Ventricular dysfunction in a family with long QT syndrome type 3

Yoran M. Hummel1*, Arthur A.M. Wilde2, Adriaan A. Voors1, Silvia Bugatti3, Hans L. Hillege4, and Maarten P. van den Berg1

Aims
Long QT syndrome (LQTS) type 3 is characterized by prolonged ventricular repolarization due to persistent sodium inward current secondary to a mutation in SCN5a, the gene encoding for the α-subunit of the sodium channel. We speculated that by disrupting calcium homeostasis the persistent sodium current in patients with LQTS type 3 might cause derangement of diastolic function. We aimed to identify functional myocardial alterations in a family with a sodium channelopathy with a phenotype of both LQTS type 3 and Brugada syndrome.

Methods and results
The study group comprised 12 SCN5a mutation carriers (SCN5a-1795insD), 9 females and 3 males, mean age 35.7 ± 7.3 years, and 12 healthy controls. In addition to conventional echocardiographic measurements, two-dimensional speckle tracking was performed to assess tissue properties. Mean e’ was lower in the patients compared with the controls (5.6 ± 0.75 vs. 6.7 ± 0.98 cm/s, P = 0.006). Onset QRS to maximum s’ was longer in the patients than in the controls (0.20 ± 0.04 vs. 0.15 ± 0.05 s, P = 0.007), and the number of segments with post-systolic shortening was higher (6.58 ± 2.54 vs. 1.83 ± 1.64, P < 0.001).

Conclusion
Patients in this family with LQTS type 3 showed post-systolic shortening, as well as both left and right ventricular diastolic dysfunction. The underlying mechanism remains to be elucidated but the persistent sodium inward current leading to calcium overload might play a role, in particular regarding diastolic dysfunction.

Keywords
Long QT syndrome • SCN5a • Echocardiography • Speckle tracking • Post-systolic shortening • Sodium channel • Persistent inward current

Introduction
Long QT syndrome (LQTS) is a genetic disorder characterized by prolonged ventricular repolarization, predisposing to ventricular arrhythmias and sudden death. The two most common forms are LQTS type 1 (LQT1) and LQTS type 2 (LQT2), caused by mutations in KCNQ1 and KCNH2, respectively. These genes encode the α-subunits of two potassium channels which carry the slow and rapid component of the outward rectifying potassium current, IKS, and IKr, respectively. Interestingly, although they are considered ‘primary electrical diseases’, several studies have shown that subtle alterations in myocardial function may occur in patients with LQT1 and LQT2.1–4 L QTS type 3 (LQT3), the least common form of the three main forms of LQTS, is caused by mutations in SCN5a, the gene encoding for the α-subunit of the cardiac sodium channel which carries the sodium current (INa). Mutations in SCN5a, however, are not only associated with LQT3, but have also been linked to other arrhythmias, such as Brugada syndrome, sick sinus syndrome, conduction disease, and atrial fibrillation. In addition, evidence is accumulating that they can also be associated with cardiac fibrosis, dilation, and hypertrophy.5–12 In the present study, we extensively evaluated ventricular function, by using state-of-the-art echocardiographic techniques including two-dimensional (2D) speckle tracking echocardiography (STE), in a family with LQT3 due a mutation in SCN5a (‘sodium channelopathy’). We speculated that by disrupting calcium homeostasis the persistent inward sodium current might cause derangement of diastolic function.

*Corresponding author. Tel.: +31 50 3612355; fax: +31 50 3614391, E-mail: y.m.hummel@umcg.nl

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Methods

Study subjects
The study group consisted of 12 adult patients (≥18 years), all members of a previously reported family with features of both LQT3 and Brugada syndrome, and all of them being carriers of the mutant gene (SCN5a-1795insD). The control group consisted of 12 healthy subjects drawn from a large database of control subjects who had served as controls in a previous study. All patients had received a VVI pacemaker. Based on data obtained after interrogation of the pacemaker, only carriers with ≥10% of ventricular pacing were included in the study. Exclusion criteria were hypertension, significant valvular dysfunction, previous myocardial infarction, and use of cardiovascular medication. The study conformed to principles defined in the Helsinki Declaration and informed consent was obtained.

