Pleomorphic Ventricular Tachycardia and Risk for Sudden Cardiac Death

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Increasing implantable cardioverter-defibrillator (ICD) use in response to broad indications in recent years has heightened the need to better refine selection for patients most likely to benefit. Although no single test adequately predicts sudden cardiac death risk, it seems intuitive that the best markers should be those that directly reflect electric instability and abnormalities of the underlying myocardial substrate. The advanced recording capacity of ICDs allows detailed investigation of spontaneous ventricular tachycardia (VT) episodes that would previously have been inaccessible and to potentially aid in documenting characteristics of clinically significant VTs. Different VTs occurring in the same patient can vary in stability, duration, and hemodynamic consequence. The ability to document and monitor for certain distinguishing features might provide new insights into the underlying pathophysiology and thus help to inform assessments of risk. Although ICDs discriminate between VTs primarily based on differences in rate, stored electrograms (EGMs) also have been used to help identify the arrhythmia origin and in a recent study, to help discriminate likely regions of origin for different “clinical” VTs while pace mapping in patients postinfarction.

In this issue of Circulation: Arrhythmia and Electrophysiology, Hadid et al1 analyze stored EGMs to evaluate the incidence and predictive value of pleomorphic VT and multiple VT morphologies among patients enrolled in the DATAS (Dual Chamber and Atrial Tachyarrhythmias Adverse Events Study) trial,2 in which ICDs were implanted under standard class I indications according to the 1998 American College of Cardiology/American Heart Association guidelines, as well as for MUSTT (Multicenter Unsustained Tachycardia Trial) criteria after November 2001. This study is the first to use ICD EGMs to systematically study pleomorphic VT, which was defined as a single VT episode having >1 stable ICD EGM morphology, each lasting at least 6 consecutive beats. The incidence of pleomorphism in a largely secondary prevention population consisting of men with coronary heart disease and prior myocardial infarction was relatively high (20% of those with monomorphic VT). The presence of pleomorphism was associated with a greater number of episodes of monomorphic VT and independently predicted total mortality (odds ratio, 5.33; P=0.009). Interestingly, the median time from the development of pleomorphic VT to death was a short 1.5 months.

Monomorphic VT following myocardial infarction has been demonstrated to be due to reentry, and pleomorphism was first reported by Josephson et al,4 who proposed that the same reentry circuit with different exit sites could produce morphologically distinct VTs (Table). Subsequent mapping studies suggested that distinct VTs can arise from either the same circuit or the adjacent circuits within 1 to 2 cm in proximity, with regions of shared conduction.5 Specifically, changes in VT morphology might result from changes in the reentry path, using varying portions of the same common isthmus region. Alternatively, pleomorphism may relate to activation differences at sites outside or distal to the shared isthmus. Pleomorphism due to temporally distinct clinical VTs also has been demonstrated through reversal of conduction within the same reentry circuit.6 Importantly, the changing patterns that manifest as pleomorphism may occur not only as a consequence of structurally fixed circuits, but also in the setting of functional block that dynamically alters isthmus lengths or exit sites. Distinct VTs that originate from anatomically removed regions of the heart also can initiate each other, causing pleomorphism.

There are clues that sometimes help to distinguish between the different mechanisms. Pleomorphism caused by a change in exit site rather than from the interplay of 2 distinct circuits should exhibit an initial change in tachycardia cycle length accompanying the change in morphology followed by an immediate return to the original cycle length. Figure 1A of Hadid et al7 shows an example of pleomorphic VT with 2 morphologies separated by a fusion complex. The cycle lengths of the 2 morphologies are slightly different, suggesting that 2 different structural or functional circuits are involved. Figure 4C of their article demonstrates monomorphic VT, which appears to be a fusion of the 2 morphologies from the pleomorphic VT shown in Figure 4A from the same patient, consistent with a figure of 8 reentry mechanism.

Table. Mechanisms of Pleomorphism in VT

| • Single VT circuit with >1 exit site |
| • Distinct circuits in proximity with shared isthmus |
| • Activation differences in regions outside a shared isthmus |
| • VTs from remote regions that activate or trigger each other |
| • Dynamic functional block giving rise to changes in isthmus length or exit sites |
| • Conduction reversal within the same reentry circuit (requires extra stimulus) |

