Modulated dispersion of activation and repolarization by premature beats in patients with cardiomyopathy at risk of sudden death

Anandaraja Subramanian, Adrian Suszko, Raja J. Selvaraj, Kumaraswamy Nanthakumar, Joan Ivanov, and Vijay S. Chauhan
Division of Cardiology, University Health Network, Toronto, Canada
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FREQUENT PREMATURE VENTRICULAR beats are associated with an increased risk of sudden cardiac death in patients with left ventricular dysfunction (18). Critically timed premature beats can initiate ventricular tachycardia and fibrillation by providing a depolarizing trigger during the vulnerable period of cardiac repolarization. Premature beats can also modulate activation and repolarization gradients, creating zones of slow conduction and prolonged refractoriness, leading to unidirectional conduction block and reentry (8, 11). These gradients have been evaluated in response to programmed ventricular extrastimulation in patients with preserved ventricular function along the endocardium (9, 15, 24, 25) and the epicardium during intraoperative mapping (7, 17). Based on these clinical studies, repolarization heterogeneity is minimized by the close coupling of activation to repolarization along the propagating wavefront, and premature beats increase repolarization dispersion by reducing activation-repolarization coupling. Activation time and repolarization time restitution further interact with activation-repolarization coupling to alter repolarization dispersion in these patients (9). Unlike normal hearts, activation and repolarization dynamics in response to extrastimuli have not been studied in the patients with cardiomyopathy, particularly those at risk of sudden death. The myopathic human heart exhibits nonuniform electrical remodeling with altered repolarization reserve (1, 13, 14, 16, 28).

Therefore, we sought to determine the effect of premature ventricular beats on activation and repolarization dispersion along a propagating wavefront in conscious patients with cardiomyopathy at increased risk of sudden death. High-risk patients were selected based on inducible ventricular tachycardia and fibrillation programmed stimulation or the presence of microvolt T wave alternans, which are markers for arrhythmic events and death (3, 6). We further sought to evaluate the contribution of activation-repolarization coupling and restitution in premature beat-modulated dispersion in these patients.

MATERIALS AND METHODS

Study population. Patients with left ventricular (L.V) ejection fraction <40% by echocardiography or radionuclide angiography were considered for the study if they were undergoing invasive electrophysiology testing for prophylactic defibrillator risk stratification. The electrophysiology study was performed in the postabsorptive state after all antiarrhythmic drugs were discontinued for 5 half-lives and consisted of microvolt T wave alternans evaluation and/or programmed ventricular stimulation. The Heartwave system (Cambridge Heart, Bedford, MA) was used to evaluate microvolt T wave alternans during atrial pacing at cycle length (CL) 600, 550, and 500 ms for 5 min at each CL. Programmed ventricular stimulation was performed from the right ventricular (RV) apex using up to three extrastimuli at two drive CL. Only those patients with positive microvolt T wave alternans at pacing CL of 550 ms (based on the Cambridge Heart criteria) (2) or inducible ventricular tachycardia (with up to 3 extrastimuli) or ventricular fibrillation (with up to 2 extrastimuli) were considered high risk and included in the study. Patients were excluded for the following reasons: 1) NYHA IV, 2) unstable angina, 3) class I or III antiarrhythmic medications, 4) myocardial infarction within one month, 5) revascularization within three months, or 6) atrial fibrillation. The study was approved by the research ethics board at Mount Sinai Hospital, Toronto, and all patients provided written consent.

Intracardiac recording. Following the clinical electrophysiology study, a quadripolar pacing catheter ( Biosense Webster, Diamond Bar, CA) was placed in the RV apex for programmed ventricular stimulation (Fig. 1). Two multielectrode catheters were then positioned in proximity to and remote from the pacing catheter to evaluate activation and repolarization dynamics across a broad region of the heart during programmed stimulation. Access to these recording sites was

