Published in final edited form as:

Heart Rhythm. 2008 February ; 5(2): 241–245.

Electromechanical coupling in patients with the short QT syndrome: Further insights into the mechanoelectrical hypothesis of the U wave

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Abstract

BACKGROUND—Patients with a short QT syndrome (SQTS) are at risk of sudden cardiac death (SCD). It is not known whether abbreviation of cardiac repolarization alters mechanical function in SQTS. Controversies persist regarding whether the U wave is a purely electrical or mechanoelectrical phenomenon.

OBJECTIVE—The present study uses echocardiographic measurements to discriminate between the hypotheses for the origin of the U wave.

METHODS—Diagnostic work-up including echocardiography and electrocardiogram was performed in 5 SQTS patients (39 ± 19 years old) from 2 unrelated families with a history of SCD and 5 age-matched and gender-matched control subjects.

RESULTS—QT intervals were 268 ± 18 ms (QTc 285 ± 28 ms) in SQTS versus 386 ± 20 ms (QTc 420 ± 122 ms) in control subjects ($P < .005$). In SQTS patients, the end of the T wave preceded aortic valve closure by 111 ± 30 ms versus −12 ± 11 ms in control subjects ($P < .005$). The interval from aortic valve closure to the beginning of the U wave was 8 ± 4 ms in patients and 15 ± 11 ms in control subjects ($P = .25$). Thus, the inscription of the U wave in SQTS patients coincided with aortic valve closure and isovolumic relaxation, supporting the hypothesis that the U wave is related to mechanical stretch.

CONCLUSION—Our data show for the first time a significant dissociation between the ventricular repolarization and the end of mechanical systole in SQTS patients. Coincidence of the U wave with termination of mechanical systole provides support for the mechanoelectrical hypothesis for the origin of the U wave.

Keywords

Short QT syndrome; Sudden cardiac death; Electromechanical dissociation; Isovolumic relaxation; U wave

Introduction

The short QT syndrome (SQTS) represents a primary electrical disease characterized by a substantial shortening of the QT interval and shortening of atrial and ventricular effective refractory periods.^{1–3} The aim of the present study was to evaluate the relationship between the mechanical and electrical systole in patients with SQTS and to correlate these events with the inscription of the T wave and the occurrence of the U wave.

The T wave reflects ventricular repolarization. Termination of the T wave is usually coincident with the closure of the aortic valve and termination of mechanical systole. The U wave, first shown in an electrocardiogram (ECG) tracing by Einthoven,⁴ follows the T wave as a separate wave under physiological conditions and begins with the second heart sound at the beginning of ventricular relaxation.⁵ The U wave is usually monophasic positive, best visible within a heart rate range of 50 to 100 beats/min and the amplitude seldom exceeds 0.2 mV. Unlike the QT interval, the interval from the end of the T wave to the apex of the U waves is nearly rate independent.⁶ After a sudden increase of the cycle length during atrial fibrillation or after premature beats, the timing of the U wave does not change. However, it leads to an encroachment of the T wave by the U wave.⁷ The U wave is often difficult to differentiate from the T wave under pathophysiological conditions such as long QT syndrome. The origin of the U wave has long been a matter of debate, and controversy persists regarding whether the U wave is a purely electrical or a mechanoelectrical phenomenon. The 3 major hypotheses for the origin of the U wave are that it is caused by (1) repolarization of the His–Purkinje system, (2) repolarization of certain regions of the ventricular myocardium such as the papillary muscle or M cells, or (3) stretch-induced delayed afterdepolarizations caused by distension of the ventricular wall during diastole, the so-called mechanoelectrical hypothesis.^{6,8,9} The theories relating the U wave to ventricular repolarization are difficult to reconcile with the characteristics of a normal U wave. Arguments against the His–Purkinje hypothesis include the fact that the tissue mass is too small to register on the surface ECG. Moreover, the interval between the end of the T wave and the apex of the U wave is constant at different heart rates, whereas the difference between Purkinje action potential duration and that of ventricular muscle increases as heart rate slows and decreases at faster rates.¹⁰

Midmyocardial M cells, more abundant in mass and possessing delayed repolarization characteristics similar to those of Purkinje fibers, could be responsible for the inscription of the U wave, particularly the pathophysiologic U wave appearing under long QT conditions.¹¹ Arguing against this hypothesis are experimental findings showing that the M cells are responsible for a second component of the T wave, often confused as an accentuated or inverted U wave.^{12,13} Antzelevitch et al^{13–15} suggested use of the terms T1 and T2 to describe the 2 contiguous repolarization waves or bifurcated T wave, which is distinct from the U wave.

