Racing to the flatline: heart rate and β-adrenergic stimulation quicken the pace

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ASYSTOLE, IDENTIFIED AS a flatline in all ECG leads, is a nonshockable rhythm that is associated with high mortality. Patients with coronary artery disease who suffer a sudden occlusion may progress to asystole through a sequence of events initiated at the onset of the occlusion: local ischemia, ventricular tachycardia (VT), ventricular fibrillation (VF), global ischemia, and asystole. Defibrillation has the highest efficacy when applied during VF, well before asystole. Prognosis is dim for patients suffering from out-of-hospital cardiac arrest (OHCA) who are found in asystole. An analysis of the Swedish OHCA registry has shown that patients who were found in a nonshockable rhythm had an average one-month survival rate of 1.3% (8).

Several retrospective studies have analyzed the incidence of lethal arrhythmias in OHCA and found that the incidence of arrest with VT/VF as the first recorded rhythm has steadily declined while the incidence of non-VF arrest, including asystole, has markedly increased (10, 13). The decline in VF arrest could be the result of reduced incidence of VT/VF as the cause of OHCA, likely because of increased use of implantable cardioverter defibrillators and β-blockers. Interestingly, the incidence of asystole as the first recorded rhythm increased substantially from 1992-2002 in Milwaukee, WI, with the increase offsetting the decline in VT/VF arrests. Overall, the total incidence of OHCA remained constant over the period of that study (13). Observed increases in non-VF OHCA in the United States and Europe have lead to speculation that VF in OHCA is quickly deteriorating into another rhythm, primarily asystole (10). There is further speculation that β-blockers could be the culprit in the accelerated deterioration of VF to asystole (10).

In this issue of the American Journal of Physiology-Heart and Circulatory Physiology, Garg and colleagues (6a) present the results of investigations into factors that influence electrical function’s degeneration to asystole during global ischemia. They hypothesized that both rapid heart rate and β-adrenergic stimulation would accelerate electrical failure. They studied isolated rabbit hearts in which contraction had been pharmacologically arrested. The hearts were paced at cycle lengths of either 300 or 200 ms and either were or were not exposed to 30 nM of the β-adrenergic agonist isoproterenol. Global no-flow ischemia was initiated, and the resulting progression of electrical failure was monitored with optical mapping. They found that a rapid heart rate and β-adrenergic activation synergistically accelerated the development of regional loss of excitability, which was tightly correlated with the onset of VF and, ultimately, the complete loss of excitability (asystole).

Although measured during global ischemia, the activation rate data of Garg et al. may provide new insight into clinical observations that elevated basal heart rate is associated with increased cardiovascular risk factors (2, 5, 12), including sudden myocardial infarction (7) and VF (1). These data support clinical efforts to maintain lower heart rates in patients with coronary artery disease. It is reasonable to hypothesize that acute local ischemia within the context of high heart rate and increased β-adrenergic activity would be correlated with increased risk of VF and possibly a fast progression to asystole. Thus, during a coronary event, reduced basal heart rate may lengthen the time to asystole, thereby increasing the likelihood of observing a shockable rhythm in OHCA. β-Blockers may further lengthen the time to asystole; however, this point could be debated (10).

In previous animal studies, slowing of sinus rate and blocking β-adrenergic activity delayed the time to onset of VF during ischemic events, presumably by preserving myocardial energy status (21). Studies by Vaillant and colleagues (21) measured the time to VF after acute myocardial ischemia in pigs. From the onset of ischemia, the time to VF was prolonged when a pacemaker current (I\text{Kr}) inhibitor (ibivadoline) was administered to reduce heart rate. When a β-blocker (propranolol) was administered, time to VF was also prolonged, but not nearly as much as that with I\text{Kr} inhibition. The isoproterenol results of Garg et al. corroborate these earlier findings. Phosphocreatine-to-ATP ratios measured by Vaillant et al. (21) at the onset of VF were also higher during I\text{Kr} inhibition, indicating improved preservation of myocardial energy stores. In the clinic, heart rate reduction in patients with angina pectoris increases the time to ST-segment depression and prolongs the onset of angina symptoms (15, 20). These beneficial effects are attributed to improved myocardial energy status, including reductions in myocardial oxygen consumption and improved coronary perfusion secondary to a longer diastolic interval (2).

