EDITORIAL COMMENT

The Cardiologists' Worst Nightmare

Sudden Death From "Benign" Ventricular Arrhythmias*

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The right ventricular outflow tract (RVOT) is the site of origin of the most common type of ventricular tachycardia (VT) occurring in patients without organic heart disease (1). This RVOT-VT has a distinctive morphology (QRS complexes with left-bundle branch block pattern and tall R waves in the inferior leads) and, in general, does not lead to hemodynamic decompensation. Therefore, in patients presenting with palpitations (in the absence of heart disease), recording of extrasystoles that appear to originate from the RVOT is reassuring. This procedure follows the reasoning that any sustained arrhythmia originating from the RVOT, if it ever occurs, will be well tolerated.

However, the RVOT also is a site of origin of ventricular fibrillation (VF) in patients with Brugada syndrome (2,3) and idiopathic VF (4,5). Although patients with these polymorphic arrhythmias present with syncope or cardiac arrest and have rare extrasystoles with a uniquely short coupling interval (with extrasystoles falling on the peak of the T-wave) (4,6,7), those with the more common monomorphic VT present with palpitations and have frequent extrasystoles with a long (away from the T-wave) coupling interval (1). Thus, distinguishing patients with benign (monomorphic) RVOT-VT from those with malignant (polymorphic) arrhythmias originating from the RVOT has not been a clinical problem. Not until now.

We recently recognized three patients with otherwise-typical "benign RVOT ectopy" who went on to develop spontaneous VF or polymorphic VT (8). Again, the coupling interval of the extrasystoles (falling on the descending limb of the T wave) offered clues to their malignant nature because it was "intermediate" (longer than the coupling interval in idiopathic VF but shorter than that of truly benign monomorphic RVOT-VT) (8). Now, Noda et al. (9) report, in this issue of the *Journal*, the largest series of

patients with polymorphic VT originating from the RVOT (16 patients) and compare them with 85 patients with monomorphic RVOT-VT. Most patients were between 30 and 50 years of age and had thousands of extrasystoles per day, but neither the number nor the coupling interval of the extrasystoles distinguished patients with the malignant (polymorphic) RVOT-VT from those with truly benign (monomorphic) RVOT-VT. Yet, five (31%) of patients with polymorphic VT had cardiac arrest with VF. Not surprisingly, the ventricular rate during polymorphic VT was faster (mainly 220 to 276 beats/min) than the rate of monomorphic VT (generally <230 beats/min). Finally, radiofrequency ablation applied to the site of arrhythmia origin in the RVOT was curative for most patients in both groups (9).

POLYMORPHIC RVOT-VT: WHAT SHOULD WE CALL IT AND HOW CAN WE EXPLAIN IT?

In isolated cases, extrasystoles with short coupling interval were observed to initiate polymorphic RVOT-VT (5,8). We named that arrhythmia "short-coupled variant of RVOT-VT" (8) in analogy to the "short-coupled variant of torsade de pointes," a term used by Leenhardt and the late Philippe Coumel for idiopathic VF (7). Our term would not fit the series reported here because the coupling interval triggering polymorphic VT was long (9). "Idiopathic VF originating from the RVOT" would not be a good term either because the latter term implies spontaneous extrasystoles with an ultrashort coupling interval (6) and easy induction of VF with programmed ventricular stimulation (10), neither of which were observed here (9). Finally, polymorphic VT in adult Japanese patients (9) brings to mind Brugada syndrome. However, the Brugada-pattern electrocardiogram was absent even after a flecainide challenge, and traits of the Brugada syndrome, such as familial sudden death, male predominance, and easy induction of VF (11), were absent in the Noda et al. series (9). We are therefore left with the terms "idiopathic polymorphic RVOT-VT" or "malignant idiopathic VT."

