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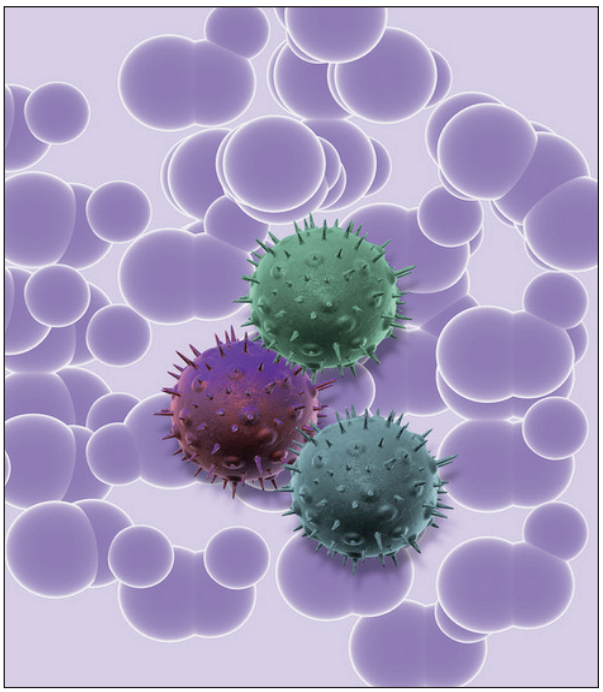

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Towards a New Understanding of the Molecular Mechanisms of Cardiovascular Disease

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Abstract: In this article, we review a process put forward in former publications by which fatty acid micelles and vesicles with an acidic core can develop, and the physiological manifestations of such process in the human body. The process allows the understanding of arterial calcification, why coronary arteries, aorta, and carotids are the most affected vessels, and the preferential distribution of plaques on the areas of the endothelium where shear stress is lower. Also reviewed are the role of systemic buffers in the control of blood pH, and the effects of pollutants, namely heavy metals, diet, and ethanol intake, on cardiovascular risks. The most important cardiovascular risk factors are explained based on their effect on either lowering blood pH or increasing blood FFA concentration, or both. Cardiovascular risk protection factors also find an explanation within the proposed framework. As a final point, the importance of knowing blood pH and concentrations of free fatty acids and albumin concentrations in the blood is emphasized in developing a strategy of prevention of cardiovascular disease. [*Discovery Medicine* 28(154):1-6, 2019]

Introduction

For decades, lowering low-density lipoprotein cholesterol (LDL-C) to circumvent cardiovascular disease (CVD) has been the cornerstone of preventive cardiology. However, the cholesterol hypothesis has a reduced explanatory capacity regarding the understanding of the multiple manifestations of cardiovascular disease (DuBroff, 2018). Consequently, from time to time, some researchers call for a reappraisal, or turn their attention back to other actors considered to be implicated in CVD, such as triglycerides (Pradhan, 2019). On the other hand, understanding of the acute events (myocardial infarction, stroke, sudden cardiac death) based only on the idea of occlusion of arteries proves to be very difficult and complicated (Rothberg, 2013).

In recently published articles (Reis, 2016; 2017), it was put forward a new framework for the development of CVD in which major cardiovascular risks could be easily understood. In addition, that framework allows us to understand the clinical manifestation that is characteristic of each acute cardiovascular event.

In this paper, we add further evidence and broaden our understanding of other CVD risks within the proposed framework.

New Framework for the Understanding of Cardiovascular Disease

Fatty acids (FA) are one of the most important sources of energy in the body. Compared to the same amount of glucose, they produce about 2.5 times more energy. It is therefore a high-quality fuel that is used on special occasions (e.g., fight or fly), which plays a very important role in human physiology (Newsholme and Leech, 2010).

An interesting fact is that fatty acids are esterified in the liver and the adipose tissue to form triacylglycerol (also known as triglyceride) by binding three fatty acids to a glycerol molecule. They are then transported in the blood by lipoproteins, namely VLDL and chylomicrons.