Echocardiography
All echocardiographic studies were performed on a GE Vivid7 (General Electric) by a single sonographer (Y.M.H.), using a 2.5–3.5 MHz probe for image acquisition. All echocardiographic measurements were performed during sinus rhythm. Standard parasternal and apical views were acquired and digitalized for offline evaluation on an EchoPAC station (General Electric). Cardiac dimensions were measured and left ventricular (LV) ejection fraction, LV mass, and left atrial volumes were calculated and indexed to body surface area. Pulsed wave Doppler recordings of mitral valve inflow were acquired to study ‘transmitral’ diastolic LV function. Tricuspid annular plane systolic excursion (TAPSE) was measured through M-mode echocardiography. All echocardiographic measurements were performed according to standard recommendations. Two-dimensional Speckle tracking echocardiography software (EchoPac; General Electric) was used for the assessment of longitudinal LV and right ventricle (RV) tissue deformation, tissue velocity and time intervals. Proper care was taken to avoid apical foreshortening and sampling of the pericardium as described in the recent expert consensus statement on utilization of STE. The measurements consisted of myocardial longitudinal peak systolic strain, systolic tissue velocity (s′) and early diastolic tissue velocity (e′), and time intervals. All measurements were performed offline by STE software in apical four- and two-chamber views, at 61.3 ± 7.8 frames/s. Twelve segments were analysed of the LV myocardium (septal, lateral, anterior, and inferior; at the basal, mid, and apical level) and three segments of the RV myocardium (RV free wall; at the basal, mid, and apical level). For each measurement the mean three cardiac cycles was taken. For the LV as a whole the mean of the 12 individual segments was calculated and for the RV as a whole the mean of the three individual segments was calculated, resulting in a percentage of global longitudinal systolic strain (GLSS). Peak systolic strain and s′ were measured as the maximum value independent of timing within the cardiac cycle. Global longitudinal systolic strain is expressed as percentage and s′ and e′ are expressed in cm/s. On the generated strain and velocity curves the following time intervals in the LV were measured: onset QRS to s′ and onset QRS to peak systolic strain. Finally, the strain curves were used to evaluate the presence of post-systolic shortening. Post-systolic shortening was considered present in case peak systolic strain occurred after aortic valve closure. For this purpose, aortic valve closure was visually marked in an apical three-chamber view.

Statistical analysis
All data are expressed as mean ± SD in case of a normal distribution, and as median with interquartile range in other cases. Comparison of groups was performed using Student’s t-test and correlations were analysed using Pearson’s test. Two-tailed P values < 0.05 were considered significant. The analyses were performed using SPSS (SPSS 18.0, SPSS Inc.).

Figure 1  Echocardiogram with four-chamber apical view (left panel) and two-chamber apical view (right panel). The LV myocardium is divided into 12 segments: 1, basal septum; 2, mid septum; 3, apical septum; 4, apical lateral; 5, mid lateral; 6, basal lateral; 7, basal inferior; 8, mid inferior; 9, apical inferior; 10, apical anterior; 11, mid anterior; 12, basal anterior.
Results

Study subjects

The patient group (‘patients’) consisted of three male and nine female subjects, mean age 35.7 ± 7.3 years. None of them had cardiac symptoms. The control group (‘controls’) consisted of five males and seven females, mean age 35.3 ± 6.2 years. Mean heart rate and mean body surface area in the patients were 64 ± 11 b.p.m. and 1.90 ± 0.24 m², respectively. Mean heart rate and mean body surface area in the controls were 68 ± 11 b.p.m. and 1.95 ± 0.15 m², respectively. The differences between the two groups were not significant (P > 0.05), and the two groups were thus well-matched (Table 1). Mean QTc in the patients and the controls was 0.475 ± 0.050 and 0.397 ± 0.023 s, respectively (P < 0.001). Mean QTc dispersion (precordial leads) in the patients and the controls was 0.048 ± 0.027 and 0.030 ± 0.021 s, respectively (P = 0.097).

General measurements

Data on LV end-diastolic dimension, LV mass, and left atrial volume are shown in Table 1. There were no significant differences between the patients and the controls in any of these three parameters.

