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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

with high pH flows to the left atrium of the heart via the pulmonary veins.

Because binding of calcium to proteins increases with pH, it displaces fatty acids (FA) from albumin binding sites, which leads to lowering of free calcium levels in the blood together with increased concentration of FFA. Additionally, due to Bohr–Haldane effect, the high pH locally enhances affinity of hemoglobin to oxygen, and for that reason blood entering the left atria is close to the oxygen saturation point.

At low pH fatty acids are fully protonated and form an oil phase, while at high pH they are fully deprotonated and form FFA micelles [21–24]. Micelle formation rate is strongly increased when blood flow becomes turbulent, as it is well known that shaking promote rapid micelle formation [24].

Mild endothelial activation and atherosclerosis

As explained above, hyperventilation, as a compensatory mechanism to restore normal blood pH levels in the whole blood, induces local pulmonary alkalosis that entails significant changes in the properties of the blood flowing from the lungs to the left atrium of the heart. Therefore, blood entering the left atrium must have a high pH, low free calcium (due to high albumin binding affinity) increased FFA content, hemoglobin close to the oxygen saturation point, and contain FA micelles.

Blood flow into the left atrium is highly turbulent and, together with high FFA concentration, creates the conditions to accelerate FA micelle formation. On the other hand, blood pH is maximal at the alveoli and decreases downstream as it comes into contact with tissues with lower pH. This aspect induces new transformations in the blood as if flows within the heart and downstream:

(a) Blood coming from the lungs as a fatty acid micellar solution shifting to lower pH spontaneously generates vesicles with a broad size distribution [26]. FFA vesicles are formed by FA in such a way that the hydrophilic "head" is in contact with surrounding blood while the hydrophobic single-tail region points to the micelle center. Because of the pH partition effect, vesicles formed in alkaline conditions are likely to have an acidic core, due to deprotonation of FA [21–23,25–27].
(b) Number of FA vesicles can increase exponentially, because they grow spontaneously when alkaline micelles are added to already existing vesicles. Spontaneous assembly of FA vesicles from alkaline micelles diluted into buffered solution is an autocatalytic process [28].
(c) Partial pressure of oxygen progressively increases, therefore enhancing concentration of ion superoxide (O_2^-) and reactive oxygen species (ROS), which easily forms in highly oxygenated blood environment [28,29];
(d) Free calcium ion concentration increases due to progressive loss of affinity to albumin with decreasing pH.
(e) Pulmonary vasodilatation is directly favored by local alkalemia, while systemic acidemia favors vasodilatation of the peripheral arteries [30]. However direct vasodilatation is offset by the indirect sympathetically mediated vasoconstriction and cardiac stimulation during mild acidosis [31].

The consequences of such transformation in the blood are the activation of the endocardium, and the endothelia of the arteries that first receive the blood ejected from the left ventricle: the coronary arteries, the aorta, and the nearby distributaries (brachial, carotids, subclavian, hepatic, gastric).

Fatty acid vesicles are supramolecular structures, in which the molecular components are in rapid dynamic equilibrium with the surrounding solution and with each other [25]. Because of this feature together with the high affinity between the FA vesicle membranes and cell membranes they easily fuse with endothelial cells, thereby delivering them the acidic core. Alternatively, because protons can pass through some membranes they can deliver the acidic core by diffusion rather than by direct fusion with the cells [32]. The result is a marked increase in the local acidity at the sites where FA vesicles attach to the endothelium, which disrupts many important ion exchange processes, namely trafficking of Ca^{2+}, K^+, and Na^+ [33]. These ions control vital cell processes, and namely calcium ions control contractibility of smooth muscle in the arteries [6], and also of the myocardium as it is known that this muscle is also controlled by the endocardium [34].

Local acidity also strongly reduces binding affinity of albumin to calcium ions which are released at the sites where FA vesicles attach to endothelium, and react with acids to form calcium salts, and other calcium derived molecules. This partially explains artery calcification.

Local acidity also reduces affinity of hemoglobin to oxygen (Bohr–Haldane effect [35]), therefore strongly increasing local production of ion superoxide (and other ROS), which is toxic to endothelial cells in the absence of adequate levels of the various superoxide dismutase enzymes (SODs) [36].

As a consequence, endothelial cells at the vesicle attachment sites become damaged or die, hence liberating cytokines that mobilize both the immune and repair systems to the affected site. The result is endothelial remodeling, which entails plaque formation (see Section Thromboembolic stroke below).

