Long-Term Improvement of QT Dispersion is Unaffected by Short-Term Changes in Blood Pressure During Treatment of Systemic Hypertension with Enalapril

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Background: We report the reduction of QT and QT_c dispersion in patients treated for 7 years with enalapril for systemic hypertension with left ventricular (LV) hypertrophy. We assess the correlation between QT dispersion and LV mass during this period and at the end of an 8-week period of suspension of enalapril treatment after 5 years.

Methods: Twenty-four previously untreated patients with this condition took enalapril (20 mg twice daily) for 7 years, except during an 8-week period following 5-year follow-up. Cardiovascular parameters were determined by two-dimensional guided M-mode echocardiography, and QT interval was measured, in a pretreatment placebo phase, 8 weeks and 1, 3, 5, and 7 years after the start of the therapy, at the end of the 8-week suspension effected after 5 years, and 8 weeks after the end of the suspension.

Results: Therapy rapidly reduced blood pressure (BP) from 156/105 mmHg to normal values: 134/84 mmHg after 8 weeks' treatment, 130/84 mmHg at 7-year follow-up ($P < 0.001$ with respect to the placebo phase). LV mass index decreased progressively until at 5-year follow-up the reduction had reached 39% ($P < 0.001$), after which neither LV mass nor any other structural parameter underwent any further significant change. During this time, QT dispersion (Δ QT) and the dispersion of "corrected" QT (Δ QT_c) decreased significantly: Δ QT (from 61 ± 21 to 37 ± 13 ms) and Δ QT_c (from 67 ± 27 to 41 ± 16 ms). After suspension of treatment for 8 weeks following 5-year follow-up, Δ QT was 40 ± 14 ms and Δ QT_c was 44 ± 17 ms; there were no significant changes either in Δ QT and Δ QT_c or LV hypertrophy although BP had returned to pretreatment values (BP: 150 ± 16 ; 101 ± 10 mmHg).

Conclusions: Long-term enalapril treatment of hypertensive patients with LV hypertrophy induces marked regression of LV mass and improvement of QT dispersion. These improvements occur on a longer timescale than improvement in BP, and are not affected by transient changes in BP values.

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hypertension; QT dispersion; left ventricular mass; enalapril

The QT interval is the total electrocardiographically measured duration of ventricular electrical activity, including depolarization and repolarization. QT dispersion (Δ QT) is defined as the difference between the largest and the smallest of the 12 QT values afforded by a 12-lead electrocardiogram (ECG), and is a measure of regional variation in ventricular repo-

larization.^{1,2} As such, Δ QT is believed to be of value for prediction of the risk of ventricular arrhythmias: increased Δ QT has been proposed as a predictor of future arrhythmic events in patients with idiopathic long QT syndrome,³ previous myocardial infarction,^{4,5} idiopathic dilated cardiomyopathy,^{6–8} hypertrophic cardiomyopathy,⁹ electrolyte

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abnormalities,¹⁰ and chronic exposure to certain drugs.^{11,12} High ΔQT has also been observed in hypertensives with LV hypertrophy (LVH). However, ΔQT has been questioned as a marker of heterogeneity of repolarization. These authors argue that inhomogeneity of ventricular repolarization could be related to a greater variability in T-loop morphology (width, amplitude, and axis of T wave) and this could be connected with an increase in ΔQT .¹³

In this study, we evaluate the evolution of ΔQT and ΔQT_c over 7 years in a group of hypertensives with LVH who were being treated with enalapril.^{14,15} We found that improvement of QT dispersion largely occurred on a longer timescale than changes in BP, and was closely related to regression of LVH.

METHODS

Patients

We studied a group initially composed of 28 previously untreated hypertensives (20 men and 8 women aged 50 ± 10 years in the range of 35–64 years) who gave their informed consent. All were diagnosed as having essential arterial hypertension on the basis of seated diastolic blood pressure (BP_s) between 95 and 114 mmHg in three triplicate measurements over a period of 3 weeks, absence of symptoms, and absence of signs and history of any other cardiovascular disorder.