The T wave and U wave are separate deflections, as could be shown in patients with acute myocardial ischemia, in which the monophasic transformed ventricular complex is independent of the shape and timing of the U wave.⁶

The end of the T wave coincides with the second heart sound.⁵ The mechanoelectrical hypothesis suggests the origin of the U wave as afterpotential that is caused by stretching of the circular muscle layers of the left ventricle. Direct support for the mechanoelectrical hypothesis is lacking as well. Support for this hypothesis derives principally from the coincidence of the U wave with ventricular relaxation.¹⁰

Clear separation of the T wave and U wave in patients with SQTS provides a unique opportunity to obtain further insights into the origin of the U wave. In the present study, ECG recordings and echocardiographic measurements were obtained in patients with SQTS to get further insights into the generation of the U wave.

Methods

The clinical characteristics of the SQTs patients were previously described in detail.² The control group comprised 5 healthy volunteers who were matched according to gender and age. In all normal probands structural heart disease was excluded. Standardized transthoracic echocardiography was performed in accordance with the recommendations of the American Society of Echocardiography.¹⁶ The echocardiograms were recorded with a VIVID 5 or VIVID 7 system (GE Medical Systems, Horten, Norway). The examinations were obtained during calm respiration in the left lateral decubitus position. Mean Doppler velocity tracings were obtained in a circular region placed in the Doppler sector of the basal interventricular septum to determine exact timing of mitral valve and aortic valve opening and closing. The region of interest was tracked spatially throughout the cardiac cycle to avoid sampling of the left ventricular cavity. Offline measurements were performed using dedicated software (EchoPAC, GE Medical Systems). Echocardiographic parameters of ventricular systole and diastole were determined and correlated to electrical repolarization. Single-lead ECG as recorded with echocardiograms is not suitable for reliable U wave delineation. Therefore, 12-lead ECG was registered immediately after termination of the echocardiographic examination in the supine position. After the slight change of the upper body position, a potential discrete volume shift and an effect on the surface ECG could not be definitely excluded, but seems to be unlikely. The amplitude gain was increased to 20 mm/mV to calculate the offset of the U wave, which was best visualized in the precordial leads V2/V3/(V4) and correlated to the hemodynamic parameters with the identical R-R interval.

The following parameters were analyzed: heart rate, QT interval, heart-rate-corrected QT interval according to the Bazett formula (QTc), isovolumic contraction (IVC, interval from closure of the mitral valve to opening of the aortic valve), ejection period, end systolic volume, end diastolic volume, ejection fraction, isovolumic relaxation (IVR, interval from closure of the aortic valve to opening of the mitral valve), interval from the end of the T wave to aortic valve closure, interval from the Q wave to the beginning of the U wave, interval between the end of the T wave to the start of the U wave, interval from the beginning of the Q wave to closure of the aortic valve, interval from the aortic valve closure to the beginning of the U wave. The data are expressed as mean values $\pm$ SD. A Student *t* test was performed to test for statistical differences between 2 unpaired mean values. A value of $P < .05$ was considered to be statistically significant (MS Excel version 2002 SP3, Microsoft, Redmond, Washington).

Results

Five patients from 2 unrelated European families were evaluated (2 men and 3 women, 39 ± 19 years old) and compared with a gender-matched and age-matched control group (2 men and 3 women, 41 ± 18 years old). Underlying structural heart disease was excluded in SQTs patients and control subjects. QT intervals were significantly different between SQTs patients (268 ± 18 ms, QTc 285 ± 28 ms) and control subjects (386 ± 20 ms, QTc 420 ± 22 ms, $P < .005$). The end systolic, end diastolic volume and ejection fraction were normal in patients and control subjects (Table 1). SQTs and control groups displayed similar heart rates, isovolumic contraction, and isovolumic relaxation (Table 1). The systolic ejection time was similar as well (265 ± 29 ms versus 272 ± 12 ms, $P = .6$). The end of T wave preceded the closure of the aortic valve by a mean of 111 ± 30 ms in patients with SQTs (Figure 1), whereas in the control group the aortic valve closed during the terminal portion of the T wave (-12 ± 11 ms).

The U wave was generally discernible at resting heart rates in patients and control subjects (Figure 2). The interval between the Q wave and the beginning of the U wave was 388 ± 27 ms in SQTs patients. The interval from the end of the T wave to the inscription of the U wave in patients was 106 ± 17 ms. The interval between the Q wave and the beginning of the U wave

was 389 ± 20 ms in control subjects, whereas the interval from the end of the T wave to the start of the U wave was 3 ± 12 ms. The interval between the Q wave and aortic valve closure (beginning of isovolumic relaxation) was 389 ± 16 ms in patients and 374 ± 13 ms in control subjects ($P = .14$). The interval from the aortic valve closure to the beginning of the U wave was 8 ± 4 ms in patients and 15 ± 11 ms in control subjects ($P = .25$). Thus, the timing of the inscription of the U wave coincides with the timing of aortic valve closure and the beginning of isovolumic relaxation (Figure 3).

