Effect of physiological mechanical perturbations on intact human myocardial repolarization

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Abstract

**Objective:** The objective of this study was to investigate the relationship between acute decreases in right ventricular volume during Valsalva strain (with resultant changes in autonomic neural tone) and measures of local endocardial repolarization time independent of heart rate and autonomic neural tone. **Methods:** Patients implanted with a stimulus to T wave (Stim-T) sensing pacemaker specially adapted to output a validated measure of beat to beat local repolarization (*n*=9) performed Valsalva manoeuvres (40 mmHg for 15 s) while paced at a cycle length of 500 ms. Stim-T intervals were measured before and after autonomic blockade (Block: 0.03 mg/kg i.v. atropine±0.15 mg/kg propranolol). Right ventricular end diastolic volume was estimated by simultaneous 2D-echocardiography. **Results:** Without autonomic blockade, compared to baseline, repolarization significantly prolonged during Valsalva strain (1.1±0.7%) and shortened during release (−2.1.4±1.0%). After block, strain related repolarization prolongation was also observed (1.0±0.6%), with significantly less release related repolarization shortening (−0.8±0.8%) compared to pre-block (*P*<0.05). Right ventricular end diastolic volume decreased during strain by 11±10 and 9±16% from baseline, pre- and post-block respectively (*P*<0.05). **Conclusion:** In a chronically instrumented human model, an acute physiologic volume reduction modestly prolongs right ventricular repolarization independent of changes in rate or autonomic tone. © 2000 Elsevier Science B.V. All rights reserved.

**Keywords:** Pacemaker/AICD; Autonomic nervous system; Stretch/m-e coupling; Ventricular arrhythmias; Ventricular function

This article is referred to in the Editorial by M.R. Franz (pages 263–266) in this issue.

1. Introduction

The effect of ventricular loading on the time course of myocardial cellular repolarization, is termed mechano-electrical feedback (MEF) [1,2]. This phenomenon may be responsible for the observations that patients with volume or pressure overload commonly have ventricular arrhythmias [3–6]. Mechanically induced electrical phenomena may also be responsible for termination of ventricular arrhythmias, by manoeuvres that alter mechanics of the ventricle [7].

To date, the demonstration of this phenomenon in humans, has been limited to either non-physiological volume changes or in acute invasive studies [8–11]. In addition, both autonomic activity and prevailing heart rate can influence the timing of repolarization, and thus accurate and reliable measure of repolarization duration is difficult. Hence, a human model using unambiguous measurements with concomitant control of heart rate and autonomic neural tone is needed to study the independent effect of mechanical perturbation on myocardial cellular repolarization [12]. Combined (parasympathetic and sympathetic) autonomic blockade during either head up tilt or Valsalva manoeuvre have been previously used to isolate the effect of cardiac volume/size on cardiovascular vari-

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ables [11,13], especially those related to reflex increase in sympathetic tone [14,15].

This study used a non-invasive, reliable measure of repolarization duration in a chronic, ambulatory human heart model, using a pacemaker that measures local repolarization. Rate responsive pacemakers with specially developed software to display all stimulus to T wave (Stim-T) intervals (Vitatron Inc, Holland) allow measures of endocardial repolarization on a continual basis without invasive instrumentation. This tool allows an unbiased and accurate local assessment of beat to beat cardiac repolarization from the same population of ventricular myocytes over long periods. The paced stimulus to T interval measure used in the proposed study has been validated against the simultaneously recorded extracellular APD_{90} (action potential duration at 90% duration) from our laboratory [16].

We hypothesized that: (a) acute decreases in right ventricular volume prolong local endocardial repolarization time, independent of heart rate and autonomic tone, and also that (b) increasing sympathetic tone shortens repolarization, independent of heart rate. The objective of this study was to measure cardiac repolarization without autonomic blockade, using endocardial stimulus to T intervals during constant ventricular pacing with strain phase of the Valsalva maneuver and head up tilt to test hypothesis (b), and to perform the above measurements with autonomic blockade to test hypothesis (a).

2. Methods

2.1. Patient population

Patients were recruited from St. Michael’s Hospital, Toronto and University Hospital, London, Ontario based on the following inclusion and exclusion criteria. All patients gave informed consent and the study protocol was approved by the ethics review committee at St. Michael’s Hospital, Toronto. The investigation conforms with the principles outlined in the Declaration of Helsinki (Cardiovascular Research 1997;35:2–3).

