

Ventricular Arrhythmias in Heart Failure Patients

Ronald Lo, MD, Henry H. Hsia, MD, FACC*

Division of Cardiovascular Medicine, Stanford University School of Medicine, Cardiac Electrophysiology and Arrhythmia Service, Stanford University Medical Center, 300 Pasteur Drive, H2146, Stanford, CA 94305-5233, USA

Heart failure is a significant major health problem in the United States. An estimated 5 million patients are afflicted by this disease, with an additional 550,000 new cases diagnosed annually. It is a major source of morbidity and mortality and is associated with an increasing number of hospitalizations [1]. Mortality in the heart failure population is primarily by pump failure or by sudden cardiac death (SCD), of which more than 75% is associated with ventricular tachyarrhythmia [2]. There are an estimated 400,000 to 460,000 deaths attributable to SCD in the United States each year, representing an incidence of 0.1% to 0.2% per year in the adult population [3].

Epidemiology

Heart failure can be considered a degradation of systolic or diastolic function. The diagnosis of heart failure is most commonly classified as an ischemic etiology secondary to coronary artery disease and prior myocardial infarction, or as a nonischemic etiology with a variety of causes such as infiltrative, infectious, metabolic, or hemodynamic insults (Box 1) [4]. Ventricular ectopy and nonsustained ventricular tachycardia (VT) are common in patients who have cardiomyopathies and heart failure. It has long been known that the frequency of ventricular ectopy is a risk factor for SCD. Patients who suffered a prior myocardial infarction with frequent premature ventricular complex (PVCs) or nonsustained VT are at a higher risk of SCD irrespective of their

ejection fractions. Increasing frequency of PVCs greater than 10 per hour are linked to an even greater SCD risk in patients who have heart disease [5,6]. Despite recent pharmacologic advancements in treatment, mortality remains unacceptably high, with sudden, “unexpected” death occurring in up to 40% to 70% of patients [7,8]. Although the total mortality among patients who have mild heart failure is low, the relative proportion of patients dying suddenly is significant. Patients who have more advanced heart failure have a substantial annual mortality of 40% to 60%; however, the relative proportion of sudden death amounts to less than 30% of all causes of death (Fig. 1) [7,9].

Pathophysiology

Multiple studies have shown that in most patients who have ischemic and nonischemic cardiomyopathies, mechanisms of VT and ventricular fibrillation include myocardial reentry, reentry using the specialized conduction system such as bundle branch reentry (BBR) or intrafascicular reentry, and focal automaticity/triggered activity.

Abnormal automaticity

Ventricular arrhythmias may arise from disturbances in automaticity in myocardial cells. Normal automaticity often originates from cells with “pacemaker activity,” which is determined by the rate of phase 4 depolarization of the cardiac action potential. It is a normal property of the sinus node, the atrioventricular node, and the His-Purkinje system. Abnormal automaticity that causes VT has also been demonstrated in subendocardial Purkinje fibers that survive ischemic

* Corresponding author.

E-mail address: hhsia@cvmed.stanford.edu
(H.H. Hsia).

Box 1. Etiologies of cardiomyopathy*Ischemia*

Acute and chronic coronary artery disease

Infections

Bacteria
 Spirochetes
 Rickettsia
 Viruses (including HIV)
 Fungi
 Protozoa
 Helminthes

Granulomatous diseases

Sarcoidosis
 Giant cell myocarditis
 Wegener's granulomatosis

Metabolic disorders

Beriberi
 Selenium deficiency
 Carnitine deficiency
 Kwashiorkor
 Familial storage disorders
 Uremia
 Hypokalemia
 Hypomagnesemia
 Hypophosphatemia
 Diabetes mellitus
 Hyperthyroidism
 Hypothyroidism
 Pheochromocytoma
 Acromegaly
 Morbid obesity

Drugs and toxins

Ethanol
 Cocaine
 Anthracyclines
 Cobalt
 Tricyclic antidepressants
 Phenothiazines
 Catecholamines
 Cyclophosphamide
 Radiation

Other

Tumors
 Connective tissue disorders
 Familial disorders
 Hereditary neuromuscular and neurologic disorders
 Peripartum

myocardial injury [10]. Studies in experimental animal models and in failing human hearts have demonstrated abnormal calcium handling. The abnormal calcium metabolism results in decreasing the calcium available to the sarcoplasmic reticulum for release, leading to mechanical dysfunction. Alterations in calcium cycling have also been implicated in the development of arrhythmias by a focal, nonreentrant mechanism in the heart failure population [11]. Pogwizd and colleagues [12,13] studied the role of abnormal calcium handling using three-dimensional mapping of spontaneously occurring VT in human hearts and showed that 100% of VT in nonischemic cardiomyopathy and 50% of VT in ischemic cardiomyopathy may be caused by a focal nonreentrant mechanism.

Triggered arrhythmias

Triggered arrhythmias may occur when there are abnormalities of action potentials that trigger another electrical event by way of abnormal depolarization. The most common abnormality causing triggered arrhythmias are early and late depolarizations, often associated with a prolonged repolarization phase. Early afterdepolarizations (EADs) usually occur in late phase 2 or phase 3 of the action potential. An EAD may occur with an imbalance between the inward and outward currents that favors a net inward current. The EADs may be manifested when there is a decrease in the outward potassium channel or an increase in the inward sodium or calcium currents. EADs may occur when the heart rate is markedly slowed, reducing the outward current from the delayed rectifier potassium channel [14]. EADs are easily inducible in experimental settings with bradycardia or during pauses and are thought to initiate torsades de pointes [15]. Experimental animal models with isochronal mapping have shown that torsades de pointes is consistently initiated first as a focal subendocardial activation, with subsequent beats due to a reentrant mechanism [16].

Delayed afterdepolarizations (DADs) occur in late phase 3 or early phase 4 when the action potential is almost fully repolarized. The development of a DAD is related to conditions that increase intracellular calcium concentrations. With catecholamine stimulation and activation of the beta-adrenergic receptors, an increased intracellular concentration of cAMP results in an increased calcium current and an increased

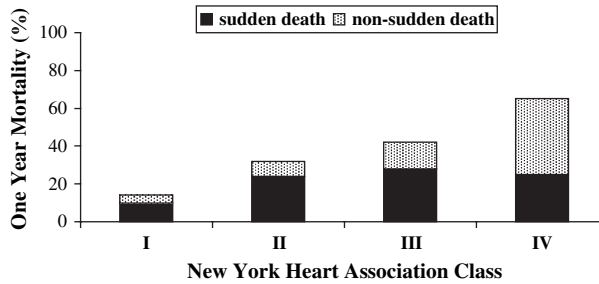


Fig. 1. Annual mortality of heart failure. Prevalence of sudden death and non-sudden death by New York Heart Association functional class and 1-year mortality. (From Hsia HH, Jessup ML, Marchlinski FE. Debate: Do all patients with heart failure require implantable defibrillators to prevent sudden death? *Curr Control Trials Cardiovasc Med* 2000;1(2):98–101.)

calcium release from the sarcoplasmic reticulum. The elevated intracellular calcium subsequently activates the calcium-sodium exchanger, ultimately leading to transient inward sodium current (I_{Ti}) and the DAD (Fig. 2).

Adenosine by way of antiadrenergic effects is able to terminate cAMP-mediated triggered arrhythmias by decreasing the concentrations of intracellular cAMP [17]. Termination of VT by adenosine may be pathognomonic for outflow tract VT caused by cAMP-triggered DADs. In contrast, in other conditions that promote cardiac calcium overload, such as digitalis toxicity, the DADs are mediated by the inhibition of the

sodium potassium ATPase, which secondarily increases intracellular calcium by way of a shift in the equilibrium of the sodium-calcium exchanger. These different mechanisms of DADs may be supported by data showing that adenosine abolishes DADs caused by cAMP stimulation but has no effect on digitalis-induced DADs [18].

