QT Interval Response to Exercise in Children with Syncope

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Recurrent syncopal episodes in children and adolescents are a common occurrence. Orthostatic testing is widely accepted as a useful method for evaluating these patients.[1,2] The response to the orthostatic challenge can be vasodepressor (an initial decrease in blood pressure followed by bradycardia), cardioinhibitory (asystole for several seconds or severe bradycardia), or mixed. Autonomic dysfunction has been postulated as a possible underlying mechanism for these syncopal episodes; cardiac and peripheral vascular autonomic control appear to play a role.[3,4] Patients with tilt test–induced syncope (tilt+) have been noted to have a significantly greater prolongation in their corrected QT interval (QTc) in response to isoproterenol infusion than those who did not develop syncope in response to the same tilt test (tilt−).[4] Moreover, subjects with autonomic dysfunction, i.e., familial dysautonomia, have a prolongation of the QTc with changes in position as well as a failure of QTc shortening with exercise.[5] This study evaluates the response of the QTc to exercise in tilt+ and tilt− patients. We hypothesize that the effects on cardiac repolarization observed with isoproterenol infusion in tilt+ patients will also be seen in the tilt+ subjects in response to exercise (presumably because of endogenous catecholamines).

The 14 patients (8 females and 6 males, mean age 12.9 years [range 6.5 to 17]) who were evaluated had a history of at least 1 episode of syncope. All patients had a thorough history and physical examination. All except 1 patient with mitral valve prolapse had a normal cardiac examination. Echocardiograms were obtained in 12 patients. With the exception of the patient with mitral valve prolapse, all echocardiograms were normal. No patient had an arrhythmia at rest. Three of the patients had a neurologic evaluation that included clinical evaluation as well as electroencephalogram, computerized tomography, or magnetic resonance imaging of the head; all were normal.

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TABLE I Hemodynamic Measurements

	Heart Rate	Systolic BP (mm Hg)	Diastolic BP (mm Hg)
Tilt+			
Supine	76 ± 12	116 ± 15	63 ± 7
Standing 1 minute	105 ± 33 *	112 ± 15 **	64 ± 6
Syncope	71 ± 50	73 ± 40 *	42 ± 23
Tilt−			
Supine	79 ± 13	116 ± 15	70 ± 15 †
Standing 1 minute	92 ± 21 †	122 ± 22 *	71 ± 14
Standing 20 minutes	101 ± 15	120 ± 17	70 ± 7

*p <0.05; †p <0.01.
BP = blood pressure.

The syncope evaluation was performed in the outpatient setting. Testing was performed in the midmorning after a light breakfast. In the exercise laboratory, a heparin lock was placed in the forearm or anticubital fossa. Electrocardiographic leads were placed to obtain a 12-lead electrocardiogram and to facilitate monitoring during the tilt and exercise tests. After spending 1 hour in the supine position, the patients were moved smoothly to the erect position; minimal movement was encouraged. The patients were maintained in the erect position for 20 minutes, or until syncope or intolerable symptoms developed. Heart rate was monitored constantly. At 1-minute intervals, blood pressure was measured using a Dinamap monitor (model 1846 SX, Critikon Inc., Tampa, Florida) with a cuff of appropriate size. In addition, 3-lead electrocardiograms were recorded. In the event of syncope, the patients were allowed to recover in the supine position. Otherwise, a period of rest for a few minutes was allowed before maximal exercise testing using a cycle ergometer. Electrocardiogram recordings were obtained at rest, during standing and hyperventilating, and at the end of every 3-minute stage of exercise, as well as at 1, 3, and 5 minutes after exercise. Patients exercised to maximal voluntary effort. The QT and corrected QTc ($QT/\sqrt{RR}$) intervals were measured from each electrocardiogram. The QT was measured from the beginning of the QRS complex to the intercept point of a tangent to the downslope of the T wave and the isoelectric line[5] (Figure 1).

TABLE II QT and QTc Intervals with Position Changes and During and After Exercise (ms)

	Tilt+		Tilt−	
	QT	QTc	QT	QTc
Supine	393 ± 25	424 ± 34*	379 ± 48	415 ± 34
Standing	356 ± 20	458 ± 29	354 ± 32	426 ± 34
Peak exercise	233 ± 32	406 ± 28*	245 ± 26	410 ± 36
After exercise				
1 minute	257 ± 29	409 ± 15*	280 ± 29	413 ± 20
3 minutes	283 ± 31	420 ± 20*	310 ± 30	415 ± 17
5 minutes	313 ± 23	425 ± 26	334 ± 26	416 ± 21

*p <0.04 (for tilt+ patients when compared with standing QTc).

