Ventricular transmural repolarization sequence: its relationship with ventricular relaxation and role in ventricular diastolic function

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Aims
We investigated the role of ventricular repolarization sequence in ventricular diastolic function.

Methods and results
Arterially perfused canine left ventricular wedge preparation with simultaneous recording of action potentials and isometric contractile force was used to establish the relationship between ventricular repolarization and relaxation sequences. An isolated rabbit working heart model was used to investigate role of ventricular repolarization sequence in ventricular diastolic function. Under controlled conditions, similar to transmural dispersion of repolarization (TDR), there existed a time difference between initiation of epicardial and endocardial relaxation (TREpi–Endo, 47.4 ± 13.9 ms) with epicardium relaxing earlier. There was a strong correlation between TDR and TREpi–Endo (r² = 0.99, n = 5) and the interventions that changed transmural repolarization sequence led to parallel changes in transmural relaxation sequence. In isolated rabbit working hearts, reversal of the transmural repolarization sequence that manifested as negative T wave was associated with a significant increase in isovolumic relaxation time (from 49.2 ± 19.1 to 76.4 ± 12.1 ms, n = 5, P = 0.001).

Conclusion
There is a strong correlation between transmural repolarization and relaxation sequences. A positive T wave that denotes transmural repolarization sequence from epicardium to endocardium is essential for normal diastolic function of ventricle and the reversal of such sequence is associated with ventricular diastolic dysfunction.

Keywords
T Wave • Ventricular repolarization • Ventricular relaxation • Diastolic function

Introduction
The primary function of the heart is mechanical: pumping of the blood through the circulatory system. Normal pump function of the heart depends not only on the excitation–contraction coupling at the cellular level, but also on correct spread of electrical excitation to coordinate heart muscles as a syncytium.1,2 Propagation of electrical impulses can be detected and recorded on the body surface electrocardiogram (ECG). On the ECG, the QRS waveform represents ventricular electrical depolarization that initiates ventricular contraction and ejects the blood out of the ventricles, whereas the T wave represents ventricular electrical repolarization that is associated with ventricular relaxation that allows blood to fill the ventricular cavity.

The fact that the polarity of T wave is the same as that of the QRS complex under physiological conditions, i.e. a positive T wave, has puzzled scientists for almost a century.3–7 An increasing number of studies have demonstrated that a positive T wave is an electrocardiographic manifestation of the ventricular repolarization sequence from the epicardium to the subendocardium/endocardium that is opposite to that of the ventricular activation sequence.8–10 In other words, ventricular depolarization normally starts with the subendocardium (or endocardium) and spreads across the ventricular

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wall to the epicardium, whereas the repolarization initiates at the epicardium and propagates towards the subendocardium (or endocardium). Many studies have demonstrated that abnormalities in the ventricular repolarization, detected as changes in the T wave morphologies, play an important role in the genesis of ventricular arrhythmias. However, the physiological significance and pathophysiological implications of the ventricular repolarization sequence for ventricular mechanical function remain poorly understood.

We have recently demonstrated that the repolarization time and the dispersion of repolarization across the wall of a particular chamber of the heart is closely proportional to the wall thickness of that chamber.11 Across species, an increase in the body mass is accompanied by an increase in thickness of the wall of the left ventricle and by a proportional prolongation of the QT and Tp–e intervals. In larger species with thicker left ventricles, a longer QT interval is associated with a relatively prolonged Tp–e interval, therefore, not only is the total repolarization time prolonged but the transmural dispersion of repolarization (TDR) is increased as well.11 This raises several critical questions: What is the physiological significance of a normal upright T wave on the ECG that denotes a physiological repolarization vector from the left ventricular (LV) epicardium towards the inner cavity? Is this normal ventricular repolarization sequence essential to the pumping function of the left ventricle?

With the above questions in mind, we planned a study investigating the mechanical counterpart of the electrical T wave. We hypothesized that ventricular repolarization from the epicardium to the endocardium, which manifests as a positive T wave on the ECG, is a physiological requisite for adequate LV relaxation and the reversal of this physiological sequence that registers as a negative (or inverted) T wave is associated with impairment of ventricular relaxation hence with ventricular diastolic dysfunction.