| Table 1: Echocardiographic measurements |
|-------------------------------|-------------------|-----------------|-----------------|
|                                | SCN5A mutation   | Controls        | P value         |
|                                | carriers (n = 12) | (n = 12)        |                 |
| LV end-diastolic dimension (cm²/m²) | 2.46 ± 0.23      | 2.46 ± 0.24     | 0.993           |
| LV mass (g/m²)                  | 69.1 ± 16.6      | 71.3 ± 18.7     | 0.764           |
| LA volume (mL/m²)               | 26.5 ± 6.9       | 30.5 ± 8.1      | 0.209           |
| LV systolic parameters          |                   |                 |                 |
| LV ejection fraction (%)        | 0.60 ± 0.06      | 0.56 ± 0.05     | 0.103           |
| Mean s’ (cm/s)                  | 4.75 ± 0.67      | 4.73 ± 0.82     | 0.959           |
| GLSS (%)                        | 21.59 ± 2.81     | 21.33 ± 2.29    | 0.811           |
| LV diastolic parameters         |                   |                 |                 |
| E-wave (m/s)                    | 0.82 ± 0.17      | 0.99 ± 0.15     | 0.024           |
| A-wave (m/s)                    | 0.58 ± 0.11      | 0.59 ± 0.17     | 0.821           |
| E/A ratio                       | 1.40 ± 0.33      | 1.74 ± 0.37     | 0.067           |
| DT (ms)                         | 225 ± 30.6       | 197.8 ± 35.74   | 0.057           |
| IVRT (ms)                       | 91 ± 15          | 85 ± 10         | 0.285           |
| Mean e’ (cm/s)                  | −5.6 ± 0.75      | −6.7 ± 0.98     | 0.006           |
| RV parameters                   |                   |                 |                 |
| TAPSE                           | 25.3 ± 5.2       | 22.0 ± 4.2      | 0.096           |
| Mean RV e’ (cm/s)               | 5.4 ± 1.22       | 7.6 ± 2.5       | 0.038           |
| Mean RV s’ (cm/s)               | 6.8 ± 1.41       | 7.1 ± 2.23      | 0.766           |
| RV GLSS (%)                     | 31.4 ± 5.59      | 30.2 ± 6.13     | 0.684           |
| Time intervals                  |                   |                 |                 |
| Onset QRS to peak systolic strain (s) | 0.39 ± 0.04  | 0.39 ± 0.03     | 0.989           |
| Onset QRS to s’ (s)             | 0.20 ± 0.04      | 0.15 ± 0.05     | 0.007           |

LV, left ventricle; LA, left atrium; RV, right ventricle; GLSS, global longitudinal systolic strain; DT, deceleration time; e’, early diastolic tissue velocity; IVRT, isovolumetric relaxation time; TAPSE, tricuspid annular plane systolic excursion.

Left ventricular systolic function

Left ventricular ejection fraction was comparable in the patients and the controls. There were also no significant differences in mean s’ and global longitudinal systolic strain (GLSS, Table 1).

Left ventricular diastolic function

E-wave velocity was significantly lower in the patients compared with the controls (0.82 ± 0.17 vs. 0.99 ± 0.15 m/s, P = 0.024) and mean e’ was also significantly lower in the patients compared with the controls (5.6 ± 0.75 vs. 6.7 ± 0.98 cm/s, P = 0.006). Representative examples are shown in Figure 2. The other diastolic parameters were not significantly different in the two groups (Table 1).

Right ventricular function

Right ventricular s’ and RV GLSS, as measures of systolic RV function, were comparable in the patients and the controls (Table 1). However, RV e’, as a measure of diastolic RV function, was significantly lower in the patients as compared to the controls (5.4 ± 1.22 vs. 7.6 ± 2.5, P = 0.038).

Time intervals

Onset QRS to peak systolic strain was comparable between the two groups, but onset QRS to maximum s’ was significantly longer in the patients than in the controls (0.20 ± 0.04 vs. 0.15 ± 0.05 s, P = 0.007) (Table 1). For the evaluation of post-systolic shortening, curves of all 12 wall segments were considered separately and we determined the total number of segments showing post-systolic shortening. Patients showed a significantly higher number of segments with post-systolic shortening as compared with the controls; mean values were 6.58 ± 2.54 vs. 1.83 ± 1.64, P < 0.001. Representative examples are shown in Figure 3. Finally, the number of segments showing post-systolic shortening was significantly correlated with both E-wave velocity and e’ (r = 0.46, P = 0.025 and r = 0.43, P = 0.039 respectively).

Discussion

In the present study we investigated ventricular function in a family with LQT3. We found no abnormalities in the patients in terms of LV mass, LV dimension, and LV systolic function. However, the patients showed significant post-systolic shortening as well as diastolic dysfunction of both ventricles. The novelty of our study is that it is the first to show that LQT3 is associated with derangement of ventricular function.

To characterize myocardial function beyond routine echocardiographic techniques we applied STE software which allows direct assessment of the deformation of myocardial tissue (‘strain’) as intrinsic part of myocardial performance. Left ventricular systolic tissue velocity (s’) and GLSS were not different between patients and controls. However, STE software also allowed us to assess the duration of contraction. Onset QRS to s’ was significantly longer in the patients than in the controls. This is a novel finding in patients with LQT3, although it is not surprising given the fact that LQT3 (like LQTS in general) is obviously characterized by prolongation of the action potential and prolongation of contraction can thus be expected. A noteworthy finding is that we provide evidence for the presence of excessive post-systolic shortening in our LQT3 patients.
patients. To a certain extent persistent shortening of individual myocardial segments beyond aortic valve closure is a normal phenomenon, as also demonstrated by our controls (1.83 ± 1.64 of the 12 segments of the LV). However, in the patients the number of segments with post-systolic shortening was much higher (6.58 ± 2.54, P < 0.001). Post-systolic shortening has been documented before in other pathological conditions, including ischaemic or scarred myocardium. In addition, post-systolic shortening has also been shown by Haugaa et al. in patients with LQT1 and LQT2, and it thus appears that more extensive post-systolic shortening is a distinct feature of patients with LQTS. At present, it is unclear how to explain post-systolic shortening in LQTS, but it is probably related to inhomogeneous prolongation of the action potential and hence contraction, some segments showing even more prolongation compared with other segments, even beyond closure of the aortic valve.

