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Sudden Cardiac Death in Heart Failure
The Role of Abnormal Repolarization

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Abstract Congestive heart failure is a common, highly lethal cardiovascular disorder claiming over 200,000 lives a year in the United States alone. Some 50% of the deaths in heart failure patients are sudden, and most of these are probably the result of ventricular tachyarrhythmias. Methods designed to identify patients at risk have been remarkably unrewarding, as have attempts to intervene and prevent sudden death in these patients. The failure to impact favorably on the incidence of sudden death in heart failure patients stems largely from a lack of understanding of the underlying mechanisms of arrhythmogenesis. This article explores the role of abnormalities of ventricular repolarization in heart failure patients. We will examine evidence for the hypothesis that alteration of repolarizing K⁺ channel expression in failing myocardium predisposes to abnormalities in repolarization that are arrhythmogenic. The possible utility of novel electrophysiological and ECG measures of altered ventricular repolarization will be explored. Understanding the mechanism of sudden death in heart failure may lead to effective therapy and more accurate identification of patients at greatest risk. (Circulation. 1994;90:2534-2539.)

Key Words • heart failure • tachyarrhythmias • action potentials • tachycardia

Over 2 million Americans suffer from congestive heart failure (CHF), and 200,000 or more die annually. The majority of patients with chronic heart failure have not suffered a myocardial infarction, suggesting that classic reentrant ventricular tachycardia (VT) may not be the principal mechanism of sudden cardiac death. Despite therapeutic advances that improve exercise tolerance and survival in these patients, heart failure remains a highly lethal disease, with annual mortality rates as high as 50%, 3-7 Of the patients with heart failure who die, 35% to 50% of the deaths are sudden and unexpected.2,8 Fig 1 shows the actuarial survival curves from the first Vasodilator in Heart Failure Trial (V-HeFT I). The largest single cause of death over the first 60 months of follow-up was sudden death. Furthermore, the percentage of deaths that are sudden tends to be highest early, presumably in patients with the least severe disease.9 Even if the progression of pump failure were to remain unaltered, effective prevention of sudden cardiac death in the existing heart failure population would extend life by as much as 1 million person-years. Large multicenter trials of heart failure therapy have demonstrated the efficacy of vasodilators in delaying overall mortality, yet few therapeutic interventions have decreased the sudden death rate,4,10 and none has done so selectively. Despite intensive evaluation, the mechanism of sudden death in heart failure remains ill defined.8 Likewise, there are no reliable strategies to evaluate patients at risk, and therapeutic interventions remain ineffective.

In this article, we will explore the evidence for the following hypothesis: Human heart failure is characterized by abnormalities of cardiac repolarization, and these abnormalities increase the risk of sudden cardiac death. We focus our attention on patients with heart failure without an obvious substrate for reentrant tachycardia (eg, prior myocardial infarction).

Action Potential is Prolonged and Repolarization is Delayed in Heart Failure

An elementary and distinctive signature of any given excitable tissue is its action potential profile. Myocardial cells possess a characteristically long action potential (Fig 2); after an initial rapid upstroke, there is a plateau of maintained depolarization before repolarization. The duration of the action potential is primarily responsible for the time course of repolarization of the heart; prolongation of the action potential produces delays in cardiac repolarization. Cells isolated from failing animal and human hearts consistently reveal a significant prolongation of action potentials compared with those in normal hearts, independent of the mechanism of CHF.11-14 In animal models of pressure overload–induced heart failure, this prolongation is progressive and generally occurs in the absence of other electrophysiological abnormalities such as changes in resting membrane potential, action potential amplitude, or upstroke velocity.11,15-17 The importance of this simple finding is difficult to overstate. The plateau phase of the action potential is known to be quite labile: this is a time of high membrane resistance, during which small changes in current can easily tip the balance either toward repolarization or toward maintained depolarization. As
a rule, the longer the action potential, the more labile is the repolarization process.\textsuperscript{15}

