Effect of Calcium Channel Block on the Wall Motion Abnormality of the Idiopathic Long QT Syndrome

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Background We recently showed the frequent occurrence of an unusual ventricular wall motion abnormality, assessed by echocardiography, in patients with the idiopathic long QT syndrome (LQTS). Two new quantitative indexes were developed: Th1/2 (time needed to reach half of the maximal systolic thickening), which was smaller in LQTS patients than in controls; and TSTh (time spent at a very low thickening rate before rapid relaxation), which was much greater in LQTS patients, indicating the presence of a slow contraction in the late thickening phase. This marked late systolic “plateau,” either rectilinear or with a peculiar double peak pattern, was significantly more frequent in patients with a history of syncope or cardiac arrest. The mechanism underlying this puzzling phenomenon remained unexplained.

Methods and Results The present study assessed the effects of the calcium channel blocker verapamil on the contraction pattern in 10 LQTS patients (9 females and 1 male; mean age, 19±7 years) with a marked plateau pattern and in 6 healthy controls (4 females and 2 males; mean age, 28±5 years). Either verapamil (0.1 mg/kg) or saline was randomly injected over 2 minutes. Saline had no effect. In LQTS patients, verapamil increased Th1/2 by 27%, from 16.9±3.2% to 21.4±3.9% of the cardiac cycle (P=.005), and dramatically reduced TSTh by 92%, from 13.7±5.3% to 1.08±0.6% of the cardiac cycle (P=.0001). At the peak effect of verapamil, the contraction pattern of all patients was normal. In healthy control subjects, verapamil did not significantly change either Th1/2 (from 17.6±2.5% to 18.5±3.5% of the cardiac cycle) or TSTh (from 0.92±0.47% to 1.17±0.74%).

Conclusions This study demonstrates that the wall motion abnormality of LQTS is completely abolished by verapamil. These results suggest that symptomatic LQTS patients may have an abnormal increase in the intracellular calcium concentration before relaxation has completed, possibly linked to an early afterdepolarization, and that the contraction abnormality may be the mechanical equivalent of an early afterdepolarization. (Circulation. 1994;90:2126-2132.)

Key Words • torsade de pointes • death, sudden • depolarizing • verapamil • echocardiography

The idiopathic long QT syndrome (LQTS) is a well-defined clinical entity characterized by ECG signs of prolongation and dispersion of ventricular repolarization, the occurrence of malignant ventricular arrhythmias, and a high mortality among untreated patients. With the exception of the typical alterations present in the ECG, traditional cardiological examination, including cardiac dimensions and dynamics, has always been considered normal in LQTS patients.

In contrast with this traditional view, we have recently shown in a case-control study that unusual ventricular wall motion abnormalities occur frequently in LQTS.8 These anomalies were present in more than 50% of the affected patients. Two new measurements were developed to quantitatively assess the abnormalities. The first, Th1/2, is the time needed to reach half of the maximal systolic thickening; this was smaller in LQTS patients, indicating that the early contraction phase was more rapid than in control subjects. The second, TSTh, is the time spent at a very low thickening rate (<1 cm/s) before rapid relaxation; this was much greater in LQTS patients, indicating the presence of a slow contraction in the late thickening phase. This marked late systolic “plateau” in the contraction pattern was the most prominent characteristic of LQTS patients and appeared either to be rectilinear or to have a peculiar double peak pattern that was never observed in control subjects. Interestingly, this abnormality was significantly more frequent in patients with a history of syncope or cardiac arrest. Thus, that study also provided the first evidence that a noninvasively detected cardiac abnormality was associated with a higher risk for syncope or cardiac arrest.