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This study by Hadid et al is intriguing in that it is the first to report an increased mortality associated with pleomorphism. How pleomorphism translates into increased mortality is not completely clear. A relatively high rate of VT recurrence and appropriate ICD shocks in the group with pleomorphic VT suggests that pleomorphism is a peculiar manifestation of an active arrhythmogenic substrate. Reentry circuits in proximity or activation wavefronts that are dynamically changing might create the electrically heterogeneous and spatially unstable reentrant conditions that favor degeneration into ventricular fibrillation. In this study, increased cardiac mortality may have been presaged by the higher proportion of cardiac arrest before inclusion in patients who had pleomorphism as opposed to multiple morphologies, although this was not directly compared statistically. The shorter cycle lengths of the pleomorphic VT (median, 330 ms versus 350 ms; \( P=0.044 \)) might also be clinically meaningful. Conversely, pleomorphism may reflect the degree of underlying myocardial dysfunction or deterioration. Pleomorphism previously has been related to extent of coronary heart disease and the presence of multiple infarctions as well as to compromised ejection fraction and an unusually high incidence of left ventricular aneurysms. One might hypothesize that pleomorphism in the setting of functional barriers that are not fixed can arise during ischemia, which generally does not play a role in monomorphic VT.

The study overall has small numbers and will require further corroboration and elucidation of some incomplete details. Total and cardiac mortality were predicted by the presence of pleomorphism, but there were insufficient numbers to assess the impact of arrhythmic mortality. However, whether arrhythmic mortality can even be properly classified in populations with ICDs is debatable. All pleomorphisms may not be the same or carry the same risk. As redepicted in the Venn diagram in the Figure, pleomorphism appears to largely be a subset of VT with multiple morphologies of monomorphic VT, which is not surprising given the presumption that circuits that can sustain pleomorphic VTs also can readily manifest each morphology separately. Multiple morphologies of monomorphic VT also occurred in 17 (85%) out of 20 patients with pleomorphism, and it is this subgroup of patients with both pleomorphism and multiple morphologies that had the highest mortality on follow-up, although the absolute numbers (4 deaths) are very small. The authors reasonably suggest that the mortality of the subgroup with multiple morphologies was driven by patients with concomitant pleomorphism. One could alternatively speculate that pleomorphic VT alone in the absence of multiple morphologies portends low risk.

The authors acknowledge important limitations. There is a lack of longitudinal clinical data with respect to potential confounders. Specifically, potential triggering factors such as ischemia, heart failure, or metabolic issues were not systematically analyzed. Changes in antiarrhythmic medications as well as interim treatments would modify risk in an unquantified manner. Notably, 2 of the 4 deaths in patients with pleomorphism occurred in patients who underwent VT ablation. There is also the potential for underdetection of multiple VT morphologies with the use of only 1 EGM configuration. Conversely, polymorphic VT, such as torsade de pointes, may appear transiently monomorphic in a single lead but then switch to another morphology to appear pleomorphic. That some pleomorphism might in fact be a veiled manifestation of polymorphic VT may explain increased mortality. The extent to which this occurs also can be influenced by antiarrhythmics; Horowitz et al and Buxton et al both demonstrated that class I agents can convert polymorphic tachycardia to a monomorphic tachycardia in patients with prior myocardial infarction.

More studies will be needed to elucidate the prevalence and nature of spontaneous pleomorphism and perhaps expose evidence for pleomorphic VT degenerating into polymorphic VT or ventricular fibrillation. In conjunction, carefully conducted electrophysiological studies can clarify the mechanisms and prognostic relationship between spontaneous and inducible pleomorphism. The implications for clinical practice will then depend on the degree to which specific treatments based on findings of pleomorphism can actually improve outcome. In general, patients with multiple VT morphologies have experienced less success with surgical treatment and less efficacy with antiarrhythmic drugs. Prior studies have suggested that inducibility of pleomorphic VT during programmed stimulation identified patients at higher risk for subsequent recurrence of VT. Although patients with pleomorphic VTs might seem ideal candidates for ablation of a common isthmus, they also tend to have poorer results with catheter ablation. Unstable regions of functional block might be difficult to identify by mapping at times remote from the event. Nevertheless, aggressive intervention seems warranted because it is often the higher risk groups that benefit the most.

The findings of Hadid et al should more generally focus attention on the importance of better characterizing myocardial arrhythmogenicity in understanding risk and targeting VT therapies more precisely. Restratifying traditional at-risk groups with heterogenous substrates and dynamically changing risk profiles likely requires synergistic integration of anatomic/imaging, clinical, and electrophysiological compo-
ents, and this has thus far proved difficult. Analysis of stored EGMs might eventually help to connect some dots by translating observations between the electrophysiology laboratory and the real-world outpatient arena. Trials that form the basis for current ICD indications were not designed to optimize ICD use, and in returning full circle, ICDs are fast becoming an indispensable tool to better study the arrhythmias for which they provide protection.

Disclosures
Dr Josephson is on the consultant/advisory board for Medtronic.

References
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