Stretch mechanoreceptors may also alter the electrophysiologic properties of the myocardium in heart failure. Stretching or stress in the left ventricle in the normal heart has been shown to shorten the local action potential duration while increasing local spontaneous automaticity and triggered activity [19]. These effects are more

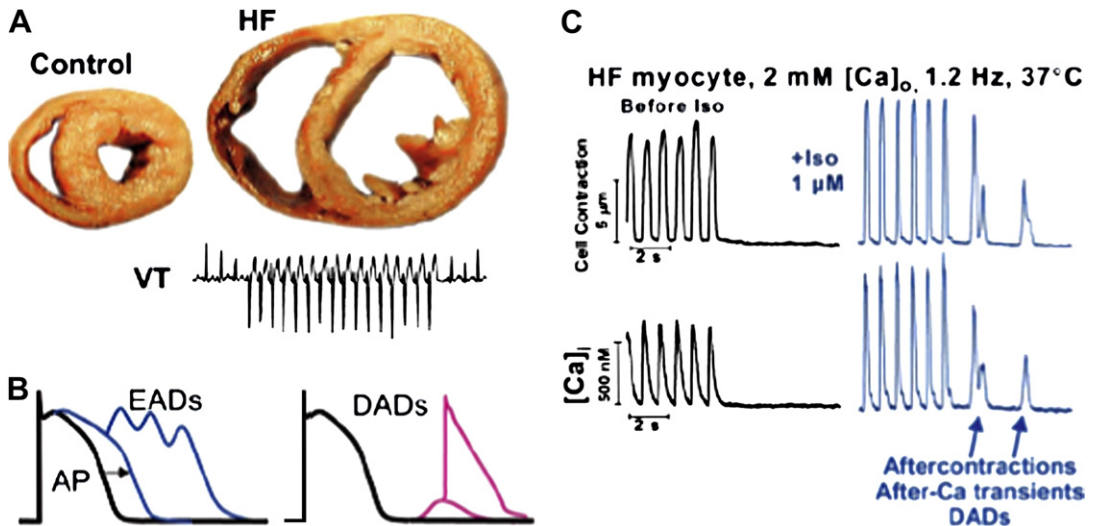


Fig. 2. Cellular basis of triggered arrhythmia in heart failure (HF). (A) Cross sections of control and failing hearts in a rabbit HF model. Holter recording of nonsustained VT was seen in 90% of HF versus 0% of control rabbits. (B) Diagram of EADs and DADs. AP, action potential. (C) Spontaneous aftercontractions (top, in μm) and changes in intracellular calcium transients concentration (bottom, in nM) in HF myocytes were observed after exposure to isoproterenol (Iso) under 1.2-Hz stimulation (37°C). (From Pogwizd SM, Schlotthauer K, Li L et al. Arrhythmogenesis and contractile dysfunction in heart failure. *Circ Res* 2001;88:1161; with permission.)

pronounced in structurally abnormal hearts, with greater heterogeneity of action potential durations leading to a wider dispersion in tissue excitability and refractoriness that facilitate unidirectional conduction block [20]. Transient stretch during diastole has been shown to cause local depolarization and trigger action potentials. In dilated canine hearts, stretch mechanoreceptors were reproducibly able to produce spontaneous PVCs [21]. Characterization of stretch-related mechanoreceptors has been located to a nonselective cation channel and related potassium channels [22].

Reentry

Reentrant ventricular arrhythmias represent most of the clinically significant tachycardias. The hallmark of reentrant ventricular arrhythmia is slow conduction, most often due to structural heart disease with scar-based anisotropic conduction abnormalities. Conduction velocity, however, is also mediated by the local cell-to-cell coupling by gap junction proteins such as connexin 43. These connexins are more common along the longitudinal axis than the short axis of the myocytes, leading to a faster conduction velocity along the long axis compared with a slower impulse propagation perpendicular to the cellular syncytium. Disorganization of gap junction distribution and down-regulation of connexins, however, are typical features of myocardial remodeling in hypertrophied or failing hearts, which may play an important role in the development of reentrant arrhythmogenic substrates in human cardiomyopathy [23].

Reentrant VT is characterized by reproducible initiation and termination with programmed stimulation. A stable monomorphic VT can usually be induced from multiple sites in the ventricle. The presence of an excitable gap is a hallmark of stable reentry, with implications that the size and location of the VT circuit is relatively fixed and, at least in part, anatomically defined [24].

Cardiomyopathy

Ischemic

The predominant mechanism of ventricular arrhythmias in patients who have structural heart disease is reentry. Much of what is known about ventricular arrhythmias is based on studies of patients who have coronary artery disease or animal models of myocardial infarction. The pathologic process caused by ischemia or infarct

leads to extensive myocyte death and results in aneurysm formation, especially if the infarct is large or transmural [25]. Reentrant arrhythmias typically occur in areas of infarcted myocardium that are adjacent to dense scar. Residual myocardial fibers survive on the endocardium, probably due to perfusion from the ventricular cavity or retrograde perfusion through sinusoidal channels [26]. The surviving myocytes become embedded within regions of fibrosis or scar that constitute substrate for abnormal nonuniform anisotropy, often with conduction block and propagation barrier that promote reentry. Fractionated, long-duration electrograms are commonly recorded from the peri-infarct regions with abnormal, non-uniform anisotropy. Low-level late potentials detected by signal-averaged ECG have been correlated to localized areas of delayed endocardial activation in humans [27–29].

Nonischemic

The anatomic and electrophysiologic substrates for nonischemic cardiomyopathy are less well described. In contrast to ischemic cardiomyopathy in which a distinct scar is present, ventricular myocardium in nonischemic cardiomyopathy often has multiple patchy areas of fibrosis and myofibril disarray with various degrees of myocyte hypertrophy and atrophy [30]. Myocardial dysfunction in nonischemic cardiomyopathy may be secondary to hypertension, diabetes, and metabolic, autoimmune, and infectious causes. Necropsy studies in patients who had idiopathic dilated cardiomyopathy showed that there was a high incidence of endocardial plaque (69%–85%) and myocardial fibrosis (57%) without significant visible scar (14%) [31]. Histologic specimens commonly reveal variable amounts of fibrosis and myofiber disarray that correlate with the degree of nonuniform anisotropic conduction and generation of reentrant wave fronts. In hearts with mild to moderate activation abnormalities, interstitial fibrosis with linear collagen deposition was primarily observed with an overall preserved tissue architecture and cellular alignment. In hearts with severe anisotropy, disturbed activation patterns were observed in areas of dense scar that had muscle bundle disruption similar to the pathologic specimens from patients who had ischemic heart disease and prior myocardial infarction [32].

The mechanism of ventricular arrhythmias in nonischemic cardiomyopathy patients is primarily myocardial scar-based reentry. There is a greater

degree of myocardial fibrosis in patients who present with sustained monomorphic VT compared with those presenting with nonsustained arrhythmias [33–35]. Focal initiation of VT, however, may also result from triggered activity with EADs or DADs. Pogwizd and colleagues [13] demonstrated that focal activation can arise in the subendocardium or the subepicardium, with variable interstitial fibrosis. Pathologic findings demonstrated that sites of conduction delay or block consist of areas of extensive interstitial fibrosis with scar formation.

The relationship between inducible arrhythmias and the extent of abnormal endocardial and epicardial substrate in patients who have nonischemic cardiomyopathy was initially evaluated during surgical epicardial defibrillator patch placement [35]. In patients who had inducible sustained monomorphic VT, a significantly higher incidence of abnormal electrograms was recorded

at epicardial and endocardial layers (47% and 38%, respectively) compared with patients who did not have inducible VT (6% and 18%, respectively). Although a wide individual variation in epicardial electrogram abnormalities predominated in some patients, endocardial abnormalities predominated in others.

