Adrenergic stimulation increases repolarization dispersion and reduces activation–repolarization coupling along the RV endocardium of patients with cardiomyopathy

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Aims

Dispersion of repolarization (DOR) in the human heart is minimized by activation–repolarization coupling. Adrenergic stimulation can be proarrhythmic in patients with impaired left-ventricular function and its effect on repolarization dispersion has not been systematically investigated. Our objective was to study the effect of dobutamine on repolarization dispersion and activation–repolarization coupling in patients with cardiomyopathy.

Methods and results

Activation recovery intervals (ARI) and activation times (AT) were measured from unipolar electrograms at 10 sites along the apicobasal right ventricle (RV) in 14 patients with cardiomyopathy (LVEF < 40%). These measurements were made during control, dobutamine 2.5–5.0 μg/kg/min, and a recontrol phase while maintaining constant heart rates with atrial pacing. Dispersion of repolarization was calculated from the total recovery time (TRT, AT + ARI). Activation–repolarization coupling was assessed by linear regression of ARI and AT. Dispersion of repolarization across all 10 sites and between adjacent sites increased with dobutamine compared with control (whole DOR: range 15 ± 2 vs. 12 ± 2 ms, P = 0.06 and standard deviation 5.5 ± 0.9 vs. 4.3 ± 0.9 ms, P = 0.04; adjacent DOR: 5.9 ± 0.8 vs. 4.5 ± 0.6 ms, P = 0.04). This was associated with shallower ARI/AT slopes (2 ± 0.3 vs. 2 ± 0.8, P = 0.05) and a decrease in ARI–AT correlation (R² 0.4 ± 0.1 vs. 0.6 ± 0.1, P = 0.05) with dobutamine compared with control.

Conclusion

Adrenergic stimulation increases apicobasal RV DOR and reduces coupling between activation and repolarization in patients with cardiomyopathy. This may provide a mechanism for the proarrhythmic potential of heightened adrenergic states in these patients.

Keywords

Repolarization dispersion • Activation repolarization coupling • Adrenergic stimulation • Cardiomyopathy

Introduction

The repolarization moment is nearly synchronous in the normal heart and an increase in the dispersion of repolarization (DOR) can form the substrate for ventricular arrhythmias. Dispersion of repolarization is minimized by the dependence of action potential durations (APD) on the sequence of activation such that regions activated earliest tend to have longer APD while those activated latest have shorter APD. Activation–repolarization coupling in this manner has been demonstrated in patients with preserved ventricular function3–5 and in those with cardiomyopathy at low risk of ventricular arrhythmias.6 However, certain disease states such as ventricular hypertrophy,7 arrhythmogenic infarcted myocardium,6,8 or therapeutic LV epicardial pacing9 can reduce activation–repolarization coupling. Under these circumstances, DOR may increase significantly, creating the substrate for reentrant ventricular arrhythmias.10,11

Dispersion of repolarization can be modulated by adrenergic activation, which is also a potent trigger for ventricular arrhythmias in experimental models of heart failure and infarction.12,13 In the
normal ventricle, sympathetic stimulation increases apicobasal repolarization gradients and the effect is more pronounced with stellate ganglion stimulation than systemic catecholamines due in part to inhomogeneities in regional sympathetic innervation.14–16 Similarly, apicobasal repolarization gradients in the canine infarct model increase with norepinephrine due to sympathetic denervation supersensitivity.17

In patients with structural heart disease, heightened adrenergic states are associated with the development of ventricular arrhythmias and sudden cardiac death,18,19 but it is unclear if this is due to increased repolarization dispersion. The response of repolarization dispersion to circulating catecholamines in humans has not been consistent. While dobutamine increases endocardial repolarization dispersion by shortening repolarization time in ischaemic myocardium without affecting non-ischaemic regions,20 norepinephrine produces no change in epicardial repolarization dispersion when measured in ischaemic and non-ischaemic zones of sympathetically denervated myocardium.21 A limitation of these in vivo and intraoperative human studies is that global repolarization gradients were quantified from only 3 to 4 widely spaced recording sites. The effect of adrenergic stimulation on DOR in a localized myocardial segment has not been determined, and this may be more relevant to the pathogenesis of reentrant ventricular arrhythmias.10,11

Therefore, our objective was to study the effect of adrenergic stimulation on DOR and activation–repolarization coupling in patients with ventricular dysfunction using higher spatial resolution mapping than previously reported.20,21 We hypothesized that DOR would increase with adrenergic stimulation associated with a decrease in activation–repolarization coupling. To test this hypothesis, we measured activation times (AT) and activation recovery intervals (ARI) simultaneously from 10 sites along the apicobasal right ventricular (RV) endocardium in patients with cardiomyopathy before, during, and after dobutamine infusion.