All the patients took 20 mg of enalapril every 12 hours for 5 years (59 ± 1 months). Only two patients required less than 40 mg/day to achieve normal BP; these two exceptions achieved normal BP with 20 mg/day within 6 weeks treatment, but similar to the others took 40 mg/day thereafter. At that time the treatment was interrupted for 8 weeks, after which it was resumed (the 12-hourly dose being increased progressively from 2.5 to 20 mg). At their 7-year check-up all the patients had normal BP_s .

During the 7-year course of the study (87.1 ± 1.4 months), full clinical histories were obtained, arterial blood pressures were determined, and echocardiography was performed at the following times: after a pretreatment placebo period, at 8 weeks and 1, 3, and 5 years after the commencement of therapy, after the 8-week suspension of therapy, 8 weeks after the resumption of therapy and 6 years (74.2 ± 1.4 months) and 7 years (87.1 ± 1.4 months) after the commencement of treatment.

Two of the 28 patients abandoned the study in its early stages: one after 2 months because of irritant cough and the other after 4 months due to gastrointestinal problems. Two more were excluded during the 6th year when they were taken off enalapril and put on a calcium antagonist, persistently hypertensive blood pressures (diastolic $BP_s > 100$ mmHg) having failed to respond to the combination of enalapril and a low dose of a thiazide. A fifth patient underwent surgery for breast cancer after enalapril treatment for 4 years, but is still in the study group.

BP Measurements

BP was measured with a mercury sphygmomanometer 12 hours after the latest dose of enalapril. All measurements were made on the same arm. Resting BP_s were taken with the patient seated. The values used in subsequent statistical analyses were the means of three measurements taken at intervals of at least 5 minutes, starting 10–15 minutes after the patient had sat down. Systolic BP and diastolic BP were determined during Korotkoff sounds 1 and 5, respectively. Heart rate (beats/min) was determined by palpation of the radial artery for 60 seconds.

Echocardiography

M-mode echocardiography with a Siemens Sonoline CD echograph and 2.5 MHz transducer was used to measure (in mm) the diastolic thicknesses of the interventricular septum and the posterior wall of the left ventricle, and the diastolic and systolic diameters of the cavity; two-dimensional images taken from longitudinal or transverse parasternal views were used to insure that all measurements were made at the same level (just above the papillary muscles). The values used in subsequent calculations were the means of four to six measurements made during successive heartbeats. All echocardiographic recordings were made and interpreted by the same cardiologist (J. R. G-J.), who was ignorant of the treatments of the patients and their participation in this study. The intraobserver coefficients of variation of septal thickness (7.2%), LV wall thickness (6.0%), and diastolic LV diameter (3.1%) were calculated as the medians, over all patients, of the coefficients of variation calculated for each patient, these intrapatient coefficients of variation being calculated as $100 \times$ (the difference between the values measured at the

beginning and end of the placebo period/the mean of these two values).

LV mass in grams was calculated, following Devereux and Reichek,¹⁶ as $1.04 \times ((\text{diastolic LV diameter} + \text{septal thickness} + \text{LV wall thickness})^3 - \text{diastolic LV diameter}^3) - 13.6$; LV mass index as LV mass divided by body surface area in square meters; and relative LV wall thickness as $(\text{LV wall thickness} + \text{septal thickness})/\text{diastolic LV diameter}$. LV fractional fiber shortening (%) was calculated as $100 \times (\text{diastolic LV diameter} - \text{systolic LV diameter})/\text{diastolic LV diameter}$; circumferential fiber shortening velocity (circ/s) as $\text{LV fractional fiber shortening}/(100 \times \text{ejection time})$, (LV ejection time in seconds was determined from M-mode measurements of the aortic root); and LV ejection fraction (%) as $100 \times (\text{diastolic LV diameter}^3 - \text{systolic LV diameter}^3)/\text{diastolic LV diameter}^3$.