Electroanatomic mapping provides a unique insight to the endocardial electrophysiologic substrate for uniform VT in patients who have nonischemic cardiomyopathy. The endocardial substrate is marked by a modest and variable distribution of abnormal low-voltage recordings rarely involving more than 25% of the total endocardial surface area. Furthermore, the predominant distribution of abnormal endocardial electrogram recordings is located at the ventricular base, frequently involving the perivalvular regions (Fig. 3). VTs in these patients typically originate from the basal region of the left

Electrophysiologic Substrate for Reentrant VT in Nonischemic Cardiomyopathy Basal Endocardial Voltage Abnormalities

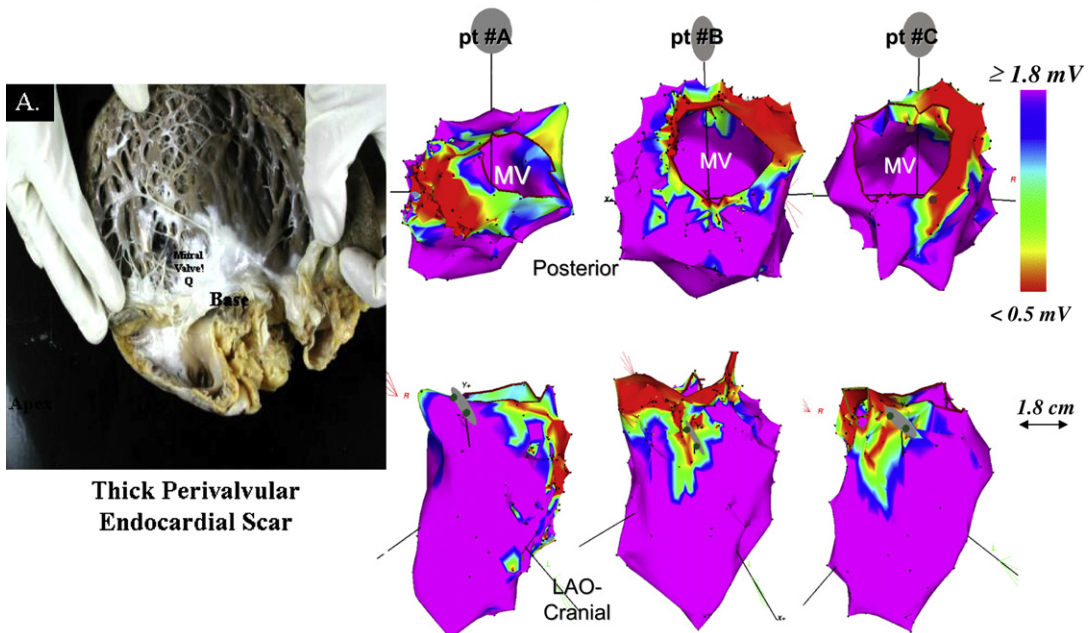


Fig. 3. Endocardial three-dimensional electroanatomic mapping in patients who had nonischemic cardiomyopathy presenting with monomorphic VT. Purple areas represent normal endocardium (amplitude $\geq 1.8\text{ mV}$), with dense scar depicted in red (amplitude $< 0.5\text{ mV}$). The border zone (amplitude $0.5\text{--}1.8\text{ mV}$) is defined as areas with the color gradient between red and purple. The voltage maps typically demonstrate modest-sized low-voltage endocardial electrogram abnormalities or scar, located near the ventricular base in the perivalvular region. On the left is a pathologic specimen that demonstrates perivalvular scarring at the ventricular base and corresponds to the observed low-voltage areas on the voltage maps. LAO, left anterior oblique; MV, mitral valve. (Adapted from Hsia HH, Mofrad PS. Mapping and ablation of ventricular tachycardia in nonischemic cardiomyopathy. In: Wang P, Hsia H, Al-Ahmad A, et al, editors. Ventricular arrhythmias and sudden cardiac death. Oxford (UK): Wiley-Blackwell; 2008; with permission.)

ventricle, corresponding to the locations of the anatomic endocardial substrate (Fig. 4). In comparison to patients who have ischemic cardiomyopathy, the endocardial scar region is significantly smaller in nonischemic cardiomyopathy patients, with a predilection for scar in the base of the heart [34,36,37].

In patients who have dilated cardiomyopathy and fail endocardial ablation, epicardial mapping has demonstrated significant areas of low-voltage scar such that the scar area may be larger on the epicardial surface than on the endocardial surface [38]. In contrast, in patients who have cardiomyopathy due to coronary artery disease, the area of scar has been found to be approximately three times larger in the endocardium compared with the

epicardium. Small islands of viable epicardial myocardium may be observed, located opposite to the corresponding endocardial dense scar region. There is, however, no such relationship between the epicardial and endocardial scars in patients who have nonischemic cardiomyopathy [39].

Ventricular tachycardia related to the His-Purkinje system

BBR is usually seen in patients who have structural heart disease. BBR is a macroreentrant VT involving anterograde conduction by way of the right or left bundle branch, transeptal intramyocardial conduction, and retrograde conduction along the other bundle branch. The

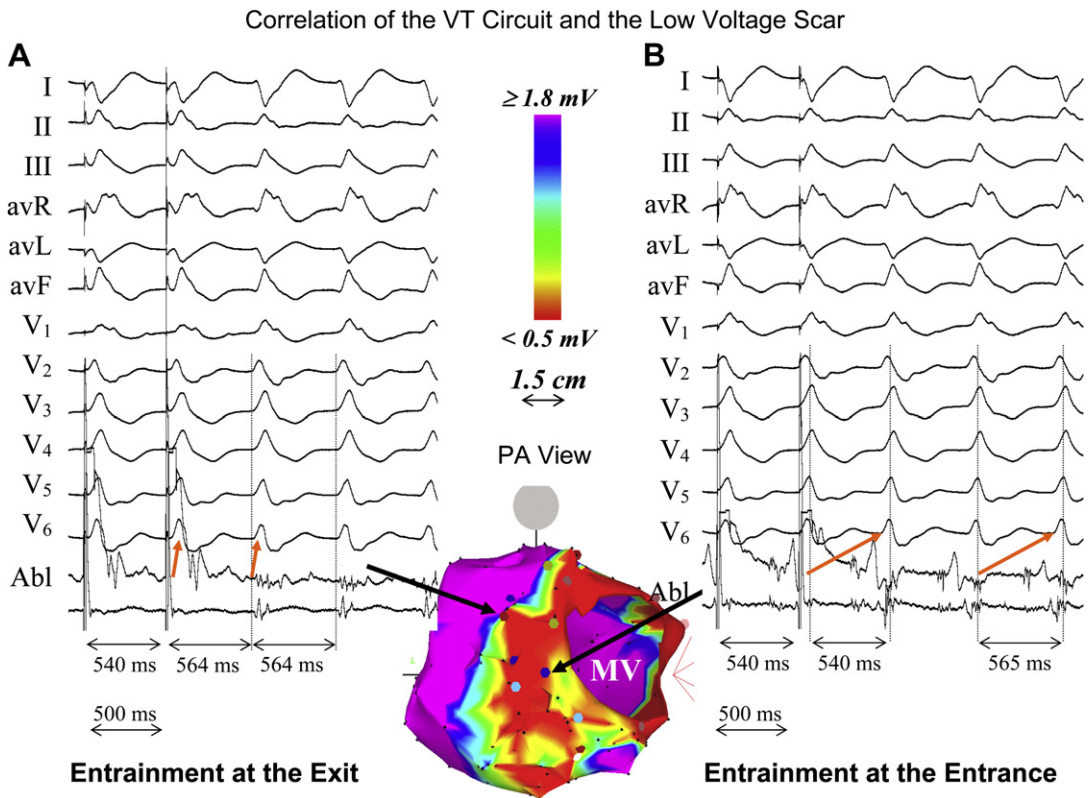


Fig. 4. Electroanatomic voltage map coupled with entrainment mapping for localization of VT circuit. The color gradient corresponds to the left ventricular endocardial bipolar electrogram amplitude as described in Fig. 3. (A) Entrainment with minimal surface fusion was observed near the exit site with a short stimulus–QRS interval. (B) The entrance site was identified with perfect entrainment and concealed fusion and a long stimulus–QRS interval that matched the electrogram–QRS interval. The VT circuit was located near the left ventricular base, corresponding to the locations of the abnormal endocardial substrate at the perivalvular region defined by the voltage map. MV, mitral valve; PA, posteroanterior. (From Hsia HH, Callans DJ, Marchlinski FE. Characterization of endocardial electrophysiological substrate in patients with nonischemic cardiomyopathy and monomorphic ventricular tachycardia. *Circulation* 2003;108(6):708; with permission.)

prerequisite for BBR VT is conduction delay in the His-Purkinje system, and the average H–V interval in patients who have BBR VT is 80 milliseconds (range, 60–110 milliseconds) [40]. The patients commonly present with a left bundle branch pattern or a nonspecific intraventricular conduction delay on ECG; however, BBR with a right bundle branch block morphology or interfascicular reentry can also be observed [41]. Although BBR is prevalent in patients who have dilated nonischemic cardiomyopathy and present with monomorphic VT, this arrhythmia can occur in cardiomyopathy of any etiology and often coexists with other myocardial reentrant arrhythmias in patients who have structural heart disease [42]. BBR VT accounts for up to 40% of induced sustained arrhythmias in nonischemic cardiomyopathy patients compared with only 6% in patients who have ischemic cardiomyopathy [43]. BBR, however, is also seen with other disorders such as mitral or aortic valve surgery due to close proximity to the His-Purkinje system [44]. Proarrhythmic effects due to conduction delay from flecainide have also been reported to cause BBR [45].