Address for reprint requests and other correspondence: V. S. Chauhan, PMCC 3-522, Toronto General Hospital, 150 Gerrard St. W., Toronto, ON M5G 2C4, Canada (e-mail: vijay.chauhan@uhn.on.ca).
limited to the right heart because of ethical considerations, since arterial instrumentation was not clinically indicated. Recordings near the pacing site were made with a 10-pole catheter (Livewire; St. Jude Medical, Minnetonka, MN) positioned percutaneously along the anteroseptal RV endocardium. Recordings remote from the pacing site were achieved with a 16-pole catheter (Pathfinder; Cardima, Fremont, CA) advanced percutaneously in the coronary sinus via a guide sheath (Shuttle; Bard) in the great cardiac vein over the LV epicardium. For the research study, programmed ventricular stimulation was performed at a pulse width of 2 ms and stimulus strength of 2$\times$ diastolic threshold. Following a 5-min stabilization period of constant RV apical pacing at CL 500 ms, single ventricular extrastimuli (S2) were delivered after a drive train of 10 beats (S1) at a CL of 500 ms. The S1S2 coupling interval was decremented by 20 ms from 400 to 300 ms, followed by 10 ms from 300 ms down to the effective refractory period.

**Activation and repolarization evaluation.** Unipolar electrograms (0.05–500 Hz, 1,000-Hz sampling rate) were simultaneously recorded from the 16-pole and 10-pole catheters during programmed ventricular stimulation. Local activation time (AT) of the extrastimulus was defined as the minimum dV/dt of the unipolar QRS complex. Local repolarization time was defined according to the modified Wyatt method as the minimum dV/dt of the upright unipolar T wave or maximum dV/dt of the inverted unipolar T wave. For biphasic T waves, local repolarization was computed from the midpoint between the two phases of the T wave (20, 24, 25). Although Coronel et al. (5) have argued that the original Wyatt method more accurately measures the end of local repolarization in isolated pig hearts, in vivo human studies (4, 26) have consistently shown significant underestimation with this method when the T wave is positive. In these studies, the modified Wyatt method provided better correlation with monophasic action potential duration (MAP$_{90}$) than the original Wyatt method, so the former approach continues to be implemented to define the local repolarization in humans (10). The activation repolarization interval (ARI) provided an estimate of action potential duration, measured from local activation to local repolarization, and has been validated previously (4). The AT was defined as the interval from the pacing stimulus to local activation. Total repolarization time (TRT) was computed as the sum of AT and ARI. The diastolic interval (DI) was calculated from local repolarization of the last drive train beat to local activation of the extrastimulus beat. For tightly coupled S1S2 where local repolarization of the last drive train beat could not be reliably annotated, local repolarization of the penultimate drive train beat was used instead (Fig. 2) (20). Analysis was only performed for drive trains without contaminating spontaneous ectopic beats. Extrastimuli with low-amplitude T wave or ST segment elevation without discernable T wave upstroke were also excluded because local repolarization times could not be determined reliably.

Dispersion of the AT, ARI, and TRT was calculated separately as the difference between the maximum and the minimum value and normalized to the distance over which the recordings were made. The 16 unipolar epicardial electrograms and the 10 unipolar endocardial electrograms were recorded over a distance of 58 and 30 mm, respectively. For each S1S2 coupling interval, activation-repolariza-
tion coupling was evaluated from the linear regression slope of the AT vs. ARI relationship. A slope of −1 implied complete coupling, and slopes less negative or more negative than −1 indicated reduced activation-repolarization coupling.

AT restitution was evaluated from the AT vs. DI relationship fitted to the monoeponential function, $AT = a \cdot \exp(-DI/\tau) + b$, where $a$ and $b$ are regression coefficients, and $\tau$ is the time constant. The restitution slope ($AT_{RI}$) was derived from this monoeponential function at the minimum DI ($DI_{min}$) as follows: $AT_{RI} = -a/\tau \cdot \exp(-DI_{min}/\tau)$. AT restitution slope heterogeneity was defined by the range of AT restitution slopes. ARI restitution was characterized by plotting ARI vs. DI, and the restitution slope was defined as the steepest linear slope of a moving 40-ms window containing at least three points (20, 22, 25). ARI restitution slope heterogeneity was represented by the range of ARI restitution slopes.

