Reversible Causes of VT/VF: Fact or Fiction? Case presentation and review of the literature

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ABBREVIATIONS USED

AVID – Antiarrhythmics Versus Implantable Defibrillators Trial

CASH – Cardiac Arrest Study Hamburg

CAST – Cardiac Arrhythmia Suppression Trial

CHF – Congestive Heart Failure

CIDS – Canadian Implantable Defibrillator Study

DINAMIT - Defibrillator in Acute Myocardial Infarction Trial

GUSTO I – Global Utilization of Streptokinase and Tissue Plasminogen Activator in Occluded Arteries Trial

ICD – Implantable Cardioverter Defibrillator

LVEF – Left Ventricular Ejection Fraction

MADIT II – Multicenter Automatic Defibrillator Implantation Trial

SCD – HeFT – Sudden Cardiac Death – Heart Failure Trial

VF – Ventricular Fibrillation

VT – Ventricular Tachycardia

SUMMARY

This overview begins with a case presentation and then reviews the concept of ventricular tachyarrhythmias with reversible causes. Myocardial ischemia, electrolyte disorders, proarrhythmic drug reactions, and other circumstances have been considered transient and correctable causes of life threatening ventricular tachyarrhythmias. Conventional wisdom, as it is embodied in current guidelines, suggests that recurrent ventricular tachyarrhythmia can be prevented if these causes are identified, corrected, and prevented, obviating the need for an implantable defibrillator. However, an analysis of the largest published cohort of patients with sustained VT and VF, namely, the AVID Registry, demonstrates that patients whose ventricular tachyarrhythmias were attributed to these "reversible causes" have an outcome that is the same or worse than that of those with primary VT/VF. A precis of the literature concerning ischemia, electrolyte disorders and pro-arrhythmic drug reactions as potentially reversible causes of VT/VF, with an emphasis on the AVID Registry analysis is presented. Proarrhythmic drug reaction may be a reversible *cause* of VT/VF. Hypokalemia and hypomagnesemia should be considered recurrent *risk factors* for VT/VF. The role of ischemia is complex and can be recurrent in spite of treatment. Physicians should exercise caution when attributing VT/VF solely to these three conditions. Further research is required to identify "truly reversible" causes of VT/VF and the role of ICD therapy in these settings.

CASE PRESENTATION

A 54 year old woman initially presented with hemodynamically stable, sustained monoform VT at a rate of 160 per minute. Her first recorded blood pressure was 130/60 mm Hg. Although she felt unwell and was aware of palpitation, she had not had presyncope or syncope. She had no recent anginal chest pain and did not have chest pain during ventricular tachycardia. She was electrically cardioverted.

Her VT occurred in the setting of multiple medical problems including the following:

- Anterior Q-wave myocardial infarction 15 years ago
- Non-ST elevation myocardial infarction 1 year ago
- Angiography 2 years and one year ago showing chronically occluded left anterior descending coronary artery and all other stenosis ≤50%
- Intermittent CHF for 12 years, worsening over the last few months and in CHF on presentation
- LVEF after treatment for heart failure was 0.23
- Bifascicular block (Right Bundle Branch Block and Left Anterior Fascicular Block)
- Diabetes mellitus
- Chronic renal failure

- Obesity and hirsutism
- Obstructive sleep apnea
- Chronic renal failure
- Bronchiolitis obliterans organizing pneumonia

The patient was referred for assessment for an ICD.

She had increasing symptoms of congestive heart failure at home over a few days and had been instructed to increase her daily furosemide dose two days prior to admission. At admission, her troponin was normal, there were no new ECG findings, her serum potassium was 4.1 mmol/L and her serum magnesium was 0.74 mmol/L. Her serum creatinine was over 500 µmol/L, whereas it had recently been hovering around 250 µmol/L.

There are a number of issues that could be discussed in the context of this case. The first would be the basis for deciding an ICD was needed. The secondary prevention trials (AVID, CASH, CIDS) did not include patients with hemodynamically stable VT. Nevertheless, the patient fits the criteria for an ICD on the basis of primary prevention (MADIT II and SCD-HeFT) and has several features suggesting she is likely to benefit (remote myocardial infarction, widened QRS and left ventricular ejection fraction <0.30) from an ICD for primary prevention. In this respect, her physicians felt her survivability from death due to her other problems for the next 2 years was very good. Another issue is consideration of the need for cardiac re-synchronization therapy. A tissue Doppler echocardiographic study showed no evidence of dyssynchrony.