Intrafascicular reentry has been less commonly described (but may be present in patients who have BBR) and typically has a right bundle branch block pattern. A right axis deviation may be observed when there is anterograde conduction down the left anterior fascicle and retrograde conduction up the left posterior fascicle. A left axis deviation may be observed when the reverse path is taken.

The QRS morphology during BBR VT commonly resembles that during sinus rhythm. The diagnosis of BBR is based on carefully detailed electrogram recordings (including recordings from the bundle branches and the His) during the initiation and the sustained reentry. During BBR VT, the onset of the QRS is often preceded by the right bundle potential or the His deflection, with an H–V interval typically equal to or longer than that during sinus rhythm (Fig. 5). Cycle length oscillations of the V–V intervals are preceded by similar changes in the H–H intervals. Entrainment of the bundle branch circuit movement reentry can be achieved by pacing and capturing the right bundle branch or the left fascicle.

Catheter ablation of the right or left bundle branches interrupts the circuit and provides an effective treatment of this arrhythmia [46]; however, a comprehensive electrophysiologic evaluation is essential in patients who have cardiomyopathy because VTs related to the

His-Purkinje system often coexist with other myocardial reentry arrhythmias.

Other cardiomyopathies

Sarcoidosis

Sarcoidosis is a granulomatous disease of unknown etiology. It is characterized by multisystem granulomatous infiltration or discrete fibrosis. Myocardial involvement may be focal or multifocal and the granulomas may become foci for abnormal automaticity and increase the likelihood of reentrant arrhythmias. VT is the most frequently noted arrhythmia in cardiac sarcoid and is the terminal event in 67% of cardiac sarcoid patients [47,48]. Programmed stimulation may induce monomorphic VT, suggesting a reentrant mechanism in patients who have cardiac sarcoid [49]. MRI may also be useful in revealing areas of inflammation in patients who have minimal ventricular dysfunction [50].

Arrhythmogenic right ventricular dysplasia/ cardiomyopathy

Arrhythmogenic right ventricular dysplasia/ cardiomyopathy (ARVD/C) is a distinct pathologic diagnosis primarily involving fibrosis and fatty infiltration of the right ventricle. Mutations in genes encoding for desmosomal proteins that impair cell adhesion may lead to fibrofatty replacement of myocytes [51]. Additional myocardial mechanical stress may explain the typical phenotypic expressions of ARVD/C that include (1) a strikingly high incidence of the disease in athletic individuals, (2) a latent period for the development of clinical manifestation in early adulthood, and (3) a predilection for the disease to primarily affect certain locations of the right ventricle [52,53].

The extent of right ventricular (RV) involvement may vary from diffuse RV involvement to localized dysplastic regions. Left ventricular or biventricular involvement can also be observed with more recent evidence, suggesting that left ventricular involvement may precede RV involvement [54]. Infiltration of fibrous tissue and fat into regions of normal myocardium, analogous to infarct-related aneurysms in ischemic heart disease, form the arrhythmogenic basis for development of reentrant VT [55]. The extent of RV involvement can vary markedly. Although diffuse RV enlargement and hypokinesis may be present, localized abnormalities consisting of bulging or sacculation of the RV free wall are more characteristic and predominantly involve the

Clinical management

Risk stratification

By far, the highest total mortality appears to be in patients who have a depressed ejection fraction and symptoms of heart failure. Sudden, presumably arrhythmic death accounts for a significant proportion of total mortality in patients who have mild symptoms of ventricular dysfunction, whereas progressive hemodynamic deterioration and pump failure are the major causes of death in patients in advanced stage of heart failure (see Fig. 1). A large number of risk factors for arrhythmia recurrence and SCD have been identified in patients who have structural heart disease; however, developing a comprehensive risk stratification strategy remains a challenge.

A depressed ejection fraction remains the most consistent predictor of SCD in patients who have structural heart disease, irrespective of etiology. Patients in the follow-up Multicenter Automatic Defibrillator Implantation Trial (MADIT-II) who had an ejection fraction less than 30% had a rate of SCD of approximately 9.4% at 20 months [60]. In a similar population of patients, however, an ejection fraction greater than 35% and history of myocardial infarction conferred only a 1.8% risk of SCD [61].

The presence of ambient ventricular ectopy also carries prognostic significance. In patients who had prior myocardial infarctions, the presence of frequent PVCs (>10/h) or nonsustained VT was associated with an increased risk of SCD [62]. In contrast, patients who had prior infarctions but no ventricular ectopy had a less than 1% incidence of SCD [63]. A similar observation was made in patients who had nonischemic dilated cardiomyopathy in the GESICA-GEMA trial. In patients who had heart failure and an average ejection fraction of 19%, the presence of VT was associated with an increased risk of SCD, whereas the absence of VT indicated a lower probability of SCD [64].

Prolongation of the interlead QT interval reflects a dispersion of myocardial repolarization. Such a prolonged vulnerable phase during myocardial recovery and regional heterogeneity has been associated with occurrences of ventricular arrhythmias [65]. The normal QT interval dispersion is around 30 to 70 milliseconds. A measured QT dispersion greater than 80 milliseconds post myocardial infarction was associated with VT with a sensitivity of 73% and a specificity of 86% [66].

T-wave alternans or beat-to-beat variation in the T-wave morphology is believed to be due to regional disturbances in action potential duration leading to dispersion in repolarization and propensity to develop arrhythmias [67]. Microvolt T-wave alternans (MTWA) measures microvolt changes in the T-wave amplitude in alternate beats and has also been found to be a significant predictor of VT events [68]. Abnormal MTWA in patients who have congestive heart failure has been associated with an increased mortality rate [69]. Application of the MTWA test to patients who fit MADIT-II criteria demonstrated that patients who had an abnormal MTWA test had a significantly increased 2-year mortality rate (17.8%) compared with patients who had a normal MTWA (3.8%) [70]. A major limitation of such an MTWA test, however, is the high proportion of indeterminate results.

The autonomic nervous system has also been implicated in causing ventricular arrhythmias. Heart rate variability and baroreflex sensitivity (BRS) are two noninvasive tests used to estimate the function of the autonomic nervous system. Decreased heart rate variability has been shown to be a powerful predictor of mortality and perhaps arrhythmic events in patients who have myocardial infarctions [71,72]. The Autonomic Tone and Reflexes After Myocardial Infarction trial was designed to evaluate the prognostic utility of BRS and heart rate variability in postmyocardial infarction patients. A depressed BRS (defined as <3 ms/mm Hg) significantly predicted cardiac mortality over an average 21-month follow-up period [73].

The signal-averaged ECG is a high-resolution ECG technique designed to determine the risk of developing VT by measuring the low-amplitude, high-frequency surface ECG signals in the terminal QRS complex that cannot be detected by a standard ECG machine [74]. These late potentials have been correlated to localized areas of delayed endocardial activation in humans, and reflect the substrate for ventricular reentry [27–29]. In patients who have coronary artery disease, signal-averaged ECG has an overall low positive predictive value ranging from 7% to 27%, whereas it has a very high negative predictive value ranging from 96% to 99%. Its utility as a prognostic tool remains controversial in patients who have idiopathic nonischemic cardiomyopathy. An abnormal signal-averaged ECG in patients who have nonischemic cardiomyopathy

has been associated with a significantly higher cardiac event rate, with the predominant cause of mortality being sudden death [75].

The diagnostic and prognostic values of an electrophysiology study depend on the underlying pathologic substrate and the spontaneous arrhythmia presentations. The inducibility of monomorphic VT is a powerful marker of risk for SCD, especially in patients who have a history of prior myocardial infarction and reduced ejection fraction or syncope. Programmed electrical stimulation has a sensitivity of about 97% in those who have spontaneous sustained monomorphic VT and a positive predictive value of 65% [76]. In patients who have nonischemic cardiomyopathy, the inducibility of ventricular arrhythmias is much lower. Although the overall sensitivity of programmed stimulation is similar to that in patients who have coronary artery disease, noninducibility in patients who have nonischemic cardiomyopathies does not confer a good prognosis, and patients are still at high risk of SCD [77].

