Mechanisms Underlying Spontaneous and Induced Ventricular Arrhythmias in Patients With Idiopathic Dilated Cardiomyopathy

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Background—To define the electrophysiological mechanism(s) of inducible and spontaneously occurring ventricular arrhythmias associated with nonischemic cardiomyopathy, 3-dimensional intraoperative mapping from 156 intramural sites was performed in 6 patients with idiopathic dilated cardiomyopathy undergoing cardiac transplantation.

Methods and Results—Electrode density was sufficient to determine the mechanism for 52 of 74 beats of nonsustained ventricular tachycardia (VT) induced by programmed stimulation and 9 of 11 beats of spontaneous ventricular arrhythmias. The first, second, and third extrastimuli (S2 through S3) conducted with progressively greater degrees of conduction delay (total activation times [TAs] of 144±5, 166±5, and 194±5 ms, respectively) owing to slow conduction and on occasion intramural block. The first beats of induced VT arose from subendocardial or subepicardial sites distant from areas of marked conduction delay by a focal mechanism on the basis of the absence of intervening electrical activity between the termination of the last extrastimulus and the initiation of VT (123±31 ms). Subsequent beats arose by a focal mechanism and conducted with a TA of 127±6 ms (P<NS versus initiating beats of VT [118±9 ms]). Spontaneous ventricular arrhythmias initiated in the subendocardium by a focal mechanism and conducted with a TA of 138±5 ms. Tissue analysis demonstrated a variable degree of interstitial fibrosis at sites of focal activation. Sites of conduction delay or block typically exhibited marked interstitial and/or replacement fibrosis but were spatially distant from sites initiating VT.

Conclusions—Spontaneous and induced ventricular arrhythmias in patients with end-stage idiopathic cardiomyopathy can arise in the subendocardium or subepicardium by a focal mechanism. (Circulation. 1998;98:2404-2414.)

Key Words: tachycardia • heart failure • mapping

Patients with idiopathic dilated cardiomyopathy (IDCM) demonstrate a high incidence of ventricular arrhythmias1 and are at increased risk of sudden death from ventricular tachycardia (VT) and ventricular fibrillation.2 Treatment with pharmacological agents has been empirical, ineffective, and frequently proarrhythmic and limited by the paucity of data on electrophysiological mechanisms.3

Myocardium from patients with IDCM demonstrates altered epicardial conduction,4,5 especially in response to programmed electrical stimulation, suggesting, albeit indirectly, a substrate for reentrant rhythms. However, nonreentrant mechanisms such as triggered activity arising from delayed afterdepolarizations (DADs) or early afterdepolarizations (EADs) could initiate ventricular arrhythmias, especially in light of findings that DADs and EADs can be induced in myocardium obtained from patients with end-stage cardiomyopathy.6

We have previously performed 3-dimensional cardiac mapping in patients with coronary artery disease undergoing surgical ablation of VT.7,8 We demonstrated that sustained and nonsustained VT induced by programmed stimulation initiated by intramural reentry in half the cases and by a focal mechanism in half the cases. In the present study, we performed intraoperative mapping just before explantation of the heart in patients with IDCM undergoing cardiac transplantation to define the mechanism(s) of initiation for beats of VT induced by programmed stimulation and for spontaneously occurring ventricular arrhythmias.

Methods

Patients Studied
Six patients (5 men, 1 woman) with end-stage IDCM undergoing cardiac transplantation were studied. Their mean age was 50±4 years. All patients demonstrated premature ventricular complexes (PVCs), ventricular couplets, and nonsustained VT (≤11 beats) on Holter monitoring (Table). Patient 2 had syncope. None was being treated with antiarrhythmic agents. The mean left ventricular ejection fraction was 15±4%. The protocol was approved by the Institutional Review Board at Washington University. Informed consent was obtained from each patient.