Attachment of vesicles occurs at sites where flow shear stresses are minimal, because they correspond to minimal entrainment in the blood stream (minimal lift force). This is made clear in the mapping of arterial plaque distribution [37]. This aspect also explains why plaques develop at preferred sites rather than being distributed uniformly on the inner artery wall. Not surprisingly, plaque composition includes "incrustation around individual microvesicles of lipids eventually coalescing to larger clumps of calcification" [38].

If this process keeps developing at low intensity for years, it may promote progressive arterial calcification, with growing number of plaques of increasing dimension covering the inner surface of affected arteries. The fact that arteries most affected by calcification are just those that receive the altered blood ejected from the left ventricle (the coronaries, aorta, and the carotids) [37] adds credit to the process above described.

Heart attack

When spikes of FFA occur in a context of acidemia, exceptionally strong activation of the endocardium and the endothelia of the arteries may occur. We stress again that spontaneous formation of FA vesicles from alkaline micelles is an autocatalytic process [25]. Hence when FFA concentration peaks to high values we must expect a stormy development of FA vesicles in the left atrium and ventricle together with very intense and acute activation of the endocardium and endothelium, namely in the coronaries, the aorta, and the carotids.

If endocardium in the left atrium and ventricle is severely damaged, the myocardial function is also compromised in what respects to contractibility and electric activity [39]. Due to local acidemia the coronaries constrict, hence lowering blood flow into the myocardium [31]. Additionally, severe local acidemia due to high FA vesicle concentration sharply decreases affinity of hemoglobin to oxygen, which is released into the blood, then promoting formation of ion superoxide and ROS in the acidic blood stream that feeds the myocardium. In regions perfused by this toxic blood with low pH, and carrying FA vesicles together high concentration of ion superoxide and ROS, myocardial cells might die (Contraction Band Necrosis – CBN), albeit oxygen is available locally. This might

explain why in many cases of heart failure, oxygen was found at almost normal levels in the myocardium [3]. It explains also how ischemia can develop albeit no thrombus is found blocking the coronary arteries [3]. In the present context the extent of myocardial ischemia depends both upon the extent of the region bathed by the toxic blood and the ability of the cardiac veins to collect and return blood to the right atrium through the coronary sinus.

We speculate that toxic FFA vesicles might be responsible for myocardial CBN, by rupturing sarcolemma, the cell membrane of the myocardium striated muscle fiber cell. In fact, at the sites where FFA vesicles release their acidic core, an acidic spot must be created that decreases calcium binding affinity to albumin, and thereby high free calcium levels are likely to be present at these sites. By quoting [40]: "massive Ca^{2+} entry from the plasma reperfusing the tissue (causes) an enormous cell swelling, contraction bands, and mitochondrial hydroxyapatite accumulation. Thus, the mitochondria of myocytes reperfused early in the phase of irreversible injury exhibit significant energy-linked function manifest by the accumulation and deposition of calcium phosphate. After reperfusion, such mitochondria could open the mitochondrial permeability transition pore, thereby releasing some of the accumulated Ca^{2+} and accelerating cellular disintegration". As noted by known cardiologists: "in other specific diseases where CBN is found, an adrenergic stress is part of their natural history" [3].

Differences between heart attack and mild endothelial activation is only a matter of intensity. Due to the stormy development of FA vesicles that is thought occur during a heart attack they are most likely formed at higher degree within the left atrium and ventricle, while during mild endothelial activation they are likely formed within the nearby arteries, and in lesser degree.

Despite the above process might explain ischemia development without arterial occlusion, thrombi may be concomitantly formed as the consequence of activation of prothrombotic factors (see Section Thromboembolic stroke) and then block the coronaries. In such a case, hypoxia leads to pyruvate formation from conversion of glucose, or fatty acids (through a reaction with acetyl-CoA). Lactate is then produced from the pyruvate faster than the body can process it, causing lactate concentrations to go up, therefore explaining why acid lactic is found in the myocardium in many cases of heart attack [41].

Here a question remains: Why a state of acidosis (and blood acidemia) is not always followed by heart attack? We remark that acidosis/acidemia originates from various factors, and may develop at low levels of FFA, though FFA must be present in adequate concentration in the blood for micelles and then vesicles to form. This aspect points to the essential role of FA metabolism, namely the hormones that promote lipolysis and discharge of FFA into the blood. As referred before the liver takes up FFA from the blood esterifies and releases them into the blood packaged as triglycerides into VLDL particles. Therefore, concentrations of VLDL and triglycerides in the blood are markers of FFA trafficking and may be viewed as surrogates of blood FA concentration in the blood. Long ago, blood levels of VLDL and triglycerides have been considered as risk factors for cardiovascular diseases. Yet, in the above framework, blood levels of VLDL and triglycerides (as surrogates for FFA level), only become dangerous if superimposed to acidemia.