The focus of the discussion in the present context, however, is the potential for a number of factors in the case to be transient or reversible causes for her ventricular tachycardia. There were no overt electrolyte abnormalities and no objective signs of ischemia. However, she was in heart failure before ventricular tachycardia had started, she was hypoxemic, and her creatinine had recently increased. One had to suspect that there might have been progression of her ischemic heart disease. Coronary angiography, however, showed no obvious change in her coronary anatomy.

A dual chamber ICD was implanted. Routine device checks showed two episodes of ventricular tachycardia that were pace-terminated with the first programmed anti-tachycardia pacing therapy within the first two months after implant. No further arrhythmias were noted at the routine 6 month follow-up visit. Eight months after her initial presentation she was placed on chronic hemodialysis. A month later she was seen because of a shock from the ICD during hemodialysis. Interrogation of the device showed 42 episodes of ventricular tachycardia since hemodialysis was started. The shock therapy was a successful low energy cardioversion after all programmed anti-tachycardia pacing therapies had failed to terminate ventricular tachycardia. The serum potassium at that time was noted to be 2.5 mmol/L. This occasion was the only time low

potassium was noted. After correction of hypokalemia, she had no further shock therapies. However, over the next 4 months she had 13 more episodes of ventricular tachycardia – all terminated by the first pacing therapy and all occurred during hemodialysis. Review of the records and patient history showed that on those days she held her carvedilol dose until after dialysis (for reasons that were not clear) and always became hypotensive during dialysis. Coronary angiography showed no change in her coronary anatomy. However, it was hypothesized that hypotension during dialysis led to transient ischemia and/or changes in autonomic tone which triggered ventricular tachycardia. Irbesartan was held on the days of dialysis and the cardvedilol dose was reduced slightly, although she was instructed to take it one hour before dialysis. Adding amiodarone was considered but not done because of underlying chronic pulmonary disease. Since then she has not been hypotensive during dialysis and has had no further ventricular tachycardia over 4 months. She is currently contemplating having coronary artery bypass graft surgery.

Thus, the case illustrates the difficulty in identifying transient or reversible causes for ventricular tachyarrhythmias but also the problem that even when identified, transient or reversible causes of ventricular tachyarrhythmias are likely to recur.

INTRODUCTION

Current guidelines discourage ICD implantation among patients with VT or VF thought to be due to a transient or reversible disorder[1], reflecting the conventional wisdom that these patients should have a low risk of recurrent VT/VF if the cause is corrected. However, when outcomes of patients with and without a putative transient or correctable cause for their VT/VF were compared in the AVID Registry, no mortality difference was found [2]. The purpose of the present overview is to review that analysis and other literature regarding myocardial ischemia, electrolyte abnormalities, and proarrhythmic drug effects as potentially reversible causes of VT/VF.

The AVID Registry

The AVID trial was a prospective, randomized comparison of antiarrhythmic drugs (mostly amiodarone) versus the ICD in patients with life-threatening sustained ventricular arrhythmias[3]. Patients qualified for randomization with i) VF, ii) sustained VT with syncope, or iii) sustained VT causing angina, pre-syncope, hypotension, or CHF and had a LVEF $\leq$0.40. Patients were excluded from randomization, but followed in the AVID Registry[4] when the principal investigator at that site felt that the VT/VF had a transient or correctable cause. The nature of the putative reversible cause was classified as follows: i) new Q-wave MI, ii) new non-Q-wave MI, iii) other ischemic event, iv) proarrhythmic drug reaction, v) electrolyte imbalance (hypokalemia or hypomagnesemia), or vi)

other cause. Registry patients' initial treatment strategy, chosen by their own physicians, was recorded. Patients were excluded from the Registry and randomization if the qualifying event occurred in-hospital within 5 days after presentation with myocardial infarction. The AVID Registry is the largest published cohort of patients with sustained VT/VF (n=4,450, including both randomized and non-randomized patients). Its design allows comparison of total mortality of patients with an identified transient or correctable cause for VT/VF with that of patients with primary VT/VF. A group of 2,013 registry patients and a group of 278 patients with a transient or correctable cause, whose primary arrhythmias occurred out-of-hospital and in a context similar to those randomized, were identified[2].

