Journal of the American Heart Association

EDITORIAL

Tapping on Pulseless Electrical Activity: An Opportunity for Improving Resuscitation Outcomes?

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Approximately 356 000 individuals experience an episode of out-of-hospital sudden cardiac arrest every year in the United States.[1] Emergency medical services attempt cardiopulmonary resuscitation in ≈67%; and of these, only 8.4% survive and recover with good neurological outcome.[1] Accordingly, the likelihood of surviving an episode of sudden cardiac arrest today remains disappointingly low for most individuals. Thus, continuous efforts to gain further understanding of the pathophysiological characteristics of cardiac arrest while identifying more effective resuscitation interventions represent an important public health undertaking, as also recognized by the National Academy of Medicine recommending structured and comprehensive steps forward.[2]

See Article by Ambinder et al.

On the basis of the electrical and mechanical activity of the heart, episodes of sudden cardiac arrest can be grouped into those that present with a "shockable" rhythm, to include ventricular fibrillation (VF) and pulseless ventricular tachycardia, and nonshockable rhythms, to include pulseless electrical activity (PEA) and asystole. The outcomes among these "rhythms" vary considerably, with the best outcome associated with VF/pulseless ventricular tachycardia followed by PEA and asystole.[3] Although much is known about VF, its predisposing conditions, its mechanisms, and its most effective treatments, less is known about PEA. PEA is characterized by the severe and rapid interruption in the ability of cardiomyocytes to effectively contract despite the existence of an action potential. PEA was originally described as electromechanical dissociation, evolving into the more practical term of PEA, requiring the presence of an organized cardiac electrical activity (often with a wide QRS and slow rate) and the inability of detecting a peripheral pulse in an unresponsive individual. Yet, the inability to detect a peripheral pulse does not indicate absence of left ventricular contractile activity. With the use of cardiac ultrasound, a weak left ventricular activity can be detected despite the absence of a peripheral pulse in a subset of patients with PEA, a condition that has been termed pseudo-PEA and is associated with a higher likelihood of successful resuscitation.[4]

PEA is a common mechanism of cardiac arrest associated with severe hypoxemia, circulatory shock, blunt trauma, pulmonary embolism, opioid overdose, and other similar nonprimary cardiac conditions.[3,5,6] These conditions have in common the abrupt and critical reduction in oxygen delivery to the myocardium, leading to its inability to sustain an effective contractile function, compromising forward blood flow and the corresponding driving pressure for coronary perfusion. However, there is incomplete understanding of the mechanisms leading to PEA in the absence of

Key Words: Editorials ■ Ischemia-reperfusion injury ■ left ventricular function ■ preconditioning ■ pulseless electrical activity ■ swine

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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systemic events responsible for critical reduction of myocardial oxygen delivery, which most likely represent the predominant mechanism of PEA outside the hospital.

In this issue of the *Journal of the American Heart Association* (*JAHA*), Ambinder et al[7] used a swine model of coronary occlusion to study mechanisms associated with PEA, specifically determining whether the underlying contractile state of the myocardium could determine the mechanism of cardiac arrest. Occlusion of the left anterior descending (LAD) coronary artery in swine with previously healthy hearts led to VF after an average of 23.5 minutes in 18 of 34 animals. During this period, no changes in blood pressure occurred, suggesting that hemodynamic function was largely preserved. Yet, LAD coronary artery occlusion in swine that had been subjected to sequential myocardial infarctions within the preceding 2 weeks by a 2-hour occlusion of the right coronary artery and the left circumflex artery 1 week apart resulted in rapid decline in left ventricular function, resulting in PEA within an average of 1.7 minutes in each of 18 animals. These animals had a prearrest left ventricular ejection fraction of 15%, presumably with most of the contractile activity generated by the myocardium supplied by the LAD coronary artery. Accordingly, in this model, interruption of blood flow toward the remaining contractile myocardium rapidly and severely compromised left ventricular function, resulting in the almost immediate PEA. VF in this group followed after 17.6 minutes.

