Inflammation, coagulation, weather and arrhythmogenesis: Is there a linkage?

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The role of inflammation and coagulation in the pathophysiology and triggering of cardiac arrhythmias is a matter of debate. In commenting on our article [1] about external triggers of supraventricular tachycardia, Yalta and the coauthors [2] discussed some mechanisms regarding this issue. They noted that, among other mechanisms, weather conditions may induce a systemic inflammatory and hypercoagulable response facilitating arrhythmogenesis in susceptible patients. They also suggested that the association of short-term meteorologic situations with occurrence of cardiac arrhythmias could be involved in the seasonal variation and winter increase in the frequency of cardiac arrhythmias [2]. However, several important points should be discussed in this regard.

Acute and chronic risk factors. Factors contributing to the occurrence of acute cardiac events could be defined as chronic, i.e. long-term acting (months, years), and acute, short-term acting (up to several hours) [3]. Chronic risk factors include hypertension, hyperlipoproteinemia, diabetes, smoking and other factors which create a pathomorphological substrate for a cardiac event by promoting the development of coronary atherosclerosis, cardiomyopathia or other structural changes. Acute factors, or triggers, are external factors, activities or situations responsible for determining the very moment of onset of cardiac events [3] in a significant number of patients [4,5].

Our research on triggering supraventricular [1,6] and ventricular [7,8] arrhythmias accounted for chronic cardiovascular risk factors, but was specifically designed to examine acute external triggers including physical activity, emotional stress and meteorologic elements such as atmospheric pressure, relative air humidity and temperature. We investigated the occurrence of arrhythmias within a 2-hour frame for absolute static levels of meteorologic elements, and a 3-hour frame for change in the level of meteorologic elements. Therefore, we researched short-time associations and acute triggering effect and extrapolation of our results to long-term seasonal meteorologic influences cannot be made.

Inflammatory disorders and cardiac arrhythmias: the hypothesis. The idea of a link between inflammation and arrhythmias has originated from clinical observations that heart rhythm disturbances are associated with inflammatory conditions affecting the heart such as myocarditis, pericarditis and post-pericardiotomy syndrome [9]. In children, cardiac arrhythmias may be secondary to infections with Coxackie B2 [10], influenza B [11], influenza A and enterovirus [12], varicella [13] and respiratory syncytial virus [14], particularly in the presence of myopericarditis.

The majority of data to support this idea resulted from the research on atrial fibrillation, an arrhythmia that has its specificities in development and perpetuation [15]. Inflammatory disorders that have been linked to atrial fibrillation include the presence of psoriasis [16], rheumatoid arthritis [17], herpes simplex infection [18] and celiac disease [19]. However, in all of the above cases, infection and inflammation are not triggers in a typical manner; they over a certain period create histopathological changes that underlie arrhythmias.

Inflammatory mechanisms and arrhythmogenesis. A bulk of evidence associates inflammation with cardiac arrhythmias. On the systemic level, several inflammatory mediators, such as C-reactive protein, tumor necrosis factor-α, interleukins 2, 6 and 8, monocyte chemoattractant protein-1 and YKL-40 have been associated with a greater risk of atrial fibrillation [15,20–22]. A study performed on 47,000 participants has suggested that increased plasma CRP per se does not increase the risk of atrial fibrillation because while CRP was robustly associated with the risk, genetically elevated CRP was not [23]. Therefore, the association is not quite simple and needs further exploration.

Besides soluble markers, patients with atrial fibrillation have an increased expression of monocyte Toll-like receptor [24] and T cell activity [25]. In contrast to systemic inflammation, an observation of higher CRP levels in the left atrium than in the coronary sinus during atrial fibrillation implies a role of local inflammatory processes [26]. The inflammatory properties and the ability of epicardial adipocytes to modulate the electrophysiology of atrial myocytes could be also involved in local mechanisms of supraventricular arrhythmias [27,28].