Statistical analysis. SAS Version 8.2 (SAS Institute, Cary, NC) was used for all data analyses. Continuous variables are reported as means ± SE. Categorical variables are reported as frequencies. The relationship between dependent variables and S1S2 coupling intervals was evaluated for each recording site by linear regression and a one-way ANOVA. If the one-way ANOVA was significant, Scheffé's post hoc tests were used to test the differences between coupling intervals. A repeated-measures analysis of covariance was used to test the main effects (early/late activated site, S1S2 coupling interval, and the interaction of site-coupling interval). If there was a significant interaction, post hoc t-tests were used to identify the coupling intervals with significant differences between sites. Statistical significance was established with a two-tailed $P$ value ≤0.05.

RESULTS

Study population. The study was completed in 15 patients; however, 4 patients were excluded because of poor-quality intracardiac electrogram recordings [prominent atrial pacing artifact interrupting unipolar T wave ($n = 2$), low amplitude unipolar T waves ($n = 2$)]. Another four patients were excluded because of frequently induced ventricular beats following the programmed extrastimulus, which precluded reliable annotation of S2’s local repolarization. Thus the study population included seven patients (57 ± 10 yr, 6 males) with an LV ejection fraction of 31 ± 7% (Table 1). The etiology of cardiomyopathy was ischemic ($n = 4$) and nonischemic ($n = 3$). Unipolar electrogram recordings were analyzed from a total of 70 early sites and 112 late sites in these patients. Only electrograms that were free of artifact and suitable for measurement of the local AT and repolarization time without ambiguity were included in the final analysis, which totaled 67 early and 103 late sites.

AT, ARI, and TRT intervals. During the basic RV apical drive train of 500 ms, the mean AT of the 16 LV epicardial recording sites was longer than that of the 10 RV endocardial sites (115 ± 15 vs. 38 ± 4 ms, $P = 0.0027$), consistent with activation from the RV endocardium to LV epicardium. The mean ARI of the late activated sites was shorter compared with the early activated sites (255 ± 15 vs. 306 ± 6 ms, $P = 0.0059$). RV apical effective refractory period was 224 ± 6 ms.

The relationship of mean AT, ARI, and TRT as a function of the S1S2 coupling interval is shown separately for early and late sites in Fig. 3. In the case of early sites, shorter S1S2 increased AT (36 ± 4 to 68 ± 7 ms, $P < 0.0001$), decreased ARI (301 ± 5 to 249 ± 17 ms, $P < 0.0001$), and decreased TRT (337 ± 7 to 317 ± 20 ms, $P < 0.0003$). At late sites, AT increased (113 ± 15 vs. 148 ± 30 ms, $P = 0.02$) and ARI decreased (244 ± 13 vs. 228 ± 18 ms, $P = 0.039$) with shorter coupling intervals. However, unlike early sites, there was no significant change in TRT with S1S2 shortening (358 ± 10 vs. 376 ± 26 ms, $P = 0.32$).

AT, ARI, and TRT dispersion. During the basic drive train of 500 ms, normalized AT dispersion was larger in early than late sites (1.0 ± 0.1 vs. 0.6 ± 0.1 ms/mm, $P < 0.05$). In contrast, no differences were evident between early and late sites with respect to normalized ARI dispersion (0.5 ± 0.1 vs. 0.8 ± 0.2 ms/mm, $P = 0.11$) or TRT dispersion (1.0 ± 0.2 vs. 0.8 ± 0.1 ms/mm, $P = 0.17$). Figure 4 shows the normalized dispersion data for early and late sites in response to ventricular extrastimuli. AT dispersion remained fairly constant along early and late sites at long coupling intervals (400–300 ms), and AT dispersion at early sites remained larger. However, at tighter coupling intervals (300–240 ms), AT dispersion at early sites progressively increased while there was minimal change at late sites. Across all coupling intervals from 400 to 240 ms, AT dispersion was significantly greater at early compared with late sites.

ARI dispersion did not significantly increase at early or late sites with shorter coupling intervals, and there was no difference in ARI dispersion between early and late sites when all coupling intervals were considered.

