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EDITORIAL COMMENT

Mystery of Biphasic Defibrillation Waveform Efficacy

Is it Calcium?*

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In this issue of the *Journal*, Hwang et al. (1) proposed that differential effects on the calcium transient underlie the greater efficacy of biphasic over monophasic waveforms for cardiac defibrillation. Biphasic waveforms have supplanted monophasic ones in internal as well as external defibrillators, yet despite extensive investigation, the mechanism for the greater superiority of selected biphasic type shocks remains debated. The biphasic mystery is part of the larger uncertainty over the mechanism of defibrillation itself, with critical mass (2), upper limit of vulnerability (3,4), and refractory period extension and/or synchronization (5,6) theories posited. The effects of a shock grow increasingly complex as one takes into account extracellular and intracellular space with cable theory (7,8), gap junctions and potential oscillations of membrane potential ("saw tooth" effect), active ion channels using biodomain theory (9), transient membrane porosity or electroporation (10,11), or even nonmyocardial vascular and connective tissue structures (12,13). A better understanding of defibrillation and of biphasic superiority could potentially allow development of still more effective waveforms.

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Proposed mechanisms for differential efficacy for the biphasic waveform include: 1) reduced impedance for the second phase due to reduction of electrode polarization caused by the first phase; 2) the large change in peak to peak voltage between the first and second phase; 3) reduced detrimental effects of biphasic shocks in high gradient fields (14); 4) greater ability to stimulate refractory myocardium; 5) restoration of sodium channel activity by the first phase of the biphasic shock; 6) enhanced refractory period extension by biphasic shocks (5,15); 7) virtual electrode effect; and 8) charge burping theory (16–18). The first explanation does not hold, because the impedance effect is smaller than the defibrillation threshold (DFT) difference and also because some biphasic shocks actually have higher DFTs despite retaining a lower second phase impedance. Against the second potential explanation is the observation that the 2 phases can be separated by up to 6 ms, eliminating the change in peak voltage without a loss of biphasic superiority. Third, although it is true that biphasic shocks have less adverse effects, a very weak second phase biphasic remains "gentler" still than a moderate-strength second phase biphasic but has a higher DFT than the latter, optimal type biphasic (14). Fourth, initial data by Jones et al. (19) suggested that biphasic waveforms were better able to stimulate refractory myocardium, but subsequent studies were conflicting (20–22). Fifth, the channel restoration theory does not explain why asymmetric biphasic shocks (i.e., having either a shorter second than first phase or vice versa) might be either more or less effective, respectively, than monophasic shocks, along with other difficulties (16). Sixth, biphasic shocks seem to be less potent in extending refractory periods, making their greater efficacy unexplained by this mechanism (23). When biphasic or monophasic shocks were delivered in sinus rhythm and stimulation performed immediately thereafter to measure refractoriness, greater homogeneity of post-shock repolarization occurred after biphasic shocks, and this was suggested as an explanation for biphasic superiority (23). However, at least 1 subsequent experiment presented data against this explanation (24). Virtual electrodes (i.e., regions of hyperpolarization straddling a depolarized region closest to a cathode) have been documented with optical mapping of shocks. Virtual electrode polarization has been proposed as a mechanism for failure of defibrillation shocks and for the greater efficacy of biphasic shocks (25). The presence of adjacent depolarized and hyperpolarized tissue might contribute to defibrillation failure with a shock-induced critical point or phase singularity generating an activation wave front able to propagate into the hyperpolarized regions (26,27). With optical mapping in a Langendorf model, Efimov et al. (25) noted a relative absence of virtual electrode polarization in mapped tissue for biphasic shocks having a second phase somewhat weaker than first phase. Such asymmetric biphasic shocks had previously been found optimal for defibrillation. Conversely, distinct virtual electrode regions occurred for: 1) monophasic; 2) very weak second phase biphasic; or 3) excessively strong second phase biphasic shocks. The related "charge burping" theory proposes that the second phase of the biphasic eliminates the areas of virtual anode or virtual cathode in the myocardium generated by the first phase, thus minimizing the chance of generating re-entrant wave fronts. Support for this theory came from studies exploring the change in the capacitor size when the wave constant of the defibrillator exceeds the time

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constant of the myocardium (18). It was predicted that a shorter second phase of a biphasic would outperform a long second phase biphasic. In contrast, with a low-capacitance shocking device, manifesting a device time constant shorter than the myocardial time constant, a longer second phase was predicted and found to be preferable (18).