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And, there is a good reason why until FA are oxidized in mitochondria, they are kept esterified as triglycerides. In fact, when free in solution, the fatty acids undergo phase transformations with changes in pH. Close to normal blood pH (7.38-7.43), fatty acids are fully protonated and form an oil phase, while at higher pH they become deprotonated and form free fatty acid (FFA) micelles (Wald *et al.*, 2006; Morigaki and Wald, 2007; Zhu *et al*., 2013; Hentrich and Szostak, 2014). When in the bloodstream micelles flow turbulently to a lower pH zone, a new transformation occurs, giving rise to fatty acid vesicles in an autocatalytic process (Markvoort *et al*., 2010; Musacchio and Torchilin, 2013).

Due to deprotonation of fatty acids, vesicles formed in alkaline conditions have an acidic core (pH partition effect) (Chen and, Szostak, 2004; Wald *et al.*, 2006; Morigaki and Wald, 2007; Musacchio and Torchilin, 2013; Hentrich and Szostak, 2014). Fatty acid vesicles easily fuse with the endothelia (Cevc and Richardsen, 1993), then deliver their acidic core, and damage ion channels (Nilius and Droogmans, 2001) therefore disturbing endothelial functioning. This is critical in the case of the heart because damage to the cardiac endothelium compromises myocardial function (Brutsaert *et al*., 1998). Vesicle attachment may also occur on the endothelia of the arteries. At the site of vesicle attachment, an acid spot is created due to the release of the acidic core, therefore, lowering local pH. Calcium is released at this acidic spot due to loss of affinity between albumin and calcium ions. Continued aggression of the FA vesicles to the endothelium leads to progressive calcification on the affected areas (Reis, 2016).

One may wonder if such changes in pH do occur in human blood. In fact, there are very special conditions where this can occur, as we will see in the following.

Human physiology controls blood pH very effectively so that it is not out of the narrow range 7.38-7.43. This control is accomplished by systemic buffers (carbonic acid-bicarbonate system, hemoglobin, protein system, and phosphate system), renal function, and excreting excess acid through sweating, urine, etc. [for a more detailed analysis see Reis (2017)].

The buffer that most quickly reacts to a pH lowering is the carbonic acid-bicarbonate system by increasing the respiration rate (hyperventilation) to increase carbon dioxide release, and thereby favoring the rapid return to normal pH levels. By increasing the release of carbon dioxide from blood in the lungs, hyperventilation induces local blood alkalemia, and therefore creates the conditions needed for the development of fatty acid micelles. Additionally, under alkaline conditions albumin loses affinity for fatty acids, releasing them in the blood as FFA, while increasing affinity for calcium whose blood concentration decreases (Newsholme and Leech, 2010). This further increases the concentration of FFA in the alveolar blood, an effect additionally reinforced by the fact that oxyhemoglobin generated in the alveoli is a buffer for fatty acids weaker than deoxyhemoglobin (Thomas and Lumb, 2012).

Blood flowing from the lungs to the left atrium where pH is lower may generate fatty acid vesicles as described above, which may damage the inner walls of the left atrium and ventricle, and the endothelium of nearby arteries (namely the coronaries, the aorta, and the carotids). The process and the occurrence of acute events (myocardial infarction and thromboembolic stroke) are described in detail in Reis (2016). However, it should be noted that for fatty acid vesicles to originate, the concentration of FFA in the blood must be high, though the threshold level is not yet known.

Another situation in which unrestrained hyperventilation occurs is during intense sports practice, e.g., in basketball and soccer games. If the blood concentration of FFA is very high and exceeds a critical ratio to albumin concentration (see below), a process of rapid formation of micelles and fatty acid vesicles may occur, which by the above process can cause myocardial disturbances, namely disruptions in electrical conduction. This might lead to sudden cardiac death (SCD), even in the absence of atherosclerosis. As referred by some authors "Cardiovascular-related sudden death was the leading cause of death in 45 (56%) of 80 medical cases, and represented 75% of sudden deaths during exertion. … .Data from our pathology unit demonstrate a high prevalence of SCDs with a morphologically normal heart (23%), with no other cause of death found at autopsy" (Sheppard, 2012), and "Unexplained death with a structurally normal heart is the most common finding after suspected sudden cardiac death in NCAA athletes" (Harmon *et al*., 2014).

Sudden Unexplained Nocturnal Death Syndrome (SUNDS) might also find an explanation in the above context, since it was noticed that "Gurgling, gasping, or labored respirations appeared in some victims before death" (Zheng *et al*., 2018). In fact, if acidemia occurs during sleep, the fastest way to bring blood pH to normal values is by increasing the removal of CO_2 through

the acceleration of the respiratory rate, together with the increase in urine production.

