

Autonomic function and ventricular tachyarrhythmias during acute myocardial infarction

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important arrhythmogenic mechanism in this setting, is being actively investigated, aiming at the advent of preventive strategies. Recent experimental studies have shown vagal withdrawal after anterior myocardial infarction, coinciding with high incidence of VTs, followed by more gradual sympathetic activation coinciding with a second arrhythmia peak. This article summarizes recent knowledge on this intriguing topic, generating hypotheses that can be investigated in future experimental and clinical studies.

Key words: Sudden cardiac death; Acute myocardial infarction; Ventricular tachyarrhythmias; Ventricular fibrillation; Delayed arrhythmogenesis; Ventricular tachycardia; Early arrhythmogenesis; Vagal activity; Sympathetic activity; Arrhythmogenic mechanisms

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Core tip: Autonomic dysfunction in response to acute myocardial infarction is subject of continuous investigation. Recent experimental data indicated vagal withdrawal, followed by more gradual sympathetic activation, coinciding with early and delayed arrhythmogenesis, respectively. These findings call for further research on the pathophysiologic role of the autonomic nervous system on the ischemic ventricular myocardium.

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Abstract

Most cases of sudden cardiac death are attributed to sustained ventricular tachyarrhythmias (VTs), triggered by acute coronary occlusion. Autonomic dysfunction, an

INTRODUCTION

Sudden cardiac death is a major health-related problem worldwide, accounting for more than half of cardiovascular mortality^[1]. It is invariably caused by sustained ventricular

tachyarrhythmias (VTs), occurring in the setting of acute myocardial infarction (MI). The high incidence and the ominous prognosis of ischemia-related VTs dictate ample research efforts toward in-depth understanding of the underlying mechanisms, aiming at the advent of preventive strategies^[2].

During acute-MI, epinephrine is released in the ischemic myocardium, followed by activation of chromaffin cells in the adrenal medulla^[3]; epinephrine, either locally released or circulating, alters ventricular electrophysiology and has been long known to exert a prominent role in genesis of VTs^[4]. Acute-MI is also often accompanied by marked autonomic dysfunction, but its precise time-course along the acute phase of MI and the ensuing arrhythmogenic effects remain incompletely understood. This article briefly summarizes recent knowledge on this topic that may offer further insights into the complex pathophysiology of sudden cardiac death.

AUTONOMIC DYSFUNCTION DURING MI

Afferent stimuli

Although cardiogenic reflexes were first recognized in the mid-19th century, studies on the autonomic effects on the ischemic myocardium and their impact on VTs were systematically performed only a century later^[5]. These led to early clinical reports introducing the role of autonomic dysfunction on ventricular electrophysiology following acute coronary occlusion^[6]. The activation of ventricular afferent fibers in the ischemic myocardium was subsequently demonstrated, mediated by hemodynamic changes induced by acute-MI, as well as by the local production of chemical stimuli^[7]. This process is dynamic, determined by the time-course of left ventricular hemodynamics and by the balance between the rate of production and metabolism of various mediators.

Sympathetic afferents are mainly nonmyelinated, with only occasional thinly myelinated A δ -fibers, that form a network over the epicardium^[8]. Most sympathetic afferents are activated by adenosine triphosphate and are classified as ischemia-sensitive^[7], although the pathophysiologic significance of those not responding to adenosine triphosphate remains unknown. Afferent activation depends on the location of the ischemic myocardium, as shown by experimental^[9] and clinical^[10] data; in this regard, vagal A δ - and nonmyelinated C-fibers, located in the inferior left and right ventricular wall, are frequently activated during ischemia involving these walls.

Efferent autonomic activation

Afferent stimuli reach the nucleus tractus solitarius, which acts as an integrative center, signaling emergency changes in the central nervous system. In this structure, a series of sensory nuclei, embedded in the medulla oblongata, form circuits with other nuclei in the brainstem and with a large number of other central regions. The medulla contains sympathetic cell bodies, with respective nerves travelling along the spinal cord; from there, sympathetic fibers synapse with sympathetic ganglia, and postganglionic

fibers ultimately synapse at their target sites. The parasympathetic cell bodies exit the medulla as long preganglionic efferent fibers that form synapses with postganglionic fibers within the myocardium.

The effects of the autonomic nervous system on ventricular electrophysiology during myocardial ischemia have attracted rigorous research efforts^[11-14]: Sympathetic activation shortens the ventricular action potential and the refractory period under normal conditions, but these actions vary in the ischemic ventricular myocardium. Thus, in addition to ionic imbalance, sympathetic activation enhances the dispersion of repolarization across the energy-depleted ischemic myocardium and lowers the fibrillation-threshold^[11], perhaps without altering local conduction^[12]. By contrast, parasympathetic stimulation prolongs the action potential duration and the effective refractory period^[13]; hence, vagal activation exerts potent anti-fibrillatory actions on the ischemic myocardium, although transmural dispersion of repolarization seems unaffected^[14].