ISCHEMIA AND INFARCTION

Acute ischemia creates heterogeneity of electrophysiologic properties between ischemic and bordering non-ischemic zones that may act as a *substrate* for re-entrant VT/VF. It also causes changes in transmembrane ion channel kinetics, cellular energy metabolism, and releases catecholamines, producing a biochemical milieu favouring abnormal automaticity, which can act as a *trigger* for VT/VF. In a rat model, the resolution of "electrical instability" parallels reperfusion after a period of ischemia [5] and is independent of myocardial salvage, supporting the notion that acute ischemia is a reversible cause of VT/VF. Ischemic proarrhythmia may be modulated by genetic factors, explaining familial clustering of sudden death as the initial manifestation of acute myocardial ischemia[6-8].

Scarring from chronic coronary artery disease capable of supporting re-entry at the penumbra of ischemia between *dead* (scar) and normal myocardium[9] poses a *constant* substrate for re-entrant ventricular arrhythmias. In these patients, acute ischemia, autonomic influences[10] and other factors may serve as the milieu for VT/VF.

Patients with ischemic proarrhythmia may sequentially present with non-arrhythmic manifestations of acute ischemia such as angina, or heart failure and then develop VT/VF. Alternatively, cardiac arrest or sustained VT may occur without prior symptoms.

Patients who first present with acute myocardial infarction

A large body of information suggests that patients who present with acute myocardial infarction and develop VF within 48 hours have a good long term prognosis, if they survive to be discharged from hospital[11-18].

The same cannot be said of patients who develop VT prior to discharge after acute myocardial infarction. Among 41,020 patients enrolled in the GUSTO I study, 4188 patients

developed VT, VF, or both in association with acute myocardial infarction[18] (Table I). The 1-year mortality of 30-day survivors with early (within 48 hours of admission) VT was nearly 3 times that of patients without VT/VF (7.1 vs. 2.7%). Thirty-day survivors with late VT (>48 hrs after admission) had the highest 1-year mortality (24.7%), while thirty-day survivors with late VF also had increased risk (1-year mortality = 6.1%). As found in the earlier literature, thirty-day survivors with early VF had mortality similar to that of patients without ventricular arrhythmias (2.7% vs. 2.9%). Thus, VT and VF that develop later in the course of acute myocardial infarction (*particularly VT*) should not be considered "reversible", probably because their substrate is more stable, and therefore, more capable of supporting future arrhythmic events. Also, early VT may not be as benign as early VF.

Table I. Mortality after acute myocardial infarction by early and late ventricular arrhythmias[18]

	VT		VF		Both VT & VF		Neither
	Early	Late	Early	Late	Early	Late	
1-year mortality of 30-day survivors, %	7.1	24.1	2.7	6.1	6.4	4.7	2.7

Early < 2 days; Late > 2 days; VT=ventricular tachycardia; VF=ventricular fibrillation

These observations must be tempered with the knowledge that non sudden death is an important contributor to total mortality in the early phase after myocardial infarction. The DINAMIT Trial randomized patients after a recent myocardial infarction (6-40 days) who had not had VT/VF, but were thought to be at high risk for VT/VF, to ICD therapy or best medical therapy[19]. It demonstrated a reduction in sudden death associated with ICD therapy, but no reduction in overall mortality. Thus, in the acute phase, simply focussing on the risk of arrhythmic death may not translate into a meaningful clinical benefit. Underlying coronary artery disease and left ventricular dysfunction may themselves portend an increased risk of non sudden death and in this setting VT/VF in some may be a marker for a heart that is not capable of survival when VT/VF is terminated.