The present study was undertaken to gain further insights into the potential mechanism of the plateau morphology. The hypothesis was made that the contraction abnormality could be related to an abnormal increase in intracellular calcium that occurred before rapid relaxation. This, together with the anecdotal suggestion of the efficacy of calcium antagonists in patients with prolonged QT interval and torsade de pointes,9 led us to the evaluation of the effects of the calcium channel blocker verapamil on the contraction pattern of LQTS patients with marked thickening abnormalities. Preliminary data have been presented.10

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Methods

Study Population

Ten LQTS patients were included in the present study because of well-marked wall thickening abnormality (9 females and 1 male; mean age, 19±7 years). They all had a prolonged ventricular repolarization (QTc, 545±75 milliseconds12); 6 of 10 were affected by the familial type of LQTS. A history of documented syncope or cardiac arrest was present in 8 of 10 patients. At the time of the study, treatment was as follows: 2 patients were without therapy, 4 were on β-blockers, 1 had undergone left cardiac sympathetic denervation,13 and 3 had undergone left cardiac sympathetic denervation and were also on β-blocker therapy. The β-blocker was either nadolol or propranolol, 1.5 to 3 mg/kg.

Six healthy volunteers (4 females and 2 males; mean age, 28±5 years) with no cardiac abnormality and a normal QT interval (QTc, 414±14 milliseconds12) were also studied to specifically address the effects of verapamil on TSH in healthy subjects.

Echocardiographic Procedure

The procedure was that used in our previous study (Aloka SD 830 echocardiograph).8 Since the most relevant measurements were performed in the M-mode long-axis parasternal view, great care was taken to obtain uniform and good-quality recordings with the ultrasound beam directed perpendicular to the posterior wall. For these measurements, we used a recording of the left ventricular posterior wall in which the endocardium could be identified with precision. The investigator responsible for the identification of the endocardial contour was blinded as to the infused drug. The endocardial movement of a 100-mm/s recording was followed with a graphic pen (Cardio 200, Kontron Instruments). The signal was stored in the built-in computer that also calculated the first derivative of wall thickening. We then obtained the two measurements developed in the previous study.8

The first, Th12, is derived from the endocardial tracing and corresponds to segment AB in Fig 1. The second, TSH, is calculated from the first derivative of the endocardial tracing. The reversal of the movement of the endocardium, ie, the point at which the first derivative definitively crosses the zero line in the downward direction, was taken as the end of this period. TSH is represented by segment CD in Fig 1. Because of the possibility that different heart rates might influence the comparability of these indexes, they were presented as percentage of the cardiac cycle unless otherwise specified.

Drug Administration

A venous line was placed in all patients, and the drugs were infused as a slow bolus of 5 mL over a period of 2 minutes. The drug administered was either verapamil (0.1 mg/kg) or saline, in randomized order. In 4 of the 10 patients, one saline and two verapamil bolus infusions were administered to assess the reproducibility of the effects of verapamil. Also, in 2 patients, a further test was performed in which nitroglycerin (15 μg/kg) was injected to assess the effects of unloading and of reflex tachycardia on the indexes studied. At least 20 minutes was allowed between tests to facilitate a return to baseline. The investigator was asked to choose a recording of the left ventricular posterior wall in which the endocardium could be identified with precision at the following experimental times: baseline, “peak effect” (approximately 1 minute after the end of the drug infusion; range, 30 to 90 seconds), and “recovery” (at least 15 minutes after the end of the infusion). The peak effect measurement will be considered as the result of the drug administration throughout the study.

Data and Statistical Analysis

Unless stated differently, the two echocardiographic indexes are expressed as percent of the cardiac cycle. Mean comparison was performed by Student’s t test on paired or unpaired samples as required. Data are expressed as mean±SD. A value of P<.05 was considered the limit for significance.

Results

Hemodynamics and ECG

Saline had no effect on either blood pressure or heart rate. Verapamil slightly decreased systolic blood pressure (an average of 10 mm Hg [range, 5 to 15 mm Hg] at its peak effect, in both patients and control subjects) and caused a slight but significant increase in heart rate (from 72±15 to 82±15 beats per minute in LQTS patients and from 74±14 to 85±12 beats per minute in control subjects, both P<.005).

Saline had no effect on the ECG variables. In LQTS patients, verapamil, besides increasing heart rate, caused a prolongation of the PR interval from 150±12 to 179±24 milliseconds, P<.005. The QT interval showed a trend toward a decrease in duration after verapamil infusion (QTc from 545±75 to 530±66 milliseconds, P=.063). A modest decrease in the amplitude of the T wave was observed in all patients. This decrease occurred also in the second component of a notched T wave12 in the four patients who clearly showed this abnormality in control conditions. However, this phenomenon could not be reliably quantified, because of the unconventional position of the precordial electrodes and the oblique position of the patients (because of the echocardiographic examination). In control subjects, verapamil tended to increase the PR interval, from 153±24 to 163±32 milliseconds (P=.076), and had no significant effect on the QT interval.