Early clinical reports have underscored the involvement of both arms of the autonomic nervous system post-MI^[15]; however, the precise time-course of sympathetic and vagal alterations and their contribution to arrhythmogenesis remain incompletely understood^[2]. This can be explained by the marked individual variation, attributed to the size and location of MI, its hemodynamic sequelae, and to the magnitude of the accompanying symptoms of pain and anxiety. Moreover, accurate pathophysiologic conclusions are hindered by the inevitable delays in monitoring patients in coronary care units, coupled with the confounding effects of treatment.

VTs during acute MI

In response to acute coronary occlusion, two temporally distinct peaks have been described in various species, with several lines of epidemiological data pointing towards a similar curve in man^[1,2]. Although this topic has been long debated, classification into VTs linked to reversible ischemia versus those occurring during evolving necrosis is based on firm pathophysiologic differences; more importantly, classification into early and delayed VTs is clinically sound, as it corresponds to the pre- and in-hospital phases, respectively, carrying profound consequences on survival rates and potential treatment strategies. As noted above, scarce data exist in humans on the incidence of early-phase VTs and concurrent autonomic responses. Therefore, the investigation on the underlying mechanisms of ischemia-induced VTs relies largely on *in vivo* animal models; indeed, these models offer clear-cut advantages in monitoring physiologic parameters during specific periods after coronary ligation, in the absence of the confounding effects of various interventions.

ANALYSIS OF RECENT EXPERIMENTAL STUDIES

Our group recently examined the autonomic responses

and the incidence of VTs in the *in vivo* rat-model, by comparing sham-operated controls with an animal-group post-ligation of the left coronary artery^[16]. Continuous electrocardiographic recording was performed in conscious rats *via* implanted telemetry transmitters, and autonomic indices were derived by heart rate variability techniques; specifically, sympathetic activity was assessed by detrended fluctuation analysis, and vagal activity by time- and frequency-domain analysis. Frequent VTs were observed post-ligation, following the typical pattern of an early prominent peak and a more prolonged delayed arrhythmogenic window. Vagal activity decreased markedly immediately post-ligation and remained low throughout the 24 h-observational period. The pattern of sympathetic activation differed, showing a progressive rise; it became significant at a later stage post-MI and remained elevated until the end of the recording. Using micro-neurographic recordings, such delayed sympathetic activation post-MI was also observed by Jardine *et al*^[17] in the ovine-model, in which enhanced cardiac sympathetic nerve-activity was observed only after the first hour post-ligation. These findings support the notion of attenuated parasympathetic, rather than enhanced sympathetic-inputs, contributing to early-phase VTs, given the aforementioned anti-fibrillatory vagal effects on the ischemic myocardium^[14].

Two recent studies lend further support to this hypothesis: in the canine-model^[18], no antiarrhythmic effect was found after suppression of the left stellate-ganglion for 60 min post-MI, except from experiments in which its action was completely abrogated. Likewise, a study from our group^[19] examined the incidence of VTs post-ligation in rats pretreated with clonidine, a centrally acting inhibitor of sympathetic preganglionic-neurons; treated rats displayed a lower incidence of VTs occurring during the delayed phase post-MI, but early phase arrhythmogenesis was unaffected^[19].

PERSPECTIVE

Autonomic dysfunction, commonly observed during acute MI, contributes to the genesis of VTs. Autonomic responses vary, depending on several modulating factors, some of which remain incompletely understood; hence, the precise nature and time-course of such responses during the acute phase of MI is subject of continuous investigation. Early-stage VTs are at the center of research-efforts, because they invariably occur prior to medical attendance and they are responsible for most cases of sudden cardiac death. Recent *in vivo* experimental studies have drawn the attention toward vagal withdrawal, associated with pro-fibrillatory effects in the ischemic ventricular myocardium. Such decreased parasympathetic inputs appear to occur swiftly in response to ischemia, whereas sympathetic activation is more gradual and coincides with a second cluster of VTs. These studies provide further insights into the pathophysiology of acute MI and sudden cardiac death. Nonetheless, these findings should be viewed as hypothesis-generating research that warrants further

validation in animal models and, ultimately, in patients. The investigation of autonomic dysfunction during acute MI is an intriguing topic of high clinical importance that may unravel further aspects of the interrelation between the brain and the heart.

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