Chapter 4.4

The Virtual Electrode Hypothesis of Defibrillation

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Introduction

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 has evolved to become the only effective therapy against sudden cardiac death. Highly detailed knowledge of ion channel biophysics and cell signaling cascades has allowed for the development of numerous specific agonists and antagonists, but as of yet, has failed to deliver safe and effective antiarrhythmic therapy. In contrast to this approach, electrotherapy is steadily improving its efficacy and safety.

Despite major improvements over the past several decades, defibrillation is not free from side effects, which may include both contractile and electrical dysfunction. In addition to physical damage to the heart, defibrillation is also associated with psychological side effects. Therefore, reduction of defibrillation energy is highly desirable. However, the basic mechanisms of defibrillation still remain debatable a century after its inception, which has slowed further improvement of the therapy. This chapter explores one of the leading hypotheses of defibrillation, the virtual electrode hypothesis, which has emerged over the past decade through the successes of novel research methodologies, including optical mapping and bidomain modeling.

Historical Overview of Defibrillation Therapy

The motivation to explore the relationship between electrical activity of the heart and that of external electric stimuli began in the late nineteenth century, presumably due to the increasing electrification of urban areas. In 1899, while studying induction of ventricular fibrillation in the dog heart, physiologists Prevost and Batelli working at the University

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of Geneva discovered that they could defibrillate a dog heart by applying an appropriate high current shock directly to the surface of the myocardium: “We have shown that the fibrillatory tremulations produced in the dog, in which they are definitely established can under certain circumstances be arrested, the heart re-established its beats, if one submits the animal to passages of a high current of high voltage (of 4800 volts, for example).”

In 1946 Russian physiologists Gurvich and Yuniev\(^8\) reported defibrillation of the mammalian heart, with a capacitor discharge applied externally across the closed chest. The next year Beck et al.\(^9\) reported the first successful human defibrillation in which they used two 110-V, 1.5-A alternating current (AC) current shocks to resuscitate a 14-year-old boy who suffered cardiac arrest during elective chest surgery. In 1956 Zoll et al.\(^10\) performed the first successful human external defibrillation using a 15-A AC current that produced 710 V applied across the chest for 0.15 s. However, the superiority and safety of direct current (DC) over AC for defibrillation were demonstrated by several investigators such as Kouwenhouven and Milnor,\(^11\) Lown et al.,\(^12\) and Gurvich.\(^13\) In 1969 Mirowski et al.\(^14,15\) began research on the implantable cardioverter-defibrillator (ICD). In 1980 the first ICD was implanted in a human patient at Johns Hopkins Hospital. Since the advent of ICD technology, survival for those at high risk for ventricular tachycardia/fibrillation (VT/VF) has greatly improved.

Despite profound advancements in defibrillation therapy over the past century, little was known about the basic mechanisms of defibrillation until the past two decades due to the advent of fluorescent optical mapping with voltage-sensitive dyes. In parallel, advancements in numerical simulations using the bidomain model of cardiac tissue provided the theoretical means to interpret these complex experimental findings.

**Bidomain Model**

The bidomain model is now widely accepted for numerical and theoretical studies of cardiac electrophysiology. The tissue is represented by two interpenetrating intra- and extracellular domains with each of them having different conductivities along and across the direction of the fibers.\(^16,17\) The state variables describing the system are intracellular \((\phi_i)\) and extracellular \((\phi_e)\) potentials defined everywhere in the domain of interest \(\Omega\). The transmembrane potential is defined as \(V_m = \phi_i - \phi_e\). The following coupled reaction-diffusion equations constitute the bidomain model:

\[
\nabla \cdot (\hat{\sigma}_i \nabla \phi_i) = I_m, \quad \text{in } \Omega,
\]

\[
\nabla \cdot (\hat{\sigma}_e \nabla \phi_e) = -I_m - I_o, \quad \text{in } \Omega,
\]

where \(\hat{\sigma}_i\) and \(\hat{\sigma}_e\) are intra- and extracellular conductivity tensors, respectively, \(I_m\) is the volume density of transmembrane current, and \(I_o\) is the volume density of the stimulation or shock current.

The transmembrane current is described as a sum of capacitive, ionic, and electroporation currents\(^18\):

\[
I_m = \beta \left( C_m \frac{\partial V_m}{\partial t} + I_{\text{ion}}(V_m, t) + G(V_m, t) \cdot V_m \right),
\]