Electrocardiogram Evaluation

Standard 12-lead ECGs were recorded at a paper speed of 25 mm/s and these data were fed into a personal computer in digital form using an optical scanner. For three consecutive cycles in the record of each of the 12 electrocardiographic leads, two blind observers used calipers to measure QT, the interval from the onset of the QRS complex to the end of the T wave (defined as the return to TP baseline; when a U wave was present; the return to baseline was taken as the point of intersection between the baseline and the tangent to the descending limb of the T wave). The QT for each lead was calculated as the mean over the three cycles, and the absolute QT dispersion (ΔQT) was calculated by subtracting the shortest of these 12-lead-specific QTs from the longest. This value was converted into a percentage ($\%\Delta\text{QT}$) by dividing ΔQT by the shortest lead-specific QT interval and multiplying by 100 ($\%\Delta\text{QT} = ((\text{QT}_{\text{max}} - \text{QT}_{\text{min}})/\text{QT}_{\text{min}}) \times 100$). Each lead-specific QT was "corrected" for the patient's heart rate using Bazett's formula ($\text{QT}_c = \text{QT (ms)}/(1000 \text{ ms}^{-1} \text{ RR (ms)})^{1/2}$,¹⁷ and an absolute QT_c dispersion (ΔQT_c) was calculated by subtracting the shortest lead-specific QT_c from the longest, subsequently expressed as a percentage ($\%\Delta\text{QT}_c = ((\text{QT}_{c\text{max}} - \text{QT}_{c\text{min}})/\text{QT}_{c\text{min}}) \times 100$). The QT dispersion ratio (ΔQT_r) was calculated as QT dispersion (ΔQT) divided by the cycle length in milliseconds and multiplied by 100.

The reliability of the QT measurements was checked by numbering and duplicating 20 ECGs in which they were measured independently by

the two observers. The average percentage differences in QT measurements for the same ECG were 4–5% for within-observer variability and 5–7% for between-observer variability.

Statistical Analysis

Results are expressed below as means $\pm$ standard deviations. Normal distributions were identified by the Shapiro-Wilk test. The significance of differences between groups was estimated using Friedman's test. Proportions were compared using Fisher's test.

RESULTS

One of the criteria for inclusion in the study had been that normal BP should be achieved within 8 weeks of the start of enalapril treatment. After 5 years, all the patients remained normotensive, but 8-week suspension of treatment sufficed to return resting BP values that, for the group as a whole, did not differ significantly from pretreatment values ($150 \pm 16/101 \pm 10$ mmHg after 5 years, $156 \pm 14/105 \pm 6$ mmHg at pretreatment). Only six patients remained normotensive, with diastolic $\text{BP}_s < 95$ mmHg. Eight weeks after the resumption of enalapril therapy, all except four patients were normotensive again, with resting blood pressures of $128 \pm 12/82 \pm 5$ mmHg (Fig. 1). Four patients were put on enalapril plus low dose of thiazide treatment.

LV mass index fell by 39% during the first 5 years treatment, from 148 ± 34 to 90 ± 16 g/m²

Figure 1. BP during 7 years of enalapril treatment. Eight-week suspension of treatment after 5 years raised BP to pretreatment values.

($P < 0.001$), and septal thickness and LV wall thickness also fell significantly during this time, whereas LV fractional fiber shortening and LV ejection fraction were significantly greater after 5 years treatment than during the pretreatment placebo phase ($P < 0.01$ and $P < 0.05$, respectively). At no subsequent examination did either the LV mass index or any index of the LV structure or function exhibit any significant difference from the values recorded at 5-year follow-up; in particular, the 8-week suspension of treatment following 5-year follow-up had no significant effect (Table 1 and Fig. 2).

Serum glucose, cholesterol, creatinine, and Na^+ concentrations remained unaltered over the 7 years of the study (during which no patient received treatment for antihyperlipemia). K^+ concentration underwent a marginally significant increase from 4.1 to 4.9 mEq/L during the 1st year ($P = 0.048$), but thereafter returned to lower levels. There were no statistically significant changes in blood cell count and related parameters (hemoglobin, hematocrit, platelet count, and total and specific leukocyte counts) (data not shown).

During the placebo phase, LV mass was significantly correlated with ΔQT ($r = 0.65$, $P < 0.0001$) and ΔQT_c ($r = 0.62$, $P < 0.0001$). Table 2 shows the evolution of QT and related parameters over the following 7 years. Five years enalapril treatment was accompanied by a progressive fall in QT, QT_c , and the dispersion measures to significantly lower values ($P < 0.01$) that were maintained during the following 2 years. Similar to the measures of LV structure and function, QT, QT_c , and their dispersions were not significantly affected by the 8-week suspension of treatment that was tried after 5 years and was found to cause a return of BP to pretreatment values, and at no subsequent examination was any significant difference from the values recorded at 5-year follow-up detected (Fig. 3). The results are rate-corrected by Bazett's formula. Recently, it has been reported that ΔQT remains unchanged during atrial pacing up 120 bpm and submaximal exercise.¹⁸ Furthermore, correction by Bazett's formula results in prolongation of ΔQT_c yielding values that may be misleading.¹⁹ We have measured both values having a similar fall in ΔQT and ΔQT_c during follow-up.

