Sudden cardiac death (SCD) triggered by ventricular tachycardias (VTs) is a major public health issue worldwide. The annual incidence of SCD in the United States is estimated to be 69 per 100,000 in the general population (9). In patients with a history of myocardial infarction (MI), its frequency is even higher.

Initial electrophysiological studies, including the analysis of activation patterns during sinus rhythm in patients with VT and cardiac arrest, were performed three decades ago (12, 27). Their findings paved the way for the concept that areas of slow conduction and lines of block are the electrophysiological milieu for reentry circuits, the most common mechanism for VT following MI.

It is now widely accepted that endocardial and epicardial local abnormal ventricular activations and late potentials which are seen within or after the QRS complex, respectively, can serve as surrogate markers of abnormal or delayed electrical propagation. Their abolition has been found to be effective end points of VT ablation, improving patient outcome (15, 26, 29). Importantly, recent experimental and human studies using high-resolution mapping demonstrated that barriers forming the critical part of VT circuits consist of functional rather than fixed lines of block and are not always present in sinus rhythm (4).

For more than a century, the autonomic nervous system of the heart has been known to tightly modulate ventricular electrophysiology and arrhythmogenesis (13, 20). However, whether and how the sympathetic nervous system serves as a functional driver that contributes to the initiation and perpetuation of VT in the healthy and scarred myocardium by dynamically modulating conduction is not fully understood.

**Sym pathetic control of ventricular electrophysiology.** Sympathetic activation from the neuraxis modulates ventricular electrophysiology: it shortens refractory periods (17, 18), changes action potential duration (25, 31), increases dispersion of refractoriness (21), increases heterogeneity of repolarization (28), and induces early afterdepolarizations (8, 32). These physiological changes are directed by neural networks located at the level of the insular cortex to the heart (5, 24). The efferent postganglionic neural input is supplied by numerous intrathoracic sympathetic nerves (6) that originate mainly from the cervical and stellate ganglia with lateral specificity. Although it is functionally not fully explored yet, it becomes evident that the right stellate ganglion predominantly innervates the anterior and the left stellate ganglion innervates the posterior wall of the heart (30). Importantly, efferent nerve fibers from the left and the right side are intertwined at the base of the heart, interact with intracardiac neurons and transverse down to the apex (16, 30). The branched projections of these neurons result in an extensive transmural network of delicate fibers that interact with the cardiomyocytes (Fig. 1).

Following MI, myocardial scarring goes along with functional and morphological neuronal remodeling of the extrinsic and intrinsic cardiac autonomic nervous system (22). In the peri-infarct zone, sympathetic nerve sprouting can result in regional hyperinnervation and related VT (11). In the scar tissue itself, sympathetic reinnervation has been shown to beneficially modulate arrhythmogenesis despite cellular demise and the multiplicity of remodeling processes (14). This underscores the delicate interplay between 1) the functional substrate of modulated sympathetic activity and 2) the morphological substrate of scarred myocardium following MI, resulting in the initiation of VT.

**Impact of sympathetic modulation on cardiac arrhythmogenesis.** In the current issue of the American Journal of Physiology-Heart and Circulatory Physiology, Ajijola et al. (2) provide several novel insights on how sympathetic activation can modulate ventricular electrophysiology and arrhythmogenesis in healthy and infarcted hearts.

First, by using ventricular epicardial mapping on the anterior left ventricle of the healthy pig heart, the authors demonstrate that stimulation of the right stellate ganglion, but not the left, leads to an increase in conduction velocity. These data support the concept that the right stellate ganglion provides greater functional control of the anteroapical left ventricle than the left stellate ganglion. While the underlying molecular mechanisms were beyond the scope of the present study, the authors present evidence that these effects are mediated by β-adrenergic signaling and involve gap junction coupling, as supported by pharmacological studies with esmolol and carbexolone. This finding is of interest since only limited knowledge exists regarding the short-term influence of β-adrenergic signaling on gap junctions (10), even though it should be noted that carbexolone might influence neurons itself (23).

Second, the authors show that sympathetic stimulation can influence sinus rhythm activation and repolarization in the peri-infarct region 6–8 wks after left anterior descending...
coronary embolization. Fiber disarray in that region was confirmed via diffusion tensor magnetic resonance imaging and histological staining. While no differences in activation recovery intervals (ARI) and activation times were detectable at baseline, sympathetic stimulation of the left and right stellate ganglion led to a shortening in ARIs and an increase in heterogeneity of activation. Even though the effect of the right stellate was more pronounced, left stellate stimulation now had a detectable effect, too. This suggests that not only an increase in sympathetic excitability but also adaptations regarding the laterality of the nervous supply took place here. This is surprising since MI-induced neurochemical and structural remodeling occurs in both stellate ganglia (3). Whether these changes in laterality originate from higher (increase of sympathetic activity post MI) or lower [release of growth factors and (co)transmitters in the peri-infarct area] levels of the neuronal hierarchy needs to be identified.

As another key finding of these laudable investigations, Ajijola et al. (2) demonstrate that putative circuits of VT can be influenced by sympathetic stimulation. Changes in propagation were demonstrated by studying late potentials as indicators of slow conduction in areas related with these putative circuits. The authors show in this MI model that stimulation of the right stellate ganglion induced heterogenous changes in a region that exhibited late potentials, e.g., prolongation of activation time post MI) or lower [release of growth factors and (co)transmitters in the peri-infarct area] levels of the neuronal hierarchy needs to be identified.

Inspired by the present findings, one might speculate that endo- and epicardial substrate mapping with and without sympathetic stimulation might improve the identification of VT circuits and subsequent ablation strategies. However, this needs to be investigated in more detail in experimental and first human studies. In addition, the findings of the present study might facilitate ongoing investigations that address the question of whether and when right or bilateral cardiac sympathetic denervation should be preferred to sole left-sided denervation to prevent VT in selected patients. Finally, percutaneous (1) or intracardiac electrical neural stimulation using catheter-based techniques (7, 19) might open up new avenues to study “the sympathetic heart and its scars.” This might hopefully pave the way for the development of elegant therapeutic approaches translating into improved outcome of patients with VT in ischemic heart disease in the future.

REFERENCES