Echocardiographic Analysis

All LQTS patients had a marked abnormality in baseline conditions and, specifically, a prolonged plateau phase in wall thickening before rapid relaxation.

The administration of saline had no effect on left ventricular contraction. Left ventricular diameters, fractional shortening, and the indexes of contraction pattern (Th12 and TSH) were unchanged.
In LQTS patients, verapamil administration caused no significant effect on left ventricular diameters: end-diastolic diameter was 45.8±4.5 mm in control conditions and 44.9±4.2 mm after verapamil; end-systolic diameter was 29.8±2.9 mm in control conditions and 29.6±3.8 mm at the peak effect of the drug. The shortening fraction was also not affected by verapamil (34.8±2.5% before and 34.2±5.2% after verapamil).

By contrast, the administration of verapamil caused a marked change in LQTS patients in the pattern of left ventricular contraction and modified both indexes of contraction pattern. TH1/2 was increased after verapamil by 27%, from 16.9±3.2% to 21.4±3.9% of the cardiac cycle (P<.0005). The most striking effect, however, was on the measure of the slow-speed thickening in late systole, TSTh. This was dramatically reduced, by 92%, from 13.7±5.3% to 1.08±0.6% of the cardiac cycle (P<.00001). Thus, verapamil caused the complete abolition of the plateau morphology, so that at its peak effect the contraction patterns of all patients were normal. Fig 2 illustrates the effect of verapamil on both indexes of contraction pattern.

Figs 3 and 4 show the effect of verapamil in two patients. Fig 3 depicts the most marked abnormality observed in our population. This figure also clearly shows that the contraction abnormality was not confined to the posterior wall but rather was clearly visible in the septum as well. Verapamil completely abolished the plateau morphology both at the posterior wall and at the septal level. The effect was transient, and the contraction pattern returned to its baseline aspect within 20 minutes after verapamil administration.

When these indexes are examined as to actual duration, rather than as a percentage of the cardiac cycle, the increase in TH1/2 is substantially diminished, because of the shorter cycle length after verapamil (146±38 milliseconds in control conditions and 160±35 milliseconds after verapamil, P=NS). Conversely, the main change observed, i.e., the decrease in TSTh, is further magnified (120±65 milliseconds in control and 8±4 milliseconds after verapamil, P<.00001).

In the four patients in whom two verapamil bolus infusions were administered, the effect of the drug was reproducible. Specifically, TSTh was 0.82±0.16% of the cardiac cycle after the first bolus and 0.98±0.33% after the second bolus, indicating the complete disappearance of the plateau morphology in both cases.

In two patients, the effects of verapamil and nitroglycerin were compared to assess whether the effects observed after verapamil were dependent on its unloading effect and the consequent reflex tachycardia. In these two patients, mean systolic blood pressure was reduced from 95 to 79 mm Hg by nitroglycerin and to 83 mm Hg by verapamil. The tendency toward a greater unloading with nitroglycerin was supported by smaller cardiac diameters (mean left ventricular end-diastolic diameter was 40 mm and 42 mm with nitroglycerin and verapamil, respectively; mean end-systolic diameter was 23.5 and 25.5 mm, respectively) and higher heart rates.
(87 versus 80 beats per minute after nitroglycerin and verapamil, respectively). The response of the contraction index, however, was completely different. Mean Th1/2 increased with verapamil from 14.36% in baseline conditions to 18.51%, whereas it decreased with nitroglycerin to 12.95%; more importantly, mean TSTh was markedly reduced, as expected, from 11.80% to 1.77% with verapamil but actually tended to increase to 12.69% of the cardiac cycle with nitroglycerin.

No significant effect of verapamil was noted on either index of contraction in the control group. Th1/2 was 17.6 ± 2.5% in baseline conditions and 18.5 ± 3.5% after verapamil, whereas TSTh was 0.92 ± 0.47% in baseline conditions and 1.17 ± 0.74% of the cardiac cycle after verapamil. Also, systolic and diastolic diameters and shortening fraction were not affected by verapamil in the control subjects.

