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 S4) 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 arrhythmias and are at increased risk of sudden death from ventricular tachycardia (VT) and ventricular fibrillation. Treatment with pharmacological agents has been empirical, ineffective, and frequently proarrhythmic and limited by the paucity of data on electrophysiological mechanisms.

Myocardium from patients with IDCM demonstrates altered epicardial conduction, 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.

We have previously performed 3-dimensional cardiac mapping in patients with coronary artery disease undergoing surgical ablation of VT. 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. Surface ECGs I, aVF, and V₅₆ 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

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**Figure 1.** Diagram of heart from patient 1 demonstrating location of plunge electrodes in the left and right ventricles and interventricular septum.

**Figure 2.** CI versus TA (in ms) for each extrastimulus (S2 ▲, S3 ■, and S4 ○ and first beat of induced VT [T1] ◆) for patients 2 (top) and 6 (bottom).

SuVT indicates sustained VT; NSVT, nonsustained VT.
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 ≥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 ventricular 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) conducted throughout the heart with a TA of 143±3 ms. The first, second, and third extrastimuli (S₂ through S₄) 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 immediately adjacent sites A (in level 3) and B’ (in level 2) in patient 2 during the last S₁ beat took 53 ms. However, during S₂, S₃, and S₄ (S₄ is shown in Figure 3), there was intramural conduction block between sites A and B’, with slow conduc-
As shown in Figure 4, S₄ initiated at a subendocardial site in the apex (level III). Activation spread basally, terminating at a subendocardial site in the base of the lateral left ventricle with a TA of 159 ms. T₁ initiated at an endocardial site in the apex in level III 142 ms later, with no intervening electrical activity. This observation is also shown in Figure 5, in which the site of terminal activation of S₄ is labeled A and the site of initiation of T₁ is denoted as S; there was no intervening electrical activity at intramural sites B-R or any other site in the heart.

In 5 VTs, T₁ arose focally in the subepicardium. In each instance, the initiation site was the same as the site of earliest activation for S₄ (located 3 to 5 mm away from the left ventricular epicardial pacing plaque). As shown in Figure 6, S₄ initiated in the apical subepicardium in level IV and propagated basally, terminating 200 ms later at the base of the left ventricle. T₁ arose at the same apical epicardial site as S₄ by a focal mechanism with no intervening electrical activity from the termination of S₄ to the initiation of T₁. Spread of activation to immediately adjacent (2.5 to 8 mm) intramural electrodes was rapid with no evidence of slow conduction, fractionation, or conduction block.

The T₁s conducted with a TA of 118±9 ms, significantly less than that of the preceding terminal extrastimulus (186±8 ms, P<0.001), and a prolonged CI of 317±16 ms. As Figure 2 shows, the extent of conduction delay of T₁ varied among patients but was inversely related to its CI. Even areas of marked conduction delay and intramural block during the extrastimuli demonstrated rapid activation during the late coupled initiating beat of VT. In Figure 3, T₁ initiated by a focal mechanism at a CI of 362 ms. In contrast to the marked conduction delay (TA, 216 ms) and block between A and B during S₄, conduction during T₁ was rapid (TA, 73 ms) with no block between A and B’.

**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, beat T₇ 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.

**Initiation of VT by Programmed Stimulation**

All the VTs initiated in the subendocardium or the subepicardium by a focal mechanism on the basis of the absence of intervening electrical activity between the termination of the preceding beat and the initiation of the next (123±31 ms). In every case, the site of focal initiation was surrounded on all sides by closely adjacent electrodes.
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 ($T_5$) 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 ($T_6$) 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 ($\approx370$ 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

Figure 6. Activation sequence of third extrastimulus (S3) and first beat of 3-beat VT induced in patient 1. S3 initiates (†) at subepicardial site in apex and propagates basally. After termination of S3 in posterolateral base of left ventricle (+), first beat of VT (T1) initiates (†) by focal mechanism at same apical epicardial site in level IV where S3 initiated. Calibration bar=300 ms.

Figure 7. Top, Surface ECG of last drivetrain beat (S1), 3 extrastimuli (S2 through S4), and 7 beats of VT induced in patient 1. A through D represent sites of initiation for each beat. Bottom, Diagram of heart showing location of initiation sites A through D. Beats T1 through T6 initiated by focal mechanism. Calibration bar=300 ms.
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 nonsus-
tained VTs induced by programmed stimulation or occurring
spontaneously in patients with end-stage IDCM initiate pri-
marily 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 re-
ported 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 arrhyth-
mias in patients with IDCM. Thus, approaches to the preven-
tion 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 mor-
phology 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 demon-
stration 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 nonische-
ic cardiomyopathy.

Focal Mechanisms
Although focal initiation arises primarily in the subendocar-
di um, 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

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Figure 8. Top, Surface ECG of 3-beat VT induced in patient 1. Box highlights third beat of VT whose
activation map and electrograms are shown at bottom. Middle, Activation map of level III for beat
T3 with site of initiation (*) in the midmyocardial and schematic of level III with selected sites A
through E whose electrograms are shown below. Bottom, Bipolar electrograms for sites A through
E demonstrating initiation of T3 at midmyocardial site B followed by subsequent activation at sites
A and C through E, as well as adjacent basal site F (in level II) and adjacent apical site G (in level
IV). Calibration bar = 300 ms.
underlying nonsustained \(^8,9\) and sustained monomorphic VT \(^7\) 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.\(^{15}\) 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\(^{16}\) ) that could contribute to EADs.\(^6\) 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,\(^{17}\) and more recently increased expression of sodium-calcium exchange.\(^{18}\) 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.\(^5,17\)

**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.\(^{11}\)

Our findings of conduction slowing and block expand on the results of Anderson et al.\(^3\) 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 in specific areas was associated with the presence of microreentrant circuits in some hearts.
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 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. 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 IDCM in this study had a prior history of syncope, and none had sustained VT. Sustained VT is induced by programmed stimulation in ≈15% of patients with nonischemic cardiomyopathy, whereas nearly one half of all patients with cardiomyopathy will ultimately suffer sudden death. 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 substrate\(^7\)\(^–\)\(^9\) 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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![Diagram](image-url)
References


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