Methods

We used two experimental models in our study to investigate the hypothesis of interest: (1) arterially perfused canine left and right ventricular wedge preparations were used to define the relationship between ventricular repolarization and ventricular relaxation sequences; and (2) an isolated working rabbit heart model was used to investigate the role of the ventricular transmural repolarization sequence in normal ventricular relaxation and effects of reversal of normal repolarization sequence.

Arterially perfused canine ventricular wedge preparation and electrophysiological recordings

The Institutional Animal Care and Use Committee at the Lankenau Institute for Medical Research approved the use of animals in this project. Fifteen adult beagle dogs were included in experiment and 15 wedge preparations were prepared (5 LV and 10 right ventricular wedges). Surgical preparation of the ventricular wedge from the canine heart has been described in detail in previous publications.13–14 Briefly, a transmural wedge preparation was dissected from the canine ventricular free wall (right or left depending on experiment), and cannulated via a coronary artery and perfused with Tyrode’s solution buffered with the following composition (mM): NaCl 129, KCl 4, NaH₂PO₄ 0.9, NaHCO₃ 20, CaCl₂ 1.8, MgSO₄ 0.5, glucose 5.5, insulin 1U/L, buffered with 95% O₂ and 5% CO₂ (35.7 ± 0.1°C). The preparation was then suspended in a tissue chamber and surrounded by H₂O-saturated atmosphere consisting of 95% O₂ and 5% CO₂ (35.7 ± 0.1°C). The perfusate was delivered to the artery by a roller pump. Perfusion pressure was monitored with a pressure transducer and maintained between 35 and 50 mmHg by adjustment of the perfusion flow rate.

The preparations were stimulated from the endocardial surface at a basic cycle length (BCL) of 1000 ms using bipolar silver electrodes insulated except at the tips. A transmural pseudo-ECG signal was recorded using extracellular silver/silver chloride electrodes placed on two small sponges attached to epicardial and endocardial surfaces of the preparation. Transmembrane action potentials were simultaneously recorded from the epicardium and subendocardium (on the cut surface of the wedge that was about 1 mm from the endocardial surface). For all of the preparations, impalements were obtained from positions approximating the transmural axis of the pseudo-ECG recording. The Tp–e interval, an index of TDR, was defined as the interval between the peak of the T wave and the end of the T wave.

Two force transducers were connected to the wedge, one each at the endocardial and the epicardial surface across the long axis of the preparation as demonstrated in Figure 1A. The epicardial and the endocardial isometric contraction loops were recorded with isometric transducers from Kent Scientific as previously described.15 The ‘beginning of relaxation’ was defined as ‘a point in isometric contraction loop at which dT/dt (change in tension as a function of time) not only becomes zero but also shows continuous decline thereafter’. A continuous decline in dT/dt after it becomes zero—is an imperative part of above definition, as in our experience, the endocardial isometric contraction loop shows a plateau phase, where dT/dt remains zero for multiple time points before it starts decreasing. The beginning of relaxation of endocardium and epicardium was calculated as defined above from respective isometric contraction loops. The transmural dispersion of beginning of relaxation (TREp–Endo) was defined as the time difference between the onset of relaxation of the epicardium and the endocardium.

Any preparation that showed persistent ST segment abnormality (elevation or depression) and/or spontaneous arrhythmia (ventricular tachycardia or fibrillation) after equilibration period of 30 min, were excluded from study protocol. The success rate of wedge preparation in our experiments was 100%.

The isolated rabbit working heart model and assessment of left ventricular diastolic function

The isolated working rabbit hearts were prepared as shown in Figure 1B in the ways similar to that used by others.16,17 Five adult white New Zealand rabbits were used. Briefly, the isolated rabbit heart was cannulated through the left atrium, which was then connected to a reservoir containing Tyrode’s solution buffered with 95% O₂ and 5% CO₂ at 37 ± 0.1°C. The pulmonary veins were ligated at the ostia to the left atrium and aorta was cannulated and connected to a small elastic container that simulated the peripheral vascular trees. The heart was then suspended in a tissue bath chamber containing oxygenated Tyrode’s solution. The sinus node and surrounding tissue were removed and the heart was paced through the right atrium at a BCL of 500 ms.

