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On the etiology of cardiovascular diseases: A new framework for understanding literature results

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ABSTRACT

The interpretative framework presented here provides a rationale for many well-known features of cardiovascular diseases. Prolonged acidemia with high blood levels of free fatty acids is proposed to shape the basic context for formation of fatty acid micelles and vesicles with an acidic core that fuse with the endothelia, disrupt vital cell processes, and initiate atherosclerotic plaque formation. It offers an explanation for the distributed localization of atherosclerotic lesions, and how mild cases of occurrence of fatty acids vesicles formed within the heart and the arteries close to the heart may cause such lesions. It provides a rationale for how acute events, namely heart attacks and strokes, may arise from stormy development of fatty acid vesicles within the heart. Additionally, a process is proposed for clot development from the existing fatty acid vesicles.

Introduction

According to a recent study [1], peer-reviewed publications in the field of medical and health sciences amounted to 12,796,558 in the period from 1980 to 2012, and currently are growing at rates of 8–9% per year. This huge body of scientific literature is usually interpreted in line with established paradigms that provide rationales, and guidance for future research. Paradigms are helpful, but also have a great inertia, and lack of flexibility when facing research results conflicting with their axiologies. Therefore, research results can be found in all fields that were misinterpreted, overlooked, or even discarded due to lack of explanation in the context of existing paradigms. This is also true in the field cardiovascular diseases. Additionally, due to the current fast publication rate, and the need to keep up-to-date with mainstream lines of research, researchers almost exclusively take into consideration the most recent literature, not paying much attention to older results. However, the results that conflict with current paradigms are of utmost importance, because they may trigger new ways of thinking, redirect research priorities, and open new ways to the solution of old problems.

In short: the current paradigm of etiology of cardiovascular diseases [2] is based on two fundamental assumptions: (i) damage to endothelium of blood vessels causes lesions, local inflammation with mobilization of white blood cells, lipoproteins and other substances, which lead to development of fibrofatty atherosclerotic plaques, thereby causing narrowing of arteries (stenosis or closure of the lumen); (ii) rupture of the atherosclerotic plaque with clot formation may lead to arterial occlusion thereby stopping blood flow (and oxygen) to a part of the heart causing damage to the heart muscle (myocardial infarction) or to a part of the brain (thromboembolic stroke).

Below we list some features of cardiovascular diseases picked from a review by Baroldi and Silver [3] that hardly find a rationale within the current paradigm of etiology of cardiovascular diseases:

- An occlusive coronary thrombus was found in about half of infarct cases and in a minority of sudden/unexpected death cases;
- In contrast to spleen, kidney, brain, etc, where cholesterol emboli are often seen, in more than 14,000 myocardial sections of all groups, only one atheromatous embolus was found in a small intramural arteriole;
- Infarct size did not correlate with the number or degree and length of severe stenoses present in the whole coronary arterial system;
- It must be noted that in 37% of our cases, an infarct involved the adjacent vascular territories of vessels that were not occluded;
- The presence of acute or organized thrombotic coronary occlusion without a related infarct;
- In people that die accidentally from carbon monoxide intoxication, the acute hypoxia results in myocardial cell relaxation without any other change (vacuolization, edema, pathological contraction bands, etc);

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- Old total coronary occlusions were found in "healthy" subjects who died from accident but had no ischemic heart disease clinically, nor any significant myocardial fibrosis;
- A higher frequency of sudden death in patients with a resting heart rate $\geqslant$65 beats per minute (indicating low parasympathetic activity) vs. $\leqslant$65 beats without relation with other risk factors;
- An assumption proved is that normal subjects who undergo surgical ligation of a lacerated coronary artery following a chest wound do not develop a myocardial infarction.

In what follows we propose an explanatory framework for the main aspects of cardiovascular diseases, and namely the facts reported above, by taking into consideration the literature published from the beginning of the sixties of the last century until the present time.

The hypothesis

We put forward the following hypothesis:

(i) Cardiovascular diseases are the result of persistent states of acidemia, paralleled with peaks of blood concentration of free fatty acids (FFA);
(ii) Spikes in FFA concentration due to enhanced catabolic imbalance of lipids, in a context of local (compensatory) pulmonary alkalosis originate formation of FFA micelles, which travel to the heart where due to local blood acidity they transform into FFA vesicles with an acidic core;
(iii) FFA vesicles easily fuse with the membranes of the endothelial cells then liberating the acidic core, which impairs local ion transport (namely Ca^{2+}) and damage the endocardium and the endothelia of the aorta and nearby arteries;
(iv) Development of the resulting local inflammation, with mobilization of clotting factors, immune system, and repair processes, in which LDL particles and endothelial progenitor cells (EPC) play an important role, results in plaque formation;
(v) Acute crises such as myocardial infarction or stroke result from increased local blood acidity that impairs calcium, sodium and potassium ion exchange (among others), and promote clotting factors and therefore thrombus and clot formation within the blood stream, and in the damaged epithelia at the sites most affected by vesicle adhesion.