Finally, we remark that the clinical symptoms of acidemia and of heart attack have much in common [42]. All the main symptoms of heart attack are easily understood in the framework developed above:

(a) "Chest discomfort or pain (feel like a tight ache, pressure, fullness or squeezing in the chest); Pain or discomfort may spread beyond the chest to the shoulders, arms, back, neck, teeth or jaw; Pain or discomfort may spread beyond the chest to the shoulders, arms, back, neck, teeth or jaw; Pain may extend downward into the abdominal area. Nausea and vomiting". The symptoms perfectly match development of micelles and vesicles, attachment and damage to endocardium and the endothelia of arteries of the heart (damage to myocardium), chest and arms, the whole aorta and upper distributaries (pain in the back, neck, teeth or jaw), lower distributaries (nausea and vomiting), which are bathed by toxic blood with FA vesicles, superoxide ions, and ROS ejected from the left ventricle.
(b) "Shortness of breath (patients may pant for breath or try to take in deep breaths)". This symptom is characteristic of acidosis/acidemia, and it is worth noting that "try to take in deep breaths" (Kussmaul breathing) is characteristic of severe acidemia;
(c) "Lightheadedness" appears as the result of vasoconstriction of arteries in the brain due to acidemia;
(d) "Anxiety" as the result of activation of the sympathetic system facing a threat to whole body;
(e) "Excessive sweating" as a means for the body to get rid of excess acid.

Additionally it is well known that people that suffered heart attack often felt tired in the days before. This may be a symptom of developing acidemia since muscle fatigue comes with acidemia because "intracellular acidosis affects many aspects of muscle cell function; for instance it reduces maximal Ca^{2+}activated force and Ca^{2+} sensitivity, slows the maximal shortening velocity and prolongs relaxation" [43].

Thromboembolic stroke

It is well established that thromboembolic stroke is caused by occlusion of an artery in the brain either by a locally formed thrombus or by an embolus generated elsewhere upstream. From now on we use the term clot as a general designation for both thrombus and embolus. The simplest definition of clots is that they are composed of platelet aggregates in a mesh of fibrin, which includes also other components (macrophages, foam cells) [44].

There is a huge body of literature dealing with clot formation [45]. The actual paradigm of clot formation relies on the activation of atherosclerotic plaques by factors present in the blood, which produce an inflammatory state in the course of which clot is formed and released into the blood stream. In what follows we present another process by which clots may be formed.

Emboli most usually arise from the heart especially during atrial fibrillation events [46,47]. It is not difficult to understand clot formation within the present framework. The abnormal heart rhythm with rapid and irregular beating that is characteristic of atrial fibrillation strongly shakes the blood within the left atrium and ventricle hence creating the conditions propitious to FA vesicle formation, in case of adequate level of FFA [21,23,24]. FA vesicles are not clots, because not only their composition is very different but also because they are very small and not likely to reach dimension characteristic to clots. However, because they are clusters of FA, they have the ability to activate blood coagulation factors, namely Factor VII (Hageman Factor) and Factor XII. This aspect has been observed more than fifty years ago [48–54]. At the epoch it was found that "concentrations of soaps comparable to the concentration of free fatty acids found in human plasma shorten the recalcified clotting time and accelerate the formation of artificial thrombi in vitro the clot-promoting properties of the soaps of long-chain saturated fatty acids" [53]. Connor and Poole demonstrated that "sodium soaps of long-chain saturated fatty acids dramatically accelerated the recalcified clotting time of whole blood in silicone-coated tubes or in rotating plastic loops". Additionally, it is of great significance that it was referred that: "the data presented

suggest that the clot-promoting properties of the soaps are unlikely to be significant under the conditions present in circulating blood". From the above quotations it is also of note that rotating plastic loops dramatically accelerated clotting. Actually, as referred above, FFA soaps are micellar solutions that when strongly shacked rapidly form FA vesicles. Also of note is the reference to the fact that under the conditions present in circulating blood it is unlikely the formation of blood clots. Interestingly, it was also observed that there was a rapid net uptake of FFA by human platelets when long-chain FFA, bound to human serum albumin were incubated with platelet suspensions [55], and that platelet aggregation promoted by long-chain saturated FA is only observed when the molar ratio FFA/albumin is greater than 2 [56], therefore confirming that a high blood FFA level is required to induce platelet aggregation.