Three-Dimensional Intraoperative Mapping
Transmural and transseptal ventricular mapping was performed as described previously.7,9 Surface ECGs I, aVF, and V5 were monitored. Twenty minutes before explantation, 39 plunge-needle electrodes were placed in the left and right ventricles and interventricular...
Electrodes were evenly distributed. Interelectrode distance averaged 0.5 to 1.5 cm between endocardial sites, 1 to 3 cm between epicardial sites, and 2.5 to 8 mm between sites of focal initiation and immediately adjacent sites. Each electrode contained 4 bipolar pairs separated by 2.5 mm, with an interbipole distance of 500 μm. Electrograms were recorded from 156 intramural sites. Epicardial pacing plaques were sutured to the right and left ventricles. Programmed stimulation from the right and left ventricles was performed (basic cycle length, 400 ms) with single, double, and triple extrastimuli for ≤15 minutes until the donor heart arrived in the operating room. Bipolar electrograms were sampled at 2 kHz, filtered (40 to 500 Hz), amplified, digitized, and stored on a high-density recorder.7–9 The recipient heart was removed with the electrodes in place. Electrode localization (Figure 1), electrogram analysis, and construction of 3-dimensional activation maps were performed as previously described.7–9

Beats during induced or spontaneous arrhythmias were assigned a macroreentrant mechanism7–12 when (1) there was continuous depolarization from the preceding beat, (2) the site of initiation of a beat was adjacent to the site of termination of the preceding beat, and (3) the conduction velocity of the activation wave front from the site of focal initiation was 80% of the control value.

Figure 1. Diagram of heart from patient 1 demonstrating location of plunge electrodes in the left and right ventricles and interventricular septum.
of termination of the preceding beat to the site of initiation of the
ectopic beat was similar to the conduction velocity of the terminal
portion of the activation wave front of the preceding beat. A
mechanism was defined as focal7–9,12 when the site of initiation
demonstrated radial spread of activation and was remote from the
site of termination of the preceding beat with no intervening
depolarizations despite

$\frac{4}{4}$ intermediate recording sites. The finding
of a focal mechanism was not considered to exclude the possibility
of microreentry.

The coupling interval (CI) of beat n was the difference in
activation times between the initiation of beat n and that of the
preceding beat (n−1). Total activation time (TA) was the difference
between the activation times recorded at the sites of latest and
earliest activity.

Histological Analysis
After explantation and electrode localization, hearts were fixed in
formalin (including perfusion of the coronary arteries). On the basis
of analyses of the activation maps, 1×1×0.3-cm blocks of myocardium were excised from selected sites of focal activation, sites of
slow conduction and block, and sites that were neither. Paraffin-fixed
sections (12 µm thick) were cut and fixed with hematoxylin and
eosin or Masson’s trichrome stain for light microscopy.

Statistical Analysis
Data are presented as mean±SEM unless otherwise stated. Student’s
$t$ test was used to identify significant differences ($P<0.05$) in CIs or
TAs of programmed extrastimuli or induced or spontaneous ventric-
ular arrhythmias.

Results
Nineteen VTs (74 VT beats) were induced. The longest was
7 beats, and the average length was 3.9±1 beats. Electrode
density was sufficient to define the mechanism for 52 VT
beats.

Extrastimuli
Drivetrain beats (S1, S2) conducted throughout the heart with a
TA of 143±3 ms. The first, second, and third extrastimuli (S2
through S3) conducted with progressively greater conduction
delay (Figure 2) (TAs of 144±5, 166±5, and 194±5 ms,
respectively). Conduction delay during the last extrastimulus
was as high as 223 ms. Progressive delay in response to
closely coupled extrastimuli was due to slow conduction and
intramural conduction block and was observed in 58% of
cases. As illustrated in Figure 3, conduction between imme-
diately adjacent sites A (in level 3) and B' (in level 2) in
patient 2 during the last S2 beat took 53 ms. However, during
S3, S4, and S5 (S5 is shown in Figure 3), there was intramural
conduction block between sites A and B', with slow conduc-
Conduction delay between adjacent sites A and B of up to 145 ms (during S4) occurred with progressively more premature extrastimuli. In contrast, conduction between sites A and B during the first (T1) (Figure 3) and subsequent beats of VT (data not shown) was rapid.