In the Noda et al. series (9), typical monomorphic RVOT-VT was documented in 5 of the 16 patients who also had polymorphic VT, and the coexistence of these two arrhythmias has been reported (8,12). Thus, monomorphic and polymorphic RVOT-VT could share an underlying mechanism, i.e., delayed afterdepolarizations (DADs)-induced triggered activity (13). In addition, catecholaminergic polymorphic VT, a genetic disorder also leading to malignant VT (14), also appears to originate predominantly from the RVOT (15) and also appears to involved DAD-induced triggered activity (14). The preponderance of M cells (which more readily develop DADs) in the RVOT (16) may explain why all these tachyarrhythmias originate from this limited area. Moreover, the cellular mechanisms underlying the transition of monomorphic VT to polymorphic

VT recently were studied in an animal model of cat-echolaminergic polymorphic VT that used caffeine and isoproterenol to disrupt calcium homeostasis (17). In this canine right ventricular wedge preparation, either mono-morphic VT, bidirectional VT, or slow polymorphic VT developed as a consequence of DAD-induced triggered activity (17). Bidirectional VT resulted from alternation of DAD-induced extrasystoles between epicardium and endo-cardium, whereas slow polymorphic VT was a consequence of the gradual migration of the origin of DAD-induced beats across the ventricular wall. All DAD-induced rhythms had relatively slow rates (≤200 beats/min), rates that would be expected to be well-tolerated.

However, in some wedge preparations, DAD-induced triggered beats originated in epicardium, leading to a reversal of the direction of activation (from epicardium to endocardium instead of the normal endocardial to epicardial activation). Such reversal in activation sequence leads to a dramatic increase in transmural dispersion of repolarization because the epicardial areas, who have shortest action potential, are now activated first instead of last (18). A vulnerable window across the ventricular wall is thus cre-ated, allowing closely coupled extrasystoles to induce rapid polymorphic VT/VF. These experimental findings are con-sistent with the following clinical observations of Noda et al. (9): The RVOT extrasystoles leading to monomorphic or polymorphic VT had similar (long) coupling intervals. Yet, when polymorphic VT occurred, the second or third extra-systoles had a very short coupling interval (9). One could speculate that DADs from the endocardium or M-cell layer of the RVOT trigger monomorphic RVOT-VT with a stable rate. However, DADs originating from the RVOT-epicardium not only initiate VT but also create the substrate for reentry by increasing dispersion of repolarization (18). An extrasystole from any source arriving during the vulner-able period so created could precipitate circus movement reentry in the form rapid polymorphic VT.

"BENIGN" ARRHYTHMIAS THAT KILL

The worst nightmare for electrophysiology consultants is reassuring a young patient (and his or her family) about the benign nature of the arrhythmias only to find out that he or she later died suddenly. The present study makes such a nightmare more tangible because patients with a malignant course were not different, at the time of presentation, from patients with benign RVOT-VT (9). Having said that, it is clear that recommending aggressive therapy for all patients with RVOT-ectopy would be counterproductive because RVOT-ectopy is common, malignant RVOT is rare, and therapy for RVOT-arrhythmias is not without risk. We would argue that radiofrequency ablation should be recom-mended early, rather than late, for patients with these high-risk characteristics: 1) a history of syncope (9); 2) very fast VT (because ventricular rates >230 beats/min are associated with polymorphic VT) (9); 3) extremely frequent

ectopy (>20,000 extrasystoles/day) because such degree of ectopy causes cardiac desynchronization and may eventually lead to cardiac dilatation (19); and 4) ventricular ectopy with short coupling interval (because the shorter the coupling interval, the higher the probability for polymorphic arrhyth-mias) (5,6,8), noting that the absence of short coupling intervals is no guarantee against polymorphic RVOT-VT (9).

Efforts to exclude subtle forms of disease with adverse prognosis, particularly right ventricular dysplasia, could include signal averaged electrocardiography (20) and/or T-wave alternans (21) in addition to imaging techniques and a maximal exercise stress test. And to conclude, a word of caution: Our approach to patients with asymptomatic ventricular arrhythmias is based on the dictum that arrhyth-mias occurring in patients with organic heart disease, particularly left ventricular dysfunction, potentially are ma-lignant and need aggressive therapy, whereas similar ar-rhythmias generally are benign, and can be left untreated, when there is no evidence of heart disease or genetic disorders (1). Although this approach is well-supported by guidelines (22), the data supporting the two aspects of this dogma are not comparable: Although the notion that impaired left ventricular function worsens the prognosis in patients with ventricular arrhythmias is supported by nu-merous studies, each one involving thousands of patients (22), the dictum on the excellent prognosis of patients with ventricular arrhythmias and normal ventricles is based on isolated studies involving only a few dozen patients (23–25). This reservation should be part of every consult on "benign ventricular arrhythmias."

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