2.2. Inclusion criteria

All patients with either a Vitatron Diamond or Saphire (Vitatron Inc, Holland) pacemaker were eligible. All pacemakers had a passive fixation, bipolar endocardial pacing electrode implanted in the right ventricular apex. The pacemakers had to have been implanted at least 3 months before enrollment (chronic functioning) and prior determination of appropriate pacing function had to be established.

2.3. Exclusion criteria

Patients older than 80 years of age with unstable angina, New York Heart Association Classification 3 or 4, or significant recent heart failure were excluded. Also, patients with a history of reactive airway disease, bronchospasm, glaucoma and obstructive urinary symptoms were excluded because of the proposed autonomic blockade. Patients thought not to be able to perform Valsalva maneuvers were excluded from the study. Due to the possibility that antiarrhythmic drugs may influence MEF, patients on 13-blockers, calcium channel blockers, digoxin or amiodarone therapy were excluded from the protocol.

2.4. Design

A prospective, single blinded, acute study was planned. Consenting patients meeting inclusion/exclusion criteria were recruited two weeks prior to study by the pacemaker clinic. Patients were asked to come to the electrophysiological service after fasting overnight. Patients were allowed a light breakfast prior to the procedure, and were asked not to have coffee, tea or cigarettes. Patients were acclimatized to the procedure room, given instructions for performing the Valsalva procedure and were oriented to the tilting procedure. Patients were then asked to rest quietly in a supine position.

2.5. Electrophysiological set-up

Skin electrodes were placed across the pacemaker header and external chest wall and stimulation was performed while the device was in VVT mode. Patient discomfort was minimized using 10 ms pulse width, 2 mA stimulus to the chest wall [17]. A stimulus to the chest wall resulted in patients being paced at a constant cycle length of 500 ms. The Vitatron relay header was taped to the chest wall over the pacemaker and the programmer was then linked to an IBM compatible portable computer.

Specialized software stored all beat to beat measures of the paced Stim-T intervals and each beat’s simultaneously measured stim–stim interval to a floppy disc. The software allowed markers to be placed to identify precise times of the strain phase of Valsalva, head up tilt, run in period and points at which echocardiographic measurements were made. Once the electrophysiological set up was completed, training Valsalvas were performed. The patients were then paced at a constant cycle length of 500 ms. There was a run in period of 7 min of conditioning pacing after which the baseline Stim-T data was recorded. Also during this time the baseline echocardiographic measurements were made. The first Valsalva was performed, and after an interval of 4 min a second Valsalva was performed. If the Valsalvas did not reach 40 mmHg, or did not last 15 s, the Valsalva was repeated. Four minutes after the two Valsalvas were completed, patients were tilted to 60°. The initial 2 min after the tilt was used for the post-tilt values. The echo measurements were made 5 min after tilt. Seven minutes after the tilt, patients were asked to perform a Valsalva while still in head up tilt position. After total tilt
duration of 10 min, patients were returned to supine position and pacing was terminated. Soon after autonomic blockade was instituted the above-mentioned protocol was repeated.

2.6. Stimulus to T wave validation

In a separately published validation study, Stim-T intervals were measured and compared with the simultaneous monophasic action potential duration, in the cardiac catheterization laboratory for both steady state and acute rate change protocols. Monophasic action potential duration 90 (MAP$_{90}$) has been validated as a reliable indicator of the time course of cellular repolarization [18]. For the range of paced cycle lengths tested, in a steady state pacing protocol the slopes of either the MAP$_{90}$ or Stim-T cycle length were similar (slope 0.96 or 0.95, respectively) [16]. As well, the standard deviation of the mean differences between APD$_{90}$ or Stim-T at each cycle length had a Gaussian distribution with 93.5% of the differences within 2 S.D. of the mean.

2.7. Method for measurement of right ventricular volume

The echocardiographer and the patients were oriented to the protocol. The right ventricular end diastolic and end systolic dimensions were measured from stop frame images according to maximum and minimum dimensions, respectively. The measurements were made (first preference) from the apical four chamber view at the level of the tips of the tricuspid valve or from the parasternal long axis window (second preference if apical images were poor). Right ventricular dimension measurement by the cine loop method has been previously shown to correlate with right ventricular volume [19–21]. Measurements were made at baseline, strain phase of Valsalva and 5th minute of tilt. All comparisons within each patient were made from the same measurement. These measurements were made before and after autonomic blockade.