Although on average ΔQT and ΔQT_c fell faster than LV mass index during the 1st year of treatment (especially during the first 8 weeks, coinciding with the normalization of BP), the difference was not statistically significant (Fig. 4).

Table 1. Left Ventricular Structure and Systolic Function in Hypertensive Patients Treated with Enalapril

Follow-up	LV Mass (g)	LV Mass Index (g/m ²)	Septal Thickness (mm)	LV Wall Thickness (mm)	LV Ejection Fraction (%)	LV Mass Index Regression (in Each Period) (%)
Placebo	271 ± 40	148 ± 34	12.8 ± 1.3	11.5 ± 1.0	74.6 ± 5.1	—
8 weeks (57 ± 5 days)	259 ± 38	142 ± 29	12.4 ± 1.1	11.2 ± 0.9	74.8 ± 5.4	4.05 ± 0.8
1 year (11 ± 1 month)	230 ± 33 ^a	127 ± 26 ^b	11.7 ± 1.2 ^a	10.6 ± 0.8	75.1 ± 6.2	10.1 ± 2.1 ^b
3 years (37 ± 1 month)	193 ± 25 ^c	106 ± 18 ^c	10.5 ± 1.1 ^c	9.3 ± 0.7 ^c	76.4 ± 5.2	14.2 ± 2.8 ^c
5 years (59 ± 1 month)	166 ± 23 ^c	90 ± 16 ^c	9.3 ± 0.8 ^c	8.1 ± 0.5 ^c	77.6 ± 5.0 ^a	10.8 ± 2.1 ^c
8 weeks without treatment (56 ± 3 days)	174 ± 28 ^c	95 ± 20 ^c	9.5 ± 0.9 ^c	8.2 ± 0.6 ^c	77.5 ± 5.9 ^a	−3.4 ± 0.6 ^c
8 weeks with treatment (96 ± 4 days)	167 ± 29 ^c	92 ± 19 ^c	9.3 ± 0.9 ^c	8.2 ± 0.6 ^c	76.9 ± 5.5 ^a	2.0 ± 0.4 ^c
6 years (74 ± 1 month)	160 ± 30 ^c	90 ± 18 ^c	9.2 ± 0.9 ^c	8.1 ± 0.5 ^c	77.2 ± 5.1 ^a	1.3 ± 0.3 ^c
7 years (87 ± 1 month)	164 ± 28 ^c	91 ± 18 ^c	9.3 ± 0.9 ^c	8.2 ± 0.7 ^c	77.6 ± 5.2 ^a	0.7 ± 0.2 ^c

^a $P < 0.05$; ^b $P < 0.01$; ^c $P < 0.001$ with respect to the pretreatment placebo period.

Figure 2. LVMI during 7 years of enalapril treatment. The 8-week suspension after 5-year follow-up had no significant effect.

None of the patients suffered any clinically detectable cardiovascular accident at any time during the 7-year duration of the study.

DISCUSSION

Epidemiological studies have confirmed that patients with hypertension are more prone to cardiac death and sudden cardiac death if they exhibit LVH, and the combination of LVH and complex ventricular ectopies worsens prognosis.²⁰⁻²² In

Figure 3. Δ QT and Δ QT_c during 7 years of enalapril treatment. They were not affected by the 8-week suspension of treatment after 5 years.

this study, 5 years enalapril treatment of hypertensives with LVH was accompanied by a progressive decrease in LV mass, improvement in LV systolic function indices, and reduction in QT and QT_c dispersion. The values of structural, functional, and electrical parameters that had been achieved after 5 years were maintained during further treatment for 2 years. In particular, suspension of treatment for 8 weeks after 5 years caused no regression of the improvement in either QT-derived parameters or parameters of LV structure and systolic function, even though BP_s returned to pretreatment values. This strongly suggests that LV structure and