This liability may be manifest as variability in duration and/or secondary depolarizations that interrupt action potential repolarization, early afterdepolarizations (EADs) that can initiate triggered arrhythmias including torsade de pointes VT. A variety of conditions common in patients with heart failure can affect either outward (repolarizing) or inward (depolarizing) currents, resulting in action potential prolongation and the propensity for EADs. Such factors include hypokalemia, hypercalcemia, acidosis,\textsuperscript{18,19} and exposure to a variety of antiarrhythmic drugs. Animal models of cardiac hypertrophy exhibit an increased propensity to EADs,\textsuperscript{11,15} possibly due to suppression of K\textsuperscript{+} currents.\textsuperscript{20}

Increasing inward current will also favor the production of afterdepolarization-mediated triggered activity, as might occur with \(\beta\)-adrenergic stimulation of Ca\textsuperscript{2+} current or after release of endogenous lipid metabolites that interfere with Na\textsuperscript{+} channel inactivation.\textsuperscript{21} Stretch-responsive channels have been described in ventricular myocardium\textsuperscript{22,23} and have been proposed to contribute to EADs in heart failure,\textsuperscript{11,15} but their physiological significance remains controversial.

The ability to isolate viable human ventricular myocytes has recently enabled the dissection of the changes in membrane current that occur in myocardial failure. The inward Na\textsuperscript{+} and Ca\textsuperscript{2+} currents do not appear to be altered, at least under basal conditions. Sakakibara et al\textsuperscript{24} found no disease-related changes in the time course or amplitude of Na\textsuperscript{+} currents in human ventricular cells. Measurements of dihydropyridine binding sites\textsuperscript{25} and inward Ca\textsuperscript{2+} current\textsuperscript{24,26} in ventricular myocytes from failing hearts reveal no changes relative to nonfailing control cells despite a modest decrease in steady-state messenger RNA levels.\textsuperscript{27}

Human ventricular myocytes contain at least two distinct classes of voltage-dependent K\textsuperscript{+} channels. The inward rectifier K\textsuperscript{+} current, \(I_{kr}\), sets the resting membrane potential and contributes to the terminal phase of repolarization. The density of \(I_{kr}\) is reduced by nearly 40\% in cells from myopathic ventricles compared with controls; this reduction occurs in the absence of changes in the voltage dependence of gating.\textsuperscript{28} Another important K\textsuperscript{+} current is the transient outward current, \(I_{to}\). Unlike the inward rectifier, \(I_{to}\) is expressed in heart cells in a species- and cell type-specific fashion. This current plays a crucial role in the early phases of repolarization and in determining the voltage of the plateau of the action potential, which in turn influences all currents active during the remainder of the action potential. Ventricular myocytes from the midportion of the ventricular wall have a substantial \(I_{to}\) that is specifically blocked by 4-aminopyridine (4-AP). Fig 2 shows the 4-AP-sensitive \(I_{to}\) recorded from normal (top) and failing (bottom) ventricular myocytes. The amplitude of this current is significantly reduced (35\% to 40\%) in cells isolated from failing ventricles, and, as in the case of \(I_{kr}\), there is no other significant change in the current.\textsuperscript{28} Similar depression of \(I_{kr}\) has been noted in diseased human atria,\textsuperscript{29} chronically infarcted canine ventricle,\textsuperscript{30} and hypertrophied rat ventricle,\textsuperscript{31} all of which are arrhythmogenic substrates.

The heart failure–associated prolongation of the action potential alone would not necessarily suffice to produce reentrant ventricular arrhythmias, particularly if the prolongation were homogeneous. Variations in action potential duration would, however, create dispersion of repolarization and refractoriness that could be arrhythmogenic.\textsuperscript{32} Regional differences in the density of K\textsuperscript{+} currents, particularly \(I_{to}\), have been described in several experimental animal models.\textsuperscript{33} Human hearts have recently been reported to exhibit similar gradients of K\textsuperscript{+} currents, with \(I_{to}\) being much larger in the subepicardium than in the subendocardium.\textsuperscript{34,35} It is plausible that reduction in repolarizing K\textsuperscript{+} current density does not occur uniformly in heart failure. Thus, enhanced regional variability and disease-related
changes in K⁺ current density may conspire to produce large spatial inhomogeneities of repolarization. Another plausible contributor involves the influence of the autonomic nervous system, which figures prominently in the heart failure phenotype. Heterogeneity of sympathetic innervation is well described in cardiomyopathy patients and has been correlated with heterogeneity of recovery of excitability.