2.8. Autonomic blockade

Autonomic blockade was achieved by 0.03 mg/kg of i.v. atropine and 0.1 mg/kg of i.v. propranolol. These doses of pharmacologic autonomic agents are standard in the literature and have been shown in other validation studies to abolish heart rate changes to standard autonomic challenges, produce a marked shift in the isoproterenol dose–response curve, and also have been used to block autonomic effects in ventricular refractoriness in humans [22–24]. These doses approximate autonomic blockade from extracardiac autonomic neural input. The effects of these agents on intracardiac ganglionated neural structures are unknown [25]. Both were given simultaneously and the measurements made within 5 min thereafter.

2.9. Statistical methods

The baseline phase for each patient was defined as the 50 consecutive beats prior to the onset of the Valsalva manoeuvre. The strain phase was defined as the 30 consecutive beats from the onset of Valsalva, and the release phase was defined as the 50 beats after Valsalva termination. To illustrate the relationship between decreased right ventricular volume (during strain phase of Valsalva) and prolongation of repolarization time, each patient’s data was averaged across the 30 beats of the strain phase and expressed as percentage change as a function of their respective mean baseline values. Similarly, the 50 beats denoting the release phase of the Valsalva were averaged and expressed as a percentage of the average baseline value for each patient. All data are expressed as mean±standard deviation.

The statistical analysis was performed separately for each patient using a Student’s paired t-test comparing the raw baseline repolarization measures to the strain and release phases of the Valsalva. To examine overall differences between phases in all patients, each patient’s baseline, strain and release measures were normalized to the first beat of their baseline phase (i.e. beat −50), and analysis of variance was used to compare the baseline to the strain and release phases of the Valsalva across all patients.

A comparison of the rate of recovery of the release phase (slope) of the Valsalva manoeuvre before and after autonomic blockade was used to further elaborate the effect of mechanical influence on repolarization. For the head up tilt protocol, the baseline phase for each patient was once again defined as the 50 beats prior to the onset of tilt, and the first 30 beats after initiation of tilt was considered for comparison. A comparison of the time course of the recovery phase of the head up tilt (slope), before and after autonomic blockade was used to further elaborate the effect of mechanical influence on repolarization.

3. Results

3.1. Patients

Nine patients (five male, four female) were studied. The mean age was 62±9 years with a range of 49–76 years. Two of the nine patients were in atrial fibrillation at rates slower than paced rates and the seven others were in sinus rhythm. The median qualitative echocardiographic overall left ventricular ejection fraction was 40% with a range of 20–50%. Two patients had normal left ventricular function, and five had mildly impaired left ventricular function which derived from clinically stable coronary artery disease with past infarction. Six of the nine patients had received pacemakers for degenerative, chronically acquired AV nodal disease while the other three had received the
pacemaker for sick sinus syndrome. Two of the nine patients could not tolerate autonomic blockade due to LV dysfunction. Four of the patients who had autonomic blockade felt unwell (pre-syncope) for up to 2 h post-procedure and all patients were discharged home the same day.

### 3.2. Right ventricular dimension change

Right ventricular dimensions were measured in all patients before and after Valsalvas, however, measurements were made in only six of nine patients after autonomic blockade (two did not tolerate, one was symptomatic). Table 1 describes the mean percentage reduction in right ventricular end diastolic dimension as a percentage of baseline during Valsalva strain in supine position, during head up tilt, and also during Valsalva strain loaded during the head up tilt.

Fig. 1 shows the reduction in right ventricular volume in a typical patient during the strain phase of the Valsalva manoeuver. Autonomic blockade in supine position resulted in $3.0 \pm 4.8$ mm ($10 \pm 14\%$) reduction in RV dimension. The strain phase of the Valsalva prior to ANS blockade and after ANS blockade resulted in a significant reduction in right ventricular volume $3.3 \pm 3.9$ and $1.8 \pm 0.6$ mm ($-11 \pm 10$ and $-9 \pm 16\%$, respectively). Similarly head up tilt showed reduction of $4.3 \pm 4.3$ mm ($-15 \pm 16\%$) prior to, and $3.7 \pm 2.6$ mm ($-17 \pm 14\%$) after blockade. The biggest reduction was seen when patients performed Valsalvas in head up tilt position $7.6 \pm 4.2$ mm ($-24 \pm 12\%$) and this was maintained after autonomic blockade $3.8 \pm 5.8$ mm ($-20 \pm 20\%$).