In support of the above framework, several recent studies have associated sudden cardiac death with high FFA levels (Pilz *et al*., 2007; Havmoeller *et al*., 2014).

The framework presented above also allows us to understand the symptoms that come with myocardial infarction: "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; shortness of breath; lightheadedness; anxiety; excessive sweating." For a detailed analysis, see Reis (2016). It also allows us to understand why atherosclerotic plaques are preferentially distributed through the coronary arteries, the aorta, and the carotids, which are the vessels that first carry left atrial and ventricular blood where fatty acid vesicles develop (Reis, 2016). Additionally, it is possible to understand why atherosclerotic plaques in the arteries occur in the areas where shear stress is low, because it is precisely in those areas where the lift force is lower, thus allowing fatty acid vesicles to attach more easily to the endothelium (Reis, 2016).

In this context, we can also explain the occurrence of myocardial infarction, even without the existence of clots obstructing the coronary arteries, an aspect that has long been observed by cardiopathologists (Baroldi and Silver, 2004; Abdelghani *et al*., 2015). Yet, clots may appear in the blood due to changes in the various blood components owing to the presence of high concentrations of FFA, and then provoke arterial occlusion. In fact, high blood FFA levels favor thromboxane formation, vasoconstriction (though not all FFA do it at the same degree), significantly elevate lipoprotein(a), activate plasminogen activator inhibitor-1 (PAI-1), and the coagulation factors VII and XII. However, it has long been known that platelet aggregation promoted by long-chain saturated fatty acids only starts to be observed when the molar ratio of FFA/albumin is greater than 2 [see Reis (2016) for details]. This explains why not every condition in which both acidemia and FFA are present leads to formation of fatty acid micelles and vesicles, and clots. Nevertheless, albumin is crucial as a fatty acid carrier, because low concentrations of albumin may originate a higher concentration of FFA in the blood. Not surprisingly, a low blood albumin concentration predicts mortality, at least in nonagenarians (Yanagisawa, 2010).

A Rationale for Cardiovascular Disease Risks

Concerning the so-called cardiovascular risks, the above framework also provides a consistent explanation. The term "cardiovascular risk" is a definition of statistical nature, representing the set of indicators that in a statistically significant manner were associated with CVD. Although the statistical method detects associations of certain indicators with CVD, it does not distinguish between those that are causal in nature and those that are simply consequences.

Even in this context, a comprehensive explanation for the vast majority of cardiovascular risks can be found. In general, known risk indicators that really shape the context for cardiovascular events originate in the body in the form of either acidemia or a large release of FFA in the blood, or both. Actually, because both high levels of FFA and acidemia must come together to develop CVD, if one of these conditions is already in place, then the probability of the simultaneous occurrence of both conditions and therefore of a cardiovascular event is higher. As a result, the occurrence of either acidemia or a high level of FFA has to be regarded as cardiovascular risk.

Acidemia may result either from increased H^+ load or to HCO_3^- loss. Many drugs that disrupt the acid-base balance in the body and lower blood pH are listed as cardiovascular risk factors. A more detailed review of drugs that contribute to acidemia in one or the other way may be found in Reis (2016). Particular reference should be made to the most prescribed drugs, namely NSAIDs (Hunter *et a*l., 2011; Liamis *et al*., 2010), and proton pump inhibitors (PPI), which contribute to lower blood pH and have been associated with increased CVD risk (Shah *et al*., 2015). PPIs block the release of acid into stomach, therefore, reducing the body's capability to get rid of part of the acid load. Chronic kidney disease which leads to reduction in serum bicarbonate (HCO_3^-) concentration, therefore contributing to acidemia, is also listed a cardiovascular risk factor [see Reis (2017) for more details].

Diets high in proteins, carbohydrates, and sugars also contribute to the body's acid load, while fruits and vegetables have an alkalinizing effect, which may explain why they are considered as being protective against CVD (Reis, 2017).