Monophasic action potentials (MAPs) from the LV endocardium and epicardium were recorded using custom-made MAP electrodes. A transmural pseudo-ECG across the left lateral ventricular wall was recorded simultaneously at the same vector as the MAP recordings. In our experience in working with isolated rabbit heart model, end of repolarization...
of endocardial MAP coincides with the end of the T wave and end of repolarization epicardial MAP coincides with the peak of the T wave.

The pressure waveforms were recorded from left ventricle, left atrium (LA), and aorta simultaneously with three separate pressure transducers as shown in Figure 1B. The isovolumic relaxation time (IVRT) was defined as the time interval from the aortic valve closure to the mitral valve opening. During this time, cardiac muscle fibres begin relaxation, which leads to a progressive decrease in LV pressure creating a suction effect. When diastolic dysfunction occurs, isovolumic relaxation is slowed and incomplete. This leads to a decrease in early diastolic suction effect with a resultant increase in IVRT and left atrial pressure.

For a preparation to be included in the study, a minimal baseline aortic systolic pressure of 90 mmHg, as measured by the aortic pressure transducer was required. Any preparation that shows ST segment abnormality (elevation or depression) or spontaneous arrhythmia (atrial or ventricular arrhythmias) was excluded from the study. In our study, the drop out rate for any of above reasons was 0%.

Statistics
Statistical analysis of the data was performed using two-sided Student’s t-tests for paired data. Data are presented as mean ± SD. Based on our previous experience with wedge preparation and isolated working heart model, anticipated mean, common standard deviation, and standard deviation for mean of the difference between variables were calculated. The software package Power and Precision was used to calculate the power function, which reached 90% with five pairs.

The SAS procedure, Proc Multtest, was used to determine the P-value adjustment for multiplicity since eight tests were conducted independently. The option in Proc Multtest that we used allows adjustment of raw P-values based on those P-values for the eight tests.

Results
Relationship between ventricular repolarization and relaxation sequences
Previous studies have demonstrated that there is an intrinsic difference in TDR between the left and right ventricles in animals and humans and TDR can be significantly amplified by reversal of the normal activation sequence via pacing from the epicardium. In the first set of experiments, we tested the effect of endocardial vs. epicardial pacing on the difference in transmural relaxation initiating time (TR_{Epi-Endo}) and compared it between canine left and right ventricular wedge preparations.

Figure 2A shows original recordings of isometric contraction force in a canine LV wedge preparation paced from the endocardium and the epicardium, respectively. Comparison of the TR_{Epi-Endo} between two pacing sites in the left vs. the right ventricular wedges is shown in Figure 2B.

With LV endocardial pacing at a BCL of 1000 ms, the epicardium repolarized first and the T_{p–e} interval (an ECG index of TDR) was 51.4 ± 4 ms. Also, the epicardial relaxation started earlier than the endocardium and the resultant TR_{Epi-Endo} was 47.4 ± 13.9 ms (Figure 2). Epicardial pacing significantly increased the T_{p–e} interval (69.0 ± 6.5 vs. 50.6 ± 3.5 ms with endocardial pacing, n = 5, P = 0.0002) and this was accompanied by prolongation of TR_{Epi-Endo} (70.4 ± 19.5 vs. 47.4 ± 13.9 ms with endocardial pacing, n = 5, P = 0.003). Similarly, the TDR and the TR_{Epi-Endo} across the canine right ventricle changed in parallel although both values were significantly smaller when compared with those of the left ventricle (Figure 2B).