Methods

Study population

Consecutive patients with cardiomyopathy, defined as a left-ventricular (LV) ejection fraction <40% by echocardiography or nuclear imaging, who were undergoing a clinical electrophysiology study were included in the research protocol. Patients with decompensated congestive heart failure, unstable angina, myocardial infarction within the past 3 months, or atrial fibrillation were excluded. Patients taking antiarrhythmic drugs other than beta-blockers were also excluded. All patients gave written, informed consent and the study protocol was approved by the Research Ethics Board at Mount Sinai Hospital and University Health Network.

Experimental protocol

Beta-blockers were held for five half lives after the study. The research study commenced 15 min after completion of the clinical electrophysiology study. A decapolar catheter (Livewire™, St Jude Medical) was positioned along the anteroseptal RV endocardium. Unipolar electrograms referenced to Wilson central terminal were recorded from the 10 electrodes (5 mm interelectrode distance) simultaneously using a bandpass of 0.05–500 Hz and a sampling rate of 1000 Hz. All intracardiac electrograms and 12-lead ECG data were digitally archived onto an electrophysiology workstation (Cardiolab™, GE) and extracted for offline analysis.

A quadripolar catheter (Avail™, Biosense Webster) was advanced into the right atrium and atrial pacing was commenced at 80% of the spontaneous sinus cycle length during a (i) control phase (4 min), (ii) dobutamine 2.5 μg/kg/min (4 min), (iii) dobutamine 5.0 μg/kg/min (4 min), and then a (iv) recontrol phase (7 min). The pacing rate was kept constant during control, dobutamine, and recontrol phases. Unipolar electrograms and non-invasive blood pressures were recorded during the last minute of each phase. Recordings during the recontrol phase were obtained 3 (recontrol 1) and 7 min (recontrol 2) after the dobutamine infusion had been discontinued.

Data analysis

Action potential duration at each recording site was estimated by measuring the ARI of the corresponding unipolar electrograms.22,23 Activation recovery interval was defined as the interval between local activation and local recovery. Local activation corresponded to the minimum dV/dt of the QRS complex. Local recovery was defined according to the modified Wyatt method, as the minimum dV/dt of a positive T wave, the maximum dV/dt of a negative T wave, or the midpoint between the two peak derivatives for a biphasic T wave. Although Coronel et al.24 have argued that the original Wyatt method may more accurately measure the end of local repolarization based on findings in isolated pig hearts, in vivo human studies25,25 have consistently shown significant underestimation of the APD with this method when the T wave is positive. In these studies, the modified Wyatt method provided better correlation with monophasic action potential duration (MAP90) than the original Wyatt method, so the former approach continues to be implemented for ARI measurements in humans.26

Activation time was measured as the interval from earliest QRS onset in any surface ECG lead to local activation. Total recovery time (TRT) was defined as the sum of the AT and ARI. Beat-to-beat ARI, AT, and TRT analysis was performed on a consecutive 7-beat segment with no ectopics. Unipolar electrograms with significant ST elevation, excessive noise, or very low amplitude T waves were excluded from analysis. In addition, unipolar electrograms with minimum dV/dt less negative than 0.3 mV/ms, which suggested local inexcitability or poor electrode-tissue contact were also excluded. The ARI, AT, and TRT at each of the 10 recording sites were calculated by discarding the two outlying measurements and taking the mean of the remaining five measurements. All measurements were made automatically and verified manually using custom interactive software written in Matlab (Matlab 7.3 for Windows, Mathworks Inc.).

Apicobasal DOR was defined as the range and standard deviation of TRT along the 10 recording sites. Adjacent DOR was measured as the largest difference in TRT between any two adjacent recording sites. In order to assess regional differences in activation and repolarization times, the recording sites were divided into apical (electrodes 1–3) and basal (electrode 8–10) segments.
The extent of activation–repolarization coupling was evaluated from the linear slope and Pearson correlation coefficient of ARI plotted as a function of AT for the 10 recording sites. In the presence of complete activation–repolarization coupling, a linear slope of $-1$ and a correlation coefficient of 1 would be expected, while a slope and correlation closer to 0 would indicate progressively less coupling.

**Statistical analysis**

All continuous variables are expressed as mean ± SEM. Comparison of continuous variables across groups was made using the paired t-test. A two-tailed $P$-value $\leq 0.05$ was considered significant.