Hwang et al. (1) studied the calcium transients after biphasic defibrillation shocks, expanding on their prior work with this model (28). Seeking to explain the source of activations after failed defibrillation shocks after the controversial quiescent period or isoelectric window (4,29–31), they found that the earliest activation originated from a region of relative low intracellular calcium (Ca_i), a calcium "sinkhole," 50 to 60 ms after the shock, possibly via phase 2 re-entry or reverse excitation-contraction coupling. Comparing an unsuccessful monophasic to an equal voltage successful biphasic shock, Hwang et al. (1) found the calcium transient to be more heterogeneous with the monophasic shock with a sinkhole-associated site of early activation. The role of the calcium transient in biphasic waveform superiority was supported by the elimination of the biphasic DFT differential with thapsigargin and ryanodine administration.

This Ca_i heterogeneity theory proposed by Hwang et al. (1) adds new insights to our understanding on why the biphasic waveform defibrillation shocks are superior to the monophasic waveform; however, some limitations exist in this study. One potential concern is that only the epicardium is evaluated. Similar to a monophasic action potential recording but in contradistinction to a single cell recording, optical mapping has a field of view that includes a population of cells ranging up to 150 to 300 μm deep (5,32). However, deeper intramural tissue cannot be evaluated, and the apparently focal activation pattern seeming to arise from calcium sinkholes could be due to focal or re-entrant activations propagating from deeper intramural tissue. Of note, in their earlier study (28) they confirmed the sinkhole phenomenon in endocardially cryoablated perfused hearts having only a surviving subepicardial region. A second limitation is that the hypothesis that biphasic shocks succeed because of more uniform calcium transients fails to explain why monophasic and biphasic shocks of the same voltage that are both unsuccessful have similar depolarization and calcium transient maps (see Fig. 3 in Hwang et al. [1]), although the timing of the peak depolarization and peak Ca_i was earlier for the biphasic shocks. This raises the possibility that the differences observed in Ca_i are secondary to another process that determines whether the shock is successful or not (e.g., refractory period extension) or the activation state of the tissue in certain regions. Lesser tendency to generate a sinkhole and delayed sinkhole formation by the biphasic are put forward by Hwang et al. (1), but for the unsuccessful biphasic shocks the time to sinkhole was actually earliest in Table 1 of the report (1).

There are several important questions that lie ahead for future investigation. First, how do the findings correlate with virtual electrode polarization? Second, what are the cellular mechanisms responsible for a more balanced effect on sarcoplasmic reticulum calcium release under the biphasic shock? Is it due to an absence of a virtual electrode polarization of the myocardium? Is this due to a decrease in the development of calcium alternans? Is this a secondary effect of the biphasic shock-mediated changes in L-type calcium channel kinetics or sodium/calcium exchange activities? Third, what is the relative impact of "calcium sinkhole" on early after depolarization and delayed after depolarization? Fourth, because gap junction inhibitors (33) have been found to elevate the DFT—in line with known effects of ischemia on DFT—what role might the gap junction play in the formation of a "calcium sinkhole?" Fifth, what are regional influences (epimyocardium, midmyocardium, and endomyocardium, site of shock, conduction velocity at different regions of the heart, and so on) on the outcomes of biphasic and monophasic shocks? Sixth, is the formation of a calcium sinkhole the cause or the effect of heterogeneous calcium transients? Last, if the calcium sinkholes are causative of failed defibrillation, rather than vice versa, is the electrophysiologic mechanism micro–re-entry, phase-2 re-entry, triggered activity, or reverse excitation-contraction coupling?

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Key Words: defibrillation ■ biphasic waveforms ■ calcium transient ■ sudden cardiac arrest ■ ventricular fibrillation.