MRI

Advances in MRI have provided unique capabilities to identify morphologic changes in the cardiac chambers in ischemic and nonischemic cardiomyopathies [78]. Applications of gadolinium-enhanced imaging provide detailed characterization of cardiac tissues and identification of areas of scar. Differences between the nonischemic and ischemic subgroups in patients who have ventricular dysfunction and heart failure can be demonstrated on cardiac MRI scans [79,80]. In the studies done by Assomull and colleagues [79] and McCrohon and colleagues [80], all patients who had coronary artery disease had subendocardial or transmural late-gadolinium enhancement, consistent with the typical locations of infarcted myocardium and scars. In contrast, patients who had nonischemic cardiomyopathy had absence of abnormal gadolinium uptake in over half of the population, and patchy or longitudinal striae of midwall enhancement patterns were observed in approximately one third of the patients. The midwall myocardial enhancement in patients who had nonischemic cardiomyopathy was similar to the focal segmental fibrosis found at autopsy. The remaining patients (13%) had a pattern of myocardial enhancement that was indistinguishable from that of ischemic heart disease. These observations were clearly different from the distribution pattern found in patients who

had coronary artery disease. Patients who had MRI-documented fibrosis had a significantly greater incidence of SCD and induction of sustained VT by programmed stimulation [81].

Pharmacologic therapy

In addition to their neurohormonal benefits in the management of patients who have heart failure, β -blockers have been shown to be antiarrhythmic and antifibrillatory. Trials using different β -blockers, including atenolol, propranolol, metoprolol, timolol, acetabutolol, and carvedilol, have shown consistent reductions in mortality after myocardial infarction [82–86]. The total mortality reduction with these agents is approximately 25% to 40%, with approximately a 32% to 50% reduction in the incidence of SCD. The benefit of reduction of total mortality, cardiovascular mortality, and sudden death risk extends beyond patients who have coronary artery disease to those who have nonischemic cardiomyopathy. It is clear that β -blocker therapy is the cornerstone of heart failure management and is indicated in all patients who have heart failure and no contraindications [87,88].

Angiotensin-converting enzyme (ACE) inhibitors have been well established to decrease the overall mortality in patients after myocardial infarction who have various degrees of systolic heart failure. ACE inhibition has been shown to reduce mortality primarily by inhibiting the progressive architectural changes that lead to inefficient left ventricular function, thus preventing or delaying pump failure. ACE inhibitors, however, were not shown to result in any significant reduction in the incidence of SCD in the Cooperative North Scandinavian Enalapril Survival Study, the Survival And Ventricular Enlargement trial, or the SOLVD trial [89–91], with the exception of the use of ramipril decreasing the incidence of SCD by 30% in post-myocardial infarction patients who had heart failure [92].

Most trials using antiarrhythmic drug therapy have resulted in worsening outcome in the drug treatment arms. The first of these trials was the Cardiac Arrhythmia Suppression Trial, which demonstrated an increased mortality despite suppression of PVCs using class IC agents, presumably due to proarrhythmia [93]. d-sotalol, a pure I_{Kr} blocker with class III antiarrhythmic effects and little β -blocking activity, also demonstrated a significant mortality increase in patients who had myocardial infarctions and New York Heart

Association (NYHA) class II to III heart failure (Survival With ORal d-sotalol trial) [94]. It was believed that this increase in mortality was due to the lack of β -blocking benefits. Other class III antiarrhythmic agents such as dofetilide appear to be neutral in regard to all-cause mortality and SCD in postmyocardial infarction patients who have heart failure (DIAMOND trial) [95].

Amiodarone, a complex antiarrhythmic drug with multiple pharmacologic actions, is one of the most widely used antiarrhythmic drugs in the heart failure population. Amiodarone does not appear to have any adverse effect on survival or heart failure. In the Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure, amiodarone had no significant impact on the incidence of SCD or on total mortality [96]; however, multiple smaller studies have shown significant mortality benefits and SCD reduction with the use of this drug [97–99]. Perhaps the largest of

the amiodarone studies are the European Myocardial Infarct Amiodarone Trial and the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial, which focused on patients who had ischemic heart disease and prior myocardial infarction. The results suggested that amiodarone may reduce arrhythmic death, but at the expense of higher mortality from re-infarction and noncardiac mortality [100,101].

Nonpharmacologic therapy (implantable cardioverters-defibrillators)

Initial therapies using implantable cardioverters-defibrillators (ICDs) were targeted at survivors of SCD. Randomized controlled trials involving implantation of ICDs in cardiac arrest survivors demonstrated a significant survival benefit in total mortality and sudden death mortality (Antiarrhythmics Versus Implantable

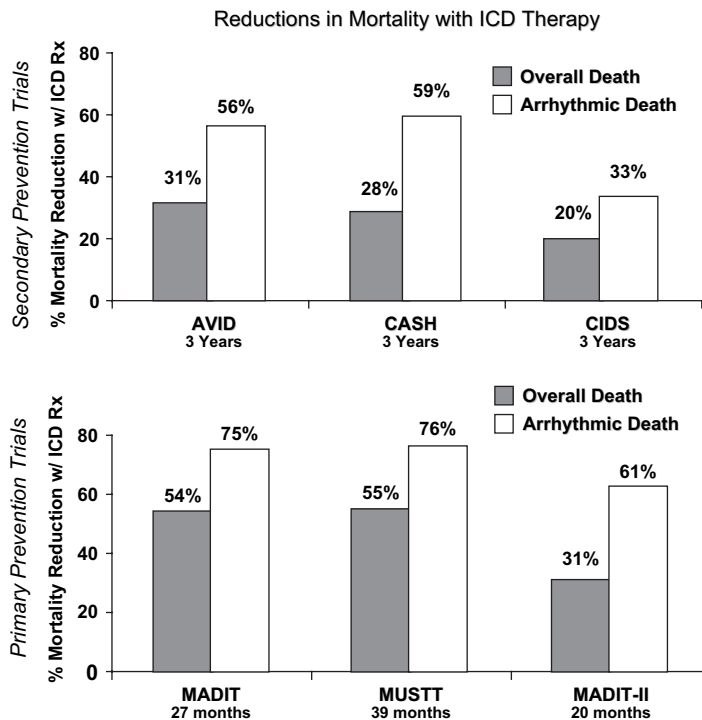


Fig. 6. Reduction of mortality with ICD trials. Randomized controlled trials (AVID, CASH, CIDS; *top*) involving ICD implantation in cardiac arrest survivors demonstrated statistically significant survival benefit in total mortality and sudden death mortality. The relative reduction ranged from 20% to 31% for total mortality and from 33% to 59% for arrhythmic death mortality. Primary prevention trials (MADIT, MUSTT, MADIT-II, *bottom*) with prophylactic ICD implantation in patients who had prior myocardial infarction and ventricular dysfunction demonstrated a relative mortality reduction ranging from 31% to 55% for total mortality and from 61% to 76% for arrhythmic death mortality. The mortality reductions with ICD in primary prevention trials are equal to or greater than those in secondary prevention trials.

Defibrillators trial [AVID] [102], Canadian Implantable Defibrillator Study [CIDS] [103], and Cardiac Arrest Study Hamburg [CASH] [104]. Meta-analysis from the combined secondary prevention trials demonstrated a 57% decrease in the risk of arrhythmic death along with a 30% decrease in all-cause mortality in survivors of SCD (Fig. 6) (Table 1) [105].

With the widespread adoption of ICDs for prevention of SCD in survivors of SCD, the focus was shifted toward prophylactic ICD use for primary prevention in patients who have ventricular dysfunction and are at high risk of sudden death. The MADIT study was the first to evaluate the prophylactic use of ICDs in patients who had prior myocardial infarction, low ejection fraction, and inducible but nonsuppressible ventricular arrhythmias. The use of ICDs in this population was associated with a 54% decrease in all-cause mortality and a 75% decrease in arrhythmia deaths [106]. The MADIT study, however, has been criticized for its small sample size and the low rate of β -blocker usage in the conventional therapy arm.