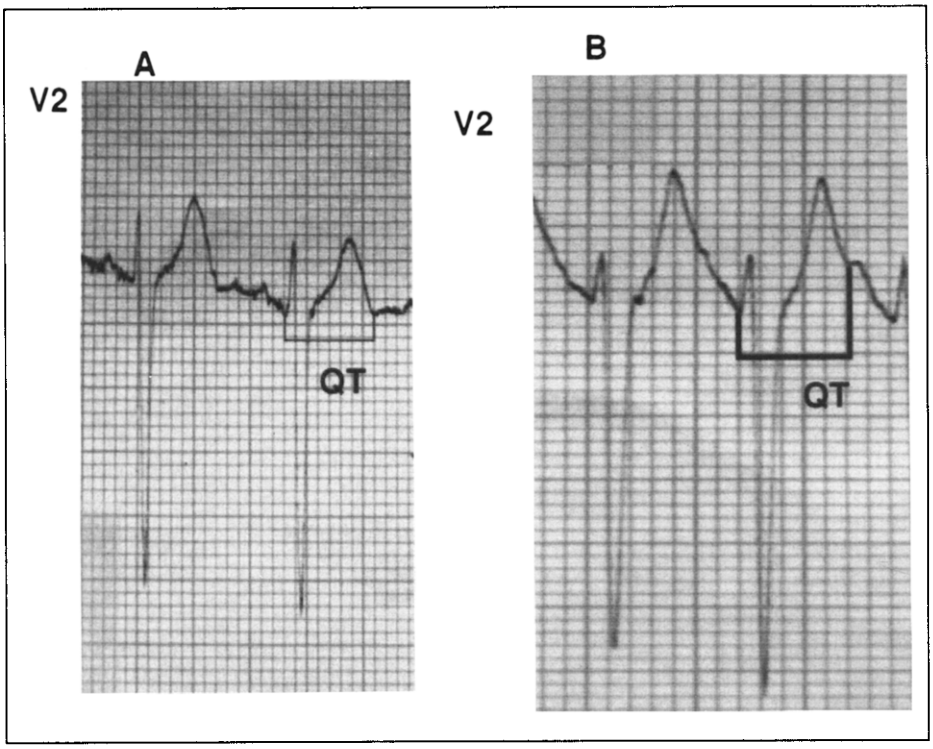

FIGURE 1. Measurement of the QT interval in a patient with syncope. *A*, at rest; *B*, at maximal exercise. The QT measurement on each electrocardiogram is shown. The paper speed is 25 mm/s.

Mean and SD were computed for each variable. Unpaired and paired Student's t *tests were used to assess differences between groups and within each group, respectively. Chi-square analysis was used when appropriate.*

Syncope in our patients was not arrhythmogenic. There were 6 tilt+ and 8 tilt− patients. Vasodepressor-type syncope was observed in 5 patients. A sixth patient had the cardioinhibitory type. There was no significant difference between the tilt+ and the tilt− groups with regard to sex distribution, age, heart rate at any stage of exercise, or exercise work load achieved, although the tilt+ patients tended to achieve higher heart rate and exercise for a longer duration. Table I depicts the hemodynamic responses during tilt testing. The tilt+ patients had a significant increase in heart rate after standing. There was no acute change in blood pressure immediately after standing, but at the time of syncope there was a significant decrease in blood pressure.

Table II lists the values of the QT and QTc during rest, standing, peak exercise, and during the recovery period after exercise. There was no significant difference in the QT and QTc between the tilt+ and tilt− groups at any phase of the testing. During exercise, the response of the QT and QTc in both groups was normal, with shortening of both intervals. The QTc in the erect position (immediately before the exercise test) was prolonged (i.e., >0.44) in 4 of the tilt+ and 1 of the tilt− patients (p = 0.053). The QTc in the tilt+ group was significantly longer during standing than at any other stage of the test (for the tilt+ group only). None of the patients had an abnormally prolonged QTc at rest or during the recovery period. No patient had any arrhythmia during exercise testing.

The autonomic nervous system has been shown to affect heart rate, blood pressure, and QT interval.[3,4] We have shown that both tilt+ and tilt− subjects demonstrate a normal QTc response during and after exercise. However tilt+ patients (patients with a significant increase in heart rate and subsequent decrease in blood pressure and heart rate) have a significant increase in QTc when brought from the supine to the standing position. This QTc shortened with exercise and remained shortened during the recovery period. The change in QTc with the assumption of the erect position is similar to that observed in patients with familial dysautonomia.[4] However, in contrast to those patients, the QTc in our subjects shortened during exercise. Glickstein et al[4] suggested a derangement in the autonomic regulation of cardiac conduction by parasympathetic overdrive as the etiology of QTc prolongation in familial dysautonomia. Our group of tilt+ patients also had evidence of parasympathetic overdrive during tilt testing. Thus, the change in QTc in our patients and in those with familial dysautonomia may be a subtle marker of autonomic dysfunction. In contrast, both isoproterenol and epinephrine infusion prolonged QTc in the tilt+ patients and in normal subjects, respectively.[3] We did not observe this QTc response during our exercise testing. Thus, this physiologic stimulation of catecholamines did not mimic the pharmacologic challenge.