The cellular electrophysiological abnormalities are consistent with the clinical arrhythmias observed in heart failure patients. Abnormalities of action potential duration and afterdepolarizations may produce arrhythmias by triggered mechanisms or may predispose the myocardium to reentry by inhomogeneous changes in excitability and dispersion of refractoriness. Except for the few patients who present with sustained monomorphic VT,59-61 evidence to support a reentrant mechanism for arrhythmias in nonischemic cardiomyopathy is scarce even in settings where inhomogeneities of action potential duration or refractoriness have been described.62-64 The failure of programmed stimulation of the ventricle to predict sudden death in either animal models or humans also argues against an excitable gap reentry mechanism for arrhythmogenesis in nonischemic cardiomyopathy.

Prognostic Indicators and Risk Stratification of Heart Failure Patients

Just as the basic mechanisms of sudden cardiac death in heart failure are uncertain, the care of patients is complicated by the limited utility of conventional clinical prognostic indicators of risk for sudden death. Ventricular ectopic activity is commonly observed in patients with left ventricular dysfunction and congestive heart failure, with up to 80% having nonsustained VT. Unlike patients with a recent myocardial infarction and ventricular dysfunction, in whom there is a clear association between ventricular ectopy and the risk of sudden death, the prognostic significance of ectopy in heart failure patients is unclear. Some studies suggest that the presence of nonsustained VT in patients with cardiomyopathy is predictive of sudden death, while others suggest that its presence is merely a marker for a failing ventricle.65-67

The controversy regarding the utility of asymptomatic ventricular ectopic activity as an independent predictor of sudden cardiac death may relate to ambiguities regarding the definition and cause of sudden death in heart failure patients. The mechanism of death in the majority of patients with organic heart disease who die suddenly is sustained ventricular tachyarrhythmias, based on studies of heterogeneous populations of patients with out-of-hospital cardiac arrest.68-70 A recently reported series of unexpected cardiac arrests in hospitalized patients with New York Heart Association (NYHA) class III or IV heart failure found 15 out of 29 cases (52%) of sudden death were due to VT/ventricular fibrillation (VF), the others resulting from bradyarrhythmias or electromechanical dissociation.71,72 However, this group of patients was highly selected, having end-stage heart failure awaiting cardiac transplantation. The authors were careful to acknowledge that the population was not representative of the majority of heart failure patients, most of whom are ambulatory.

Clearly, ventricular ectopy lacks specificity in predicting sudden death in heart failure patients irrespective of the mechanism. This has motivated a search for other modalities that might provide improved prognostic information regarding sudden death risk in heart failure patients.

Electrophysiological testing also has limited value for predicting the risk of arrhythmic death in patients with dilated nonischemic cardiomyopathy. Induction of sustained monomorphic VT in patients with dilated cardiomyopathy and no clinical history of this arrhythmia is uncommon,73,74-76. Nonspecific electrophysiological end points such as polymorphic VT and VF occur commonly but have dubious prognostic significance. Even the absence of an inducible arrhythmia in this patient population does not predict a low mortality from arrhythmia.77,78

Retrospective and prospective studies suggest that the signal-averaged ECG might be prognostically useful in patients with dilated cardiomyopathy.79,80 In a recent prospective study, patients with an abnormal signal-averaged ECG were more likely to develop sustained ventricular arrhythmias or sudden death than patients with either a normal signal-averaged ECG or bundle branch block.53 This study supports the importance of an arrhythmic substrate in predicting the survival of patients with dilated cardiomyopathy. The presence of a prolonged high frequency QRS duration was the most common signal-averaged ECG abnormality. This finding is suggestive of slowed conduction through the ventricular myocardium and most likely reflects abnormal cell-cell coupling of uncertain mechanism.

Other clinical parameters thought to be indicative of hemodynamic derangement in heart failure, such as left ventricular ejection fraction, plasma norepinephrine levels, peak exercise oxygen consumption, and cardiothoracic ratio on chest radiograph are predictors of all-cause mortality,3-6,55 but in general, these parameters do not discriminate between sudden deaths and deaths from other causes.