Patients resuscitated from out-of-hospital cardiac arrest

Victims resuscitated from out-of-hospital cardiac arrest have been sub-categorized in the literature as having acute transmural myocardial infarction (by the development of new pathologic Q-waves), ischemic events (by cardiac enzyme elevations) or primary arrhythmias (by the absence of both evolutionary Q-waves and cardiac enzyme elevations)[20, 21]. However, because transient ST changes (including ST elevation)[22] can be seen after cardioversion itself, and hypotension due

to a primary arrhythmic event can elevate cardiac enzymes, it may be very difficult to determine which came first. Undoubtedly, some patients with an acute ST segment elevation myocardial infarction develop a VF cardiac arrest, and the data cited above suggests they have a good prognosis if they survive to be discharged. However, distinguishing these patients from those likely to have a worse prognosis, namely those with a primary arrhythmic event causing transient ST segment elevation and a rise in cardiac biomarkers, may be impossible. Thus, among patients who survive out-of-hospital cardiac arrest, the evidence that the identification of acute myocardial infarction is reliable and worthwhile prognostically is incomplete[23] and a great deal of clinical judgement is needed in individual cases.

The impact of revascularization on outcomes of patients with VF or polymorphic VT, two arrhythmias well recognized as resulting from acute ischemia, also remains controversial. It is tempting to ascribe these two tachyarrhythmias occurring during exertion to acute ischemia when coronary artery disease is present, even when objective electrocardiographic or biochemical evidence of ischemia is absent. Indeed, on immediate angiography, a majority of patients who survive such an event have evidence of unstable coronary lesions, which are not well predicted by ECG changes or a pre-morbid history of angina[24]. Unfortunately, confirmation of ongoing risk by demonstration of persistent inducibility of ventricular arrhythmias or reduced risk due to clinical recurrences after revascularization is based on small studies, often with conflicting results[25-32].

In the AVID Registry[2], ischemic events were thought to be the cause of VT/VF in 183 patients. New non-Q-wave myocardial infarction accounted for approximately half of the ischemic events, while new Q-wave myocardial infarction and transient ischemia without myocardial infarction accounted for approximately one quarter each.

Table II lists the point estimate for survival at 2 years of patients with primary VT/VF and for patients who had ischemia identified as a transient or correctable cause for their VT/VF in the AVID Registry[2]. There is no apparent difference in these point estimates and no subgroup had significantly better survival (although some of the subgroups are small). Resuscitated victims of out-of-hospital cardiac arrest attributed to a new Q-wave myocardial infarction fared no better than either those without a new-Q-wave myocardial infarction, or those with primary VT/VF. This finding seems paradoxical at first glance given i) the wealth of data among patients presenting with acute myocardial infarction suggesting that early VF in this setting does not adversely affect long term mortality[11-18] and ii) previous reports of superior outcomes in resuscitated victims of sudden cardiac death with evidence of acute transmural myocardial infarction[20, 21]. However, it must be remembered that the former cannot directly be addressed by the AVID Registry analysis, since patients who presented with acute myocardial infarction and then developed VT/VF within 5 days of admission were excluded from the AVID Registry[4], which examined patients presenting with

VT/VF and were subsequently diagnosed as having a myocardial infarction. It should also be pointed out that previous reports of superior outcome from resuscitated cardiac arrest with transmural infarction were based on observations at least a decade before the AVID Registry data was collected and prior to the availability of revascularization with percutaneous coronary intervention that is now ubiquitous in non-Q-wave infarction.

Table II. Two-year survival of patients with VT/VF attributed to myocardial ischemia and patients with primary VT/VF in the AVID Registry[2] (see text for details).

Q-wave MI	80.6 ± 4.5 %
Non-Q -wave MI	83.6 ± 4.4%
Ischemic Event (No MI)	81.0 ± 8.6%
Primary VT/VF	82.9 ± 0.9%