Discussion

This study assessed, in a group of patients with idiopathic LQTS, the effects of calcium channel block on the abnormality in left ventricular wall thickening. Verapamil dramatically abolished the contraction abnormality and, specifically, the plateau morphology (rectilinear or double peaked) that is strongly correlated with a history of malignant arrhythmia. This finding points to the presence of an abnormality in intracellular calcium handling in these patients and is relevant to the understanding of the mechanism(s) involved both in the mechanical abnormality and in the occurrence of malignant arrhythmias in these patients.

Patient Population

The patients enrolled were selected on the basis of the presence of a marked contraction abnormality; it is important to note that they can be considered typical cases of LQTS. This clinical judgment was substantiated by the use of a new scoring system for the diagnosis of LQTS. According to these criteria, there is an intermediate probability of LQTS for a diagnostic score of 3 and a high probability for a score ≥4. The average diagnostic score of these patients was 5.5. Symptoms of syncope or cardiac arrest were present in 8 of 10 patients and a familial history in 6 of 10.

Characteristics of the Abnormality

The overall pattern of the abnormality in wall thickening present in more than 50% of the patients has been discussed in detail in our previous case-control study, which also describes the two indexes of contraction, Th1/2 and TSTh, used in this study.

The lack of any dyssynergy in contraction on twodimensional images suggested that the abnormality was present throughout the left ventricle. The clear visual-
ization of the abnormality in the septum in several patients in this study and, particularly, its simultaneous abolition by verapamil both at the septal and posterior wall level strongly support this concept.

The present study has also shown that the indexes previously proposed to assess the abnormality in wall thickening can adequately quantify the effects caused by an intervention. These new indexes may become useful in conditions other than LQTS. Specifically, it may become logical to measure these indexes in patients with prolonged ventricular repolarization (eg, drug-induced) and a history of syncope or cardiac arrest. The demonstration of a plateau pattern before rapid relaxation would support the hypothesis of torsade de pointes as the mechanism of syncope. Anecdotally, a markedly prolonged TSTh was found in an infant with a drug-induced QT prolongation and cardiac arrest.14

**Effects of Verapamil**

Verapamil caused a modest decrease in blood pressure, accompanied by a mild but significant tachycardia. By contrast, its effect on the plateau morphology in LQTS patients was striking and exceeded our own anticipations. It is very unlikely that this was the non-specific result of a different ventricular load, contractile state, or heart rate, for three main reasons: (1) verapamil did not cause any significant change in healthy control subjects; (2) the effects on the contraction pattern were dramatic, but no change was observed in left ventricular diameters and shortening fraction; and (3) in the two patients studied, nitroglycerin, although it caused both a greater unloading and a greater reflex tachycardia, did not reduce TSTh but actually tended to increase it, whereas verapamil completely eliminated the plateau morphology.

**Potential Mechanisms**

The complete abolition by verapamil of the wall thickening abnormality indicates that this derives from an abnormality in calcium handling. The prolonged plateau and the double peak may be the mechanical expression of either the sustained presence of elevated calcium concentrations in late systole and early diastole or, more likely, of a secondary and delayed rise in intracellular calcium.

Although the underlying mechanism causing the contraction abnormality has not yet been conclusively identified, the results of this study allow several logical speculations and the formulation of a tenable hypothesis. Under physiological conditions, the sarcoplasmic reticulum is the main store and source of cytosolic calcium.15 Calcium is actively transported into the sarcoplasmic reticulum, and this transport is markedly enhanced shortly after tension development. Calcium can also be released from the sarcoplasmic reticulum through calcium channels.16 The secondary increase in intracellular calcium concentration that appears to be at the basis of our results is likely to derive from an imbalance in these two opposite fluxes and, particularly, from an increased sarcoplasmic calcium release.

