Mechanolectric Feedback in the Ischemic Myocardium: An Interplay That Modulates Susceptibility to Fibrillation

Retroalimentación mecanoelectrónica del miocardio isquémico: un juego que modula su capacidad fibrilatoria

David Calvo and José Jalife

*Unidad de Arritmias, Hospital Universitario Central de Asturias, Oviedo, Asturias, Spain
†Center for Arrhythmia Research, University of Michigan, Ann Arbor, Michigan, United States

Article history:
Available online 11 January 2013

Changes in the medical treatment of acute myocardial infarction (AMI) over the last few decades have markedly improved patient survival. Early recognition and prompt treatment of ventricular fibrillation (VF) by emergency services and coronary units is particularly important, as VF is the underlying cause of the collapse occurring in the first few hours after AMI. Nevertheless, the most common cause of sudden cardiac death in individuals aged more than 35 years is still coronary artery disease, and its principle intermediary agent is VF. Ensuring that the patient is reached early so that effective defibrillation can be performed is the concern of healthcare organization, while preventing the mechanisms that trigger VF is a concern of science; indeed, how the mechanisms of this incompletely understood phenomenon are triggered, and in whom, is currently a topic of debate.

The clinical link between hemodynamic factors and rapid and unstable ventricular arrhythmias has been reported in several observational studies. Ventricular fibrillation occurring after the first 24 h of an AMI is known to be a predictor of poor patient outcome, mainly due to progression to heart failure and mechanical pump failure. This is not the case when VF occurs in the first few hours of AMI, when early revascularization procedures can correct acute hemodynamic disorders and improve patient survival, as demonstrated by classical studies of acute revascularization with fibrinolytic therapy and reflected by patient response in the clinical setting. Nevertheless, the roles played by hemodynamic, mechanical, and arrhythmogenic factors during the acute transmural ischemia characteristic of AMI, as well as the interactions among these factors, are unknown. In this issue of Revista Española de Cardiología, Barrabés et al. tackle these questions by studying the early local mechanical phenomena occurring in the ischemic myocardium. As a result of the depleted energy supply, there is a loss of local contractility, while the intracavitary pressure and Laplace stress work to ensure distension of the ischemic tissue. The authors show that this latter phenomenon, which is purely local, is able to modulate the general response of the heart and its susceptibility to VF induced by pacing protocols. Although the findings are observational and do not allow conclusions on cause and effect to be drawn, the association is robust and more importantly is in line with clinical experience.

At this point, the questions that can be asked diverge, with some addressing issues of basic science while others are more concerned with clinical applications. Thus, is it the creation and/or modulation of a local substrate that predisposes the heart to fibrillatory activity? Is this substrate per se the only condition required for the arrhythmia to be sustained? Is there a medical intervention that might limit its effect? These and other questions may only be answered clearly with greater knowledge of the mechanisms and phenomena that trigger and sustain VF in the human heart.

MYOCARDIAL RESPONSE TO ACUTE ISCHEMIA

After an acute coronary occlusion, the cellular physiology of the ischemic myocardium is modified, involving changes in ion homeostasis and cell–cell coupling, among other alterations. Particularly relevant in the case of arrhythmias, and also perhaps due to their historical significance, are changes in K+ ion channel homeostasis. As the extracellular concentration of this ion increases, the membrane potential attains less negative values and, as a result of the complex nonlinear dynamic interactions between ion channels and the membrane potential, the availability of the Na+ ion current is reduced. This results in reduced cellular excitability and shortened action potential although cellular refractoriness is prolonged through lengthening of the refractory period after repolarization. These effects create the conditions that probably allow the initiation and maintenance of reentry phenomena, in this functional context. Strikingly, the greater heterogeneity of extracellular K+ concentrations—and hence of secondary electrophysiological disorders—occurs at the periphery of the ischemic tissue, where gradients of both excitability and refractoriness are established. This area, known as the border zone, has received particular attention in recent years and is increasingly thought to be the center of arrhythmic activity in the heart with regional ischemia. The membrane potential gradient between the border zone and the...
normal myocardium may translate into a wavebreak when the sinus wave approaches the border zone, which could lead to the formation of vortices causing cellular reexcitation; this is one of the mechanisms proposed for the genesis of arrhythmic triggers.\(^6\) In addition to these phenomena, other factors to be considered are the extracellular increase in catecholamines, abnormalities in intracellular \(\text{Ca}^{++}\) homeostasis and heterogeneous modifications in coupling and the intercellular resistivity affecting the border zone which, as modelled by Cabo et al.,\(^7\) can act as a stabilizer of local reentry phenomena.