In addition to systolic function, we also assessed diastolic LV function. Using transmitral inflow measurements, diastolic LV function was reduced in the patients with a lower value for E-wave velocity. This was supported by diastolic tissue velocity (e'), which was significantly lower in the patients compared with the controls. Interestingly, a significant correlation was observed between the number of segments showing post-systolic shortening and diastolic function; the higher number of segments with post-systolic shortening, the more reduced diastolic function. This suggests that diastolic function was reduced at least in part secondary to systolic dysfunction, that is, post-systolic shortening impedes the diastole by encroaching on diastole. Another explanation might be intrinsic diastolic dysfunction secondary to deranged calcium homeostasis. Indeed, we have shown previously in a mouse model that the SCN5a-1795insD mutation leads to intracellular calcium-overload secondary to increased intracellular [Na⁺] caused by the persistent inward sodium current. This possibility is supported by a study by Moss et al. in patients with LQT3 (due to SCN5a-ΔKPG) on the effect ranolazine, which inhibits the late phase of the inward sodium current. In that study, which primarily focused on the effect of ranolazine on repolarization, ranolazine improved diastolic left ventricular function, although baseline diastolic function was not clearly abnormal. This possibility is also supported by previous studies in other diseases states, like atrial fibrillation, heart failure, and hypertrophic cardiomyopathy, showing that persistent inward sodium current indeed plays a role as a determinant of
diastolic function.\(^{27–29}\) In particular, the study by Coppini et al.\(^{29}\) clarifies that calcium overload mediated by increased intracellular \([\text{Na}^+]\) is responsible for the diastolic dysfunction. Obviously, since our study was merely descriptive the concept that diastolic dysfunction was due to calcium overload (secondary to persistent inward sodium current) remains rather speculative and additional studies are needed to confirm this concept.

Although we thus speculate that the observed alterations of ventricular function are due changes in ion fluxes and concentrations (functional defects) and therefore reversible, it cannot be excluded that structural defects also play a role. Indeed, subclinical fibrosis has been demonstrated in Brugada syndrome, in particular in the right ventricle.\(^6\) We did not find gross structural alterations (e.g. LV mass) in our patients but this does not exclude to possibility of subclinical fibrosis, which, if present, might have contributed to the observed alterations in ventricular function, in particular diastolic function. However, a study by van Veen et al.\(^{30}\) in heterozygous SCN5a knockout mice has shown that the process of fibrosis is age dependent, fibrosis occurring only at advanced age. In addition, very recently van Hoorn et al.\(^{31}\) published data in patients with Brugada syndrome which were evaluated by cardiac magnetic resonance imaging, including late gadolinium enhancement. They found no significant myocardial fibrosis in the patients with SCN5a mutations (mean age 45.1 ± 14.3 years) and the patients without SCN5a mutations (mean age 43.9 ± 12.5 years) compared with the controls (mean age 42.0 ± 8.7 years). In another study utilizing magnetic resonance imaging in patients with Brugada syndrome (mean age 44.8 ± 15.0 years) no evidence was found for RV fibrosis.\(^{32}\) Based on these observations and the fact that mean age in our patient group was relatively low (35.7 ± 7.3 years) we believe it is unlikely that fibrosis contributed significantly to the functional abnormalities observed in the present study.

**Study Limitations**

Speckle tracking echocardiography depends highly on image quality and in some instances it was difficult to reliably analyze all myocardial
segments (data not shown). In addition, the sonographer was not blinded to presence of absence of LQTS. These factors may have influenced the results, in particular the latter factor may have caused a bias. Furthermore, all patients carried a pacemaker for back-up anti-bradycardia pacing with a pacing lead in the RV. Right ventricular pacing may affect myocardial function, both in short term and the long term. However, since we selected patients with a very low percentage of paced beats (<10%) it is unlikely that this factor has played a role. The clinical implications of our findings are as yet uncertain. Of note, no patient suffered from (diastolic) heart failure. However, we believe it is prudent to start treatment early in case of hypertension.

**Conclusions**

In the present study, we showed subtle biventricular dysfunction in a family with a phenotype of both LQT3 and Brugada syndrome due to a mutation in SCN5a. In particular, both LV and RV diastolic function was reduced. The underlying mechanism remains to be elucidated but the persistent sodium inward current leading to calcium overload might play a role, in particular regarding diastolic dysfunction.

**Conflict of interest:** none declared.

**References**