The authors also investigated whether ischemic preconditioning could influence the effect of LAD coronary artery occlusion and specifically the development of VF. Preconditioning is known to activate myocardial protective mechanisms and is associated with translocation of protein kinase Cε from the cytosol to mitochondria,[8] as it was also shown by the authors in their swine model. Preconditioning was induced in subsets of animals within each of the groups described above by brief repetitive occlusions of the LAD coronary artery before the sustained LAD coronary artery occlusion, leading to VF or PEA arrest. In the group with preserved ejection fraction, preconditioning reduced the incidence of VF or delayed its onset. In the group with reduced ejection fraction, preconditioning also reduced the incidence of VF or delayed its onset after PEA had occurred.

The mechanism responsible for the increased threshold for VF development after preconditioning remains to be explored. In a rat model of VF, administration of erythropoietin during cardiac resuscitation led to improved postresuscitation myocardial function associated with increased protein kinase Cε phosphorylation (indicative of increased activity) in the cytosolic and mitochondrial fractions of left ventricular tissue. Protein kinase Cε phosphorylation was associated with preservation of respiratory complex IV activity, and less mitochondrial injury evidenced by lower plasma levels of cytochrome *c*.[9] In the current swine model, it is conceivable that preconditioning slowed the time and intensity of ischemic injury development in the myocardial region supplied by the LAD coronary artery after sustained occlusion. Such effect could have increased the threshold for VF by delaying electrophysiological mechanisms that predispose to VF, which involves development of action potential conduction heterogeneity and reentry.

Another important consideration raised by the study is the potential reversibility of PEA when an abrupt coronary occlusion is the culprit, with the expectation that reversal of the occlusion could create favorable conditions for successful resuscitation. This mechanism would justify a hemodynamically more, not less, aggressive resuscitation effort focused on restoring coronary blood flow. With the availability, today, of more aggressive and effective resuscitation interventions, including the use of extracorporeal circulation, the presence of PEA could be viewed as a condition susceptible to hemodynamically more aggressive and effective management. Currently, the use of extracorporeal circulation is usually limited to refractory VF because those patients are known to have a greater potential for successful resuscitation.[10] Yet, PEA might be another condition to be considered, especially if the event is witnessed.

It is also worth pointing out that most of the preclinical work in cardiac arrest has been made in animal models of VF, either electrically induced or following coronary occlusion, and in models of asphyxia induced by neuromuscular blockade. Much less work has been devoted to the development of animal models that could recapitulate the mechanisms leading to PEA in humans. To this end, the present work by Ambinder et al is meritorious and worth complimenting. Yet, the study invites discussion on the extent to which the proposed swine model of PEA recapitulates the conditions that most often lead to PEA of primary cardiac origin in humans. The animal model developed had a marked reduction in left ventricular ejection fraction to 15%, elicited after 2 sequential myocardial infarctions along the territory of the right coronary artery and the circumflex artery, with the LAD coronary occlusion triggering PEA. Clinically, such ejection fraction decrease would be expected to result in clinical manifestations of heart failure requiring medical management. It is not clear from the literature as to the incidence of preexistent heart failure in patients experiencing PEA, and whether a large percentage of the sudden cardiac arrest population lives with unrecognized severe left ventricular dysfunction or critical coronary artery disease. Thus, further work is warranted to develop variations in the model, and specifically, determine whether PEA could be elicited by coronary occlusion with less severe underlying myocardial dysfunction.

Another interesting aspect of the work to be further investigated is the fate of the myocardium. It is well established that VF is an energy-demanding rhythm that during cardiac arrest leads rapidly to intense myocardial ischemia. In the absence of VF, the energy demand of the myocardium is substantially less and therefore the possibility of better postresuscitation myocardial function should be considered and worth investigating.[11] Likewise, the assessment of whether preconditioning could facilitate the return of spontaneous circulation and lead to better postresuscitation myocardial function is also worth investigating.

In summary, the work by Ambinder et al is timely and provocative and creates incentive to further study the underlying coronary and myocardial conditions of patients presenting with PEA and determine the extent to which the model is representative of the corresponding clinical condition. It also invites work to determine whether a more aggressive hemodynamic approach to resuscitation in the setting of PEA could lead to better outcomes.

ARTICLE INFORMATION

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Disclosures

None.

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