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EDITORIAL COMMENT

Defining Tachycardia-Induced Cardiomyopathy

Life in the Fast Lane*

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Heart failure and arrhythmia of all kinds are natural bedfellows, but within cohorts of patients with systolic heart failure there lurks a group of individuals whose ventricular dysfunction is the result, and not the cause, of their cardiac rhythm disturbance. The first case reports of tachycardia-induced cardiomyopathy (TIC) appeared in the early years of the 20th century, but it was only in 1962 that Whipple et al. (1) described the first experimental model of pacing-induced heart failure. This standard model has been used in numerous large-animal experiments to create a phenotype in which the severity of pacing-induced left ventricular dysfunction relates to the rate, duration, and site of pacing, with chronic ventricular pacing being the most detrimental (2,3).

In humans, TIC is described in various settings, including atrial fibrillation (AF), incessant supraventricular tachycardia, frequent ventricular ectopy, and ventricular tachycardia (2,3). Perhaps the purest model for TIC is incessant (i.e., present ≥90% of the time) atrial tachycardia in which left ventricular dysfunction occurs in ≤10% of individuals (4). Successful treatment of the tachycardia in this setting improves left ventricular function in the vast majority of cases. A more common TIC is that associated with chronic AF with poor rate control (5). Caveats to this observation are that the estimation of ejection fraction during rapid AF is technically challenging, and studies have also suggested that the irregularity of AF may itself be detrimental to left ventricular function independent of the ventricular rate response (3,5,6). Another relatively common scenario is that of frequent premature ventricular complexes in which TIC is related to the frequency of these complexes as well as their absolute burden, ectopic coupling interval, QRS duration, and site of origin (2,3,7).

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In this issue of the *Journal*, Mueller et al. (8) report a thorough analysis of endomyocardial biopsy specimens taken from patients with a presumptive diagnosis of TIC. In a retrospective series of 189 patients with new-onset heart failure, the authors identified 19 individuals with TIC defined according to an admission heart rate >100 beats/min, rhythm other than sinus, recovery of left ventricular ejection fraction after restoration of sinus rhythm or rate control, and exclusion of other causes of heart failure. The remainder of the study population was classified as either having dilated cardiomyopathy or inflammatory cardiomyopathy in accordance with published histopathological criteria (9). Compared with healthy myocardial samples, biopsy samples taken from patients with TIC showed a focal loss of myofibrils, abnormally lobulated nuclear membranes, and marked variation in size and architecture of mitochondria. Mitochondria were also abnormally located near intercalated discs, and ribonucleic acid expression analysis revealed a distinct pattern characterized by increased expression of mitochondrial pyruvate carrier 1. Compared with dilated cardiomyopathy and inflammatory cardiomyopathy, myocardial samples from patients with TIC had greater expression of major histocompatibility complex class II molecules, infiltration of CD68+ macrophages, absent or low levels of CD3+ T cells, and less myocardial fibrosis.

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Although the cause of these changes—in particular, the macrophage infiltration—is unknown, the authors concluded that TIC is characterized by histological and biochemical features that differ significantly from other cardiomyopathies.

These intriguing findings (8) add to an existing body of evidence derived mostly from animal studies. Other than the defining changes in left ventricular cavity dimensions and function, numerous changes at a cellular level have been described, including cellular elongation, myofibrillar disruption, cardiomyocyte apoptosis, and myocardial fibrosis (2,3). Changes in the structure, distribution, and function of the coronary microvasculature are also described and have led to the suggestion that myocardial ischemia is a contributor to TIC. Reported biochemical changes in pacing-induced cardiomyopathy include reduced myocardial energy stores (creatine, phosphocreatine, adenosine triphosphate, and glycogen), increased Krebs cycle activity, and decreased activity of the sodium-potassium adenosine triphosphatase pump consistent with mitochondrial injury. Increased levels of oxidative stress accompany myocyte apoptosis in animal models of TIC, and reduction of oxidative stress (e.g., with antioxidant vitamins) attenuates cardiac dysfunction. Other reported findings include increased endothelin-1 levels and down-regulation of beta-adrenergic receptors and calcium cycling.

There are some obvious limitations to the study by Mueller et al. (8). Foremost is the retrospective design, which introduces the inevitable risk of selection bias. The second is the reliance on the admission heart rate for the definition of TIC. This will have been dependent on many factors, including severity of heart failure and the intensity of drug therapy on admission. Resting heart rate is also an unreliable measure of tachycardia burden in patients with AF in whom heart rate can rise precipitously with mild physical exertion. Finally, some of the observed changes reported are not unique to TIC but are seen in other forms of chronic heart failure where they reflect the downstream effects of elevated filling pressures and decreased cardiac output. Nevertheless, this study is the first in humans to characterize the cellular phenotype of TIC in vivo. One of the major issues in TIC is the fact that it is a diagnosis of exclusion, with no single confirmatory test. If the histological changes identified in this study can be replicated in prospective studies, endomyocardial biopsy could then have a role in selected cases when the diagnosis of TIC is in doubt. A second important message from this study is that some of the observed histological changes are probably irreversible, emphasizing the need for a high level of clinical suspicion for TIC and prompt treatment of the causative arrhythmia by using pharmacological methods or by other means. In other words, diagnosis of the cause of left ventricular dysfunction matters.

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