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REPLY: Effectiveness of Antitachycardia Pacing for Recurrent Ventricular Tachycardia in ARVC

Drs. Santangeli and Marchlinski have asked that we clarify and expand on the treatment of arrhythmias described in our recent report (1). We appreciate this opportunity to respond.

Of the 108 patients with implantable cardioverter-defibrillators (ICDs) included in the registry, 48 patients had 502 sustained and treated episodes of ventricular arrhythmia. Forty-three patients underwent antitachycardia pacing (ATP) attempts for ventricular tachycardia (VT); the other 5 patients received only shock therapy. The number of ATP attempts per patient ranged from 1 to 96; 28 patients had ≤10 attempts. Forty-two of the 43 patients had at least 1 successful ATP treatment for VT. Twenty-seven patients had only successful ATP treatment. Only 3 patients had more failed ATP attempts than successful ATP attempts. Thus, programming the ICDs to first deliver ATP resulted in the avoidance of shock treatment in a significant number of patients, and there were no fatalities. We stand by our conclusion that "all ICDs should be programmed for ATP, even for rapid VT" (1). However, ATP was not always successful, because 16 patients had at least 1 ATP failure that resulted in an ICD shock. In total, 30 patients had 89 ICD shocks (average: 3; range: 1 to 9). We are not aware of any episodes of arrhythmia that were excluded; all episodes of arrhythmias reported to us were included in our analysis. It is possible that there were episodes of ICD shocks and ATP that were not reported to us and thus could not be included in our analysis.

Drs. Santangeli and Marchlinski also requested details on ICD programming and management of recurrent VT during follow-up. In this registry, ICD programming was left to the discretion of the physician performing implantation and follow-up. We do not have details regarding the lower rate programmed for VT or the duration of VT for which the ICD would have attempted treatment. Fifty-three of the 108 patients with an ICD were treated with antiarrhythmic drugs, and the details have been reported in another paper (2). Briefly, in this patient population, 58 patients who were treated with beta-blockers did not have an increased or decreased risk of arrhythmia. Treatment with sotalol (n = 38) was associated with an increased risk of ventricular arrhythmias, and the 10 patients treated with amiodarone had a significantly lower risk of ventricular arrhythmias. Fifteen patients underwent ablation.

Drs. Santangeli and Marchlinski commented on the high efficacy of the combination of endo-epicardial catheter ablation. We agree that the reported data show 1-year efficacy of approximately 70%. We also agree that the best treatment strategy regarding recurrent VT remains to be determined, especially with regard to ablation. In the population studied, there was no attempt to prevent or promote ablation. Indeed, 15 of the patients underwent ablation during the study. However, we do not have data on whether the attempts at ablation were endo-epicardial or on the efficacy of ablation in these patients.

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Obstructive Sleep Apnea and Hypertrophic Cardiomyopathy

Obiter Dictum or More?

We read with interest the state-of-the-art paper on the present and future of hypertrophic cardiomyopathy (HCM) by Maron et al. (1), well-known

luminaries in the practice of HCM who have succinctly summarized the contemporary aspects of this challenging disease for the cardiovascular community. From genetics to clinical presentation to the less well-known aspect of transplantation in HCM, they have touched on the basic aspects of HCM well. It is also refreshing to read their description of the emergence of HCM from an era of misunderstanding, stigma, and pessimism to one of more optimism; HCM is now believed to be a treatable cardiovascular disease, with the vast majority of patients with HCM reaching normal or near-normal longevity. In addition, Maron et al. have delineated the risk stratification methodology in HCM, a field that can be disconcerting for both the physician and the patient. We are indeed pleased to see this influential group of physicians advocating the introduction and acceptance of cardiac magnetic resonance–delayed gadolinium enhancement as a risk stratification tool in their "pyramid profile" and arbitration assembly.