For ventricular arrhythmias, increased inflammatory markers including C-reactive protein [29–31], monocyte chemoattractant protein-1 [30], tissue inhibitor of metalloproteinase-1 and interleukins 6 and 8 [30,32] have been linked with the arrhythmia occurrence. In patients with structural heart disease, electrical storms, i.e. a cluster of ventricular tachyarrhythmic events, have been associated with proinflammatory activity assessed through elevated interleukin-6 and high sensitivity C-reactive protein [33]. In patients with heart failure, elevated C-reactive protein has been suggested as an independent predictor of arrhythmia occurrence and complexity, particularly ventricular tachyarrhythmias [29].

Coagulation and arrhythmias. It has been reported that patients with compared to those without ventricular fibrillation during an acute myocardial infarction have a more pronounced thrombin generation remote from the incident site [34] and an enhanced procoagulant response and platelet reactivity to inflammatory stimuli [35]. Thrombin could be the key arrhythmogenic factor of the procoagulant state (Fig. 1.). In cardiomyocytes, thrombin increases automaticity, cytosolic calcium and contractility [36,37], induces release and accumulation of lysophosphatidylcholine and activates voltage-gated sodium channels [35,38,39].

An increase in blood viscosity increases flow resistance [40,41] and decreases the blood flow which all favor tissue ischemia [42]. Subsequent compensatory mechanisms such as pressure increase or vasodilatation both increase circulatory load and in turn further increase the risk of ischemia and arrhythmia. Furthermore, increased circulatory load not only increases filling pressures in the heart cavities and through increased

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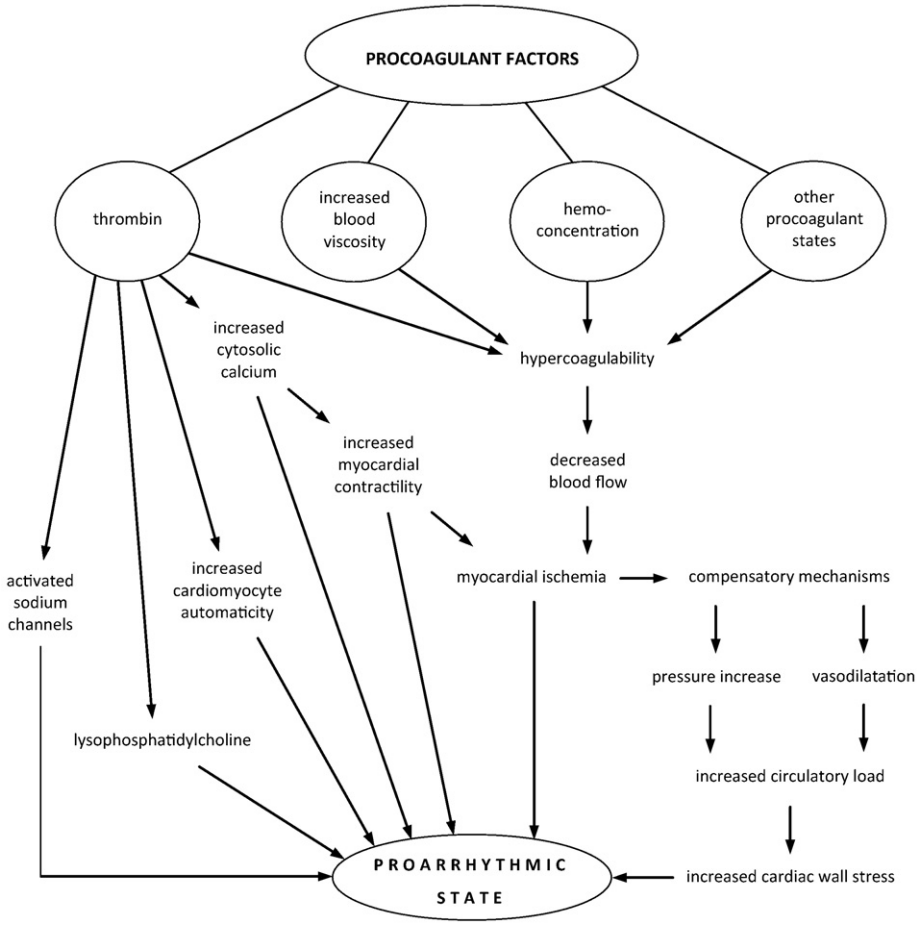