The utility of electrophysiology study to guide antiarrhythmic therapy in postinfarct patients who have low ejection fraction (<40%) and spontaneous nonsustained VT was subsequently evaluated in the Multicenter UnSustained Tachycardia Trial (MUSTT). The survival benefit associated with electrophysiologically guided therapy was entirely due to the use of defibrillators, not antiarrhythmic drugs. The risk for cardiac arrest or death from arrhythmia among patients who underwent ICD implantation was significantly lower than that among patients who did not have ICD therapy, with a relative risk of 0.24 [107]. A follow-up study, the MADIT-II, was performed in patients who had an ischemic cardiomyopathy and an ejection fraction less than 30%. There was a higher percentage of β -blocker and ACE inhibitor use. With optimized medical treatment, there was a 5.6% absolute mortality benefit and a 30% relative mortality benefit in patients who had defibrillators.

The more recent Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) included large

Table 1
Defibrillator trials

Trials	Inclusions	Interventions	Results
Primary prevention trials			
AVID	VF, VT/syncope, VT with EF \leq 40%	Amiod versus sotalol versus ICD	31% \downarrow All-cause mortality in ICD versus drugs in 3 y
CASH	Survivors of VF (no EF requirement)	Metoprolol versus amiod versus propaf versus ICD	37% \downarrow All-cause mortality in ICD versus drugs in 2 y 85% \downarrow SCD in ICD versus drugs 20% \downarrow All-cause mortality in ICD versus drugs in 3 y
CIDS	VF, VT/syncope, VT/EF \leq 35%, CL <400 ms	Amiod versus ICD	
Secondary prevention trials			
MUSTT	CAD, EF <40%, NSVT	EP versus non-EP-guided Rx, AAD versus ICD	55%–60% \downarrow All-cause mortality in ICD versus drugs in 39 mo 73%–76% \downarrow SCD in ICD versus drugs
MADIT-I	MI, EF <35%, NSVT, inducible/non-suppressible VA	Conv med versus ICD	Prophylactic ICD \downarrow overall mortality (HR: 0.46; $P = .009$), improves survival compared with conv med
MADIT-II	MI, EF <30%	Placebo versus ICD	31% \downarrow Overall mortality (HR: 0.69; $P = .016$) 61% \downarrow Arrhythmia mortality with ICD \downarrow SCD (HR: 0.20; $P = .006$) in ICD Insignificant \downarrow all-cause mortality in ICD
DEFINITE	Nonischemic CM, EF <36%, PVC/NSVT	Placebo versus ICD	
SCD-HeFT	HF/NYHA II-III, EF <35%	Placebo versus amiod versus ICD	23% \downarrow All-cause mortality in ICD versus drugs over 5 y. Amiodarone does not improve survival

Abbreviations: AAD, antiarrhythmic drugs; CAD, coronary artery disease; CL, cycle length; CM, cardiomyopathy; Conv med, conventional medical therapy; EF, ejection fraction; EP, electrophysiology; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; NSVT, nonsustained VT; VA, ventricular arrhythmia; VF ventricular fibrillation. (From Heart Rhythm 2006;3(5):page 507.)

cohorts of patients who had ischemic and non-ischemic cardiomyopathies. The enrollment criteria included only symptoms of heart failure and a depressed ejection fraction without arrhythmia indication (ejection fraction <35% and NYHA class II–III heart failure) [108]. Patients were randomized to three arms: optimal medical therapy for heart failure plus placebo, medical therapy plus amiodarone, and medical therapy plus single-lead ICDs. SCD-HeFT demonstrated a 23% mortality benefit in patients implanted with ICDs compared with amiodarone therapy or placebo.

The Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation trial focused exclusively on patients who had dilated nonischemic cardiomyopathy and ventricular dysfunction. All patients were in NYHA class I to III and received optimal medical therapy (with >85% usage of β -blockers and ACE inhibitors). The implantation of a cardioverter-defibrillator significantly reduced the risk of sudden death from arrhythmia and was associated with a nonsignificant

reduction in the risk of death from any cause in this population [109].

Meta-analysis from the combined secondary prevention trials demonstrated a 57% decrease in the risk of arrhythmic death along with a 30% decrease in all-cause mortality in survivors of SCD [102–105].

Although there is no doubt that the ICD improves survival in high-risk patients, there remains a significant increase in the rate of hospitalization for new or worsening heart failure (Fig. 7) [110]. The development of heart failure is a major determinant of subsequent mortality in heart failure patients despite receiving single-chamber or dual-chamber ICDs. Although the life-prolonging efficacy of ICD therapy is maintained among patients who receive single-chamber devices, there seems to be a significant reduction in ICD benefit after developing heart failure among patients who receive dual-chamber devices. RV pacing with a dual-chamber ICD has been shown to contribute to an increased risk of

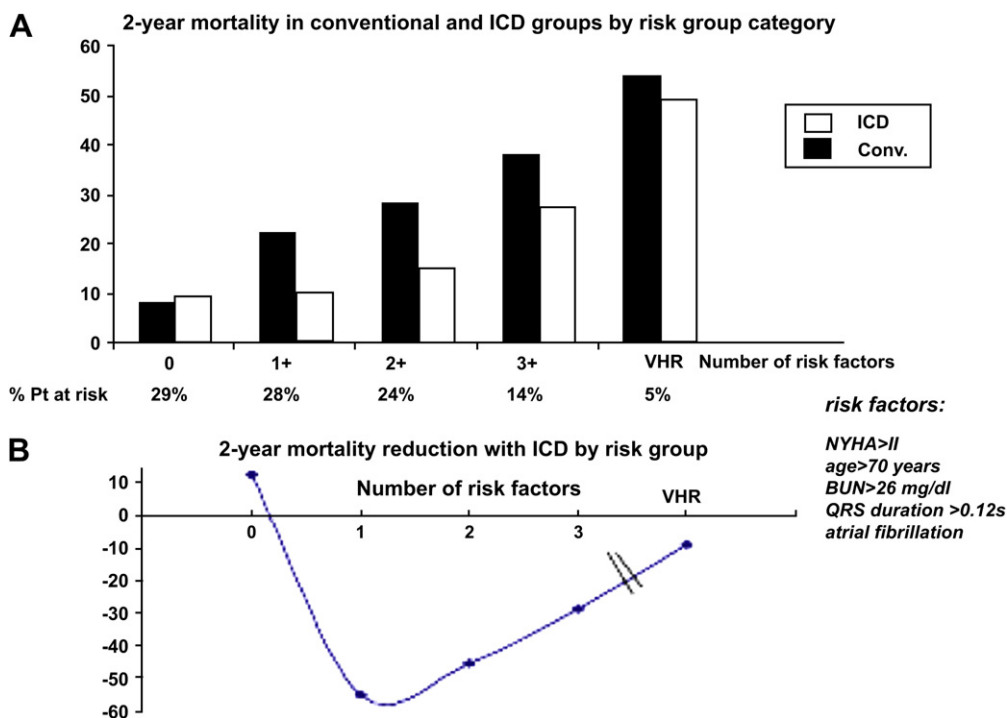


Fig. 7. U-shaped curve for ICD efficacy. Two-year Kaplan-Meier mortality rates in the ICD and conventional (Conv.) therapy groups (A), and the corresponding 2-year mortality rate reduction with an ICD, by risk score and in VHR patients ($P = .05$) (B). BUN, blood urea nitrogen; VHR, very high risk. (Modified from Goldenberg I, Vyas AK, Hall WJ, et al. Risk stratification for primary implantation of a cardioverter-defibrillator in patients with ischemic left ventricular dysfunction. J Am Coll Cardiol 2008;51:294; with permission.)

heart failure after ICD implantation [111,112]. Aggressive heart failure medical management and judicious ICD programming are essential to optimize the benefit of ICD therapy.

Ablative therapy

Prior surgical experiences for treatment of ventricular arrhythmia in patients who have ischemic cardiomyopathy have demonstrated long-term efficacy in preventing arrhythmia

recurrence [113–115]. Catheter ablation also plays an increasing role in the management of patients who have VTs because antiarrhythmic drug therapies are often inadequate to prevent recurrence [116,117]. Catheter ablation techniques, however, usually require identification of the functional components of the reentry circuit and are mostly limited to hemodynamically tolerated monomorphic VTs [118].