These features add credit to the idea that clots may form through activation of blood coagulation by FA vesicles, and therefore they have to be present in the blood prior to clot development.

Though the research line on the link between FFA soaps and blood coagulation seems to have been discontinued towards the end of the sixties of the last century, many references on other aspects of such link continued to appear in later published literature. Elevated plasma FFA levels also favor thromboxane formation [57], vasoconstriction (though not all FFA do it at the same degree) [58,59], significantly elevate lipoprotein(a) [60], activate plasminogen activator inhibitor-1 (PAI-1) [61,62], and the coagulation factors VII and XII [63,64].

All those FFA effects create the appropriate explanatory context for considering FFA vesicles as the precursors (and probably the core) of clot formation. Concomitantly all the above-mentioned aspects are consensually considered risk factors for clot formation. The common link is elevated blood FFA level. In this sense, serum VLDL levels should be viewed as a surrogate marker of a state of elevated blood FFA level. Risk of acute crises (heart attack, thromboembolic stroke) may be very high when spikes of FFA are superimposed to acidemia. Therefore, periodic checking of blood levels of FFA is of most clinical relevance.

Additional remarks

Damage to endothelium starts repair processes that involve clotting factors such as PA1-I, fibrin, lipoprotein(a), collagen precursors, among others, the immune system (white blood cells, cytokines, and other mediators) and lipoproteins (mainly LDL, and HDL) carrying several molecules, namely esterified and unesterified cholesterol . Inflammation is characteristic of the whole process, which leads to formation of atheromatous plaques mainly composed of fat, cholesterol, and calcified deposits, collagen, and elastin. Endothelial progenitor cells that are multiple different cell types circulating in the blood [65], are attracted to the lesion, and play various roles in the regeneration of the endothelium. As the result, severe narrowing of arteries may occur, thereby limiting blood flow. The actual paradigm of formation of atherosclerotic plaques assigns to cholesterol a major role, and abundant related literature may be found elsewhere, e.g. [66].

Though the process here proposed for clot development does not assign such role to cholesterol, it does not exclude the possibility of atheromatous clots to be also originated by occasional rupture of unstable plaques. Instead, in the proposed scheme plaque formation is the result of the same process that originates clots with vesicle cores, which also involves attachment of FFA vesicles to the endothelium and subsequent inflammation. This process of endothelial activation might be active in other arterial diseases.

The huge amount of observational data collected in the last hundred years enabled the identification of panoply of biomarkers that may be associated with cardiovascular diseases. If the association is statistically significant they are termed "risk factors". However, because association does not mean causation we do need to identify the real drivers of the main processes that lead to establishment of disease. Therefore a hierarchy must be established amongst risk factors such as to differentiate the respective role in the process. In the scheme here proposed, persistent blood acidemia together with high blood levels of FFA is the driver of atherosclerosis, while spikes of FFA superimposed to acidemia is the driver of acute crises, namely of heart attack and thromboembolic stroke. The remaining risk factors appear either as participants or facilitators of the process, or as collateral "imprints" left on blood composition (biomarkers), or the endothelium. VLDL particles, triglycerides, albumin, lipoprotein (a), plasminogen activator inhibitor-1, fibrin, and the coagulation factors VII and XII are examples of participants/facilitators. Inflammations, calcified vesicles, calcium salts, and other arterial deposits are "imprints" of the ongoing process that might end with an acute crisis.

This hierarchy is fundamental for the design of clinical trials, because in case of the target selected for testing its influence on some end-point, is a minor participant/facilitator of the process it is likely that the trials ends with deceptive results. Unfortunately, so far no major trial has addressed the role of FFA in cardiovascular disease.

The explanatory framework proposed here appears only as a starting point, and is not intended to tell the whole history of cardiovascular disease, although it aims at opening a new way to look at a very complex problem whose full understanding remains somehow elusive.

Conclusions

The hypothesis that prolonged acidemia with high blood levels of free fatty acids shapes the basic context for formation of fatty acid micelles and vesicles with an acidic core that fuse with the endothelia is substantiated both from the side of biomedical research, and the side of medical literature. It offers a comprehensive explanation of many known features of cardiovascular diseases. As a first step for an alternative view of cardiovascular diseases it requires further developments.

Conflict of interest

None declared.

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