A little gap junctional uncoupling too much

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See article by Pollard et al. [15] (pages 381–392) in this issue.

Ventricular fibrillation (VF) in the setting of acute myocardial ischemia and infarction remains an enormous burden for society, with ~300,000 deaths each year in the United States alone [1,2]. The chance of surviving an event of ischemia-induced VF is inversely proportional to the time elapsing until defibrillation is applied [3]. Therefore, automatic external defibrillators are now more and more being introduced in public areas. However, the vast majority of cases of sudden death occur at home [4].

Therefore, despite the numerous number of studies published in recent decades, there is still a need for better understanding of the mechanism of ischemia-induced arrhythmias. The information that is available to date concerns predominantly the mechanism of arrhythmogenesis in the first 10 to 15 min of coronary occlusion (for review see Janse and Wit [5]). However, Kaplinsky et al. reported in 1979 that premature ventricular beats, ventricular tachycardias and VF occur in two distinct phases in dogs subjected to coronary occlusion [6]. They named these immediate and delayed arrhythmias, respectively [6]. These phases of arrhythmias, now often referred to as 1A and 1B [7], are present in many species subjected to myocardial ischemia, including pig, rat and sheep although the distribution of arrhythmic event might differ in individual animals [8].

The main interest of the presence of the bimodal distribution of arrhythmias lies in the conjecture that the two early phases have different electrophysiological mechanisms. The first, 1A phase starts ~2 min after coronary occlusion and lasts until 10 min. Its mechanism relates to macro reentry that is facilitated by depression of excitability [5]. Heterogeneous increase in [K+]o is associated with different degrees of depolarization of the myocytes within the ischemic zone and with corresponding heterogeneous depressed excitability [9].

The mechanism of the 1B phase of arrhythmias is as of today not fully understood. Kaplinsky et al., in the seminal paper mentioned above, interpreted the absence of epicardial conduction delay as absence of reentrant activity [6]. There are, however, reports that confirm that intramural [10,11] and subepicardial reentry [12] does take place and might form the underlying mechanism of VF during the 1B phase.

The spontaneous occurrence of 1B-VF has been demonstrated to coincide with the onset of cellular uncoupling as measured by the rise in tissue impedance and with the second rise in [K+]o [13]. Smith et al. showed that in open chested pigs, VF occurred within a time window between 19 and 30 min of occlusion [13]. Cinca et al. demonstrated that both uncoupling (i.e. the rise in tissue impedance) as the occurrence of ventricular arrhythmias could be postponed by ischemic preconditioning [14]. These findings are of particular interest, not only because they further support the association between impedance rise and arrhythmias, but also because this might provide a therapeutic target in the future.

In this issue of Cardiovascular Research, Pollard et al. [15] report a modification of the Luo-Rudy dynamic membrane equations (LRd) [16] in which they focus on the source–sink relationships and the role of cellular coupling on the occurrence of phase 1B arrhythmias.

The authors have modified the LRd ionic concentrations, sarcolemmal currents and sarcoplasmic reticulum (SR) Ca2+ uptake and release to levels that promoted spontaneous SR Ca2+ release. Parameters were adjusted according to the degree of hyperkalemia, acidosis and hypoxia that has been reported for 15 to 25 min of ischemia. At that time, the second rise of [K+]o [17,18] and the onset of cellular uncoupling have started [19]. For detailed description of the changes imposed upon the LRd model, the reader is referred to the paper itself [15].

The modifications of the LRd model result in conditions
where spontaneous delayed after depolarisations (DADs) occurred in ‘isolated cells’. The spontaneous release from the SR caused multiple Ca$^{2+}$ currents. This inward current provided enough charge to bring the myocyte to threshold. The latency between the last paced beat and the first spontaneous SR release was shown to depend largely on [Na$^+$].

When this 1B-ischemic myocyte was coupled to a normal myocyte, that is, a model cell without 1B modifications, DAD formation was suppressed. This happened because the capacitive charging was insufficient to bring the cell to threshold, due to the coupling current toward the normal cell. DADs were suppressed at any gap junctional conductance, up to 145 MΩ, that was just less than values when propagation of the impulse to the ischemic myocyte failed.

Also in a 100-myocytes fiber, in which half of the cells were ischemic and the others normal, spontaneous DADs were suppressed at normal coupling resistance. At a slightly increased coupling resistance, however, DADs were still suppressed at the ischemic border, but became suprathreshold and triggered action potentials centrally within the ischemic segment. These action potentials then propagated toward the normal zone. In an intact heart, such premature complexes evidently could set off a sustained arrhythmia.

More severe uncoupling, that is, further increase in gap junctional resistance, still resulted in suprathreshold DADs and triggered activity within the ischemic zone, but the source current generated by these action potentials was insufficient to excite cells in the normal zone. Thus, although the spontaneous release of calcium from the SR was not suppressed within the ischemic zone, complex electrotonic interactions prevented propagation of premature depolarizations to the rest of the heart. This suggests that when gap junctional resistance exceeds a critical value, gap junctional uncoupling might in fact be arrhythmogenic.

This is an interesting observation that supplies a mechanistic explanation for previous experimental findings. For example, in the isolated blood-perfused pig heart with regional ischemia, we demonstrated that the inducibility of VF with programmed electrical stimulation was restricted to the time interval that encompasses rise in tissue impedance up to 40% of its final value (when cellular uncoupling is complete). At a rise of tissue impedance of more than 40%, VF was no longer inducible, despite the progression of ischemia and the administration of up to three short coupled premature beats [12]. In another study, we showed that premature beats during this phase of ischemia arose preferentially at the tissue neighboring the border between ischemic and normal tissue [20]. These observations are in concordance with the predictions of the simulation study by Pollard et al. Pollard et al. not only show that for arrhythmias during ischemia you need more than two cells in your heart; they also, using a sophisticated model of the 1B phase of acute ischemia, supply a mechanism for uncoupling related arrhythmias that takes us further than just the association between the two phenomena. The impact of source–sink interactions on the arrhythmogenic substrate potentially extends beyond the scope of acute ischemia. The electrotonic interactions grading suppression or propagation of triggered activity might, for example, play a role in heart failure-related arrhythmogenesis. It is well-known that this condition is associated with a redistribution of gap junctions toward the lateral ends of the myocytes [21,22]. Moreover, Peters et al. demonstrated that in the border zone of a healing myocardial infarction in the dog, sites with such gap junctional disarray co-localize with lines of functional activation block around which figure-of-eight reentry occurs [23]. We have to await further studies which demonstrate that source–sink problems underlie this arrhythmogenic substrate. The adjustment of computer models to conditions that closely resemble clinical pathophysiology, however, might bring the understanding of such arrhythmogenic mechanisms closer.

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