Published in final edited form as:
J Cardiovasc Electrophysiol. 2009 March ; 20(3): 315. doi:10.1111/j.1540-8167.2008.01330.x.

Chronaxie of Defibrillation: A Pathway Toward Further Optimization of Defibrillation Waveform?

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Editorial Comment

Despite significant research efforts of investigators in academia, medicine, and the pharmaceutical industry, no effective pharmacological alternative to defibrillation by electric shock has been developed. Thus, defibrillation, which is steadily improving its efficacy and safety, has become the only effective therapy against sudden cardiac death. However, despite major improvements over the last several decades, defibrillation is not free of side effects, which may include both contractile and electrical dysfunction.[1–3] Furthermore, defibrillation is also associated with psychological side effects.[4,5] Therefore, reduction of defibrillation energy is highly desirable, and defibrillation remains a subject of extensive research.

The basic mechanisms of defibrillation still remain debatable a century after its inception, which has slowed further improvement of the therapy. In 1899, while studying induction of ventricular fibrillation in the dog heart, physiologists Prevost and Batelli working at the University of Geneva discovered that they could defibrillate a dog heart by applying an appropriate, high-current shock directly to the surface of the myocardium.[6] Since they used very high voltage (4,800 V and more), the myocardium was incapacitated after their shocks. Thus, the initial theory of defibrillation was based on "incapacitation" effects. In 1946, Gurvich and Yuniev[7] reported defibrillation of the mammalian heart with a capacitor discharge applied externally across the closed chest. The next year, Beck *et al.*[8] reported the first successful human defibrillation using AC stimulation applied to the open heart. In 1956, Zoll *et al.*[9] performed the first successful human external defibrillation again using AC stimulation. However, the superiority and safety of DC over AC stimulation for defibrillation were demonstrated by several investigators such as Kouwenhouven and Milnor,[10] Lown *et al.*,11 and Gurvich.[12] In 1969, Mirowski and colleagues began research on the implantable cardioverter defibrillator (ICD). In 1980, the first ICD was implanted in a human patient.[13, 14] All this work led to a significant reduction of energy required for defibrillation, avoidance of myocardial "incapacitation," and, thus, the development of stimulatory theory of defibrillation.12,15 This theory postulated that defibrillation was achieved by directly stimulating and exciting the myocardium.

The stimulatory theory of defibrillation was later refined into the critical mass hypothesis in which experimentalists as well as theorists proposed that a critical mass of the myocardium (75–90%) needs to be directly defibrillated in order to fully terminate fibrillation.16–18 In 1967, Fabiato and colleagues19 demonstrated the first correlation between shock-induced fibrillation and defibrillation in a mechanism they called the "threshold of synchronous response." This idea was later extended by Chen and coworkers20 into the "upper limit of vulnerability" hypothesis. This hypothesis states that the shock must terminate all wavefronts

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of fibrillation and that, in order to be successful, the shock must produce a sufficient voltage gradient (above the upper limit of vulnerability [ULV]) everywhere in the myocardium so as not to re-induce fibrillation. This correlation was subsequently demonstrated in several experimental studies[21,22] and in humans.[23,24]

Although the concept of stimulus-induced reentry had been laid down decades earlier by Wiener and Rosenblueth,[25] Frazier and colleagues[26] were the first to obtain experimental evidence of this mechanism in 1989 in what they called the "stimulus-induced critical point" mechanism. Frazier *et al.* demonstrated that the chirality of reentry could be predicted based on the direction of the preshock repolarization gradient and voltage gradient of the applied shock. After its discovery, the critical point mechanism was held responsible for reinduction of fibrillation after a failed defibrillation shock.[27,28]

Thus, the stimulatory theory of defibrillation in all possible flavors appeared to explain many empirical phenomena. Therefore, a simple resistor–capacitor (RC) model of the heart, borrowed from pacing, has become a popular tool in explaining the interaction of electric field and cell membrane.[29] When applied to pacing, this model predicted quite well optimal pacing waveforms based on strength–duration curves. Thus, rheobase and chronaxie are commonly accepted as the principle parameters predicting the efficacy of electric stimulation. Following the same RC approach and using empirical evidence from defibrillation, several generations of investigators have worked on optimizing defibrillation waveforms. However, the RC theory had hard time explaining well-known differences between anodal and cathodal defibrillation, and between biphasic and monophasic defibrillation.[30,31]

Meanwhile, mounting theoretical and experimental evidence was showing that effects of shock are more complex than what the stimulatory hypothesis suggests. The advancement of our understanding was especially rapid after the advent of fluorescent optical mapping with voltage-sensitive dyes[32] and, in parallel, advancements in numerical simulations using the biodomain model of cardiac tissue[33,34] that provided the theoretical means to interpret these complex experimental findings.

Using these novel methodologies, numerous groups demonstrated that both positive and negative membrane polarization are induced by an applied stimulus in different areas of the heart.[35–40] Although the shock may stimulate or prolong repolarization in regions of the myocardium that are positively polarized by shock, it may be shortened or deexcited in others that are negatively polarized by the same shock. Thus, this new evidence casts doubt on the purely "stimulatory" response of defibrillation shocks with its simplistic RC framework. An alternative theory that accounts for both shock-induced excitation and deexcitation is the virtual electrode hypothesis of defibrillation.[40–42]

The term "virtual electrode" was first coined by Furman *et al.*[43] to explain the clinical observation of stimulation far from a chronically implanted pacemaker lead. Later, this term was adopted by investigators studying both pacing and defibrillation in parallel with a synonymous but more rigorously defined term "activating function" to designate the "driving force" that drives transmembrane potential in either a depolarizing (positive) or a hyperpolarizing (negative) direction following an externally applied electric field.[44,45] Over the last decade and a half, the virtual electrode hypothesis has significantly advanced our understanding of both pacing and defibrillation, showing that the reduction of the heart to an RC circuit is not an accurate representation of electric stimulation. The heart is a distributed system with RC properties ranging in space, time, and frequency domains.

In this issue of the *Journal*, Lawo *et al.*[47] show experimental evidence that suggests that strength–duration curve may offer additional insights that seem to have been overlooked so far by old theories. It is well known that stimulatory chronaxie depends on both excitable

properties of the cell membrane and the cell or tissue geometry.[46] Knowing that excitable properties are strongly affected by arrhythmia, Lawo *et al.*[47] demonstrate significant difference in chronaxie among near-field or far-field stimulation, fibrillation induction, and defibrillation, respectively. Importantly, the far-field stimulation has a chronaxie that is an order of magnitude shorter than that of defibrillation induction or defibrillation. These findings suggest that reentrant arrhythmias with large excitable gaps that are accessible to far-field stimulation may be effectively treated with stimulatory paradigm-based methods. In particular, it suggests that very short pulses (0.25–0.30 ms) as compared to that typically used in defibrillation could improve the outcome for cardioversion. Although hypothetical, this new approach may yield significant improvement in treatment of VT. Unfortunately, the study does not demonstrate such possibility and offers little mechanistic insight into the hypothetical role of the sodium channels. But this report clearly opens a new window of opportunity to both improve electrotherapy of arrhythmia and further enhance our understanding of mechanisms of electrotherapy.

Acknowledgments

Dr. Efimov has received research support from the NIH grants R01 HL074283, R01 HL67322, and R01 HL082729. He reports ownership interest in Cardialen, Inc., and serves as a consultant to Cardialen, Inc., Medtronic, Inc., and TASER, Inc.

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