors of IMT progression (34);
h) Depressive symptoms are associated with the development of atherosclerosis (35).

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 (36, 37). 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 (38, 39). Cholesterol, a vital substance produced by the human body, is the major precursor of endogenous digitalis-like compounds (40).
Many hormones, including aldosterone, insulin, thyroid hormone and catecholamines regulate not only the expression but also the insertion of Na+, K+-ATPase into the plasma membrane, according to specific physiological needs. The Na+, K+-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 (37).
In many cases, perturbation of the DLC system has been implied in pathological conditions including cardiac arrhythmias, hypertension, cancer and depressive disorders (37, 41).
Stress situations may affect the release of endogenous digitalis-like compounds by the adrenal gland (39). Also, the extracellular acidification may affect the signaling and transport of endogenous DLCs (42, 43). 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 (44, 45, 46).
Cardiac glycosides, that in higher concentrations inhibit the Na/K pump, in low therapeutic doses (147), including at nanomolar range concentration (47), 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 (48, 49). 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 (50, 51, 52, 53). It is interesting to note that studies have suggested a causal relationship between noradrenaline/adrenaline and concentrations of lactic acid (54).
We should also notice the cardiac glycosides digoxin and digitoxin may lower blood pressure in hypertensive patients (55). Paradoxically, some studies have shown that infusion of ouabain over several weeks produces hypertension in rats (56), situation in which digoxin and digitoxin can also lower the blood pressure (57). 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 (56).

Acidity Theory of Atherosclerosis

It was recently demonstrated that cardiac glycoside drugs potently block activation of NF-kB signaling pathway, providing a feasible therapeutic use for the treatment of inflammatory diseases, like in atherosclerosis (58). The activation of Nuclear factor-kappa B (NF-kB), 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 (59).

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

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 (13). The chronic or acute elevated catecholamine release, mainly from sympathetic nerve terminals in cardiac tissue (60), 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 (61)

b) Lactic acid in the blood plasma is significantly elevated during stress situations and serving as indicative of stress levels (62, 33);

c) Catecholamine may be important determinants for the development of ketoacidosis and/or lactic acid (54).

d) Lowered pH increases perfusion pressure (64, 65). Also, pH changes have profound effects on contractility of coronary arteries (65, 66), that may happens through the sodium/potassium pump and K induced relaxation channels (67);

e) Lactate, lowered pH and lactic acid induce endocardial damage (68);

f) A decreased pH may be associated with an increased blood-pressure response to salt loading (69);

g) Ingestion of glucose, fructose and other sugars may have the effect to raise blood lactic acid with this increase beingmost 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 (70, 71);

h) High carbohydrate diet may increase significantly the activity of serum lactate dehydrogenase (149, 150).

i) Lactic acid produced by anaerobic metabolism during cardiac ischemia is among several compounds suggested to trigger anginal chest pain (13), 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 (72);

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 (73);

k) Lactate accumulation predicts and determines the development and expansion of ischemic myocardial necrosis (7, 50, 74), albeit cardiotoxic catecholamines may induce myocardial necrosis -- acute contraction band lesions (75);

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 (76);

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 (77).

n) In ischemic stroke acidosis-mediated activation of acid-sensing ion channels may play a role to ischemic damage of brain tissue (78).

o) Tissue acidosis has been proposed to account for contractile failure during myocardial ischemia (79, 80) and to contribute for the genesis of cardiac dysrhythmias (81).

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Acidity Theory of Atherosclerosis

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 (13). In cats, the occlusion of the coronary artery for 5 min decreased epicardial tissue pH from 7.35 to 6.98 (82).

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 (144).

Macrophages and lymphocytes convert most of their glucose into lactate rather than oxidizing it completely to CO_2, and macrophages possess a selective transporter in their plasma membranes for lactic acid. This lactic acid may make the extrcelullar space surrounding macrophages acidic in atherosclerotic lesions (83).

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 (84).

It has been reported that lowering pH augments the oxidation of low-density lipoprotein (LDL) by releasing Fe and Cu radicals and decreasing anti-oxidant defense capacity (83, 85, 86).

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 (148).

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 (87, 88).

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 (89, 90).

It was suggested that uric acid has antioxidant and prooxidant activities towards the oxidation of native and mildly oxidized LDL, respectively (91). 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 (92). However, an elevated concentration of lactic acid in blood may inhibit renal excretion of uric acid, leading to its accumulation in the body (145).

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 (93). It has been demonstrated that plasma homocysteine levels also increase during psychological stress (94, 95, 96).

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 (97, 98, 99). 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 (100).

It is interesting to notice the evidence that, apart from its occurrence in atherosclerosis, acidity of the environment is also increased in inflammatory sites (83, 101). This raises a potential importance of acidity for inflammation results in formation of atheromas.

The timing of crystallization depends on several local physical factors, including cholesterol concentration, pH, temperature, and pressure (102). 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.

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Acidity Theory of Atherosclerosis

Hemodynamic shear stress and atherosclerosis

As the final step in this process the changes in pH may lead to mechanical forces (64, 65, 66, 67) 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 (103).

The pulsatile nature of blood pressure and flow creates hemodynamic stimuli in the forms of cyclic stretch and shear stress (6).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 (104, 105). 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 (106, 107).

The plaque rupture

The plaque instability and rupture may start a considerable time before the AMI, according some studies (108, 109). Stretching, tearing and perforation, related to cholesterol crystallization and expansion, may play a role in the process (102). 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 (110).

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

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 (112);

b) In a significant number of cases angioscopic examination continues to find thrombus on the presumed culprit lesion, at 6 months after myocardial infarction (114);

c) The frequency of an occlusive thrombus is significantly higher in the larger infarcts (115).

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 (108, 116). These findings confirm previous autopsy studies, which came to the conclusion that thrombus are a consequence not a cause of AMI (8, 111, 112).

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 (117). 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 (118). 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 (119). A third study has shown that yoga intervention retards progression and increases regression of coronary atherosclerosis in patients with severe coronary artery disease (120). 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 (121). 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 (122). 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 (123) and evidenced later by other studies (124). 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 (125). 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 (48, 49).

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) (44, 45). 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, during 23 years (46).

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 (127). 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 (128).

On the other side studies are showing that long term psychological stress is associated with progression from prehypertension to hypertension or coronary heart disease (129). 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 (130). 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 (131). Yet the elevation of plasma lactate levels may induce insulin resistance by suppressing glycolysis (132). Moreover, the autonomic nervous system is influenced by high-carbohydrate dietary, with greater sympathetic nervous activity (133, 134).

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 reduces 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 (135). Among the possible mechanisms underlying these effects is its capability to reduce the elevated blood lactic acid (136).

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 (137). 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 (138, 139). 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 (140).

Acidity Theory of Atherosclerosis

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 (44, 45) treated inside the myogenic theory of myocardial infarction, a complementary hypothesis, where psycho-emotional and physical stresses are considered to be the main triggers (7, 8).

It was demonstrated in patients taking cardiac glycosides when recovering from myocardial infarction (141), treated for congestive heart failure (142) or prophylactic in the heart not in failure (143), 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 of 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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