The “conventional mapping” strategies for ventricular arrhythmias include activation

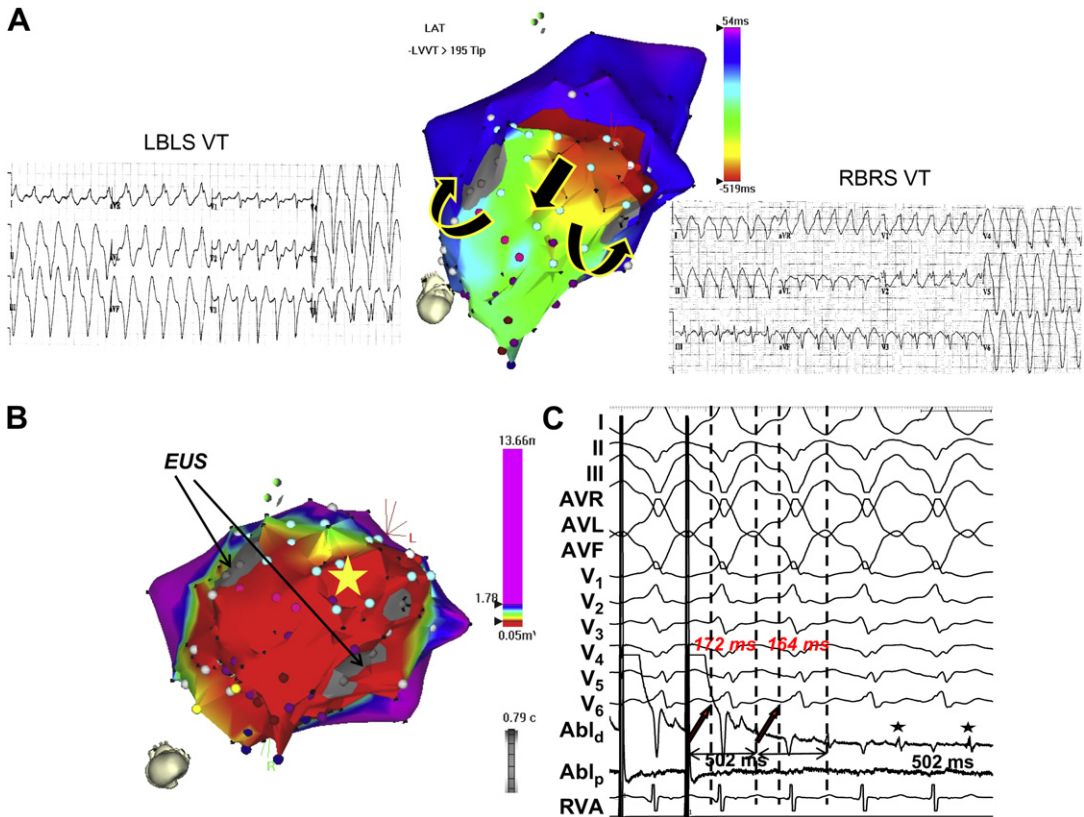


Fig. 8. Electroanatomic mapping in a patient who had a large anterolateral myocardial infarction and sustained monomorphic VT. (A) Activation mapping during VT shows a “figure-of-eight” reentry. Temporal isochronal color changes demonstrated an “early-meets-late” activation pattern, with red representing early activation and purple depicting the late area. Two different VTs were induced, with a left bundle branch block–left-superior (LBLS) and a right bundle branch block–right-superior (RBRS) QRS morphology. (B) Voltage map shows a large anterolateral scar. The color gradient corresponds to the left ventricular endocardial bipolar electrogram amplitude as described in Fig. 4. Electrical unexcitable scar (EUS) was identified by noncapture with high-output pacing and is depicted by the gray scar (arrows). Such dense scar tissues are commonly in proximity to the zone of slow conduction/isthmus of the VT circuit and are often located deep in dense scar (<0.5 mV). (C) Entrainment mapping with pacing during VT demonstrated concealed fusion that identified the isthmus site (stars), with the electrogram–QRS interval (164 milliseconds) equal to the stimulus–QRS interval of 172 milliseconds. Abl_d, ablation catheter distal; Abl_p, ablation catheter proximal; RVA, right ventricular apical. (Modified from Anh D, Hsia H, Callans D. The utility of electroanatomical mapping in catheter ablation of ventricular tachycardias. In: Al-Ahmad A, Callans DJ, Hsia HH, et al, editors. Electroanatomical mapping: an atlas for clinicians. Oxford (UK): Blackwell Publishing; 2008. p. 24; with permission.)

mapping, pace mapping, and entrainment mapping. In addition, the “site-of-origin” of VT can be identified by careful analysis of the QRS morphology on a 12-lead ECG [119,120]. Activation mapping searches for the earliest ventricular depolarization based on the local bipolar electrogram timing, a qS pattern on unipolar recordings as the wave front propagates away from the focus of ventricular activation, or both. Relative timing of recorded signals can be assessed with reference to surface R waves or intracardiac ventricular electrograms. Activation isochrones may be constructed to display the area with the earliest isochronal time as an “early spot” using three-dimensional electroanatomic mapping systems.

Pace mapping for VT localization strives to reproduce the exact QRS morphology compared with that of spontaneous arrhythmias. The method is predicated on the principle that pacing at the exit site of the VT circuit would yield the same surface ECG morphology as the clinical VT, using unipolar pacing or bipolar pacing at low current outputs from a closely spaced bipole [121]. Subtle variations in paced QRS morphology can be observed, however, which may be associated with more than one distinct focus within a limited area [122]. Although previous studies have suggested that pace mapping may be more precise in locating the site of origin compared with activation mapping for focal VTs, a more recent investigation has shown a comparable efficacy between pace mapping and activation mapping with the use of a three-dimensional magnetic electroanatomic mapping system [123].

Entrainment mapping assesses the response of a reentrant arrhythmia to pacing stimulation and is the most reliable method for defining a reentrant VT circuit. Based on the degree of surface ECG fusion, the postpacing interval, and the electrogram-to-QRS timing, one can determine the arbitrarily defined exit, central isthmus, entrance, outer loop, remote, and adjacent bystander sites within a reentrant VT circuit (see Fig. 4; Fig. 8). Entrainment mapping, however, requires that the tachycardia remains hemodynamically stable along with a stable QRS morphology and rate. Pacing during VT may accelerate, terminate, or change to a different arrhythmia, limiting the utility of entrainment mapping.

Substrate mapping

Most induced VTs are often unstable with multiple morphologies and do not permit

extensive mapping [124]. Based on the authors’ experiences in surgical resection, a recent shift of paradigm has allowed a different approach of VT ablation. This strategy depends on anatomic identification of scar, with infarcted myocardium having different electrogram characteristics than the surrounding tissue. Radiofrequency ablation deployed with reference to anatomic boundaries or myocardial scar may result in successful ablation of VT without ever inducing sustained VT. This substrate-based catheter ablation approach has been shown to be effective in eliminating or controlling scar-based reentrant VTs that were previously considered “unmappable” [125–127].

Electroanatomic mapping couples spatial locations with electrogram recordings and displays a three-dimensional anatomic construct of the cardiac chamber. Such voltage maps depict the location and characteristics of myocardial scar and facilitate mapping of scar-based VTs (see Figs. 4 and 8). The local electrogram amplitude at sites within the VT circuits was recently reported by Hsia and colleagues [128]. Entrance and central isthmus sites are predominantly (84%) located in the “dense scar,” with electrogram amplitude less than 0.5 mV. Conversely, exit or outer loop sites are more likely to be located within the border zone (0.5–1.5 mV). Almost all (92%) of the exit sites are located in abnormal myocardium of less than 1.5 mV, with more than half of the exit sites located in the border zone, with voltage between 0.5 and 1.5 mV (Table 2). Careful analysis of the voltage profile helps to identify the approximate location of the VT circuit. Ablation targeted at the scar border zone defined by

Table 2
Local electrogram amplitude for sites within the reentrant circuit

	Entrance	Central isthmus	Exit	Outer loop
Dense scar (<0.5 mV)	17	30	18	6
Border zone (0.5–1.5 mV)	2	7	26	18
Normal (>1.5 mV)	—	—	4	8
Total (136 sites)	19	37	48	32

(Data from Hsia HH, Lin D, Sauer WH, et al. Anatomic characterization of endocardial substrate for hemodynamically stable reentrant ventricular tachycardia: identification of endocardial conducting channels. *Heart Rhythm* 2006;3(5):503–12.)

substrate mapping has been shown to be effective in eliminating VT post myocardial infarction [129]. Furthermore, VT-related conducting channels that correspond to the activation wave front during reentry can be identified (Fig. 9) [128,130]. These VT-related conducting channels may be appropriate targets for ablation. Electrograms with isolated delayed components or late potentials may also serve as surrogates for anisotropic conduction delay. Identification of such late potentials during different rhythms (sinus versus paced) may be an effective adjunct to localize

the arrhythmia substrate for scar-based reentry [131].