In conclusion, pharmacologic challenges can produce changes in the QTc interval that differ from those observed under physiologic conditions. The changes in the QTc interval observed with physiologic challenges appear to be a marker of autonomic dysfunction.

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Comparison of Single Dose *Nifedipine* and *Captopril* for Chronic Severe Mitral Regurgitation

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In severe mitral regurgitation (MR), short-term treatment with intravenous nitroprusside[1] or intravenous[2] or oral[3] hydralazine reduces systemic resistance and wedge pressure and increases cardiac output. Although no long-term studies in MR have been conducted, long-term oral treatment with hydralazine in aortic regurgitation was complicated by frequent adverse effects.[4] Two newer classes of vasodilator agents, the angiotensin-converting enzyme inhibitors and calcium channel antagonists, which are better tolerated, are now widely used for other cardiovascular disorders. However, comparative studies of neither short- or long-term effects of these agents have been reported for MR. We have recently compared the hemodynamic effects of single-dose nifedipine and captopril in chronic severe aortic regurgitation,[5] but since loading conditions in aortic and mitral regurgitation are different,[6] response to these vasodilators may be different. This protocol was therefore extended to patients with chronic severe MR.

Patients who were being referred for isolated mitral valve replacement due to isolated, chronic, severe MR were recruited if they were in normal sinus rhythm, were at or older than age 14 years, and did not have echocardiographic, clinical or serologic evidence of either infective endocarditis or active rheumatic carditis. During 1992, 16 consecutive such patients were identified and gave informed consent to a protocol approved by the ethics committee of the University of Witwatersrand. Precatheterization evaluation included 2-dimensional echocardiography and Doppler color flow mapping by which all patients were judged to have severe MR: jet area >50% of left atrial area or, when jets were adherent to the left atrial wall, obvious failure of anterior and posterior mitral leaflet coaptation. Although the duration of symptoms was difficult to ascertain, no patient was believed to have acute MR, since none presented with abrupt onset of acute symptoms (<4 weeks), and all had LV enlargement. All but 4 were judged to have MR of rheumatic etiology; the mitral valve was purely or predominantly incompetent (valve area >2 cm^2) in all patients. None were currently taking vasodilator therapy. Diuretics were continued in all patients until the evening before catheterization. Digoxin was not used. None of the patients had an elevated serum creatinine or low serum sodium.

Patients were randomized in a double-blind fashion to treatment with either oral nifedipine 20 mg (n = 8) or captopril 50 mg (n = 8).

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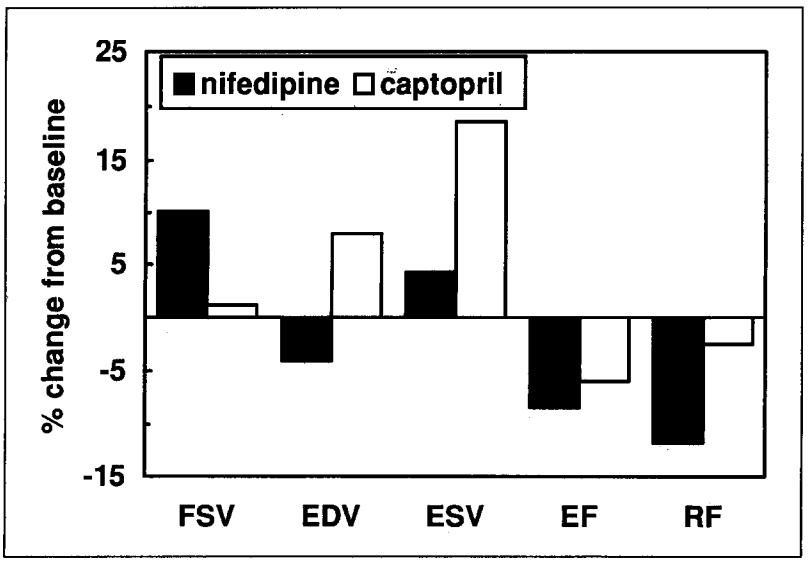

FIGURE 1. Effect of nifedipine and captopril on mean arterial pressure (MAP), systemic vascular resistance (SVR), heart rate (HR), pulmonary capillary wedge pressure (PCW) and cardiac output (CO), expressed as the mean of the individual percent changes for each patient from baseline. *Significant (p <0.05) drug effect and the p values indicate significant between-group differences as in Table I.