In this complex environment with differing effects on the central area of ischemia, the border zone, and the nonischemic myocardium, phenomena derived from mechanical abnormalities, wall distension and stress—which have been studied by Barrabés et al.\(^7\) among other authors—also need to be considered. Cardiologists can readily understand electromagnetic coupling as a one-way coupling, that is, as a mechanical response to propagation of the cell action potential. However, in this phenomenon, there is a feedback mechanism whereby a mechanical stimulus can also trigger an electrical response. In a porcine model of AMI, Coronel et al.\(^8\) demonstrated that intracavity pressure modulates the development of VF during phase 1b. In experimental Langendorff perfused hearts, the incidence of VF significantly increased when intracavitary pressure was introduced into the model. An increase in ectopic activity, which emanated mainly from the border zone, was also observed. In line with these observations, Kalifa et al.\(^9\) showed that, in the structurally normal sheep heart, manipulation of intra-atrial pressure facilitated sustained fibrillatory activity in the absence of other factors such as acetylsalicylic infusion.\(^9\) The link between mechanical stimulation and electrical response occurs through so-called stretch-activated channels (SAC), whose molecular structure is still not entirely known but whose functional behavior has been well-characterized.\(^10\) Activation of these channels promotes flow of selective cations (pSAC), permeable only to \(K^+\), or nonselective cations (nSAC), which are permeable to \(Na^+\), \(Ca^{++}\) and \(K^+\), leading to partial depolarization of the resting potential and an increase in the duration of the action potential. This activation may even enhance the activity triggered by early after-potentials, which in theory provides a mixture of triggers and an arrhythmic substrate.

Although the SAC-based hypothesis appears \emph{a priori} to be the most plausible explanation, the data reported in the literature on active participation of these channels in arrhythmogenesis mediated by tissue stretching during ischemia are still inconclusive. Kiseleva et al.\(^11\) studied a rat model of subacute myocardial infarction. As shown by Coronel et al.,\(^8\) experimental manipulation of the intracavity pressure was associated with an increase in ectopic activity emanating from the border zone of the infarction. The authors showed that continuous application of an increased pressure lengthened the duration of the action potential (APD90) of the cardiomyocytes in the border zone and provoked the development of after-potentials. Gadolinium administration, a SAC inhibitor, reversed these effects and suppressed ectopic activity. Nevertheless, other authors have not been able to reproduce these results. In previous studies by Barrabés et al.,\(^12\) intracoronary gadolinium infusion did not facilitate the suppression of ectopic activity or the onset of VF during acute ischemia. These discrepancies among authors could be explained by differences in experimental models and their limitations; however, a constant feature of these studies is their focus on the ability of mechanoelectric feedback mechanisms to trigger arrhythmias. The new study by Barrabés et al.\(^7\) adopts a different approach and proposes that the alterations in the electrophysiological properties of ischemic tissue, mediated by fiber stretching, could help create the necessary substrate and thus act as an intermediary in the susceptibility of the heart to VF. This approach helps to link the local response of the myocardium with the general fibrillatory response, as well as to broaden the discussion of the data to mechanistic theories of human VF.

**LOCAL PHENOMENA THAT INFLUENCE FIBRILLATORY ACTIVITY IN THE HEART**

One theory is that if an exclusively local modification in a tissue is able to determine its susceptibility to fibrillation, the reasons sustaining fibrillatory activity in the entire heart will depend on or be directly related to this activity. Other theories such as the mother rotor theory are gaining ground over the multiple wave theory to explain cardiac fibrillation.\(^13\) Several experimental studies have shown a high degree of spatial-temporal organization during VF, with a relatively simple configuration of frequency domains on endocardial and epicardial surfaces.\(^14\) The local activation frequencies in one domain are related to those in another domain according to Wenckebach-type patterns, which couple domains through an internally ordered system of fibrillatory conduction. In addition, high frequency periodicities that seem to dominate the general fibrillatory process are observed. Some of these have been identified in the form of rotors that generate vortex-like waves, whose high rotational frequency corresponds to the general frequency of fibrillatory dynamics observed in the heart. Moreover, their distribution seems not to be random, as there is a greater predilection for areas of the myocardium with greater structural and/or electrophysiologic heterogeneity.\(^13\) As previously explained, the border zone of an AMI undergoes the most dynamic and heterogeneous electrophysiologic transformations, thereby laying the foundations for persistent reentry phenomena. Zaitsev et al.\(^7\) showed that regional ischemia significantly increases fragmentation of the activation fronts in the border zone. When this fragmentation occurs, the rotary phenomena initiated around the singularity point could set a stable rotor in motion. Although the authors do not confirm this hypothesis by identifying rotors anchored to the border zone, the distribution in the density of fragmentation points is clearly ordered and contradicts purely random models of VF.

Thus, when studying cardiac fibrillation from a mechanical point of view, all experiments that regionalize the elements giving rise to VF in specific areas of the myocardium, such as those described by Barrabés et al.,\(^7\) are of importance. In recent years, scientific evidence has been growing and can help us approach individual phenomena that could determine fibrillatory activity in general. The importance of all this evidence lies in the paradigm shift, whereby VF is understood as an ordered and deterministic phenomenon. For example, from the therapeutic point of view, the approach may now be completely different. Some authors have shown that specific pharmologic interaction with certain ion currents prevents vortex-like reentry and thus fibrillatory activity from being sustained.\(^15\) Radiofrequency ablation may even be appropriate, locally modulating the arrhythmic substrate responsible for predisposition to VF in certain contexts.\(^16\) Finally, and linking back to the findings of Barrabés et al.,\(^7\) the mechanoelectrical pairing could also be used as a future therapeutic target. New experimental models are, however, required to determine whether correction of the mechanical abnormalities occurring locally in the ischemic myocardium could reverse susceptibility to VF during acute ischemia. A finding of such a reversal would in turn serve to confirm the interdependence between VF and myocardial ischemia.

**CONFLICTS OF INTEREST**

Dr. David Calvo Cuervo declares that he has no conflicts of interest. Dr. José Jalife: Gilead Inc., research grant; Topera, Inc.: member of scientific advisory board.
REFERENCES