In another series of experiments, the relationship between ventricular repolarization and relaxation was investigated with constant cooling of the epicardial surface of the canine ventricular wedge preparation. The continuous irrigation of epicardial surface with cold (20°C) Tyrode’s solution was used to cool the epicardial surface. The cooling of the epicardial surface prolongs the duration of action potential and delays epicardial repolarization. Figure 3 shows dynamic changes in the ventricular repolarization and relaxation sequences when the epicardium of the right ventricular wedge preparation was irrigated with cold Tyrode’s solution (20°C). As shown in Figure 3A, under a controlled condition, the epicardial action potential duration (APD) was shorter than
the endocardial APD and the transmural relaxation sequence was similar to the repolarization sequence with the epicardium relaxation starting earlier than the endocardial relaxation. The time intervals between repolarization of epicardium and endocardium \( (T_{p-e}) \) and the time interval between the onset of relaxation of epicardium and endocardium \( (TR_{Epi-Endo}) \) are marked with dotted lines in Figure 3A–D. Cooling of the epicardium led to progressive prolongation of the epicardial action potential, eventually resulting in reversal of the ventricular repolarization sequence, which manifested as a negative T wave on the pseudo-ECG (Figures 3C and D). The ventricular relaxation sequence closely followed the changes in repolarization sequence and reverted with the epicardium starting to relax later than the endocardium.
The TREpi – Endo and the Tp–e interval showed a linear relationship ($r^2 = 0.99$, 5 preparations and 28 observations, Figure 4).

Role of ventricular repolarization sequence in ventricular diastolic function

The data shown above clearly demonstrate that the ventricular repolarization sequence dictates the ventricular relaxation sequence. This raises the critical question: is the ventricular electrical repolarization sequence from the ventricular epicardium to the endocardium essential for normal mechanical function of the ventricle? To address this question, we investigated the role of ventricular electrical repolarization sequence in ventricular relaxation and diastolic function using isolated working rabbit hearts.

As shown in Figure 5, the left atrial, LV and aortic pressures were recorded simultaneously with a transmural pseudo-ECG, and epicardial and endocardial MAPs. Under control conditions, the T wave was positive, and the ventricular repolarization sequence was from the ventricular epicardium to the endocardium, identical to that observed in the isolated ventricular wedge preparations.
Figure 2. The epicardium repolarized earlier by 33.2 ± 10.0 ms than the endocardium. The IVRT, which is an index of early ventricular relaxation efficacy, was 49.2 ± 19.1 ms (n = 5). The left atrial pressure during peak atrial contraction was 6.2 ± 5.7 mmHg (n = 5).

After obtaining control recordings, ATX-II (0.01 μM), a potent toxin that enhances the late sodium current and markedly prolongs APD, was added to the bath solution of the tissue chamber (n = 5). This led to marked prolongation of epicardial APD, resulting in the reversal of the normal ventricular repolarization sequence across the lateral wall of the left ventricle (Figure 5). In other words, the endocardium repolarized earlier by 27.4 ± 10.4 ms than the epicardium, which manifested as a negative T wave on the pseudo-ECG. Interestingly, this led to a marked increase in IVRT to 76.4 ± 12.1 ms (n = 5), which was significantly longer than that observed under the controlled conditions (49.2 ± 19.1 ms; P = 0.001). The left atrial pressure, on the other hand, also increased significantly (13.4 ± 8.0 vs. 6.2 ± 5.7 mmHg, n = 5, P = 0.003; Figure 5). There was a trend towards increase in LV end-diastolic pressure but the difference was not statistically significant (5.0 ± 1.7 vs. 5.7 ± 1.5 mmHg, P = 0.097).

Discussion

Taken together, the data obtained in the present study indicate that the electrical repolarization sequence from the epicardium to the endocardium, which manifests as a positive T wave in the left precordial leads on the ECG, is essential to normal LV relaxation that begins at the epicardial surface and travels to the endocardium. To our knowledge, this is the first study to establish the relationship between ventricular repolarization and ventricular relaxation and to emphasize an important role of the electrocardiographic T wave in ventricular diastolic function.