**Results**

**Patients and haemodynamic changes**

Although 14 patients underwent the research protocol, four were excluded due to frequent premature ventricular beats or flat T waves that precluded accurate ARI measurement. The remaining 10 patients (mean age $62 \pm 5$ years, 9 males) formed the study cohort and their clinical characteristics are summarized in Table 1. The mean LV ejection fraction was $31 \pm 3\%$ and five patients had ischaemic cardiomyopathy, while the remaining five patients had non-ischaemic cardiomyopathy. The mean resting sinus cycle length was $810 \pm 42$ ms and the mean atrial pacing cycle length was $654 \pm 29$ ms. Systolic blood pressure increased with dobutamine $5 \mu g/kg/min$ ($140 \pm 24$ vs. $154 \pm 25$ mmHg, $P < 0.05$) and returned to control levels 7 min after discontinuing dobutamine ($134 \pm 15$ mmHg). All patients tolerated dobutamine $5.0 \mu g/kg/min$ for the duration of the infusion.

**ARI, AT, and TRT dynamics**

Under control conditions, mean AT was shorter at the RV apex compared with the base ($18 \pm 3$ vs. $28 \pm 3$ ms, $P = 0.05$). Activation proceeded from apex to base in three patients and base to apex in two patients, while in the remaining patients activation was earliest in the mid-endocardial electrodes. There was no significant change in AT during dobutamine infusion or recontrol (Figure 1).

**Table 1** Patient demographics

<table>
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<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Gender</th>
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<th>Infarct location</th>
<th>LVEF (%)</th>
<th>QRS (ms)</th>
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<td>M</td>
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<td>92</td>
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<td>10</td>
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<td>M</td>
<td>3 VD</td>
<td>Anterior</td>
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<td>164</td>
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<tr>
<td>Mean ± SEM</td>
<td>62 ± 5</td>
<td>9 (90%)</td>
<td>5 (50%)</td>
<td>—</td>
<td>31 ± 3</td>
<td>119 ± 9</td>
</tr>
</tbody>
</table>

LVEF, left-ventricular ejection fraction; CAD, coronary artery disease; 3 VD, three vessel disease; LAD, left anterior descending artery.

![Figure 1](https://academic.oup.com/europace/article-abstract/11/11/1529/443712)

The effect of dobutamine on apical and basal AT, ARI, and TRT are plotted. In the top panel, mean AT does not change significantly with dobutamine and recontrol. In the middle panel, dobutamine decreases apical ARI, but not basal ARI compared with control. In the bottom panel, dobutamine also decreases apical TRT, but not basal TRT compared with control. During recontrol, apical and basal TRT are both longer than control. $^aP \leq 0.05$ (apex dob 2.5 vs. apex control), $^bP \leq 0.01$ (vs. control), $^cP = 0.07$ (apex: dob 2.5 vs. control).
With dobutamine, the change in ARI was not consistent among patients. In seven patients, ARI shortened in response to dobutamine while in three patients ARI lengthened. Among all patients, mean ARI was shorter with dobutamine compared with control at the apex (dob 2.5: 285 ± 5 vs. 291 ± 6 ms, \( P = 0.03 \)), but no change in ARI was apparent at the base (Figure 1). During the recontrol phase, mean ARI at the apex and base was similar to control.

Total recovery time shortened with dobutamine in seven patients, and lengthened in the remaining three. In all patients, mean TRT was shorter with dobutamine compared with control at the apex (dob 2.5: 303 ± 14 vs. 308 ± 16, \( P = 0.04 \)), but the ARI at the base did not change. After 7 min of recontrol, TRT was significantly longer compared with control at the apex (recontrol 2: 312 ± 5 vs. 308 ± 5 ms, \( P = 0.01 \)) as well as the base (recontrol 2: 319 ± 7 vs. 315 ± 7 ms, \( P = 0.01 \)). The sequence of repolarization, defined by TRT, was the same as the sequence of activation in eight patients, while it proceeded in the reverse direction in two patients. There was no change in the sequence of repolarization with dobutamine. Figure 2 illustrates the change in AT, ARI, and TRT recorded from one representative endocardial electrode during dobutamine and recontrol.