TRT dispersion increased significantly along early sites at tighter coupling intervals, with more than a twofold increase between a coupling interval of 400 and 240 ms. In contrast, there was minimal change in TRT dispersion along late sites. At all coupling intervals, TRT dispersion at early sites was significantly greater than at late sites.

AT-ARI coupling. To account for the differences in TRT dispersion between early and late sites at short coupling intervals, the AT-ARI relationship, as a measure of activation repolarization coupling, was evaluated. The AT-ARI slopes during the basic drive train of 500 ms were −0.3 ± 0.2 and −1.1 ± 0.3 for early and late sites, respectively. The AT-ARI relationship at long, mid, and short coupling intervals is shown in Fig. 5 for a representative study patient, and summary data

### Table 1. Patient Characteristics

<table>
<thead>
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<th>Patient No.</th>
<th>Age, yr</th>
<th>Gender</th>
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<td>55</td>
<td>F</td>
<td>39</td>
<td>Ischemic</td>
<td>Yes</td>
<td>Negative</td>
</tr>
</tbody>
</table>

LVEF, left ventricular ejection fraction; VT, ventricular tachycardia; TWA, microvolt T wave alternans; M, male; F, female.
for all patients are presented in Fig. 6. At long coupling intervals of 400–360 ms, AT-ARI slopes were significantly different between early (−0.4 ± 0.1 (S1S2 400 ms) to +0.04 ± 0.2 (S1S2 240 ms)) and late (−1.5 ± 0.2 (S1S2 400 ms) to +0.3 ± 0.2 (S1S2 240 ms)) sites, particularly at 240–260 ms and became greater than zero. When all coupling intervals were compared, there was no significant difference in AT-ARI slopes between early [−0.4 ± 0.1 (S1S2 400 ms) to +0.04 ± 0.2 (S1S2 240 ms)] and late [−1.5 ± 0.2 (S1S2 400 ms) to +0.3 ± 0.2 (S1S2 240 ms)] sites, particularly at

Fig. 3. Comparison of mean AT (A), activation-recovery interval (ARI, B), and total repolarization time (TRT, C) for early vs. late activated sites in response to increasing prematurity of extrastimulus.

Fig. 4. Comparison of normalized AT (A), ARI (B), and TRT dispersion (C) for early vs. late activated sites in response to increasing prematurity of extrastimulus.
coupling intervals <300 ms when normalized TRT dispersion was greater at early sites.

AT and ARI restitution. AT rose steeply over a short DI range in all recording sites, and AT restitution fit well to a monoexponential function (early sites $R^2 0.79 \pm 0.02$, late sites $R^2 0.82 \pm 0.03$). In Fig. 7A, AT restitution is compared between base and apex along early and late sites for one study patient, showing no difference in the slopes. In all patients, mean AT restitution slopes were similar between early and late sites ($-3.5 \pm 0.7$ vs. $-4.9 \pm 1.5$, $P = 0.18$) (Fig. 7B). Furthermore, there was no difference in AT restitution slope heterogeneity between early and late sites ($4.3 \pm 0.9$ vs. $5.5 \pm 1.7$, $P = 0.35$) (Fig. 7C).

Figure 8A shows ARI restitution for one patient showing steeper slopes at the apex and at early sites. The steeper ARI restitution at these sites is related to shorter minimum DIs. Among all patients, early sites had larger mean ARI restitution slopes ($1.3 \pm 0.6$ vs. $0.8 \pm 0.6$, $P = 0.03$) (Fig. 8B) and proportionately more sites with slopes greater than one (59 vs. 20%, $P < 0.01$) compared with late sites. Steeper ARI restitution at early sites was associated with shorter minimum DIs (more negative) compared with late sites ($-25 \pm 8$ vs. $32 \pm 28$ ms, $P = 0.002$). The ARI restitution slope heterogeneity was evaluated separately for early and late sites, and slopes increased significantly from apex to base. However, mean ARI restitution slope heterogeneity did not differ between early and late sites (Fig. 8C).