Clinical Implications

Undoubtedly, acute ischemia contributes to the development of life-threatening ventricular arrhythmias. To prevent VT/VF, coronary artery disease, the commonest cause of ischemia and the commonest finding among victims of sudden cardiac death, must always be sought and optimally treated[33, 34]. All such patients should therefore have serial electrocardiograms, an assessment of left ventricular function, coronary arteriography, and revascularization when feasible. There is evidence that beta blockers[35-39] and angiotensin converting enzyme inhibitors[40], among other things, prevent sudden death in these patients. Patients with evidence of prior healed myocardial infarction will continue to carry the substrate for recurrent arrhythmias and are candidates to receive an ICD. Avoiding ICD therapy in patients with LVEF >0.35 can be considered, since a benefit from the ICD in this subgroup has been consistently absent[41, 42]. Since the DINAMIT Trial[19], the role of ICD therapy for patients who present with acute myocardial infarction and develop monomorphic VT or late VF is unclear, although such patients were not enrolled in DINAMIT. No specific antiarrhythmic therapy appears to be required for patients who present with acute myocardial infarction and develop VF within 48 hours. Finally, more research is needed to help us understand the exact interplay between the autonomic nervous system, coronary artery disease, ischemia and other factors leading to VT/VF so that the identification of truly reversible causes that obviate specific antiarrhythmic therapy may be clinically possible.

ELECTROLYTE ABNORMALITIES AND VT/VF

Potassium

Resting transmembrane potential (-90 mV) is largely determined by the closely regulated intracellular (high) to extracellular (low) potassium concentration gradient. Hypokalemia can increase the rate of spontaneous diastolic depolarization (phase 4) thereby increasing automaticity, and also increase action potential duration and refractory period. In animal models, hypokalemia has been shown to reduce the VF threshold while potassium administration raises it[43], and spontaneous VF has been observed in potassium deficient hearts[44, 45].

Among approximately 10,000 patients with acute myocardial infarction, the incidence of VT and VF was inversely related to serum potassium concentration independently of diuretic therapy [46-53]. Association does not prove causality. Nevertheless, the strength of these studies lies in the fact that potassium was measured on admission, *before* the development of VT/VF. Measurement of serum potassium just prior to the event is not usually possible among patients with out-of-hospital cardiac arrest, and the association of hypokalemia with this type of arrhythmic event is unknown. Approximately half of victims resuscitated from out-of-hospital VF are hypokalemic on admission[54, 55], but hypokalemia in this situation may be the *result* of the cardiac arrest (mediated by beta-2 adrenergic receptor stimulation), rather than part of its cause[56, 57].

Magnesium

Evidence for a role for hypomagnesemia as a cause of VT/VF is more limited than that for hypokalemia. Isolated hypomagnesemia has not been shown to have consistent effects on the electrophysiologic properties of myocytes, nor on the surface electrocardiograms of animals or humans[58]. Reports of VT/VF involving hypomagnesemia are often confounded by the presence of structural heart disease, alcoholism, antiarrhythmic drug use, or hypokalemia, making causal associations impossible. Reports of the occurrence of *torsades de Pointes* VT occurring in patients with isolated hypomagnesemia do exist[59, 60], as do reports of the efficacy of treatment of torsades de pointes VT induced by Class IA antiarrhythmic drugs with magnesium salts[60]. However, randomized trials of magnesium salts for the treatment[61, 62] and prevention[63] of ventricular arrhythmias have been negative so far.

The AVID Registry analysis

Twenty-seven patients in the AVID Registry (9.7%) had VT/VF attributed to hypokalemia or hypomagnesemia, and this subgroup had the worst prognosis in that analysis[2]. While the outcome was all-cause mortality, not recurrent VT/VF and sudden death, this finding suggests that electrolyte abnormalities should not necessarily be considered reversible causes of VT/VF. The

explanation for this observation may include the possibility that after correction, low electrolyte levels tend to recur because their root cause has not been removed.

Clinical Implications

Currently available evidence does not establish hypokalemia or hypomagnesemia as *causes* of VT/VF in most situations. Hypokalemia should be regarded as a risk factor for VT/VF, particularly among patients with myocardial infarction. On the other hand, hypomagnesemia and hypokalemia, which often co-exist, should be regarded as risk factors for torsades de pointes VT in those situations where this particular tachyarrhythmia is likely to emerge. It should also be remembered that patients prone to experience torsades de pointes VT can also have a myocardial infarction. Accordingly, all patients with myocardial infarction and/or sustained VT/VF should have measurements of serum potassium and magnesium concentrations. There is evidence among patients with acute myocardial infarction that the incidence of VT and VF is lowest when the serum potassium concentration is >4.5 mmol/L[48].