We would, however, like to point out the singular absence in this paper of mention of obstructive sleep apnea (OSA) in patients with HCM. There have been rapid advances in the past several years in the understanding of the association between OSA and cardiovascular disease and mortality (2). Recent investigations have shown the coexistence of OSA and HCM and the important contribution to drug-refractory symptoms and worsening left ventricular outflow tract obstruction in HCM as a result of heightened sympathetic nerve activity in OSA (3,4). The generally stable state of cardiovascular quiescence in sleep is interrupted in patients with OSA by intermittent surges in sympathetic nerve activity, blood pressure, and heart rate.

Several mechanisms elicited by OSA can initiate and propagate a cascade of noxious stimuli that initially and over time contribute to progression of cardiovascular disease in general and repetitive arrhythmogenic potential in particular in patients with HCM. Apnea-induced hypoxemia and carbon dioxide retention in OSA lead to autonomic dysregulation, precipitating increased sympathetic nerve activity, and parasympathetic withdrawal. These lead to peripheral vasoconstriction, myocyte injury and necrosis, renal retention of salt and water, and increased renin-angiotensin-aldosterone activity, all of which contribute to both arrhythmogenesis in HCM and its symptomatology. Furthermore, altered adrenergic signaling, a key feature of HCM, is also seen in OSA; indeed, beta-adrenergic receptor inhibition is the most common therapy for symptom relief. Apnea-induced hypoxemia also causes increased oxidative stress (increased reactive oxygen species) and platelet activation, which in turn propagate endothelial dysfunction and hypercoagulability. Both of these increase the susceptibility of the patient with HCM and small vessel disease to myocardial ischemia and its consequent attendant malignant ventricular rhythms. Recent studies involving patients with implantable cardioverter-defibrillators have shown that appropriate device discharge occurs 2- to 4-fold more frequently in those with OSA than in those without (5).

In addition to the mechanistic consideration of apnea-induced hypoxemia in arrhythmogenesis in patients with OSA and HCM, it is important to consider the effects of futile inspiratory efforts against an occluded pharynx; this mechanism is central to the generation of large negative intrathoracic pressures. The large increase in negative intrathoracic pressures affects 3 pathways in patients with OSA and HCM: 1) increased left ventricular afterload, decreased left ventricular preload with a consequent decrease in left ventricular stroke volume, cardiac output, and increased left ventricular outflow tract obstruction; 2) increased left atrial distention/dilation leading to atrial fibrillation, which is the most common arrhythmia in HCM; and 3) increased intrathoracic aortic wall stress, which is a putative mechanism for increased prevalence of aortopathy in patients with HCM (an as yet undetermined field).

In summary, there is evidence from observational and nonrandomized trial data suggesting a significant relationship (not necessarily a causal relationship) between OSA and HCM symptomatology. Mechanistic investigations also stimulate us to propose a true arrhythmogenic role of OSA in HCM in susceptible patients. Thus, it can be argued, among others, in obiter dicta that integrating OSA into the risk stratification tool in the "pyramid profile" and arbitration assembly for sudden death in HCM would strengthen the current pyramid profile. However, we understand that the most important approach to this integration will be to conduct larger-scale multicenter studies to harmonize this objective.

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REPLY: Obstructive Sleep Apnea and Hypertrophic Cardiomyopathy

Obiter Dictum or More?

We greatly appreciate the positive comments offered by Drs. Jan and Tajik regarding our contemporary review of diagnostic and management strategies for hypertrophic cardiomyopathy (HCM) (1). However, Drs. Jan and Tajik point out that we have ignored the role of obstructive sleep apnea (OSA) in the clinical course of patients with HCM. On reflection, we agree that it was perhaps an oversight not to at least mention OSA, given the increasing data suggesting that OSA may contribute to drug-refractory symptoms and left ventricular outflow gradients in this disease (2,3). On the other hand, we believe that it is probably premature to consider OSA to be a sudden death risk stratification marker in HCM, given the limited observational data that are currently available. Nevertheless, because the HCM risk factor algorithm remains incomplete (4,5), additional relevant variables would represent a significant contribution to disease management. Given its influence on clinical outcomes in a variety of cardiovascular diseases, OSA warrants further investigation in this regard.

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