DISCUSSION

The main finding of our study is that high-risk cardiomyopathy patients manifest increased repolarization (TRT) heterogeneity in response to tightly coupled extrastimuli, which is primarily due to increased AT dispersion and reduced activation-repolarization coupling while being less dependent on ARI dispersion. The increase in repolarization heterogeneity is more marked in proximity to the origin of the extrastimulus, where AT dispersion is augmented to a greater extent, than at late activated sites. Premature beats have been shown to modulate activation and repolarization gradients in the normal guinea pig heart (11, 12) and in humans with preserved ventricular function (7, 9, 24, 25). Our study extends these
observations to patients with moderate to severe LV dysfunction and further contrast activation-repolarization dynamics between early vs. late activated sites, which has not been reported previously.

The interplay between activation and repolarization is complex. With RV apical pacing, activation propagated in all patients from RV endocardium to LV epicardium, and from apex to base. During the basic drive train of 500 ms, normalized AT dispersion was already greater along the RV endocardium than LV epicardium. Because the steep portion of conduction velocity restitution is not invoked at this stable low heart rate, the differences in AT dispersion are due to the relative proximity of the RV endocardial recording electrodes to the pacing site. As activation propagates from the pacing site, local activation delays summate to generate a cumulative delay along the propagating pathway. Hanson et al. (9) also noted that the majority of the increase in AT occurred between the pacing site in the RV and the earliest activated site in the LV with a relatively small further increase during propagation over the LV endocardium in patients with structurally normal hearts. With shorter coupling intervals, the activation delay along the RV endocardium in our patients increased further and to a greater extent than the more distant LV epicardium. AT dispersion can also be influenced by heterogeneity in conduction velocity restitution, particularly when the DI preceding the premature beat is sufficiently short to engage the steep portion of the restitution curve (9). Although we did not measure conduction velocity restitution, we did find similar AT restitution heterogeneity between the RV endocardium and LV epicardium. Thus, AT restitution heterogeneity alone did not account for the differences in AT dispersion between the early and late activated sites.

Normalized ARI dispersion did not change at early or late sites, nor did it differ between early and late sites during extrastimulus testing. Because ARI is dependent on the preceding DI, which in turn is dependent on local AT, the effect
of extrastimuli on ARI dispersion requires analysis of local ARI restitution and ARI restitution heterogeneity. We found steeper ARI restitution slopes at the apex compared with the base because of shorter minimum DIs at the apex. The dependence of ARI restitution slope on the minimum DI in patients with cardiomyopathy has previously been reported by our group (19, 20) and subsequently verified in patients with preserved LV function by Hanson et al. (9). With tightly coupled S1S2, conduction velocity is reduced and activation of more distant basal sites is delayed, thereby producing longer minimum DIs and flatter ARI restitution curves. For the same reason, ARI restitution slopes are shallower at late activated epicardial sites compared with early endocardial sites. The presence of an apicobasal gradient in ARI restitution slopes minimizes any increase in ARI dispersion in response to tightly coupled extrastimuli. Because this restitution gradient is similar between early and late activated sites, their ARI dispersion is also comparable.

ARI and its rate adaptation can also be influenced by the local tissue complement of ion channels, which are known to differ between the RV/LV, apex/base, and endocardium/epicardium. For instance, greater transient outward current (Ito) in the human epicardium is responsible for shorter action potential duration and shallower action potential duration restitution when measured in an LV wedge preparation (16). Szentafrasszy et al. (21) also demonstrated shorter action potential duration in human myocytes isolated from the LV apex compared with base, associated with less slow delayed rectifier current (Iks) and Ito. In our patients, epicardial ARI was shorter than endocardial ARI during basic pacing. Although ARI restitution was measured at these sites, it was not assessed locally with LV epicardial pacing.