Magnesium concentration should be kept in the normal range. The correction of hypomagnesemia is often required for the correction of hypokalemia. One to 2 grams of magnesium sulphate, even in the absence of hypomagnesemia, can be valuable in the prevention of recurrences of torsades de pointes VT. A continuous infusion of 3 to 20 mg/min can also be used. Caution should be exercised among patients with renal dysfunction. Because of the association of diuretic induced hypokalemia with ventricular arrhythmias and sudden death, hypertensive patients managed with a low dose of a potassium wasting diuretic can be concomitantly treated with a potassium sparing diuretic, and should have potassium concentrations closely monitored[64].

PROARRHYTHMIC DRUG REACTIONS AND VT/VF

Ventricular proarrhythmia can be difficult to distinguish from drug inefficacy and spontaneous variability especially late after the drug has been started. Risk factors for the development of ventricular proarrhythmia include electrolyte abnormalities, left ventricular dysfunction, structural heart disease including coronary artery disease, a history of sustained VT, QT interval prolongation, and elevated serum drug levels (quinidine is an exception to the latter because torsades de pointes VT can occur with low levels of that drug)[65]. Many of these are also risk factors for the development of *spontaneous* VT/VF, and would be expected to persist even after the discontinuation of an offensive drug. Thus, there are significant difficulties for the identification of drug induced proarrhythmia.

Incessant ventricular tachycardia is most often seen as a proarrhythmic response to class IC agents[66-69]. This rhythm is most commonly seen in patients with left ventricular systolic dysfunction and a history of sustained VT, suggesting that the drug modifies pre-existing substrate[70-72]. The delicate balance between conduction (slowed by IC drugs) and refractoriness (minimally affected by IC drugs) in an arrhythmogenic zone can be altered, precipitating a broad bizarre monomorphic VT, which must be distinguished from aberrant 1:1 conduction of atrial flutter. It is difficult to terminate, even using electrical cardioversion. In the Cardiac Arrhythmia Suppression Trial (CAST), use of encainide and flecainide after a recent myocardial infarction in patients with frequent ventricular premature beats and modestly reduced left ventricular ejection fraction, were associated with a 3.5 fold increased risk of sudden death compared to placebo[73]. Unlike many other types of proarrhythmia, which occurs most commonly at the onset of treatment, late proarrhythmia in CAST may be responsible for the increased mortality observed throughout the follow-up period in the treatment arm. Experimental evidence and subgroup analyses of that trial suggest that recurrent ischemia may modulate the proarrhythmic response to class IC agents[74, 75]. Compared to ICD implantation, the use of another class IC agent, propafenone, was also associated with increased mortality among survivors of cardiac arrest, resulting in the discontinuation of randomization to this arm in the CASH Trial[76].

Torsades de pointes is a pause dependent polymorphic VT occurring in the setting of a prolonged QT interval. There are both acquired (usually drug-induced) and congenital forms of this tachyarrhythmia. In both forms, antiarrhythmic drugs that have been implicated as causative or facilitating agents. Drugs causing torsades de pointes VT are those whose effects include prolongation of action potential duration, namely, class IA and III antiarrhythmic agents and several other drugs that are not antiarrhythmics. Prolongation of the QT interval in itself is not all that is required however, as amiodarone, a class III agent that exhibits a wide spectrum of electrophysiologic actions including prolongation of the QT interval, rarely causes torsades de pointes VT. Thus, heterogeneity of drug effects in various layers of the myocardium and other modifiers may increase the risk (hypokalemia, hypomagnesemia, bradycardia, female gender) or decrease it (blockade of other arrhythmogenic inward currents by amiodarone). Risk factors for the development of drug-induced torsades de pointes VT in those with a disposition for this tachyarrhythmia are numerous and include: 1) diuretic use, 2) high doses or concentrations (quinidine is an exception), 3) rapid intravenous infusion of the drug, 4) recent conversion from atrial fibrillation, particularly with an ensuing pause or bradycardia, 5) baseline electrocardiogram during drug therapy showing marked QT prolongation and T-wave lability, 6) marked QT

prolongation, T-wave lability, T-wave morphologic changes, and increased QT dispersion during drug therapy, and 7) congenital long QT syndrome[65].