Table 2. Δ QT, Δ QT_c, Δ QT_r, Δ QT Reduction and Δ QT_c Reduction During 7 Years of Enalapril Treatment^a

Follow-up	Δ QT	Δ QT _c	Δ QT _r	Δ QT Reduction (%)	Δ QT _c Reduction (%)	Δ QT Reduction in Each Period (%)
Placebo	61 ± 21	67 ± 27	7.3 ± 2.2	—	—	—
8 weeks (57 ± 5 days)	52 ± 18	59 ± 24	6.1 ± 2.0	14.7 ± 4.6	11.9 ± 4.1	11.9 ± 4.1
1 year (11 ± 1 month)	46 ± 15 ^b	48 ± 20	5.6 ± 1.8	24.6 ± 8.7	28.3 ± 9.3 ^b	16.4 ± 5.2
3 years (37 ± 1 month)	41 ± 15 ^b	46 ± 18 ^b	5.1 ± 1.7 ^b	32.8 ± 10.9 ^b	31.3 ± 10.7 ^b	2.9 ± 0.8 ^b
5 years (59 ± 1 month)	40 ± 14 ^c	43 ± 17 ^c	4.8 ± 1.7 ^c	34.4 ± 11.9 ^c	35.8 ± 12.2 ^c	4.5 ± 1.1 ^c
8 weeks without treatment (56 ± 3 days)	40 ± 14 ^c	44 ± 17 ^c	4.7 ± 1.6 ^c	34.4 ± 11.6 ^c	34.3 ± 11.8 ^c	−1.5 ± 0.5 ^c
8 weeks with treatment (96 ± 4 days)	39 ± 14 ^c	44 ± 17 ^c	4.8 ± 1.7 ^c	36.0 ± 13.1 ^c	37.3 ± 13.4 ^c	0.0 ± 3 ^c
6 years (74 ± 1 month)	38 ± 14 ^c	42 ± 16 ^c	4.7 ± 1.6 ^c	37.7 ± 13.8 ^c	37.3 ± 12.8 ^c	2.9 ± 0.7 ^c
7 years (87 ± 1 month)	37 ± 13 ^c	41 ± 16 ^c	4.6 ± 1.7 ^c	39.3 ± 14.7 ^c	38.8 ± 14.2 ^c	1.5 ± 0.4 ^c

^a Δ QT and Δ QT_c in ms.

^b P < 0.05; ^c P < 0.01 with respect to the pretreatment placebo period.

Figure 4. LVMI regression (%) and ΔQT_c reduction (%) during 7 years of enalapril treatment.

function, rather than acute BP levels, are the primary determinants of QT dispersion.

Changes in BP do not imply simultaneous detectable changes in LV mass index: Manolis et al.²³ found no correlation between the extent of BP reduction and the extent of LV mass index reduction among hypertensives treated with a calcium antagonist or an inhibitor of angiotensin-converting enzyme (ACE), and in our study there was no response of LV mass index to the rise of BP that occurred during the 8-week suspension treatment. Furthermore, BP is a less reliable predictor of cardiovascular risk than LV mass index: Verdecchia et al.²⁴ found that regression of LV mass index in uncomplicated subjects with essential hypertension predicted reduced risk of subsequent cardiovascular disease, and that this association was independent of baseline LV mass, baseline clinic, and ambulatory BP and BP changes between baseline and the follow-up visit; Muiesan et al.²⁵ reported that in a group of uncomplicated hypertensives, changes in LV mass index over 10 years were more strongly related to the occurrence of nonfatal cardiovascular events than were sex, cigarette smoking, or baseline or 10-year values of BP, or of triglycerides, glucose, or total cholesterol concentrations. Although the greater predictive value of LV mass index may be due merely because it constitutes a better measure of long-term BP control than clinical BP on a single follow-up visit or ambulatory BP on a single follow-up day, it seems more likely that it derives from the LV mass index that reflects an improve-

ment in cardiac structure that directly reduces risk. The failure of some patients to achieve reduction of LV mass or regression of LVH in spite of reduction in BP may be due to the progression of coronary artery lesions and other risk factors for LVH.