Despite multiple randomized trials of therapy in heart failure, our understanding of sudden cardiac death and how to prevent it remain unclear. The role of antiarrhythmic therapy is also uncertain at best and is the subject of several ongoing multicenter trials. Our inability to identify heart failure patients who will die suddenly may be the result of the empirical approaches used to date, none of which applies our understanding of the fundamental mechanisms to the investigation of arrhythmogenesis in this patient population.

Does Evaluation of the Spatial and Temporal Inhomogeneity of Repolarization Have Prognostic Significance?

Alteration of the action potential duration is likely to produce changes in cardiac repolarization. The QT interval on the surface ECG is a readily measurable reflection of cardiac repolarization. It is possible that patients with heart failure and prolonged action potential durations will have abnormalities of the QT interval. The problem with a single measurement of the QT interval is that this is a static, global index of cardiac repolarization, which is a spatially and temporally dy-
Characteristics of Patient Cohort With Congestive Heart Failure

<table>
<thead>
<tr>
<th></th>
<th>NL (n=20)</th>
<th>CM (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>57±14</td>
<td>53±13</td>
</tr>
<tr>
<td>Sex (% men)</td>
<td>75</td>
<td>85</td>
</tr>
<tr>
<td>Leads, No.</td>
<td>10.2±1</td>
<td>7.1±2</td>
</tr>
<tr>
<td>QT, ms</td>
<td>384±27</td>
<td>380±39</td>
</tr>
<tr>
<td>QTc, ms</td>
<td>422±29</td>
<td>451±47</td>
</tr>
<tr>
<td>(\Delta QT_e), ms</td>
<td>35±13</td>
<td>59±23*</td>
</tr>
</tbody>
</table>

CM indicates cardiomyopathy. *P<.05 vs normal (NL).

The conduction process is certain to vary on a beat-to-beat basis and when measured from different body surface leads.

The syndromes of congenital and acquired prolongation of the QT interval are the prototypic clinical entities associated with abnormalities of cardiac repolarization, polymorphic VT, and sudden death. Ventricular arrhythmias characteristic of this syndrome may occur in predisposed patients even with normal QT and corrected QT (QTc) intervals on a resting ECG. These arrhythmias may be explained by temporal changes in the QT interval possibly related to changing antiarrhythmic drug regimens and/or serum electrolyte levels. Similar temporal QT variability may be operative in producing ventricular arrhythmias in patients with heart failure even in the absence of QT prolongation on a resting ECG.

The QT interval varies regionally in the heart, as has been recognized since the 1930s, although the biological significance of this variability has only recently been tested. Regional differences in repolarization, assessed by dispersion of endocardial monophasic action potential duration or QT intervals, have been documented in conditions associated with torsade de pointes and polymorphic VT. In patients with congenital or acquired long QT syndrome and acute myocardial infarction, it has been suggested that it is not the absolute duration of the single-lead QT or QTc, that predicts arrhythmia risk but rather the regional dispersion of the QT \(\Delta QT\) defined as the maximal difference in the QT intervals measured in various leads on a standard 12-lead ECG.

Regional dispersion of repolarization may, in and of itself, be arrhythmogenic, creating conditions that support reentry or permit the propagation of an afterdepolarization-triggered arrhythmia. To begin to test this idea, we evaluated the \(\Delta QT\) of the baseline ECG in a well-characterized cohort of patients with dilated cardiomyopathy using standard methods. Patients enrolled in the vensarnine trial at the Johns Hopkins Hospital were the index group; the demographics and enrolling ECG characteristics of this subgroup of the entire cohort of patients with CHF (ejection fraction ≤30%) are shown in the Table. The ECGs analyzed were obtained at initial evaluation before randomization to placebo or vensarnine. The etiology of heart failure in this group is 51% ischemic, 42% nonischemic, and the remainder unknown. The majority (~90%) of patients were taking digoxin at the time of the baseline ECG, and many (56%) had delayed intraventricular conduction. The average QT and QTc intervals were no different from those of an age-matched control group of healthy executives; however, the corrected QT dispersion (ΔQTc) was significantly prolonged. The data are not corrected for the number of leads from which the QT could be measured, but this correction would only have widened the difference in ΔQT, between the heart failure and normal groups because the QT interval could be measured reliably in fewer leads in the heart failure group. The values from the control group are consistent with other reports in the literature in which the ΔQTc was measured in a similar manner. A recent report in a small group of heart failure patients suggests that QT dispersion may be a marker of electrical instability and increased risk of sudden death. In other groups of patients with well-known repolarization abnormalities, studies suggest that the ΔQTc may be a better prognostic indicator of arrhythmic risk than the QT itself. Patients with arrhythmogenic long QT syndrome have dramatically prolonged ΔQTc (178±18 milliseconds), three- to four-fold greater than in controls; likewise, patients with class Ia antiarrhythmic drug-associated long QT and torsade de pointes have a ΔQT of 101±37 milliseconds, more than twice the pretreatment ΔQTc. Whether ΔQTc is of similar utility as a marker of susceptibility to sudden death in heart failure remains to be tested.