Fig. 1. Theoretical pathophysiological mechanisms linking procoagulant factors with increased risk of arrhythmia. Thrombin seems to be the most important factor with several proarrhythmic effects. Hypercoagulability decreases blood flow and through encumbered hemodynamics and myocardial ischemia may facilitate arrhythmia in susceptible patients.

wall stress may directly facilitate arrhythmogenesis (Fig. 1) but also enhances inflammatory processes and inflammatory cell accumulation in the left ventricle [43].

When present, inflammation itself is a strong facilitator of coagulation. Inflammation increases coagulability by inducing platelet and coagulation activation, tissue factor production by monocytes, fibrinogen expression, and endothelial dysfunction [15,44]. Increased expression of thrombocyte CD-40 ligand could be a factor specifically linking coagulation, inflammatory stimuli and malignant ventricular arrhythmias [45]. Inflammation also increases blood viscosity and stimulates aggregation between the blood cells [44,46,47]. Vice versa, endothelial dysfunction, activated platelets and platelet–leukocyte interactions initiate a positive feedback loop and further promote inflammation [15,44].

Meteorologic elements, inflammation and coagulation. Out of the meteorologic elements that have been associated with an increased arrhythmia occurrence, three have also been implicated in provoking a thrombotic or inflammatory response — air temperature, atmospheric pressure and relative humidity (Fig. 2).

An increasing incidence of tachyarrhythmic events has been reported with a temperature both decreasing below [48] and rising above 0 °C [6–8,48]. On one side of this U- or V-shaped association, cold exposure has been associated with a rapid thrombo-inflammatory response. Normal thermoregulatory adaptation to cold includes a loss of plasma fluids, increase in platelet and red cell counts, blood viscosity, and plasma fibrinogen, without compensatory increase in fibrinolytic activity [49,50]. In animal studies, acute cold stress induced a marked increase in the levels of various inflammatory markers and heat shock proteins, and produced a serious injury of the heart tissue [51,52]. On the opposite side of the temperature spectrum, higher temperatures may increase coagulability through increased blood viscosity, red cell and platelet counts [3].

Higher absolute levels of atmospheric pressure [1,6,8] and increasing air humidity [1,6,7] have been associated with a greater arrhythmic risk. A rapid inhibition of interleukin-1β, unrelated to partial oxygen pressure, has been observed in an exposure to reduced barometric pressure within several hours [53]. In addition, ascending to high altitude, i.e. hypobaric environment, has been associated with a reduced coagulability [54] suggesting a more thrombo-inflammatory activity with higher compared to lower atmospheric pressure. Increased air humidity may increase coagulability through an encumbered thermoregulation, dehydration and increased blood viscosity [3,7] (Fig. 2).

Inflammation, coagulation, weather and arrhythmias: major unresolved issues. The main question is whether inflammation is the cause or the consequence of arrhythmia. In contrast to a body of evidence described afore suggesting simply an association, observations of a decline in the level of inflammatory markers after successful ablation of atrial fibrillation imply that the inflammatory processes are at least partly a consequence of arrhythmia [55,56]. An acute episode of atrial fibrillation within minutes initiates platelet–monocyte interaction through increased expression of P-selectin on platelets and microparticles, and the response of monocytes and granulocytes to P-selectin [57].

In addition to uncertainties about local versus systemic inflammation, there is also a possibility of genetic susceptibility to the proarrhythmic effects of thrombo-inflammatory processes. For interleukin-6 −634C/G