Why shocking might be not shocking enough

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See article by Chattipakorn et al. [10] in this issue.

Sudden cardiac death remains the single most frequent cause of mortality in the industrialized world [1]. Indeed, approximately every 100 s somebody dies suddenly in the United States alone [2]. Most frequently, ventricular fibrillation (VF) associated with acute myocardial ischemia or infarction is the cause of circulatory collapse [1].

When untreated, VF is lethal within minutes because the arrhythmia precludes coordinated contraction of the ventricles and thus causes circulatory arrest. The electrophysiologic mechanism of VF is reentry. Reentrant activation was first described by George Ralph Mines who showed in 1914 that an impulse can travel around a ring of excitable heart tissue and can re-excite tissue that is no longer refractory, thus giving rise to continuous circus movement of activation [3]. Mines defined three main requirements for reentry: slow conduction, a short refractory period, and a zone of unidirectional block [3]. Slow conduction is necessary because the revolution time of the impulse should allow the tissue where the impulse started to recover from refractoriness. The shorter the refractory period, the earlier the tissue can be re-excited. Unidirectional block prevents the impulse from traveling in both directions of the tissue ring and dying out opposite from where it started. Under normal circumstances both factors are absent, but a timely delivered premature beat can initiate reentry in normal hearts.

Consequently, the wavelength of the arrhythmia, which is the mathematical product of conduction velocity and refractory period, defines the minimal size of a reentrant circuit. The wavelength forms a conceptual approach to understanding reentry: an arrhythmia has an infinite number of different wavelengths because the parameters it consists of, refractory period and conduction velocity, change continuously along the circuit. It follows that both prolongation of refractoriness and increase in conduction velocity result in a longer wavelength, which is supposed to be antiarrhythmic because less reentrant waves fit in the heart. Indeed, Garrey showed in 1914 by cutting off pieces from a fibrillating heart that a critical mass of cardiac tissue is required for sustained VF [4].

Optical mapping and multi-electrode studies showed that VF is driven by rapidly moving rotors that produce multiple wavelets [5]. Reentrant wavelets break on phase singularity points at structural or functional barriers and produce daughter wavelets that either persist or die out [5]. Vaidya et al. showed that also a single stationary rotor could produce VF in a mouse heart, thereby challenging the concepts of Garrey [6]. However, the two 90-year old reports by Mines and Garrey are still very pertinent today because they are fundamental for our understanding of fibrillation and because two important theories on the mechanism of defibrillation rely on their findings [3,4]. In short, the first “critical mass hypothesis” predicts that defibrillation can be successful even when fibrillation is not completely halted but continues in a part of the heart that is smaller than the critical mass and therefore unable to sustain VF. The second hypothesis predicts that shocks delivered during the action potential plateau can delay repolarization, which causes fibrillatory wavelets to meet refractory tissue and fibrillation to stop.

Despite our advanced understanding of the mechanism of VF, electrical defibrillation remains the only treatment applied to date. The mechanism of defibrillation has been studied extensively during recent years [7]. Successful defibrillation results from a shock that homogeneously depolarizes the heart, without launching new propagating wavefronts [7]. Defibrillation fails when VF re-establishes after initial termination. The mechanism of defibrillation failure has not been completely resolved and controversial reports have been published about how VF is re-initiated after a failed shock. For example, Efimov et al. showed that virtual electrode polarization gave rise to reentry in isolated rabbit hearts [8], whereas others have shown a focal origin...
of VF after a failed shock [9]. In this issue of *Cardiovascular Research*, Chattipakorn et al. aim at resolving this controversy [10]. They hypothesized that reentry is responsible for VF re-initiation at shocks that are well below the defibrillation threshold (DFT) and that after shocks closer to DFT focal activity might give rise to VF re-occurrence. Consequently, they induced VF with 60 Hz AC current delivered to the right ventricular apex of isolated, modified Tyrode’s-perfused porcine hearts. Ten seconds after VF had established, a defibrillator delivered a 6/4 ms biphasic shock between a platinum-coated titanium coil electrode in the right ventricular apex (cathodal first) and a titanium mesh electrode that was sutured on the right atrium (anodal first). Shocks of 100–900 V were delivered in random order with 100 V increments. The investigators recorded di-4-ANEPPS fluorescence with two CCD cameras from virtually the entire heart from 0.5 s before until 2.5 s after the shock.

Chattipakorn et al. show that reentry, suggested by the presence of phase singularity points and proven by computer animations of the activation front, underlies the mechanism of VF re-initiation at weak shocks. The number of observed phase singularity points decreased with increasing shock strength, and no phase singularities were observed at shocks of 600 V or stronger. At shocks more close to the DFT, the post-shock interval increased from zero (at shocks up to 400 V or stronger) to 62 ± 6 ms at shocks of 800 V, followed by a train of focal beats that set off VF. Successful defibrillation was reproducibly achieved only at shocks of 900 V or stronger, when no ectopic activity was observed following the shock.

Chattipakorn et al. demonstrate that there is no controversy on what mechanism re-initiates VF after failed shocks. Both reentry and focal activity can, dependent on shock strength, cause re-initiation of VF after failed defibrillation [10]. Potentially, focal activity can be suppressed with drugs that prevent the occurrence of delayed after depolarizations (DADs), thereby increasing defibrillation success. Indeed, Chattipakorn and Ideker showed previously that flunarizine, a DAD blocker, increased defibrillation efficacy [11].

The majority of cases of sudden cardiac death due to VF are associated with acute myocardial ischemia [1]. Acute ischemia changes the electrophysiological properties of the myocardium in a heterogeneous manner. Basically, these changes include a decrease in conduction velocity and excitability and an increase in $[K^+]_o$ and gap junctional resistance. These factors are arrhythmogenic but also affect DFT [12]. Sims et al. showed in a model mimicking changes during ischemia that regional gap junctional uncoupling with heptanol results in increased DFT [13]. Similarly, Moubarak et al. demonstrated that the dispersion of post-shock repolarization is related to defibrillation failure [14]. In addition, defibrillation efficacy might be affected by altered tissue architecture [15].

Chattipakorn et al. shed new light on the mechanism of defibrillation failure and VF re-induction [10]. Although in the light of the clinical problem of sudden cardiac death their findings might seem somewhat academic, they provide further insight into how defibrillation fails and why. The discovery of these pieces of the puzzle might ultimately lead to understanding how defibrillation failure can be prevented other than by just shocking harder.

References