Pharmacological Intervention to Improve Defibrillation Efficacy

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Sudden cardiac death, mainly caused by VF, is responsible for over 250,000 deaths annually in the United States.[1] Currently, electrical defibrillation is the only practical means for terminating VF. The mortality rate from sudden cardiac death has decreased in the past decade, partly due to the improvement of our understanding of the nature of this fatality as well as the development of defibrillation devices. Recent advances in implantable defibrillators, such as the use of a biphasic waveform, have led to smaller intravenous devices that have significantly benefited certain groups of patients.[2-4] Recent findings that post-shock activation always arises from area of the weakest shock field have led to the development of improved device therapy.[5-7] Despite the wide applications of defibrillators, there is still a great need to improve defibrillation. The better we understand the fundamental mechanism of defibrillation, the more likely it is that we will be able to devise strategies to improve it.

It is thought by many investigators that reentry is responsible for the resumption of VF in failed defibrillation.[8-11] Although this hypothesis is supported by most optical mapping studies which show reentrant activation fronts on the epicardium immediately after the shock,[8-11] this pattern has not been frequently observed in electrical mapping of defibrillation studies.[12-15] Instead, focal activity is frequently observed after the shock prior to its degeneration into VF.[13,15-17] Since most optical mapping studies have used a small-heart animal model with shocks that were well below the DFT, while electrical mapping studies have used a large-animal model and shocks of a strength close to the DFT, the disparity of results could be

partly due to differences in study protocols.[15,18,19] To resolve this issue, an optical mapping study using a similar protocol to that used in electrical mapping studies was performed recently in isolated pig hearts.[20-22] The results demonstrated that following failed near DFT shocks, rapid repetitive focal activations were always observed at the LV apex for several cycles before it degenerated back into VF. No reentry was observed during these cycles. These results are consistent with previous electrical mapping reports,[12-15] and led us to believe that an intervention to this small arrhythmogenic region may improve defibrillation efficacy.

Although the cause of these post-shock focal activations is not known, afterdepolarizations have been suggested as a possible mechanism for these rapid post-shock activations.[15,16,23-26] Afterdepolarizations are oscillations of the transmembrane potential that depend on the preceding action potential for their generation.[27,28] They can give rise to new activation fronts, i.e. triggered activity, if they reach a critical threshold for new activations. There are two types of afterdepolarizations; delayed afterdepolarizations (DADs) and early afterdepolarizations (EADs). DADs are oscillations in membrane potential that occur after complete repolarization of an action potential, whereas EADs are oscillations at the plateau phase of an action potential, or later during phase 3 of repolarization.[27,29] DADs are usually too small to reach threshold voltage, however with changes in heart rate or firing pattern their amplitude can change dynamically.[28] A decrease in the cycle length (an increase in the rate) has been suggested as the most important influence that causes subthreshold DADs to reach threshold.[28] DADs are believed to be induced by a transient inward current[27,30] and have been linked to intracellular Ca^{++} overload which can result from a number of conditions including increased heart

rate, enhanced sympathetic tone, ischemic reperfusion, stretch, tissue damage, and drug intoxication.[31-34] As heart rate increases or stimulation becomes more premature, DADs could become larger in amplitude until a threshold voltage is reached and a run of rapid firing or triggered activity is provoked.[28] DADs are a possible cause of rapid focal activations following failed near-DFT shocks for the following reasons. During fibrillation, heart rate is greatly elevated. Following a defibrillation shock, additional factors such as increased sympathetic tone, myocardial stretch, tissue damage, and reperfusion may be involved. These factors alone or in an additive fashion help promote DADs.[31-34] In addition, recent optical mapping studies have demonstrated that following near-DFT shocks, complete repolarization is observed followed by a 40-60 ms quiescent period after which repetitive focal activations appear on the epicardium and later degenerate into VF.[20,21,22,35] This finding suggests that the first ectopic cycle arises after complete repolarization is achieved after the shock. Recent studies have also demonstrated that the heart can be paced from the early site quickly following the defibrillation shock before the early site appears spontaneously. This suggests that DADs are a possible mechanism of the rapid repetitive post-shock activity.[17,36]

All of these findings, however, have been observed from the ventricular epicardium and may not be representative of what occurs beneath the epicardium. Although most recent studies suggest that the first post-shock activation arises on the ventricles after a short isoelectric window, it is not known whether any electrical activity underneath the epicardium exists during this isoelectric window on the epicardium. Several studies demonstrated that rapid firing from Purkinje fibers occurred immediately after the shock.[25,26] Because EADs occur in most conditions that delay repolarization and, most often, occur more readily in Purkinje fibers than in

ventricular muscle cells,[28,37] EADs could be responsible for the rapid activation fronts after the shock,. since a strong shock is known to significantly extend the refractory period as well as the action potential duration.[38,39] Therefore, EADs cannot be ruled out as the possible cause of the rapid repetitive early activations following unsuccessful defibrillation shocks.

Recently, the effect of the DAD inhibitor, Flunarizine, has been tested on defibrillation efficacy.[40] Flunarizine has been demonstrated to terminate arrhythmias due to DADs and to prevent their re-induction. It is believed that Flunarizine prevents calcium overload in the cell by blocking the Na+/Ca2+ exchanger.[33,41] It has been shown that the DFT was significantly decreased (~22% by leading edge voltage and ~39% by total energy) after the drug administration (520±90 volts vs. 663±133 volts) and returned to its control value after the drug was washed out.[40] These data strongly support the possibility that the drug will improve defibrillation and suggest that DADs could be a source of the rapid repetitive focal activation fronts after failed near-DFT shocks.

The definite mechanism by which Flunarizine prevents DADs is still unclear. Flunarizine may block the Na+/Ca2+ exchanger. It may also influence the release of calcium from the sarcoplasmic reticulum and block the transient inward current. Further studies are needed to verify its mechanism.

Conclusion

Pharmacological intervention is another useful tool in investigating mechanism of cardiac arrhythmias. Although the mechanism of defibrillation has been investigated for many decades, it's definite mechanism is still unclear. A recent defibrillation study has demonstrated the significant reduction in the defibrillation shock strength after the administration of the drug that prevents the occurrence of

DADs, suggesting that DADs may be responsible for failed defibrillation. This finding suggests that pharmacological intervention can be used as an early step in testing the mechanism of cardiac defibrillation.

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