The systemic buffers that regulate blood pH also decline with age and are affected by some diseases. The carbonic acid-bicarbonate system efficiency also decreases when lungs are affected by pollution, or by an

influenza episode, factors that have been recognized as cardiovascular risks. Aging, due to the concomitant loss of the efficiency of the carbonic acid-bicarbonate buffer, is itself a cardiovascular risk factor. The functioning of systemic buffers may be improved with physical exercise, therefore explaining why physical activity is protective against CVD (Reis, 2017). Hemoglobin, which in blood has about six times the buffering capacity of the plasma proteins, is affected by many diseases. Namely, sickle cell hemoglobin polymerizes and becomes insoluble under hypoxic conditions, causing a number of structural and functional abnormalities in affected red blood cells (Piety *et al*., 2015) thereby affecting buffering capacity. It is known that sickle cell disease increases CVD risk markedly (Akinbami *et al.*, 2019).

Heavy metals, namely lead and cadmium (Navas-Acien, 2007; Lamas *et al*., 2016), even at a slightly elevated concentration in the blood, have also been considered risk factors. Not surprisingly, both metals contribute to acidemia, specifically to renal tubular acidosis (Haque *et al*., 2012; Seifter and Chang, 2017). A causal relationship was found between lead and hypertension (Navas-Acien, 2007), and the process by which acidemia may cause peripheral hypertension was described in Reis (2017).

In recent decades, multiple studies have pointed to FFA as a cardiovascular risk factor (Carlsson *et al*., 2000; Pirro *et al.*, 2002; Pilz *et al*., 2006; Pilz *et al*., 2007; Pilz and Marz, 2008; Mathew*et al.*, 2010; Roy *et al*., 2013; Havmoeller *et al.,* 2014). FFA blood concentration may increase in response to multiple factors, though stress plays a major role here, since it induces physiological changes, namely, the activation of the hypothalamic-pituitary-adrenal axis, with mobilization of FA from the adipose tissue. Stress has long been recognized as a major cardiovascular risk factor. Negative psychological stressors (death of a family member or friend, experience of an accident or disaster, anxiety, etc.) that promote the increase FFA concentrations in blood have been implicated in CVD (Reis, 2017).

In the present framework, it is also possible to understand the increase of cardiovascular risk of menopausal women, the role of statins (they reduce the release of FFA into blood, but contribute to pH lowering) on CVD prevention, and the circadian distribution of occurrence of cardiovascular events (Reis, 2017).

Interestingly, alcohol, namely light to moderate consumption of red wine, has been found to be a factor protective against CVD, while moderate to heavy consumption is deleterious to health (Mukamal *et al*., 2010). It was found that after consumption of 38 ml of ethanol diluted in 362 ml of water, a reduction of 35-37% in FFA concentration occurred (Pownall *et al.,* 1999). This reduction is achieved in part by esterification of FFA by ethanol, producing fatty acid ethyl esters, which are toxic to the pancreas (Huang *et al.,* 2014). Concomitantly, both the cardiovascular and non-cardiovascular mortality indexes decrease in light to moderate drinkers but increase markedly for moderate to heavy consumers (Klatsky, 2010). We can interpret these results in the present context by noting that ethanol has the positive cardiovascular effect of reducing blood FFA concentration, a beneficial effect that is overshadowed by the generation of fatty acid ethyl esters that increases with ethanol consumption.

Recently, results of the PESA Study pointed to increased cardiovascular risk resulting from breakfast skipping (Uzhova *et al*., 2017). This result, which is hardly explained by the current views of CVD, finds an easy explanation within the present framework (Reis, 2018).

Conclusions

The interplay between blood pH and blood FFA concentrations in the context of keeping blood pH within the normal range offers a robust framework for explaining the occurrence of atherosclerosis and its manifestations, and for the acute cardiovascular events.

Proper functioning of systemic buffers, and other systems and organs that control blood pH, is critical to preventing cardiovascular disease. A diet that does not excessively increase the body's acid load as well as living with low levels of pollution are important factors in reducing cardiovascular risk. Also, avoiding negative psychological stress thus reducing raised FFA concentrations and spikes of concentration of FFA in the blood is also very important.

Within the framework here presented, it is exceedingly important for the prevention of CVD and its acute episodes with the timely knowledge of blood pH, FFA, and albumin concentrations in the blood, which together with the ratio between these last two values allow us to understand the degree of risk for a cardiovascular event.

Disclosure

The author declares no conflicts of interest.

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