**TRT dispersion dynamics**

Apicobasal TRT dispersion increased with dobutamine in a dose-dependent manner and decreased in the recontrol phase compared with control (Figure 3). This was apparent when TRT dispersion was measured either as range (dob 5.0: 15 ± 2 vs. 12 ± 2 ms, \( P = 0.06 \)) or standard deviation (dob 5.0: 5.5 ± 0.9 vs. 4.3 ± 0.9 ms, \( P = 0.04 \)). Adjacent TRT dispersion was also larger with dobutamine compared with control. (dob 5.0: 5.9 ± 0.8 vs. 4.5 ± 0.6 ms, \( P = 0.04 \)). Figure 4 illustrates the change in TRT dispersion with dobutamine in one patient. The grey vertical line on the left marks the QRS onset and the black horizontal bars extend from local activation to recovery for each of the 10 recording electrodes. In this representative patient, repolarization proceeded from endo 1 (apex) to endo 10 (base). With dobutamine, TRT shortened at all 10 electrodes; thereby preserving the apicobasal repolarization gradient, but greater TRT shortening at the apex compared with the base resulted in an increase in the TRT dispersion range from 24 (control) to 28 ms (dob 5.0).

**Adrenergic stimulation and activation–repolarization coupling**

Under control conditions, an inverse linear relationship between ARI and AT for the 10 recordings sites was apparent in all patients with a mean slope of \(-0.8 ± 0.2\) and a mean \(R^2\) of 0.6 ± 0.1. The absolute slope magnitude and correlation coefficient both
decreased significantly with dobutamine in a dose-dependent manner and then returned to baseline during the 7 min recontrol phase (Figure 5). At dobutamine 5.0, the slope was shallower ($20.3 \pm 0.2$, $P = 0.05$) and correlation coefficient was smaller ($0.4 \pm 0.1$, $P = 0.05$) than corresponding control values. Figure 6 is a plot of ARI as a function of AT for all 10 recording electrodes in a representative patient showing a shallower slope and lower correlation coefficient with dob 5.0 compared with control.

**Discussion**

The major finding of this study is that adrenergic stimulation with dobutamine increases apicobasal DOR along the RV endocardium and reduces activation–repolarization coupling in patients with cardiomyopathy. Significant ARI shortening in the apex, but not the base, without a change in AT contributes to the increase in repolarization dispersion. In vivo high-resolution mapping of cardiac repolarization is technically challenging in humans and studies to date have measured adrenergically mediated changes in repolarization dispersion from only 3 or 4 sequential recording sites. Simultaneous rather than sequential sampling from multiple sites is essential as time-dependent changes in repolarization can occur. We measured AT and ARI simultaneously from 10 recording sites within a localized myocardial segment in order to evaluate the effect of physiologic adrenergic stress on activation–repolarization coupling. Activation recovery intervals have been shown to accurately reflect the changes in APD during various interventions, including sympathetic stimulation.

Although prior human studies have evaluated the DOR along the entire LV epicardium or endocardium using either sequential or simultaneous measurements of ARI, monophasic action potentials, or refractory periods, apicobasal repolarization gradients have not been quantified per se. This may account for the larger DOR in these studies (26–53 ms) compared with 13 ms in our study. Consistent with these clinical studies, we found an inverse linear relationship between ARI and AT is apparent under control conditions (slope $-0.35$, $R^2 0.92$). With dobutamine 5.0 $\mu$g/kg/min, the ARI vs. AT slope becomes shallower and less linear (slope $-0.23$, $R^2 0.72$).

Dobutamine produced non-uniform changes in apicobasal ARI, while no effect was apparent on activation time. For the majority of recording sites, dobutamine shortened ARI, but in a few regions ARI either did not change or lengthened. John et al. also observed a variable effect of dobutamine on monophasic
action potential durations recorded from non-ischaemic regions of the LV endocardium in patients with coronary artery disease. In contrast, dobutamine consistently shortened APD in ischaemic zones. The potential mechanism for these differences is unclear, but likely includes (i) varying dobutamine concentrations in ischaemic and non-ischaemic regions, (ii) heterogeneous sympathetic denervation/hyperinnervation around scar,28 and (iii) non-uniform alpha/beta-receptor downregulation and G-protein uncoupling29 in the myopathic heart. In guinea-pig and porcine hearts, the modulation of repolarizing currents by beta-adrenergic stimulation is rate-dependent16,30 and this may be another explanation for the varying effects of dobutamine at different atrial pacing cycle lengths in our study.