**Maintenance of VT**

Subsequent beats of VT demonstrated a CI of 252±8 ms ($P=0.004$ versus initiating beats of VT [317±16 ms]). The TA of maintenance beats of VT averaged 127±6 ms ($P=0.376$ versus initiating beats) but ranged from 69 to 203 ms. The extent of conduction delay during VT was inversely related to the CI of the beat of VT (data not shown).

In all cases, maintenance of VT was due to focal activation often arising from multiple sites throughout the heart. Beats of VT could arise from ≥4 different subendocardial or subepicardial sites from the left or right ventricle. For example, the 7-beat VT shown in Figure 7 initiated at subepicardial site A, the next 2 beats (T2 and T3) from subepicardial site B, beats 4 through 6 (T4 through T6) from subendocardial site C in the basal left ventricle, and beat 7 (T7) from endocardial site D in the right ventricle.

In 2 instances, focal activation during the maintenance of VT arose from the midmyocardium. As shown in Figure 8, beats T4 in patient 1 initiated at midmyocardial site B and spread to adjacent subendocardial site A and subepicardial site C, as well as to adjacent sites D and E in level III and adjacent sites F in level II and G in level IV.
Termination of VT
The CI of terminating beats of VT averaged 268±16 ms (P=0.343 versus those of maintenance beats of VT). The mean TA of the terminating beats was 128±9 ms (P=0.58 versus those of maintenance beats of VT) and ranged from 64 to 195 ms. The terminal beats of VT arose in the subendocardium by a focal mechanism. As shown in Figure 9, the fifth beat of VT (T5) arose at a subendocardial site in the apex in level III, conducted basally and rightward with a TA of 156 ms, and terminated at the base of the right ventricle. The last beat of VT (T6) initiated at a subendocardial site at the base of the anterior left ventricle in level I 180 ms later by a focal mechanism; the TA of this beat was 168 ms.

Spontaneous Ventricular Arrhythmias
Holter recordings obtained from 5 patients before transplantation demonstrated PVCs (>370 beats per hour), couplets, and nonsustained VTs. During intraoperative mapping, 6 PVCs, 1 couplet, and 1 three-beat VT (a total of 11 ventricular beats) occurred spontaneously and were mapped. The ectopic beats mapped were similar in frequency and QRS morphology to those recorded (Figure 10).

Sinus beats preceding these arrhythmias initiated in the septum and conducted with a TA of 113±10 ms. The activation sequence and the TA of these sinus beats were identical to those that did not precede ventricular arrhythmias.
The mechanism of initiation could be defined for 9 of the 11 beats. In each case, initiation was due to a focal mechanism arising from the subendocardium with no evidence of reentry. The ectopic beats conducted with a TA of 138±5 ms.

The initiation of the 3-beat VT is shown in Figures 11 and 12. After termination of the preceding sinus beat (NS) in the midlateral left ventricle in level II (Figure 11), T₁ arose from an apical subendocardial site by a focal mechanism, as judged by the absence of intervening electrical activity for 665 ms from the termination of NS to the initiation of T₁ (see Figure 12). Beats T₂ and T₃ also arose by a focal mechanism from apical subendocardial sites, with T₃ initiating at the same site as T₁. Each beat terminated in the basal posterolateral left ventricle with no evidence of reentry.

Pathology
Myocardial tissues from sites of focal activation, sites of slow conduction and block, and sites that demonstrated neither focal activation nor conduction alteration were analyzed. Patchy interstitial fibrosis was a consistent finding in all hearts examined. The interstitial fibrosis predominated in the subendocardial regions and in many cases was minimal to absent in the subepicardial regions. However, in 2 patients, extensive patchy subepicardial fibrosis was noted.

Focal activation arose from a number of myocardial sites in the subendocardium and at times from subepicardial sites. These sites exhibited a variable degree of interstitial fibrosis, with some demonstrating minimal to no fibrosis (Figure 13, row 1), some showing moderate fibrosis (Figure 13, row 2), and other regions having more extensive fibrosis (Figure 13, row 3). This variability in the extent of fibrosis at initiation sites was similar to that in tissue from other sites that demonstrated neither focal initiation nor slow conduction.