It has been reported that verapamil may cross the sarcolemma and accumulate within the cardiomyocytes.17 The demonstration of a binding site for phenylalkylamines in the sarcoplasmic reticulum18,19 suggests that verapamil and closely related drugs may interfere with sarcoplasmic function. Indeed, it has been suggested that verapamil may decrease calcium release from the sarcoplasmic reticulum.20 Thus, the effect of verapamil may theoretically derive from the direct inhibition of sarcoplasmic calcium release. However, both the uncertainty of the physiological relevance in humans of the in vitro studies and the extremely short latency between infusion of the drug and effect on the contraction abnormality (peak effect within 1 minute after the injection) suggest that a direct intracellular effect is unlikely.

An alternative hypothesis suggests a role for early afterdepolarizations (EADs). The role of EADs in torsade de pointes, the typical arrhythmia of long QT interval syndromes, was suggested by the demonstration that prolongation of repolarization by cesium in the dog produces EADs and an arrhythmia indistinguishable from the clinical form of torsade de pointes.21 Subsequently, several studies supported the relation between the presence of EADs and the occurrence of torsade de pointes.22-26 Strong evidence for the presence of EADs and for their role in the genesis of prolonged and abnormal repolarization as well as of torsade de pointes has been provided in individual patients affected by both congenital27 and acquired28 LQTS.

Although EADs may be caused by any mechanism that produces an increase in inward currents or a decrease in repolarizing currents,29 January and colleagues30-32 have provided evidence that EADs originating from the action potential plateau are likely to derive from the recovery from inactivation and subsequent reactivation of L-type calcium channels. The inward flux of calcium linked to the EAD may cause a small but rapid increase in intracellular calcium, which may be sufficient to trigger the calcium-induced release of calcium from the sarcoplasmic reticulum,33 causing a much greater increase in cytosolic calcium and the occurrence of a second contraction or the prolongation of the contraction itself. This hypothesis is in agreement with the observation that, in ventricular myocytes, action potentials with EADs show greatly prolonged calcium transients.34 Also, in rat ventricular muscle subjected to moderate cellular calcium overload by rose bengal, EADs have been shown to be accompanied by a secondary contraction.35

It is on this basis that we now suggest that the LQTS patients examined in this study may have EADs mediated through L-type calcium channels that allow an inward flux of calcium, which, in turn, may induce a sarcoplasmic release of calcium and a prolonged or double-peaked contraction. Verapamil, by blocking L-type calcium channels, would markedly decrease EAD amplitude and thus block the cascade of events that leads to the contraction abnormality. This mechanism would account for the strong correlation between the plateau aspect of wall thickening and the presence of malignant arrhythmias.8 It would also fit with the anecdotally reported effectiveness of calcium antagonists in the treatment of some patients with LQTS who do not respond adequately to β-adrenergic blockade5-9 and, more generally, with that of the "natural" calcium
antagonist magnesium in the treatment of torsade de pointes.22,36

Pathogenetic and Therapeutic Implications

Our group has suggested two pathogenetic mechanisms as the potential cause of LQTS. One is the "sympathetic imbalance" hypothesis,1,2,23 and the other is the "intracardiac abnormality" hypothesis.24 In either case, the triggering event for the life-threatening arrhythmias would be a sudden increase in sympathetic activity.2,5 The findings of this study and the proposed mechanism for the effect of verapamil are in agreement with either hypothesis. A sufficient prolongation of action potential duration would allow the recovery from inactivation of L-type calcium channels and cause an EAD. In symptomatic LQTS patients, EADs may be present at subthreshold level also in basal conditions, not leading to arrhythmias but causing the contraction abnormality. An increase in sympathetic activity mediated mainly via the quantitatively dominant left-sided sympathetic nerves, as such occurs in the experimental setting,23 would bring these EADs to threshold and cause the occurrence of malignant arrhythmias.

These considerations also suggest that the antiarrhythmic efficacy of calcium antagonists should be assessed in LQTS patients who are not responsive to β-blockade and left cardiac sympathetic denervation, particularly if they show the contraction abnormality.

Conclusions

Block of the calcium channel by verapamil markedly influenced the contraction pattern of LQTS patients, completely abolishing the abnormal plateau. This suggests that these patients have an abnormal increase in intracellular calcium concentration before relaxation has completed, possibly linked to an EAD. Thus, the specific contraction abnormality we described may be the mechanical equivalent of an EAD, and calcium entry blockers may be a promising therapeutic approach in patients unresponsive to antiadrenergic interventions.

Acknowledgments

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