A substrate-based ablation strategy targeting the potential VT circuits within the myocardial scar results in successful control of recurrent VT in patients who have cardiomyopathies and heart failure [37]. Multiple linear ablations are typically required, extending from the putative VT exit site at the border zone into the dense scar, often extending up to several centimeters in length [37]. Placement of ablation lines designed to transect the VT-related “conduction channels” in

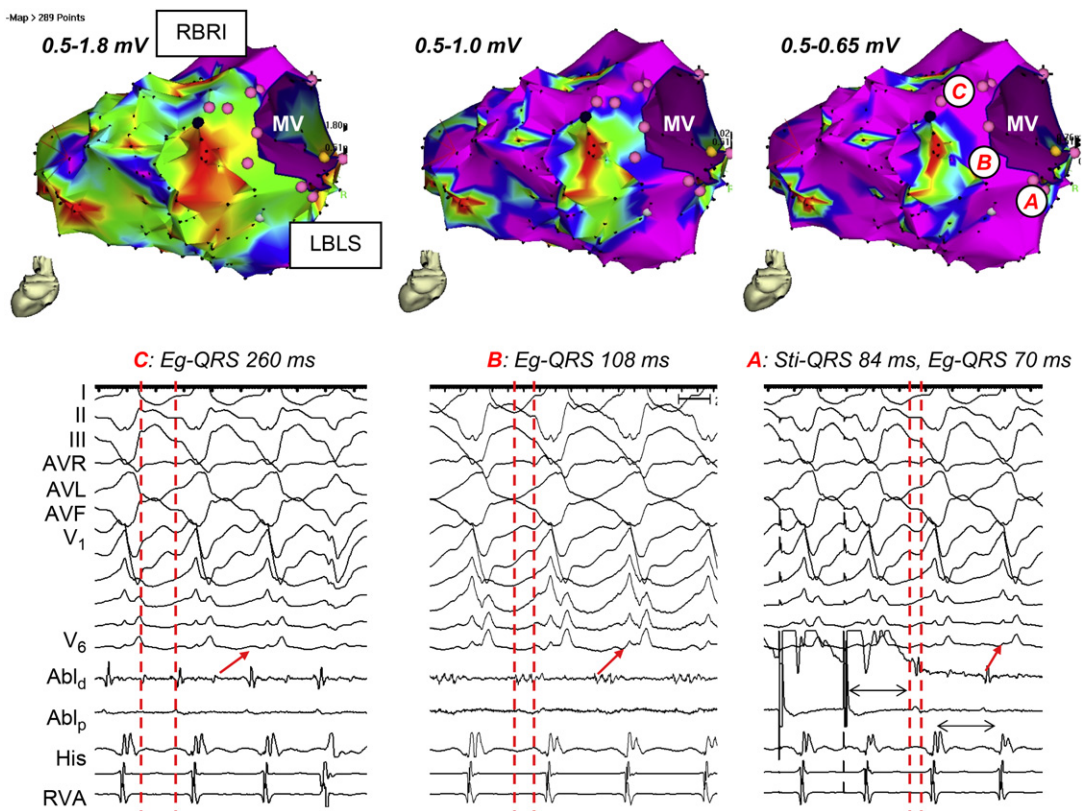


Fig. 9. Identification of a VT-related conducting channel in a patient who had prior myocardial infarctions and presented with sustained VT. Two tachycardias were documented with a right bundle branch block–right-inferior (RBRI) and a left bundle branch block–left-superior (LBLS) QRS morphology. By carefully adjusting the upper and lower color voltage thresholds on the electroanatomic voltage map (0.5–1.8 mV, 0.5–1.0 mV, and 0.5–0.65 mV), a corridor demonstrating a higher voltage amplitude than that of the surrounding areas could be visualized. Entrainment with concealed fusion within the channel was noted at multiple sites (A, B, C), with progressively longer stimulus–QRS (Sti–QRS) intervals equaling electrogram–QRS (Eg–QRS) intervals. This is an example of mitral annular VT with counterclockwise (LBLS) and clockwise (RBRI) reentry VTs around the mitral valve (MV). (From Anh D, Hsia H, Callans D. The utility of electroanatomical mapping in catheter ablation of ventricular tachycardias. In: Al-Ahmad A, Callans DJ, Hsia HH, et al, editors. *Electroanatomical mapping: an atlas for clinicians*. Oxford (UK): Blackwell Publishing; 2008. p. 25; with permission.)

abnormal scar or targeting areas with isolated delayed electrogram recordings may facilitate ablation of multiple stable and unstable VTs, even in the absence of VT induction [128,130–132].

Epicardial mapping

Mapping and ablation of VT still remains a formidable challenge in patients who have scar-based reentrant arrhythmias. The success rate depends on the underlying structural heart disease and the location of VT circuits. The presence of epicardial circuits has been considered one of the main reasons for failure of endocardial ablation. Initial reports from Brazil have demonstrated a high prevalence of epicardial circuits in patients who have Chagas' cardiomyopathy and VT related to old inferior myocardial infarctions [133,134].

In contrast to patients who have coronary artery disease, there is no predilection for sub-endocardial location of scar and VT circuits in patients who have dilated nonischemic cardiomyopathy. Only modest (approximately one third) endocardial scar is present with a predominant distribution adjacent to valve annuli [36]. Significantly large epicardial scar involvement may be found in selected patients who have nonischemic cardiomyopathy; however, marked individual variations are present [38].

The success of endocardial ablation for VT associated with nonischemic cardiomyopathy appears to be lower than that observed for ischemic VT. This difference may be the result of reentry circuits that are deep to the endocardium or in the epicardial region. Epicardial mapping has led to successful ablation in a significant proportion of these patients after failed endocardial ablation. Approximately one third of patients who have nonischemic cardiomyopathy may require epicardial ablation. The use of a combined epicardial/endocardial approach or a staged approach may improve success rates for ablation of VT [38,39].

Epicardial circuits may be difficult to approach and map using endocardial techniques. The coronary veins can be used for limited access to the epicardium, but the distribution of the coronary venous anatomy places significant constraints on catheter manipulation and placement. The sub-xiphoid transthoracic approach or a surgical approach may be used successfully to gain access to the pericardial and epicardial space to allow for unrestricted access to the epicardial surface of both ventricles [135].

Summary

Ventricular arrhythmia represents a significant cause of mortality and morbidity in patients who have heart failure. The pathophysiologic mechanisms and electroanatomic substrates of ventricular arrhythmia are slowly being elucidated.

Clinical management of ventricular arrhythmia in patients who have heart failure has progressed over the past few decades, with a shift from antiarrhythmic drugs to device therapy. Although implantable defibrillators have a clear impact in reduction of sudden death, optimization of medical neurohormonal therapy and other heart failure management strategies are essential to improve the overall mortality.

Catheter ablation of VT is an effective adjunct in the management of ventricular arrhythmia but remains a significant challenge. Better understanding of the electroanatomic substrates in different cardiomyopathies and identification of other surrogate markers for VT circuits are essential to improve the ablation outcome. Promising advances in robotic and magnetic catheter manipulation may shorten the procedural time and increase safety. Furthermore, incorporation of other imaging technologies such as CT, MRI, or ultrasound with electroanatomic mapping can enhance our ability to efficiently map and ablate ventricular arrhythmia in this patient population.

Future investigations will focus on advancing our understanding of the complex pathophysiology of heart failure. Novel anatomic/physiologic imaging modalities may provide rapid characterization of the substrate for ventricular dysfunction and arrhythmia development and the capacity for serial assessment of disease progression, improving risk stratification.

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