A consistent finding at sites of slow conduction and nontransmural block was extensive interstitial fibrosis in continuous linear bundles extending from the subendocardium to the midmyocardium (Figure 14, row 1). This finding was not evident at adjacent sites that did not demonstrate conduction alterations or at sites from other regions without conduction delay or block. Furthermore, some sites of conduction block exhibited regions of replacement fibrosis (Figure 14, row 2) that may have contributed to the altered pattern of conduction. Subendocardial and midmyocardial sites at which nontransmural conduction block occurred during the
terminal extrastimulus were also characterized by regions (1 to 3 mm thick) of extensive replacement fibrosis (Figure 14, row 3). Analysis of fiber orientation demonstrated that conduction block occurred primarily in a direction transverse to fiber orientation.

**Discussion**

The results of this study demonstrate that PVCs and nonsustained VTs induced by programmed stimulation or occurring spontaneously in patients with end-stage IDCM initiate primarily in the subendocardium by a focal mechanism without evidence of macroreentry. Although there was evidence of functional conduction delay and block in the epicardium and on occasion in the midmyocardium and subendocardium, the sites of delay and block were consistently distant from sites of focal initiation. These findings contrast with those we reported for nonsustained and sustained VT in patients with ischemic cardiomyopathy, which initiated by intramural reentry in half the cases, suggesting that focal mechanisms play a much greater role than reentry in ventricular arrhythmias in patients with IDCM. Thus, approaches to the prevention and treatment of focal mechanisms may be beneficial.

**Spontaneous Ventricular Arrhythmias**

We mapped spontaneously occurring PVCs, couplets, and beats of VT that were similar in frequency and QRS morphology to those documented by Holter monitoring. We and others have demonstrated that insertion of needle electrodes does not lead to spontaneous ectopy. Thus, the arrhythmias mapped are representative of those that these patients experienced clinically and provide the first demonstration of electrophysiological mechanisms of spontaneous PVCs and VT in the human heart. Our finding that these arrhythmias initiated by a focal mechanism is consistent with our recent observation that spontaneous PVCs and VT initiate by a nonreentrant mechanism in a rabbit model of nonischemic cardiomyopathy.

**Focal Mechanisms**

Although focal initiation arises primarily in the subendocardium, initiation of some beats in the epicardium (Figure 6) suggests that focal activation does not necessarily arise from Purkinje fibers. Furthermore, the finding that VT initiates sometimes in the midmyocardium (Figure 8) suggests, albeit indirectly, that focal activation could arise from M cells. The focal mechanism observed in this study is similar to that...
underlying nonsustained and sustained monomorphic VT in patients with coronary artery disease.

The nature of the focal mechanism remains unknown. Although microreentry is possible, our results suggest that this is unlikely. In all cases, the sites of termination and the sites of initiation of the subsequent beats were distant from each other and separated by a number of intermediate transmural recording sites that demonstrated no electrical activity in the intervening time interval. In addition, activation from sites of focal initiation propagated radially and rapidly with no evidence of conduction slowing to adjacent electrode sites that were an average of 2.5 to 8 mm away. On the basis of the refractory properties of the myocardium, the presence of a microreentrant circuit small enough that it would not be detected by our mapping technique (path length <1.5 cm) would require conduction velocities an order of magnitude slower than the slowest velocities we observed. We have found that the sites of focal activation of VT frequently vary from beat to beat, but sites of focal activation never occurred at sites of early breakthrough during sinus rhythm. Thus, bundle-branch reentry is unlikely.