Garg and colleagues provide several thought-provoking interpretations of their optical mapping data. During ischemia, diminished excitability, conduction block, and asystole are typically attributed to elevated extracellular potassium that depolarizes resting membrane potential, thereby inactivating sodium channels (3, 18). However, Garg and colleagues argue against this mechanism by suggesting that the enhanced electrical depression that they observed was caused by increased calcium loading, not the accumulation of extracellular potassium. They further suggest that the initiation of VF in their experiments was not due to early or delayed afterdepolarizations, which are usually attributed to altered intracellular calcium homeostasis (16) and are typically invoked to explain...
arhythmogenesis during β-adrenergic stimulation in nonischemic myocardium (11). Instead, they explain that the development of a spatially heterogeneous mosaic pattern of electrical depression was the mechanism of VF. Such a pattern would be expected to promote unidirectional block and reentry. As the authors speculate, the Purkinje network could play an important role in initiating the observed VF. Rabbits, the species used in this study, are similar to dogs and humans in that the Purkinje network is primarily subendocardial, making it nearly impossible to definitively associate epicardially mapped activation fronts with endocardial Purkinje activations. However, a number of studies (4, 9) have indicated that the Purkinje network is active during long duration VF, in which the heart is globally ischemic and is likely important in maintaining VF activation through a variety of focal and reentrant mechanisms. Similar mechanisms could very well be at play in the initiation of VF during global ischemia.

A benefit of optical mapping in the studies of Garg et al. was that action potential duration heterogeneity could be analyzed. This revealed differences in the time course of action potential duration shortening between the right and left ventricles, with faster shortening occurring in the left ventricle for three out of four combinations of heart rate and isoproterenol administration. This result implies a shortening of reentrant path length as well as increased dispersion of repolarization, both of which are important VF mechanisms. An important limitation of the optical mapping studies was the requirement of electromechanical uncoupling to reduce motion artifact in the optical action potentials. Interpretation of data when cross-bridge cycling is inhibited must be done cautiously because actomyosin ATPases comprise 75% of total myocardial energy consumption (23). The remaining energy consumption is attributed to the Ca$^{2+}$-ATPases (15%) and the Na$^{+}$/K$^{+}$ ATPase (9%) (17). It is likely that ATP use during both nonischemic and ischemic conditions in the studies of Garg et al. was only 24% of what it might be in an in vivo working heart. As such, it is likely that the time course of electrical events could be significantly shorter in vivo. This limitation is especially important if energy preservation is a mechanism by which lower heart rate and absence of β-adrenergic stimulation protect against the onset of VF. Inhibition of actomyosin ATPases has a large effect on physiological processes that are modulated by the balance of energy production and use, such as during increases in cardiac work and during ischemia (22). It is also worth noting that in their experiments, Garg et al. paced globally ischemia hearts at normal heart rates until VF spontaneously occurred. While this is a reasonable way to assess the effects of activation rate on the degeneration of electrical function, it does not parallel the typical progression of OHCA, which is thought to begin as an event of acute local ischemia and progress as stated in the introductory paragraph. Future optical mapping studies of local ischemia in fully contracting hearts could provide deeper insight into the initiation of VF and the progression of electrical failure.

In light of clinical data that indicates increased incidence of asystole as the first recorded rhythm in OHCA (13), there is a clear need to understand the physiological mechanisms of asystole. Garg and colleagues have provided important new insights showing that rapid heart rate and β-adrenergic stimulation accelerate heterogeneous electrical depression and quicken the pace to asystole. Many questions remain, several of which are related to the role of β-adrenergic activity. When is the best time to administer exogenous epinephrine during cardiac arrest (6, 19)? Do β-blockers prolong the maintenance of adequate levels of metabolic reserve during ischemia to maintain VF while also reducing defibrillation threshold? Could β-blockers alter mechanisms that maintain VF during ischemia and shorten the time to asystole (10) or increase defibrillation threshold (14)? Answers to these questions, and many others, will likely have significant impact on improving therapy for OHCA.

DISCLOSURES

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AUTHOR CONTRIBUTIONS


REFERENCES