We observed a consistent overcorrection of TRT after the 7 min recontrol phase despite apparent washout of dobutamine based on normalization of systemic blood pressure. This overcorrection appears to be a time-dependent phenomenon and we speculate that it may be due to residual alpha receptor activity evoked by dobutamine following beta receptor deactivation which could prolong repolarization time by augmenting inward calcium currents during the plateau phase.31,32

Dobutamine increased DOR across the apicobasal RV endocardium in a dose-dependent manner, while preserving the sequence of repolarization. The response of apicobasal repolarization gradient to adrenergic stimulation has not been reported previously in humans, but our findings are qualitatively similar to the optical mapping studies of Mantravadi et al.14 using isoproterenol in the perfused rabbit heart. In this study, isoproterenol increased the DOR without altering the sequence of repolarization. In our study, the increase in repolarization dispersion with dobutamine was due to a combination of (i) reduced activation–repolarization coupling, (ii) significant ARI shortening at the apex, but not the base, and (iii) preservation of apicobasal AT. The difference in responsiveness of the apex and base to dobutamine may relate to lower expression of the alpha (KVLQT1) and beta (minK) subunit of the IKs potassium channel in the base compared with the apex of the human heart.33 Because IKs is normally augmented by adrenergic stimulation causing APD shortening, fewer IKs channels in the base may lead to less ARI shortening in the presence of dobutamine.34 Another explanation may involve sympathetic denervation supersensitivity of the apex compared with the base, which has been demonstrated in canine infarct models to cause preferential shortening of apical refractory periods in the presence of norepinephrine,17 although Calkins et al.21 could not substantiate this phenomenon in humans using 13C-hydroxyephedrine PET imaging and intraoperative mapping.

In addition to sympathetic stimulation, repolarization dispersion can also be modulated by heart rate and premature beats. The rate adaptation of the APD is referred to as APD restitution, and an extrastimulus (S1–S2) pacing protocol can be used to measure restitution slopes or kinetics. In the normal guinea pig heart, APD restitution kinetics are not uniform over the epicardial surface.2 Although the presence of steep APD restitution (slope > 1) is associated with wavebreak and ventricular arrhythmia induction,35 restitution heterogeneity itself can be proarrhythmic by increasing APD90 dispersion in response to a tightly coupled extrastimulus.36 In our study patients, ARI restitution under basal conditions and in the presence of dobutamine could not be reliably defined due to frequent ectopic ventricular beats during the S1 drive or following the S2 extrastimulus (data not shown). Nonetheless, ARI restitution kinetics and heterogeneity may be a relevant mechanism of ventricular arrhythmogenesis in patients with cardiomyopathy.

Clinical significance

Heightened adrenergic states have been associated with an increased risk of sudden cardiac death by potentially triggering ventricular arrhythmias. The increased DOR and reduced activation–repolarization coupling observed with dobutamine may provide the arrhythmogenic substrate for reentrant arrhythmias, particularly if large repolarization gradients develop in localized myocardial segments as evident in our study patients.10,11 Reduced activation–repolarization coupling has also been observed in patients with ventricular hypertrophy and coronary artery disease at risk of arrhythmogenic death, and this is invariably associated with increased DOR.3,6–8 Thus, the extent of activation–repolarization coupling may be an important, independent metric of arrhythmia vulnerability in addition to repolarization dispersion, and therapeutic measures that enhance coupling may be antiarrhythmic.

Limitations

Activation–repolarization mapping was limited to the anteroseptal RV endocardium and more extensive mapping of the RV or LV was not performed due to ethical and technical constraints in patients. Nonetheless, our study measured in vivo human activation–repolarization gradients in response to dobutamine with higher sampling density than have been previously reported.20,21 Second, adrenergic stimulation was assessed using a sympathomimetic agent, dobutamine, rather than direct sympathetic nerve stimulation. While the latter more closely approximates physiologic stress and may increase DOR to a greater extent than sympathomimetic agents, in vivo sympathetic nerve stimulation is not possible in the conscious patient. Third, we did not have a normal control group for comparison with our cardiomyopathy patients. However, the risk of malignant ventricular arrhythmias with sympathetic stimulation is negligible in patients with preserved ventricular function, so the effect on repolarization dispersion is unlikely to be significant. Fourth, we did not attempt to correlate clinical outcomes and ventricular arrhythmia inducibility with the extent of activation–repolarization coupling or DOR, but this merits further study in a large prospective clinical trial. Finally, we did not measure conduction velocity restitution which is also an important mechanism for arrhythmogenesis.37 Such in vivo recordings will be technically challenging in patients with cardiomyopathy where ectopic beats are prevalent and activation distances cannot be accurately measured.

Conclusions

In patients with impaired LV function, adrenergic stimulation increases apicobasal DOR in the RV endocardium, which is associated with reduced coupling between the temporal sequence of activation and repolarization. This may provide a mechanism for the proarrhythmic effect of adrenergic stimulation and suggests
that therapeutic measures, which improve activation–repolarization coupling and reduce repolarization gradients, may be antiarrhythmic.

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