### 3.3. Strain phase

Seven of nine patients showed increases in repolarization measures during the strain phase of the manoeuver ($P<0.01$). The absolute increase was $3.1 \pm 2.5$ ms (range $-0.06$–$6.0$ ms). This corresponds to 1–3% of total Stim-T duration. This lengthening of repolarization during the strain phase across all patients was statistically significant ($P<0.01$) and persisted after autonomic blockade ($P<0.01$). Table 2 shows the mean change in repolarization as percentage of baseline with the corresponding change in RV dimension during the strain and release phases of Valsalva while Fig. 2 shows the typical changes seen during a Valsalva manoeuver from one patient.

![Baseline Study](image1.jpg) ![Strain Phase of Valsalva](image2.jpg)

**Table 1**
Right ventricular end diastolic volume (% change)

<table>
<thead>
<tr>
<th></th>
<th>Pre-blockade (%)</th>
<th>Post-blockade (%)</th>
</tr>
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<tbody>
<tr>
<td>Baseline</td>
<td>0</td>
<td>-10*</td>
</tr>
<tr>
<td>Valsalva strain</td>
<td>-11*</td>
<td>-9*</td>
</tr>
<tr>
<td>Head up tilt</td>
<td>-15*</td>
<td>-17*</td>
</tr>
<tr>
<td>Tilt+strain</td>
<td>-24*</td>
<td>-20*</td>
</tr>
</tbody>
</table>

* $P<0.05$, compared to baseline.

**Table 2**
Right ventricular end diastolic volume and stimulus-T intervals (mean % change from baseline)

<table>
<thead>
<tr>
<th></th>
<th>Pre-blockade</th>
<th>Post-blockade</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV dimension (%)</td>
<td>-10.7±11.8</td>
<td>-9.3±16.5</td>
</tr>
<tr>
<td>Stim-T (%)</td>
<td>1.1</td>
<td>1.0*</td>
</tr>
<tr>
<td>RV dimension (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stim-T (%)</td>
<td>-1.4</td>
<td>0.8</td>
</tr>
</tbody>
</table>

* RV, right ventricle; Stim-T, stimulus to T wave interval; * $P<0.005$ compared to baseline.
Fig. 2. Continuous beat to beat repolarization changes seen during Valsalva, before and after autonomic blockade in a typical patient. Throughout the record continuous ventricular pacing occurs at 500 ms cycle length (120 bpm). The X-axis shows the beat number (from 0–200 beats) and the Y-axis shows the stimulus to T wave interval (Stim-T) in milliseconds. The upper tracing is after and the lower tracing is before complete autonomic blockade with atropine and propranolol. The X-axis time points refer to the phases of a 40-mmHg Valsalva manoeuver at baseline. The strain phase lasts 15 s followed by the release phase (see text for further discussion).

3.4. Release phase

Significant shortening of mean repolarization during the release phase compared to baseline/rest was seen (∼4.2±3.2 ms, \( P=0.02 \)). However, the relative shortening during the release phase, post-blockade was significantly different compared to preblockade (∼0.8±0.8 vs. 1.4±1.0%, \( P=0.04 \)).

3.5. Repolarization changes during head up tilt

Head up tilt of 60° resulted in a transient prolongation of repolarization, when compared to the supine position (Figs. 3 and 4). This effect was short lived and the measure of repolarization tended towards baseline. In Fig. 3, each patients stimulus-T interval before and at the end of tilt were largely unchanged with a mean±S.D. of 289±23 ms at supine and 285±22 ms at end tilt (\( P=\text{NS} \)). In Fig. 4, one typical patients beat to beat changes are shown with a transient prolongation that normalizes close to baseline value by the end of the tilt. The return to baseline was hastened after autonomic blockade. However, in all subjects, repolarization returned to baseline more

Fig. 3. Repolarization change seen during head up tilt of 60° prior to autonomic blockade.

Fig. 4. Typical beat to beat changes in Stimulus-T interval during continuous ventricular pacing at 500 ms (120 bpm) during 60° head up tilt. At the onset of tilt, an acute increase in Stimulus-T interval occurred followed by a recovery towards baseline. The recovery was faster (slope 0.16 ms/beat, \( r=0.60 \)) before than after autonomic blockade (0.07 ms/beat, \( r=0.35 \)).
4. Discussion

The main finding in this study is that acute physiological decrease in right ventricular volume by strain phase of the Valsalva maneuver and head up tilt, resulted in modest lengthening in action potential duration in this study. This phenomenon was independent of autonomic tone or heart rate. Importantly, the measure of repolarization was made via endocardial recordings and involved the same group of myocytes. This model of electromechanical feedback is unique in that it involves ambulatory patients who have had no instrumentation and yet accurate endocardial measurement of repolarization from the same population of cells before and after the mechanical intervention. Increased sympathetic tone during the release phase of the Valsalva maneuver and during the recovery following upright tilt, resulted in shortening of action potential duration in this study. This phenomenon was also independent of heart rate and was attenuated by autonomic blockade. The physiological interventions in this study were shown to decrease right ventricular volume by simultaneous echocardiography measurement.