Recently, intracellular calcium overload has been demonstrated to play a significant role in increasing the risk of torsades de pointes VT[77, 78], possibly explaining why the risk of torsades de pointes VT is higher in patients with CHF, a condition associated with altered calcium homeostasis. Abnormalities in genes encoding transmembrane ion channels (the identification of which is recent) modulate the risk of drug induced torsades de pointes[79, 80], confirming the suspicion that certain drug-induced cases represent the unmasking of an occult genetic abnormality. Alterations in the expression of genes responsible for drug metabolism may also lead to elevated drug concentrations, which could lead to torsades de pointes VT. Many non-antiarrhythmic drugs have been associated with torsades de pointes VT, so the future impact of molecular genetics on new drug development is potentially large.

The AVID Registry analysis

Eighteen patients (6.5%) in the AVID Registry had antiarrhythmic drug reaction identified as a transient or correctable cause for their VT/VF[2]. The point estimate for survival at 2 years in this group was 94.4% $\pm$ 5.4%, which compares favourably with survival in other groups (cf. Table II). Of the various subgroups with a transient or correctable cause identified in the AVID Registry, this is the smallest, but VT/VF associated with an antiarrhythmic drug reaction in this sub-analysis seemed most likely to presage better survival. Thus, proarrhythmia may indeed be a reversible cause of VT/VF.

Clinical Implications

Class IC agents should be avoided in patients with coronary artery disease, and patients who develop monomorphic VT while on these agents should be investigated for myocardial ischemia. They should also be avoided in patients with a history of VT/VF and other significant structural heart disease.

The use of drugs that prolong the QT interval, including class IA and III antiarrhythmic agents, should be elicited from patients who develop torsades de pointes VT. A website listing these agents may be helpful (www.torsadesdepointes.org) and includes a link to report drug induced arrhythmias for inclusion in a registry. Patients who develop torsades de pointes VT while on such a drug should have the agent discontinued, but the physician should still consider the possibility of a congenital form of long QT syndrome, which may have been unmasked by the drug. The latter possibility implies, among other things, screening of family members should be undertaken. In the future, genetic testing will become more readily available than it currently is,

and molecular genetics should play a role in the development of drugs that do not pose a risk of torsades de pointes VT or identifying patients in whom some current drugs should be avoided. For now, class IA and III antiarrhythmic drugs (except amiodarone) should be avoided in patients with other known risk factors for the development of torsades de pointes VT (see above).

While ventricular proarrhythmia would appear to be an obvious explanation for the first development of ventricular tachyarrhythmias in a patient on antiarrhythmic drug therapy for supraventricular arrhythmias, such patients should also be investigated for other causes of VT/VF. In other cases, unavoidable difficulties exist in the identification of ventricular proarrhythmia, and one should always remain open to the diagnosis of late proarrhythmia. While the only real "proof" of this possibility may lie in discontinuation of the antiarrhythmic followed by a re-challenge, this approach is not advised, and therefore, the management in the situation of late proarrhythmia remains problematic. Patients who develop ventricular proarrhythmia while receiving antiarrhythmic drugs for the management of sustained VT or VF should have the drug discontinued and be offered an ICD. Even if these late arrhythmias are not proarrhythmic, their occurrence indicates failure of drug therapy to prevent VT/VF.

CONCLUSION

Currently available evidence that ischemia and electrolyte disorders are reversible causes of life threatening ventricular tachyarrhythmias, which would be associated with a low risk of future events, is incomplete. Data from the AVID Registry actually suggests otherwise. Hypokalemia and hypomagnesemia should be considered risk factors for VT/VF, and one should be cognizant of their possibility to recur. Because coronary artery disease is chronic, recurrent and can also lead to non-arrhythmic death, the influence of ischemia on total mortality is complex. Proarrhythmic drug reaction may be a truly reversible cause of VT/VF, but there are difficulties with its identification. One should therefore be cautious in attributing life threatening ventricular tachyarrhythmias to what have traditionally been considered "reversible causes". While ischemia, electrolyte abnormalities and drug therapy are certainly part of the milieu for sudden death, further research is required to identify in which situations they are *truly reversible causes* for VT/VF and for which specific antiarrhythmic therapy is not necessary.

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