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EDITORIAL COMMENT

Treatable Causes of Sudden Death: Not Really "Treatable" or Not Really the Cause?*

Sami Viskin, MD,† Amir Halkin, MD,†
Jeffrey E. Olgin, MD, FACC‡
Tel Aviv, Israel, and Indianapolis, Indiana

Ventricular tachyarrhythmias due to a "treatable" or "reversible" cause (like those due to an acute myocardial infarction [MI], electrolyte imbalance or drugs) are considered a "class III indication" for cardioverter defibrillator (ICD) implantation (1). In other words, ICD implantation is regarded as unnecessary (at best) or explicitly contraindicated for patients with ventricular tachycardia/fibrillation (VT/VF) due to a "curable cause." This is based on the premise that patients with VT/VF due to a treatable cause have a low risk of death from recurrent arrhythmias if the specific cause is treated. In this issue of the *Journal*, Wyse et al. (2) present data suggesting that patients with VT/VF due to treatable (and treated) causes may not have a good prognosis after all.

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In this study (2), >2,000 patients with "primary" VT/VF (from the Antiarrhythmics Versus Implantable Defibrillators [AVID] Study) (3) were compared to 278 patients with VT/VF that was "secondary" to a treatable cause. The last group consisted of patients who entered the AVID *Registry* by virtue of having sustained VT/VF, but were excluded from the AVID *Study* because the arrhythmia was attributed to an ischemic event, an electrolyte imbalance or a proarrhythmic drug. The 2,013 patients with "primary VT/VF" were treated according to the AVID-Study randomization (3) with either an ICD (52% of patients) or a class III antiarrhythmic (mostly amiodarone). In contrast, the treatment of patients with "correctable causes" for VT/VF included correction of the identified etiology, such as revascularization for "ischemic VF" or discontinuation of proarrhythmic drug therapy. Thus, only 20% of patients with "treatable VT/VF" had ICD implantation.

The mortality of patients with "treatable" VT/VF was unexpectedly high (27% at three years) and similar to that of patients with VT/VF for whom a curable cause could not be identified (24% at three years) (2). Among patients *not* treated with ICDs, mortality was 15% at one year and 29% at three years when a "treatable cause" was identified (and treated) versus 14% at one year and 30% at three years when such cause could not be identified (A.P. Hallstrom, personal communication, 2001).

Although AVID was a randomized trial (3), the report by Wyse et al. (2) is based in part on the AVID Registry. Since assignment to the "primary" or "treatable" VT/VF groups was not randomized, it is possible that some confounding factors affected the mortality of the last group and made it look as bad as that of patients with primary VT/VF. For example, data on the timing and mode of death are not available for patients in the Registry (those with "treatable" causes). Thus, one cannot exclude the possibility that many patients with "treatable" VT/VF died from complications of the index arrhythmic insult rather than from recurrent arrhythmias. This is unlikely, however, because all patients had to be fully conscious and in hemodynamically stable condition before entering the Registry. This suggests that the mortality figures recorded essentially reflect long-term mortality. Moreover, patients with "treatable" arrhythmias had (as a group) several characteristics associated with *improved* prognosis: they were younger, had better left ventricular ejection fraction (EF) and received beta-adrenergic blocking agents or revascularization more commonly than patients with arrhythmias not considered "treatable." Accordingly, patients with treatable arrhythmias should have done better. In fact, after correcting for these variables, patients with treatable arrhythmias appeared to do *worse* than patients with primary arrhythmias (2). How can one explain the adverse prognosis of patients with VT/VF due to treatable causes?

One explanation is that the "treatable causes" of VT/VF are not really treatable. In the study by Wyse et al. (2), the correctable cause for VT/VF most commonly identified was ischemia. Ischemic VT/VF was diagnosed in two of three cases with "secondary VT/VF" and was ascribed to a new Q-wave MI in 42% of these cases, to a "non–Q-wave" MI in 45% and to acute ischemia without infarction in the remaining 12%. Large prospective trials suggest that patients presenting with acute MI, who develop VF shortly thereafter, have an excellent long-term prognosis (4). However, data on the prognosis of patients presenting with VF, in whom an acute MI is subsequently diagnosed, are more limited. Schaffer and Cobb (5) first suggested that the long-term risk for recurrent VF is reduced when the arrhythmia is related to an acute MI. In that study, only 5% of patients with "VF due to MI"—but 33% of those with VF not occurring in the setting of acute MI—had recurrent VF at four years. It should be noted, however, that such divergence applied only when the diagnosis of MI was based on the appearance of *new* pathologic Q waves. When the diagnosis of "acute MI" was based only on cardiac enzyme

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From the †Department of Cardiology, Tel Aviv-Sourasky Medical Center, Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel and ‡Institute of Cardiology, Indiana University School of Medicine, Indianapolis, Indiana.