Discussion

The termination of the T wave coincides with closure of the aortic valve, as could be shown in the control group in the present study. Our findings show for the first time that mechanical function is unaltered in SQTs patients despite a dramatic acceleration of repolarization. Ejection times, isovolumic contraction, and relaxation were not significantly different in SQTs and control groups. These results suggest that the marked abbreviation of the ventricular action potential has little effect on the time course of the calcium transient, cell shortening, or mechanical contraction of the ventricles. Such independence of mechanical systole from changes in repolarization forces is also evident in patients with a long QT syndrome, in which the time course of mechanical systole is similar to that of control subjects.¹⁷

In patients with SQTs, electrical repolarization terminates significantly earlier compared with ongoing mechanical contraction (Figure 1). This phenomenon has previously been described in an animal study of O'Rourke et al.¹⁸ and confirmed by Sugishita et al.¹⁹ Kangaroos show a short QT interval. In these animals a striking disparity between mechanical systole and electrical repolarization could be shown (QT interval 214 ± 50 ms versus interval of Q wave to aortic valve closure of 393 ± 70 ms). Furthermore, the investigators showed that with the occurrence of extrasystoles, the myocardium of kangaroos could be excited despite the fact that contraction was not complete, thus resulting in a type of incomplete tetanus.^{18,19}

In patients with SQTs, atrial and ventricular effective refractory periods are significantly reduced.² Very short coupled ventricular premature beats are capable of inducing ventricular tachyarrhythmias in patients with SQTs.²⁰ Whether a similar incomplete tetanus contributes to arrhythmogenesis in humans with SQTs remains to be investigated.

Under physiological conditions the T wave reflects ventricular repolarization. The U wave follows the T wave as a distinct wave under physiological conditions and is often difficult to differentiate from the T wave under pathophysiological conditions such as the long QT syndrome. The electrical hypothesis considers the origin of the U wave as due to delayed repolarization of the His–Purkinje system or other parts of ventricular myocardium. In contrast, the mechanoelectrical hypothesis maintains that the U wave is caused by stretch-induced delayed afterdepolarization caused by distension of the ventricular wall during ventricular filling.^{6,8,9} In patients with SQTs, the U wave is separated from the T wave by > 100 ms, which can be documented in humans as well as in animal models of SQTs (kangaroos). Thus, the inscription of the U wave is independent of electrical repolarization and consistent with the timing of the mechanical activity of the ventricles. The timing of aortic valve closure and the start of isovolumic relaxation coincided with the beginning of the U wave. The question arises as to how isovolumic relaxation, the beginning of which is marked by closure of the aortic valve, can induce an electrical phenomenon visible in the surface ECG.

Mechanically, the cardiac cycle is traditionally divided into IVC, ejection, IVR, and diastole.²¹ Recent thorough analysis of the IVC and IVR phases has shown that these parts of the cardiac cycle are not periods of hemodynamic stasis. Rather, during these phases there is intracavitary displacement of blood and the shape of the ventricles changes. First invasive

studies with analysis of left ventricular ventriculograms described a change of the shape of the left ventricle with an outward and anterior and/or apical movement during isovolumic relaxation.²² An animal study with implantation of ultrasonic crystals in the myocardium to detect strain rate changes of the left ventricle showed that isovolumic relaxation is initiated by subepicardial fiber lengthening with a consecutive asynchronous motion and deformation of the ventricle forming a subepicardial left handed helix.²³ A recent sophisticated echocardiographic study evaluated the intracavitary blood flow during isovolumic periods using high-resolution Doppler and ultrasonic digital particle imaging velocimetry.²⁴ During left ventricular ejection, the flow was continuously in the apex-to-base direction. However, when isovolumic relaxation started with closure of the aortic valve, the intracavitary flow changed briskly in the base-to-apex direction, which was followed by a brief apex-to-base flow. As substantial intracavitary blood flow during the isovolumic phase necessarily is caused by ventricular morphology changes, it is conceivable that myocardial stretch could be the explanation for the U wave in the surface ECG as it occurs at comparable timing. Stretch activates mechanosensitive ion channels that transform changes in stretch or pressure into electrical signals through changes in membrane ion channel permeability.^{25–27} Thus, substantial stretch during the isovolumic phase may induce local membrane repolarization, generating a voltage gradient in the left ventricular myocardium detected as the U wave in the surface ECG. Although the present data favor the mechanoelectrical hypothesis of the generation of the U wave, a direct link to a stretch-induced electrical phenomenon requires further supportive invasive data.