Heterogeneity of repolarization should be even more evident in intracardiac recordings, which may prove useful for risk stratification or to evaluate the therapeutic effect of a pharmacological intervention. Regional measurements of heterogeneity of refractoriness and conduction velocity have been performed in other groups of patients. As anticipated, patients with long QT physiology and associated ventricular arrhythmias exhibited enhanced dispersion of refractoriness without significant differences in regional conduction velocity. Such methods can be brought to bear on the question of the role of regional abnormalities of repolarization and refractoriness in patients with dilated cardiomyopathy. If dilated cardiomyopathy patients exhibit long QT physiology, an abnormal dispersion of refractoriness and repolarization would be expected. We evaluated regional differences in ventricular activation and refractoriness in a group of patients with dilated cardiomyopathy. The cardiomyopathy group had similar mean local activation times and refractory periods but significantly larger regional dispersion of both activation and refractoriness compared with patients with normal ventricles studied after catheter ablation of a left-sided accessory pathway (unpublished observations). In fact, the degree of dispersion of these parameters in the patients with cardiomyopathy is comparable to that measured in patients with arrhythmogenic long QT syndrome. Both ECG and invasive electrophysiological evidence for spatial dispersion of repolarization have been documented in patients with heart failure. Although compelling, such data would have to be verified and correlated with sudden death risk in a large cohort of patients with heart failure in order to test their predictive value.

In addition to spatial heterogeneity of repolarization, there is indirect evidence for temporal heterogeneity in some situations, for example, the lability of the QT interval and the occurrence of long QT-associated arrhythmias in patients with normal resting ECGs. This lability of the QT interval is probably multifactorial but in part reflects the influence of the autonomic...
nerve system and may provide prognostic information in patients with heart failure. Heart rate variability has proven to be a very useful index of autonomic nervous system input to the heart. In patients after myocardial infarction, decreased heart rate variability is associated with low parasympathetic tone, high sympathetic activity, and a higher mortality rate. The effect of heart failure on heart rate variability has also been described. Parameters of variability in both the time and frequency domains are severely depressed in advanced myocardial failure, consistent with a reduction in vagal input and increased sympathetic input to the heart. A limitation of heart rate variability as an index of autonomic nervous system tone on the ventricle is that it is indirect, reflecting changes in the RR interval by way of reflex mechanisms mediated by the sinus node. The QT interval is an index of ventricular repolarization that is directly influenced by myocardial heart and autonomic nervous system activity. Variability of the QT interval should more directly and accurately predict cardiac risk than RR variability. New algorithms for automated quantification of the QT interval will be required for rigorous assessment of the prognostic importance of QT variability.

Summary
Heart failure remains a lethal disease, claiming a substantial number of lives suddenly. Our ability to predict the risk for sudden death is poor; likewise, there is no effective preventive strategy. On the cellular level, human and animal models of myocardial failure exhibit prolongation of action potential duration possibly as a result of decreased density of repolarizing K+ currents. The consequences of abnormalities of cellular repolarization in the intact failing human heart have not been examined despite the fact that they are potentially arrhythmogenic. Novel indices of abnormal repolarization merit further investigation as potentially useful markers for propensity to sudden death in heart failure patients. Elucidation and recognition of the fundamental pathophysiology of arrhythmias in heart failure may ultimately suggest new therapeutic strategies, including the prospect of somatic gene transfer to correct the presumed abnormalities in ion channel gene expression.

References


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