

EDITORIAL COMMENT

# Is the Hitman in Cardiac Death Hidden in the Sympathetic Nervous System Remodeling?\*



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Premature ventricular contractions (PVCs) are too-early heartbeats originating in the ventricle, disrupting the heart's normal rhythm. PVCs are very common in the general population being present in up to 75% of subjects monitored with 24-h electrocardiogram Holter (1,2). PVCs are considered benign and are usually asymptomatic in subjects without heart disease (1); however, they increase the risk of cardiomyopathy, heart failure, and sudden cardiac death in patients with structural heart disease (3). For this reason, PVCs are of great interest to both researchers and clinicians, because they represent an important risk factor requiring a better knowledge on the pathogenic mechanisms and the identification of novel treatments. Indeed, the precise mechanisms and the pathogenesis of PVC-induced cardiac dysfunction remain largely unknown. A dysfunction in the autonomic nervous system (ANS) has been associated with PVCs (4). ANS regulates key aspects of cardiovascular function, including contraction, heart rate, and blood pressure, but also several additional functions in cardiomyocytes (4). The heart is richly innervated by the autonomic terminals, with ganglion cells located either outside or inside of the heart (4,5). ANS is subdivided into the sympathetic nervous system (SNS) and

parasympathetic system (4,5). The sympathetic fibers are largely derived from major autonomic ganglia including the superior cervical, the stellate, and the thoracic, while the parasympathetic preganglionic fibers are conducted almost entirely within the vagus nerve (4,5). Experimental and human evidence have documented the pathophysiological role of SNS (4-10), showing that either hyperinnervation or denervation significantly contributes to the development of arrhythmias and sudden cardiac death (4-10). Furthermore, after myocardial infarction, stimuli that enhance neuronal outgrowth (i.e., nerve growth factor) increase nerve sprouting increasing the incidence of ventricular arrhythmias (11). The clinical relevance of abnormal neural remodeling has also been demonstrated in patients with a history of ventricular fibrillation, showing increased density of ventricular nerve fibers (11), and in patients with ischemic cardiomyopathy, showing sympathetic denervation and elevated risk of arrhythmia-related mortality independently of left ventricular (LV) function (12).

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In this issue of the *Journal*, Tan et al. (13) showed the effects of PVCs on ANS function and neural remodeling in an animal model of PVC-induced cardiomyopathy. They investigated the ANS in dogs with PVC cardiomyopathy induced by chronic (12 weeks) bigeminal stimulation, interrupted for 4 weeks to allow full recovery of LV systolic function. They monitored 24-h resting sympathetic and vagal nerve activities at baseline (sinus rhythm), at 12 weeks (a time point when PVC-induced cardiomyopathy was evident), and at the end of the study period (after recovery of LV systolic function). PVC-

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induced cardiomyopathy was associated with enhanced sympathetic nerve activity; of interest, despite a steady recovery of LV systolic function at the end of the study period, SNS function remained elevated compared with baseline values. In contrast, vagal nerve activity, which was significantly increased in PVC-induced cardiomyopathy, returned to baseline levels after cardiac function rescue. Enhanced heart rate (HR) and reduced HR variability were both observed in PVC-induced cardiomyopathy and after normalization of cardiac contractility, thus suggesting a persistent SNS hyperactivity independent from cardiac function. Of relevance from a clinical point of view, the authors observed an increased incidence of spontaneous atrial arrhythmias associated with an augmented autonomic nerve activity both in PVC-induced LV dysfunction and after LV functional recovery, although only increased sympathetic nerve activity promoted the onset of spontaneous ventricular arrhythmias. Of note, the stimulation of  $\alpha_2$ -adrenergic sympatho-inhibitory receptors via clonidine administration suppressed both atrial and ventricular arrhythmias, supporting a pivotal role of the adrenergic system (14). A further relevant finding of the present investigation is the significant sympathetic hyperinnervation (tyrosine hydroxylase staining) in both right and left stellate ganglia in PVC-induced cardiomyopathy, which also persisted after recovery of cardiac function (13). However, no difference has been observed between sham and PVC-induced cardiomyopathy in terms of cardiac sympathetic innervation. This result is of great interest, because it represents a difference with previous mechanistic models of arrhythmias such as tachypacing or systolic heart failure (6,15). However, it cannot be excluded that a longer duration of PVCs would also affect cardiac sympathetic innervation.

Moreover, despite the fact that all experiments shown in the study by Tan et al. (13) have been performed in a rigorous manner, it should be noted that the authors did not provide any data regarding circulating catecholamine levels and  $\alpha$ -/ $\beta$ -adrenergic receptor signaling (both adrenal and neural) (14). This is particularly relevant because in the presence of high catecholamine levels, adrenergic receptors undergo a process of agonist-dependent desensitization and down-regulation that represents a key pathogenic mechanism behind cardiac dysfunction (16). Although almost 5 decades of research support the pathophysiological role of SNS outflow both in the mechanisms of cardiac dysfunction and in the genesis of ventricular arrhythmias, several questions still remain. For example, although cardiac content of catecholamine is reduced and heart adrenergic receptors are dysfunctional, the SNS is hyperactive and catecholamine circulating levels are augmented (15). In this scenario, the study by Tan et al. (13) continues to support the notion that SNS hyperactivity is implicated in proarrhythmogenesis and cardiomyopathy, providing evidence that reversal of PVC-induced cardiac dysfunction is not sufficient to abrogate the proarrhythmic substrate and that other mechanisms might be involved in cardiac remodeling. The study from Tan et al. (13) represents the first report demonstrating that remodeling of the neuronal system also plays a relevant role in arrhythmias when cardiac muscle is functional, with wider implications for the development of a novel treatment approach directly targeting the stellate ganglia sympathetic hyperinnervation.

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