Conclusions

Dissociation between the ventricular repolarization and the end of mechanical systole in patients with SQTs exposes the U wave and demonstrates its independence from electrical repolarization of ventricular myocardium. Coincidence of the U wave with termination of mechanical systole provides further support for the mechanoelectrical hypothesis of the U wave.

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Figure 1.

Echocardiography of control and SQTS patient with simultaneous single-lead ECG recording (bottom line, panel B and C, paper speed 50 mm/sec). **A:** Echocardiographic sector of the parasternal long-axis view with alignment of the M-mode cursor through the aortic valve before application of M-mode echocardiography. The right ventricle (top of each panel) is close to the transducer probe, whereas the left atrium is the most distant structure (white dotted line = M-mode cursor). **B:** M-mode echocardiography of the aortic valve in a proband. Opening and closure of the aortic valve is visible by the rhombus-like echogenic reflections generated by abrupt movements of the anterior cusp and posterior cusps toward and away from the transducer. The termination of electrical repolarization (end of T wave) coincided with the end

of mechanical systole (closure of aortic valve, arrow). **C:** M-mode echocardiography of the aortic valve in a patient with SQTS. Termination of electrical repolarization (end of T wave) preceded end of mechanical systole (closure of aortic valve) by 115 ms (arrow). AV = aortic valve; ECG = electrocardiogram; LA = left atrium; RV = right ventricle; SQTS = short QT syndrome.

Figure 2.

Precordial ECG recordings from a control and a SQTs patient. Inscription of the U wave is indicated by arrow. **A:** Control: QT 360 ms, QTc 397 ms, difference of the end of the T wave to the inscription of the U wave 10 ms. **B:** SQTs patient: QT 270 ms, QTc 392 ms, difference of the end of the T wave to the inscription of the U wave 110 ms (paper speed 50 mm/sec, amplitude gain 20 mm/mV). ECG = electrocardiogram; SQTs = short QT syndrome.

Figure 3.

Tissue Doppler echocardiography recording in a patient with SQTS. Tissue velocity (yellow line, right) with sample volume positioned in the basal interventricular septum in the apical 4-chamber view (yellow circle, left lower view without and left upper view with color Doppler imaging). AVC (vertical green dotted lines) and beginning of isovolumic relaxation is correlating with beginning of the U wave. Left upper corner timings with corresponding blue dotted markers in ECG (bottom right): 1: RR interval (831 ms); 2. interval from Q wave to beginning of the U wave (398 ms, transferred timing from 12-lead ECG); 3. interval from Q wave to aortic valve closure (381 ms). Bottom right single-lead ECG (speed 50 mm/sec). AVC = aortic valve closure; ECG = electrocardiogram; SQTS = short QT syndrome.

Table 1
Electrocardiographic and echocardiographic parameters in SQTs versus control group

	SQTs	Control	P value
Heart rate (beats/min)	72 ± 9	71 ± 8	.8
QT (ms)	268 ± 18	386 ± 20	<.005
QTc (ms)	285 ± 28	420 ± 22	<.005
IVC (ms)	42 ± 15	33 ± 19	.4
Ejection time (ms)	265 ± 29	272 ± 12	.6
ESV (ml)	31 ± 8	31 ± 7	.9
EDV (ml)	85 ± 14	89 ± 18	.7
Ejection fraction (%)	63 ± 6	65 ± 6	.6
IVR (ms)	87 ± 15	75 ± 26	.4
T _{end} -AV closure (ms)	111 ± 30	-12 ± 11	<.005
T _{end} -U wave (ms)	106 ± 17	3 ± 12	<.005
AV closure-U wave (ms)	8 ± 4	15 ± 11	.25
Q-AV closure (ms)	389 ± 16	374 ± 13	.14
Q-U wave (ms)	388 ± 27	389 ± 20	.96

AV closure-U wave = interval from aortic valve closure to start of U wave; ESD = end diastolic volume; ESV = end systolic volume; IVC = isovolumic contraction; IVR = isovolumic relaxation; Q-AV closure = interval from Q wave to aortic valve closure; Q-U wave = interval from Q wave to start of U wave; SQTs = short QT syndrome; T_{end}-AV closure = interval from end of T wave to aortic valve closure; T_{end}-U wave = interval

from end of T wave to start of U wave.