Ichkhan et al.²⁶ have reported positive correlations among ΔQT , $\% \Delta QT$, and LV mass in patients with systemic hypertension. In our group, pretreatment correlation with LV mass was $r = 0.65$ for ΔQT and $r = 0.62$ for ΔQT_c ($P < 0.0001$ in both cases). Karpanou et al.²⁷ found a correlation between the regression of LVH and improvement in QT dispersion in a group of hypertensive patients treated for 6 months with an ACE inhibitor or a calcium antagonist. Mayet et al.²⁸ have reported similar results in a subset of patients treated with ramipril or felodipine. In our group of hypertensive patients treated with enalapril, ΔQT_c fell by 36% over 5 years whereas LVH, as measured by LV mass index, fell by 39%. Positive correlation between QT dispersion and LV mass index and mean aortic valve gradient has also been observed²⁹ in a group with another source of pressure overload, aortic stenosis; QT dispersion and LV mass index were furthermore reduced by valve replacement.

The correlation between QT dispersion and LV mass index among hypertensive patients, and the value of the latter for prediction of cardiovascular accidents and/or disease in the same population have led to suggestions that QT dispersion might be a readily determinable predictor of the measure of risk of sudden death. However, in a study³⁰ of several potentially useful parameters, $\Delta QT > 80$ ms was a predictor of cardiac and sudden death only in the univariate analysis and not in the multivariate analysis. The greatest QT dispersion was found among Lown Class IV patients. Bugra et al.³¹ found that different LV geometric patterns in untreated essential hypertension patients were associated with similar QT dispersion values. Mänttari et al.³² reported that in a coronary risk population increased dispersion of QT peak (QT measured up to the peak of T wave) was an independent risk factor for sudden cardiac death, but not for fatal myocardial infarction. The lack of prognostic value of QT dispersion found in these reports may be due to measurement variability and the insensitivity of ΔQT to alterations of transmural dispersion of the action potential.

The correlation between LV mass index and QT dispersion is in keeping with a number of electrophysiological results obtained with experimental

animals or biopsy tissue. Experiments with laboratory animals modeling hypertrophy due to volume overload³³ have revealed an "electrical remodeling" phenomenon (increased duration of the action potential and increased difference between its duration in the left and right ventricles) that is associated with increased susceptibility to induction of torsades de pointes arrhythmias and occurs even in the absence of increased collagen and decreased capillary/fiber ratio. Decreased uniformity of action potential duration has also been found in models of LVH due to pressure overload,³⁴ and LVH-related susceptibility to ventricular arrhythmia is attributed to associated fibrosis and ischemia. Also, biopsies of interventricular septum and papillary muscle in patients undergoing replacement of the aortic and mitral valves, respectively,³⁵ have shown positive correlation between LV mass and myocyte diameter, and negative correlation between myocyte diameter and conduction velocity; this slowing of conduction by hypertrophic myocytes is due to the increased resistivity of intercellular gap junctions, which comes about because LVH reduces the density and alters the nature of the connexins which compose the gap junctions. In addition, experiments with biopsy tissue from heart with LVH show that the action potential is of longer duration in the septum than in the papillary muscle, regardless of the myocyte diameter. Finally, regression of LVH in an experimental model,³⁶ has been observed to be accompanied by a return of action potential duration and its dispersion to basal values, and by a fall in ventricular arrhythmia inducibility and a rise in ventricular fibrillation threshold.

Increased QT dispersion in patients with LVH may be related to alteration of the ion channels involved in cardiac repolarization.^{37,38} Abnormalities in the potassium channels of hypertrophied myocytes have been shown to contribute to the prolongation of the action potential, suggesting that changes in potassium channel physiology may increase QT dispersion. Local ischemia, increased anisotropy, and stretching of myocardial fibers are among the other mechanisms that may possibly bring about increased QT dispersion in patients with LVH. The fact that in this study the fall in QT dispersion was on average initially faster than the fall in LV mass index (although the difference was not statistically significant in this small group) may therefore have been due to relaxation of the heart due to normalization of BP.

CONCLUSION

In conclusion, in hypertensive patients treated with enalapril, reduction of QT dispersion is correlated with gradual regression of LV mass index and is not immediately affected to a major extent by changes in BP, although a slight reduction may be induced by the initial normalization of BP.

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