The fact that the T wave is more prominent in species with larger body size and the Tp–e interval is directly proportional to the thickness of the LV wall indicates that a positive T wave may be important for proper ventricular relaxation, more so for the left ventricle with a thick wall than with a thin wall. From a mechanistic standpoint, the left ventricle could be considered as a 'pump' with a hollow cavity and a thick wall, which expels blood during systole/contraction and pulls it in during diastole/relaxation. It is expected that such a pump would work efficiently when the inner layer contracts earliest but relaxes last and the outer layer contracts last but relaxes first. Such co-ordination between inner and outer layers will not only generate synergistic contractile force but also ensure proper relaxation. Quite logically then, the reversal of such sequence would compromise the normal relaxation. In patients with long-standing systemic hypertension, the left ventricle becomes hypertrophic with increased wall thickness. During early stages, LV hypertrophy (LVH) is associated with an increase in the Tp–e interval. This increase in the Tp–e interval, which provides more time for completion of repolarization from the epicardium to the subendocardium (or endocardium), is likely a compensating mechanism facilitating proper LV relaxation under conditions of the increased wall thickness. When LVH progresses and physiological compensation fails, the T wave becomes inverted (negative), causing the 'strain' pattern of the T wave. Interestingly, a negative T wave in LVH often heralds frank ventricular dysfunction. Nearly all patients with diastolic heart failure have a history of long-standing hypertension, a common clinical entity that is associated with LVH.
Several lines of clinical and experimental observation have suggested an important role of the ventricular repolarization sequence in ventricular mechanical function, and are in concordance with our experimental findings. Population studies suggest that the ventricular diastolic dysfunction is more prevalent in women than men. A recent study has also shown that the T wave amplitude is smaller and less steep in its descending limb in women than men. A recent study has also shown that the T wave amplitude is smaller and less steep in its descending limb in women than men. Interestingly, it has long been recognized that the T wave amplitude is smaller and less steep in its descending limb in women than men.25,26 A recent study has also shown that the T wave amplitude is smaller and less steep in its descending limb in women than men.25,26 Additionally, digoxin, which increases myocardial contractility and impairs ventricular relaxation, is frequently associated with sagging of the ST segment and inverted T wave. Moreover, digoxin-induced abnormal diastolic function seems to be more detrimental in women compared with men.28

The reversal of the physiological ventricular repolarization sequence from the epicardium to the endocardium, in certain pacing modes of an implanted device, has been found to be detrimental to ventricular function. Right ventricular endocardial pacing in humans, which is associated with delayed epicardial repolarization, has been shown to impair ventricular relaxation. Interestingly, ventricular diastolic dysfunction induced by right ventricular endocardial pacing is accompanied by a significant increase in B-type natriuretic peptide that is released from the ventricles in response to an increased wall tension.29,30 One would expect that the ventricular wall tension would increase significantly if the endocardium starts relaxing when the epicardium is still contracting. This may partially explain why right ventricular endocardial pacing alone was associated with an increased mortality and or hospitalization for heart failure in DAVID trial.31 and why biventricular or left epicardial pacing that favours earlier epicardial repolarization improves ventricular mechanical function and relieves heart failure symptoms.32,33 In other words, improvement of ventricular mechanical function in patients with congestive heart failure (CHF) who receive biventricular pacing may have partially resulted from improved ventricular relaxation.32,33

Our results are in agreement with previous reports by Ashikaga et al who demonstrated that in the canine left ventricle, epicardium relaxes earlier than the endocardium in vivo. Similarly in isolated canine LV myocytes, the time to peak of contraction is shortest in the epicardial and longest in the endocardial cells. However, Ashikaga et al. could not establish the relationship between the ventricular repolarization and relaxation as they failed to find any TDR in the canine left ventricle possibly related to the limited ability of bipolar electrodes in accurately measuring the ventricular repolarization time.8

In the United States, there are approximately 5 million people with CHF and it is one of the leading causes of morbidity and mortality. Among people with CHF, approximately half have normal LV contractility, i.e. preserved systolic function, and therefore are diagnosed with diastolic heart failure secondary to abnormal ventricular relaxation and ventricular compliance.23,24,36,37 Therefore, our findings may have significance not only in the diagnosis and but also in the management of ventricular diastolic dysfunction. Currently, diastolic heart failure is diagnosed largely by clinical exclusion.22,38 Our study demonstrates that altered ventricular repolarization, which manifests as T wave changes on the ECG, can result in abnormal ventricular relaxation. Therefore, the T wave changes may serve as a useful diagnostic index of LV diastolic dysfunction.