The focal initiation of VT may result from triggered activity arising from either EADs or DADs. Myocardium from patients with end-stage heart failure demonstrates prolongation of action potential duration (likely the result of decreases in the transient outward current and delayed rectifier current) that could contribute to EADs. Moreover, superfused trabeculae and isolated cardiac myocytes from patients with heart failure exhibit alterations in calcium flux, including increased diastolic levels of intracellular calcium, abnormal sarcoplasmic reticulum calcium uptake, decreased expression of sarcoplasmic reticulum calcium ATPase, and more recently increased expression of sodium-calcium exchange. These alterations may contribute to elevations in intracellular calcium, activation of a transient inward current, and development of DADs that have been demonstrated in vitro.

Anatomic-Electrophysiological Comparison

No clear histological substrate characterized the sites of focal initiation. The degree of interstitial and replacement fibrosis was quite variable. These findings in the human heart are similar to those in a rabbit model of nonischemic heart failure.

Our findings of conduction slowing and block expand on the results of Anderson et al. In their study, mapping limited to 64 sites over a portion of the epicardium of the left ventricle was performed in patients with IDCM. Consequently, the extent of conduction delay during extrastimuli and beats of VT was underestimated, the contribution of intramural conduction and conduction block could not be assessed, and arrhythmia mechanisms could not be defined. Using 3-dimensional mapping, we found marked intramural conduction delay in some but not all hearts from our patients with IDCM. However, we found that marked conduction...
delay consistently occurred distant from sites at which subsequent beats of VT initiated and did not contribute to the initiation of the VTs mapped. Slow conduction and block could ultimately contribute to sustained VT or the transition to ventricular fibrillation, given that 3-dimensional mapping of the transition from VT to ventricular fibrillation under a variety of pathophysiological conditions\textsuperscript{10} has demonstrated that acceleration of VT (whether caused by reentrant or nonreentrant mechanisms) leads to the development of multiple, simultaneous intramural reentrant circuits that are the hallmark of ventricular fibrillation.

**Study Limitations**
Spatial resolution of the electrodes and the time available for mapping limited the volume of data recorded. However, spatial resolution was sufficient to delineate the mechanism for 52 of 74 beats of VT and was comparable to that in our previous studies.\textsuperscript{7-9} In those studies, we were able to define the mechanisms of arrhythmias in patients and to define intramural reentrant circuits in the left and right ventricles and interventricular septum as small as 1.5 cm in diameter. In the present study, a similar 15-minute interval was sufficient to induce 19 VTs in these 6 patients and record spontaneously occurring ventricular arrhythmias.

Although nonsustained VT was induced in 3 of the 6 patients, sustained VT was induced in none. There are 2 possible explanations. First, the period of programmed stimulation (1 cycle length, no isoproterenol) was inadequate to initiate sustained VT. Second, only 1 patient with IDCIM in this study had a prior history of syncope, and none had sustained VT. Sustained VT is induced by programmed stimulation in \textasciitilde15\% of patients with nonischemic cardiomyopathy,\textsuperscript{19} whereas nearly one half of all patients with cardiomyopathy will ultimately suffer sudden death.\textsuperscript{2} The induction

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**Figure 11.** Three-dimensional activation sequences of sinus beat and subsequent spontaneous 3-beat VT from patient 3. Calibration bar=300 ms.
of nonsustained VT, although not predictive of the development of sustained VT, nonetheless characterizes an electrophysiological-anatomic substrate7–9 ultimately leading to sudden death in many of these patients. In addition, in patients with severe heart failure, spontaneously occurring nonsustained VT is an independent marker of increased mortality and sudden death, and the absence of nonsustained VT indicates a low probability of sudden death.20 All the patients in the present study had nonsustained VT clinically.

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Beat S4 preceding 5-beat VT (level II) in patient 2. Row 3, Beat S4 preceding 3-beat VT from patient 1. Row 3, Beat T2 (level IV) of 3-beat VT from patient 2. Right, Corresponding photomicrographs of trichrome-stained sections of myocardium in vicinity of focal initiation sites demonstrating minimal conduction block. Sections in rows 1 through 3 demonstrate extensive nontransmural interstitial and replacement fibrosis at subendocardial (rows 1 and 2) and midmyocardial (row 3) sites of conduction block.

References


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