levels, the risk for recurrent VF was actually 18% (5). Goldstein et al. (6) showed similar results: among 142 patients with out-of-hospital VF due to coronary artery disease, the one-year mortality was "high" (29%) when no MI could be identified, *low* (11%) when the arrhythmia was related to an MI *defined as a new Q-wave* infarction and "intermediate" (20%) when the MI diagnosis was based on cardiac isoenzymes (6). This "intermediate risk" probably reflects the fact that patients with enzyme elevations—but no Q-wave formation—after resuscitation, probably represent a heterogeneous group that includes patients with true non-Q-wave infarction as well as patients whose enzyme elevation is due to the arrhythmia or the resuscitation (see below). Finally, the assumption that patients who developed VF during acute ischemia—without infarction—will remain free of arrhythmias if the ischemia is treated is a logical presumption that has little scientific support. Ischemia may recur (because of incomplete revascularization or disease progression) and uncertainty remains as to the risk for recurrent VF among patients who had "ischemic VF" and developed recurrent ischemia. Interestingly, one animal model of ischemic VF (involving coronary artery occlusion during exercise) suggests that some "inborn predisposition" to ischemic VF may actually exist (7). Similar arguments can be offered against the infallible prevention of VT/VF recurrence when the original insult is a proarrhythmic drug. The list of drugs that cause QT prolongation and torsades de pointes keeps expanding and patients who developed torsades when treated with one drug are prone to develop the same arrhythmia if treated with a second proarrhythmic drug. Furthermore, patients who had torsades de pointes during atrioventricular block may later develop torsades (despite a normally functioning pacemaker) if challenged with medications that prolong repolarization (8), probably reflecting an inborn repolarization abnormality (9).

A different explanation for the findings by Wyse et al. (2) may be that the identified "treatable causes" of VT/VF were not really the "cause" the arrhythmias. The criteria for defining a "reversible" cause for arrhythmia were rather vague (2). The most common reason for attributing a "reversible" category to an arrhythmia was the suspicion that the arrhythmia was due to an "ischemic event." This implies that some ST changes or a rise in cardiac enzyme levels were seen after resuscitation. However, the magnitude of these changes was not specified. This study limitation is important because ST-segment elevation and enzymes rise could be due to the arrhythmias or the DC shocks. Transient ST-segment elevation (10), QRS widening (11) and enzymes rise have been documented after elective DC cardioversion of atrial arrhythmias and it is conceivable that more severe abnormalities follow repeated DC shocks during prolonged VF. Indeed, reversible left ventricular dysfunction may result from prolonged resuscitations (12). Thus, one case of VF diagnosed as "due to non–Q-wave infarction" might be, in fact, a case of primary VF with secondary ST-changes, enzymes rise and left ventricular dysfunction. Furthermore, since the induction of monomorphic VT with programmed ventricular stimulation demonstrates persistence of an arrhythmic substrate, many clinicians would require a negative electrophysiologic study before concluding that the cardiac arrest was solely due to ischemia. Yet, this was not mandatory in the present study. Consequently, we do not know if the patients with VT/VF "due to reversible ischemia" had a bad prognosis because the "reversible ischemia" was not truly "reversible" or because the arrhythmia was not due to ischemia to begin with. The same argument holds true for "electrolyte imbalance." Physicians in AVID had the discretion to define when the arrhythmia was "caused by hypokalemia." Hypokalemia increases the risk for VF during MI (4) and facilitates *drug-induced* torsades de pointes (13). However, it is difficult to find reports in which hypokalemia was the sole cause of VT/VF. Yet, "electrolyte imbalance" (presumably hypokalemia) was the "cause of VT/VF" in 10% of "treatable cases" in this study (2). Of note, mild hypokalemia can be the result, rather than the cause, of VT/VF (14).

Patients with "treatable arrhythmias" were treated according to the physicians' judgment and 20% of them received an ICD. This implies that in many cases, the enrolling physicians were *not* convinced that the identified "reversible" cause for VT/VF was truly reversible or was truly the cause. There is one explanation for this paradox: one thing is to disqualify patients from entering a randomized trial whenever an exclusion criterion (in this case a "potentially curable cause" for VT/VF) is recognized. A different thing is to treat such patient based on that criterion. Discovery of "hypokalemia" after resuscitation could lead to the conscientious physician against enrollment of a patient to the AVID trial simply to avoid biasing the results of this important study, even if he/she was not convinced that hypokalemia had much to do with the arrhythmia. Yet, such a patient would appear in the authors' database as one with "VF due to electrolyte imbalance."

Wyse et al. (2) should be congratulated for challenging the dogma that treatment of the cause for VT/VF will consistently result in a good prognosis. The authors did *not* conclude that indiscriminate ICD implantation is the solution for all patients with VT/VF and neither should the reader. Their study has no data on the mode of death and we do not know if patients with "treated causes" of VT/VF died from recurrent arrhythmias. However, one should recognize that our ability to identify VT/VF survivors who are at low risk for recurrence (even with the aid of electrophysiologic studies) (15) is imperfect. One should be especially careful when recommending conservative management of VF survivors with severely impaired left ventricle. An EF $<35\%$ not only identifies VT/VF survivors for whom ICD implantation offers the greatest advantage (in terms of survival benefits) when no "treatable causes for the arrhythmias" are apparent (16,17). Also, a low EF also identifies patients for whom revascularization may not suffice for preventing recurrent VT/VF (18,19) even when

the original arrhythmia appeared to be due to ischemia (19). As pointed out by the authors, patients with potentially reversible causes of VT/VF need more aggressive evaluation and treatment than is currently practiced. Indeed, more research is needed to identify *the truly reversible causes* of VT/VF and the optimal way to treat them.

Reprint requests and correspondence: Dr. Sami Viskin, Department of Cardiology, Tel Aviv Medical Center, Weizman St. 6, Tel Aviv 64239, Israel. E-mail: viskin_s@netvision.net.il.

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