4.1. Autonomic tone and repolarization

The Valsalva maneuver and head up tilt were used in this study for the purpose of physiological volume reduction of right ventricular volume. However the reflex changes that occur during these mechanical perturbations are well documented and may influence repolarization. In our model, we corrected for this confounding variable seen in previous models [8–11] by comparing repolarization before and after autonomic blockade. As expected, there were reflex changes due to autonomic tone during the release phase of the Valsalva and recovery from tilt.

4.2. Valsalva and repolarization

The original descriptions of the Valsalva maneuver were mainly centered around changes in the left ventricle [15]. The complex four phased changes that occur were not described for the right ventricle. With regards to influence on this study, the neural reflex components were controlled by autonomic blockade, and the reflex changes in heart rate were controlled for by pacing at a constant cycle length. The simultaneous echocardiographic measurements of the right ventricle show reduction in volume during the strain phase, and has previously been shown to result in decrease in volume [19]. This reduction in volume is mirrored by a prolongation of right ventricular action potential duration in this study.

4.3. Head up tilt and repolarization

Head up tilt results in lowering of the transmural venous pressure proportional to the distance from the heart [14]. This pooling effect has been shown to decrease venous return and cardiac size [21]. These reductions in volume resulted in acute prolongation of repolarization. With time, the prolongation tended to normalize due to a reflex sympathetic increase. Autonomic blockade attenuated the normalization, isolating the mechanical influence on repolarization. The greatest reduction in volume was noted during the Valsalva maneuver during the head up tilt, suggesting additive effects.

4.4. Previous studies

In previous studies, attempts have been made to demonstrate the phenomenon of electromechanical feedback in humans [8–11, 24, 30, 31]. Levine et al. demonstrated that QT corrected for rate prolonged with successful balloon valvuloplasty of the pulmonary artery, in an acute study [8]. These studies have used the surface QT measure of repolarization which may not be sufficiently sensitive when considering minute changes in repolarization after correction for heart rate. In another study Taggert et al. demonstrated that discontinuation of cardiopulmonary bypass, with concomitant increase in left ventricular volume and in peak systolic pressure resulted in decrease in APD₉₀ measured in the epicardium [9]. Taggert et al. also showed that aortic occlusion with a balloon shortened the APD₉₀ [10]. These models have tended to be in the realm of non-physiological volume loads [8–11]. Taggert et al. addressed the issue of physiological volume change and left ventricular repolarization. This study was also an acutely instrumented human model without control of simultaneous autonomic tone changes [11]. In that study, a decrease in volume load resulted in shortening of action potential and lengthening was observed with volume loading. However, in patients with wall motion abnormality, the reverse was observed similar to our findings. This result may be consistent with our study, as patients with implanted leads all have wall motion abnormality of the right ventricular apex.

The explanation for changes seen during volume change are subject to few theories. Increase in diastolic stretch is known to shorten repolarization [2, 25]. However, an abrupt shortening during systole is known to lengthen APD [2, 26–28]. There are also observations from comparative studies of isovolumetric contraction versus isotonic contraction that suggest that decreased fiber excursion shortens APD [2, 25]. Our study was not designed to clarify these issues and the explanation for the changes seen are beyond the scope of this study.
4.5. Limitations

This study is limited by the small sample size with its' inherent biases. Pacing induced ventricular wall motion abnormality is inherent to the technique utilized in this study, however it is a constant within and between patients. The Stim-T measure used in this study is a relatively new research tool in repolarization research. However it has been validated against a simultaneously recorded extracellular APD recording which itself is a good surrogate for intracellular action potential [18,29] and hence we argue that Stim-T is an equally good marker of intracellular action potential duration.

5. Summary

In an ambulatory conscious human heart model, acute right ventricular physiological volume reduction, modestly prolongs right ventricular repolarization, independently of changes in heart rate and autonomic tone.

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