In what follows we provide and discuss the many evidences from the abundant biomedical literature that support the hypothesis.

Blood acidemia

Acidemia occurs when blood pH drops below 7.35. The most important causes of blood acidemia are [4–6]:

(I) Elevated cortisol levels, mainly due to chronic stress, though other hormones such as epinephrine, norepinephrine, ghrelin, growth hormone, testosterone, may further contribute to increase acidemia [6]. All these hormones increase lipoprotein lipase activity, therefore promoting lipolysis in the adipose tissue and release of FFA into the blood, some of which are taken up by cells. FFA not taken up by cells bind to albumin, which has 3 sites available for this purpose. When albumin binding sites are saturated, FFA accumulate in the blood, thereby lowering blood pH. The liver takes up FFA from the blood, and esterifies them (namely long-chain FA) to form triglycerides that are incorporated into very low density lipoproteins (VLDL), which are then released into the blood. Little by little, cells absorb triglycerides from VLDL particles, which turn into intermediate density lipoproteins (IDL), and then into low density lipoproteins (LDL) when cholesterol content surpasses that of triglycerides [6]. Spikes of blood FFA concentration may occur as a sudden increase of sympathetic activity, namely adrenergic shocks that boost lipolytic activity.
(II) Metabolic acidosis due namely to chronic kidney disease (CKD) which leads to reduction in serum bicarbonate (HCO_3^-) concentration. Metabolic acidosis develops when the kidneys are not removing enough acid from the body, as it happens with CKD. In fact, decrease in renal ammonium excretion and a positive acid balance that may lower serum bicarbonate concentration are observed in the course of CKD [7–9].
(III) Drug-induced metabolic acidosis, which occurs when drugs disrupt acid–base equilibrium. This effect may occur by two means [10,11]: (a) Drug-related metabolic acidosis owing to an increased H^+ load, such as Biguanides, Antiretroviral Therapy, Linezolid, Isoniazid, Propylene Glycol, Propofol, Adrenergic Stimulants, Nalidixic Acid, HMG-CoA Reductase Inhibitors (Statins), Antipsychotic Agents, and ingestion of Alcohols (Ethanol and Methanol), Ethylene Glycol, and other compounds; (b) Drug-related metabolic acidosis Due to HCO_3^- loss (Carbonic Anhydrase Inhibitors, Ifosfamide, and other compounds). Metformin, which is the most prescribed antidiabetic drug in the world, has been associated with acidosis [12], and severe acidosis leading to acute ST-elevation myocardial infarction [13].
(IV) Hypoventilation leading to high blood levels of CO_2 (hypercapnia), which produces carbonic acid (respiratory acidosis). It occurs when ventilation is insufficient to perform both oxygen uptake and carbon dioxide discharge by the lungs [14].

Acute blood acidemia and cardiovascular events

Hyperventilation as a compensatory mechanism to restore normal pH levels

When blood pH drops below 7.35 some compensatory mechanisms develop to restore normal pH levels. One such mechanism is hyperventilation, which consists in increased alveolar ventilation that leads to excess of carbon dioxide removal from the blood stream in relation to that the body can produce, therefore turning blood less acidic [15,16]. In a state of acidemia this is a compensatory mechanism for raising blood pH. It is very rapid and effective for this purpose because the enzyme carbonic anhydrase catalyzes the rapid interconversion of blood bicarbonate and protons to carbon dioxide and water [17]. Other mechanisms concurrent to the same objective are removal of volatile acids by the lungs through expiration, and removal of acids in the sweat, urine and feces [18].

Rapid and relatively shallow breathing (shortness of breath) is characteristic of mild up to high hyperventilation when blood acidemia has not reached extreme values, case in which it shifts to Kussmaul breathing [19]. Due to trade-off between local (respiratory) alkalemia and the sympathetic activity, pulmonary vasoconstriction occurs during hyperventilation [31]. Because hyperventilation is as a compensatory mechanism to restore normal blood pH in the whole body, it keeps on eliminating CO_2 in the alveoli despite alveolar blood pH may have reached values characteristic of alkalemia [20]. In such case, it is likely that blood