**Figure 5** (Left panel) Original recordings of pseudo-electrocardiogram, endocardial monophasic action potential, epicardial monophasic action potential, left atrial, left ventricular, and aortic pressures under control conditions. Please note that the scale for the left atrial pressure is different from that for the left ventricular and the aortic pressures. (Right panel) Similar recording obtained after continuous irrigation of the epicardial surface with ATX-II (0.01 µM). Note that ATX-II caused prolongation of epicardial action potential leading to the reversal of ventricular repolarization sequence and a negative T wave. This was accompanied by increase in IVRT and increase in left atrial pressure. Epi, epicardium; Endo, endocardium; IVRT, isovolumic relaxation time.
Limitations

Our experimental findings have two principle limitations. First, it may be argued that in the experiments involving LV wedge, cooling of epicardium with cold Tyrode solution can affect the mechanical properties of epicardium independent of APD prolongation leading to false positive findings. However, our results remained consistent in the isolated working heart model, where ATX-II was used to prolong the epicardial action potential instead of cooling. Secondly, the method for measuring contractile force in the wedge preparation is fairly novel and has not been extensively validated. As the dissection of wedge is driven by coronary anatomy, the exact orientation of endocardial and epicardial force transducers with respective myofibres is difficult to predict and less likely to be consistent across all the wedge preparations tested. However, despite variable relationship between force transducers and myofibres, earlier onset of relaxation in epicardial layers was consistently seen in all the preparations. Such variable orientation may affect the recordings of the amplitude of peak contraction but is unlikely to affect the timings of the onset of relaxation as observed by Ashikaga et al. In summary, our experimental findings suggest that a positive T wave is an ECG manifestation of the LV repolarization sequence from the endocardium and it may be essential for proper ventricular relaxation. The reversal of this repolarization sequence is associated with ventricular diastolic dysfunction.

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References

Incremental value of cardiac magnetic resonance imaging in the differential diagnosis of acute coronary syndrome in a young man

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A 21-year-old male was admitted with recurrent chest pain, dyspnoea, and elevated levels of cardiac enzymes (troponin T 0.22 μg/L). The patient had a history of periodic amphetamine abuse. One week before the admission, he had an episode of fever (39°C), chills, and diarrhoea. ECG showed normal sinus rhythm without ST-T segment abnormalities. Invasive coronary angiography demonstrated no evidence of atherosclerotic disease. However, an abnormal origin of the right coronary artery (RCA) was detected.

The differential diagnosis included subendocardial ischaemia owing to amphetamine-induced coronary spasm or to an interarterial course of the RCA and acute myocarditis.

Cardiac magnetic resonance (CMR) was performed to track the anatomical origin and course of the anomalous RCA and to help with differential diagnosis.

Images of a free-breathing whole-heart acquisition allowed the exact anatomical depiction of the RCA originating from the left sinus valsalva and passing between the ascending aorta and the pulmonary trunk (Panel A). T2-weighted images of the myocardium showed myocardial oedema of the lateral wall (arrowheads in Panel B). Corresponding delayed enhancement images demonstrated subepicardial hyperenhancement (arrowheads in Panels C and D).

The diagnosis of acute myocarditis was established on the basis of CMR criteria. Amphetamine-induced coronary spasm is a well-known cause for myocardial ischaemia and infarction. An abnormal course of the RCA between aorta and pulmonary trunk may rarely be the cause of myocardial ischaemia potentially needing bypass surgery. CMR ruled out oedema in the RCA territory and ischaemia-typical late enhancement pattern in all coronary territories, making these two other differential diagnosis highly unlikely.

This case demonstrates the usefulness of CMR in the differential diagnosis in acute coronary syndrome with clear coronary arteries.

Panel A. Multiplanar reformatted image of a T1-weighted, free-breathing whole-heart acquisition showing the exact course of the abnormal right coronary artery (RCA) with origin from the left coronary sinus passing between the aorta and the pulmonary artery (PA).
Panel B. Short-axis view of a T2-weighted image of the same patient showing signs of myocardial oedema in the posterolateral myocardium (arrows).
Panels C and D. Short-axis and four-chamber view of delayed-enhancement images, demonstrating hyperenhancement of the lateral wall, mid to epicardial, as typical sign for myocarditis (arrows).