With shorter S1S2 coupling, larger AT dispersion at early sites contributed to larger TRT dispersion. In humans with preserved ventricular function, TRT is also dependent on activation-repolarization coupling, such that reduced coupling increases TRT dispersion when measured during steady-state pacing (7, 9, 24, 25). We evaluated coupling by measuring the slope of the AT-ARI relationship, and a slope deviating from −1 indicated less coupling (7, 26). During the basic drive in our patients, the AT-ARI slope at early sites (−0.5) deviated to the same extent from −1 as the AT-ARI slope of late sites (−1.5), thereby producing similar TRT dispersion. With tighter extrastimuli, activation-repolarization uncoupled to a similar extent at early and late sites, and in some patients the slope of the AT-ARI relationship became positive. In patients with preserved ventricular function, a decrease in the AT-ARI slope has also been reported with increasing prematurity of extrastimuli, associated with an increase in TRT dispersion (9, 24). However, the magnitude of change in AT-ARI slope and
activation-repolarization coupling. Our study patients, how-
with cardiomyopathy, and the contribution of restitution and
not the purpose of the present study, which aimed to elucidate
the present study. Although this might provide information
were shown, nor was a group of low-risk patients included in
proximity to the pacing site. Finally, no clinical follow-up data
pacing, for instance, we speculate that TRT would become
and other pacing sites were not considered. With LV epicardial
stimulation, in which global mapping would not be applicable.
Risk stratification with right atrial and/or RV programmed
balloon array (25) or multielectrode epicardial sock (17).
LV mapping has been performed in patients using a noncontact
ment of the endocardium and epicardium. More global RV or
which can be sizable in the myopathic heart.
curve (19, 20). Thus the apparent heterogeneity in ARI resti-
tion with markedly reduced activation-repolarization cou-
reentrant arrhythmias (15, 23, 27). By extrapolation, critically
timed spontaneous PVCs arising in the RV may also create
similar proarrhythmic substrate, and further trigger reentry.
These gradients are not necessarily dependent on the intrinsic
heterogeneity in action potential duration or restitution in the
myopathic human heart, but it is possible that nonuniform
regional electrical remodeling may further augment the repo-
larization gradients created by wave propagation. Our results
also have important implications in the interpretation of remote
vs. local restitution kinetics in humans (17, 25). ARI restitution
slopes measured remotely from the site of pacing may be less
than those measured locally due to activation delay that length-
en the minimum DI, and effectively truncates the restitution
curve (19, 20). Thus the apparent heterogeneity in ARI resti-
tution slopes measured using a single remote pacing site may be
influenced by differences in activation delay to local sites,
which can be sizable in the myopathic heart.

Limitations. We recorded electrograms along a single seg-
ment of the endocardium and epicardium. More global RV or
LV mapping has been performed in patients using a noncontact
balloon array (25) or multielectrode epicardial sock (17).
However, our cardiomyopathy patients only required clinical
risk stratification with right atrial and/or RV programmed
stimulation, in which global mapping would not be applicable.
For the same reason, transmural recordings were not obtained,
which may be relevant in defining transmural repolarization
gradients that have been shown to develop experimentally in
response to premature beats. Nonetheless, we did perform high-density mapping with 26 recording sites in proximity to
the pacing site, which permitted high spatial resolution of
activation and repolarization gradients in this region. Second,
extrastimuli were delivered from the RV apical endocardium,
and other pacing sites were not considered. With LV epicardial
pacing, for instance, we speculate that TRT would become
larger in the epicardium because of greater AT dispersion in
proximity to the pacing site. Finally, no clinical follow-up data
were shown, nor was a group of low-risk patients included in
the present study. Although this might provide information about the prognostic value of modulated dispersion, this was
not the purpose of the present study, which aimed to elucidate
the effect of ventricular premature beats on activation/repolar-
dition dispersion along a propagating wavefront in patients
with cardiomyopathy, and the contribution of restitution and
activation-repolarization coupling. Our study patients, how-
ever, were all at risk for sudden death by virtue of their
moderate to severe ventricular dysfunction, inducible ventric-
ular arrhythmias, and/or positive T wave alternans.
In conclusion, in high-risk cardiomyopathy patients, repo-
larization (TRT) heterogeneity increases in response to closely
coupled RV extrastimuli, which may provide the substrate for
reentrant arrhythmias. This is primarily because of augmented
AT dispersion in proximity to the origin of pacing, in combi-
nation with markedly reduced activation-repolarization cou-
pling. These findings support the modulated dispersion hypoth-
esis in patients with LV dysfunction and suggest that PVC-
induced ventricular arrhythmias are more likely to arise near
the PVC origin.

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DISCLOSURES
Conflicts of Interest: none.

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