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Changes of the T-Wave Amplitude and Angle: An Early Marker of Altered Ventricular Repolarization in Hypertension

POLYCHRONIS DILAVERIS, M.D., ELIAS GIALAFOS, M.D.,* JAN POLONIECKI, PH.D., KATERINA HNATKOVA, PH.D., DIMITRIS RICHTER, M.D.,* GEORGE ANDRIKOPOULOS, M.D.,* ELENA LAZAKI, M.D.,* JOHN GIALAFOS,M.D.,* MAREK MALIK, PH.D., M.D.

Department of Cardiological Sciences, St. George's Hospital Medical School, London, England, and *the State Department of Cardiology, Hippokration Hospital, Athens, Greece

Summary

Background: The heterogeneity of ventricular repolarization is an important proarrhythmic factor. QT dispersion has been proposed to reflect the inhomogeneity of ventricular repolarization, but a poor reproducibility limits its clinical applicability. Reliable noninvasive methods to quantify abnormalities in ventricular repolarization are still lacking. The T-loop morphology analysis is a novel method aimed at quantifying ventricular repolarization.

Hypothesis: To test the ability of the T-loop morphology analysis to discriminate between hypertensive patients and healthy subjects, 105 hypertensive patients (mean age 63.6 ± 12.3 years) and 110 healthy controls (mean age 49.7 ± 14.3 years) were evaluated.

Methods: The maximum QT interval (QT maximum), the minimum QT interval (QT minimum), and their difference (QT dispersion) were calculated from a digitally recorded 12-lead electrocardiogram (ECG) in both study groups. X, Y, and Z leads were reconstructed from the 12-lead ECG, and the amplitude of the maximum T vector (T amplitude) and the angle between the maximum T vector and X axis (T angle) were calculated from the projection of the T loop in the frontal plane.

Results: T amplitude ($p < 0.001$), T angle ($p = 0.05$), and QT dispersion ($p = 0.04$) were significantly different between hypertensive patients and controls, while QT maximum ($p = 0.14$) and QT minimum ($p = 0.35$) did not differ between the groups. T amplitude was the only marker which differed between hypertensive patients without ECG criteria for left ventricular hypertrophy and controls ($p = 0.002$).

Conclusions: T-loop features and particularly T amplitude are significantly different between hypertensive patients and healthy controls and may serve as early markers of repolarization abnormalities in a hypertensive population.

Key words: T loop, maximum vector, QT dispersion, ventricular repolarization

Introduction

The heterogeneity of ventricular repolarization is a recognized proarrhythmic factor. Despite of experimental[1–3] or invasive[4] data on the importance of repolarization abnormalities, reliable and practically applicable noninvasive methods to quantify ventricular repolarization are still lacking.[5] The interlead variability of QT interval duration on 12-lead electrocardiographic (ECG) recordings, that is, the so-called QT dispersion,[6] has been suggested to offer a noninvasive measure of abnormal ventricular repolarization.[7] However, several concerns have been raised about the measurement of QT dispersion that may limit its clinical utility.[8, 9] Mainly, poor interindividual and intraindividual reproducibility of QT dispersion seems to reduce the power to assess arrhythmia risk prospectively.[10–12] The spatial aspects of the T-wave complexity, that is, the presence of biphasic or multiphasic T-wave patterns which also reflects repolarization abnormalities, have been evaluated by the so-called principal component analysis.[13, 14] Unfortunately, systematic data on this methodology are lacking.

A recent study concluded that QT dispersion is largely determined by T-loop morphology, as expressed by T-loop amplitude and width.[15] Although that study suggested that the shape of the T loop may reflect the repolarization homogeneity of the heart, no investigation was made as to whether the T-loop descriptors have any discriminative and prognostic value.

The objective of the present study was to evaluate the practical value of T-loop morphology to characterize ventricular repolarization. In particular, our study investigated the ability of the T-loop descriptors to discriminate between hypertensive

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Address for reprints:

Marek Malik, Ph.D., M.D.
Department of Cardiological Sciences
St. George's Hospital Medical School
London SW17 ORE
England

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patients with and without left ventricular hypertrophy (LVH) and healthy subjects. The study of hypertensive patients was selected because, among others, high QT-dispersion values have been previously reported in patients with systemic hypertension.[16–20] QT dispersion has also been reported to decrease when adequate blood pressure control is achieved.[19–21]

Methods

Study Population

The study population consisted of two groups: 105 consecutively recruited hypertensive patients (57 women; mean age 63.6 ± 12.3 years, range 31–88 years) (patients) and 110 healthy subjects without any cardiovascular disease or any risk factor for coronary artery disease (77 women, mean age 49.7 ± 14.3 years, range 21–86 years) (controls). Both study groups were recruited from the Rafina Study participants examined in 1997–1998. In brief, one fourth of Rafina city inhabitants, aged > 20 years, were randomly selected to undergo evaluation of cardiovascular risk factors. The type of underlying heart disease was determined from history, physical examination, 12-lead ECG, and serial blood tests. Apart from systemic hypertension, no other cardiovascular disease was present in the patient group. All patients and controls were in sinus rhythm. Routine medications were not withheld during the patients' evaluation.

Excluded from the study were patients with left or right bundle-branch block, atrioventricular block, ventricular preexcitation, history of coronary artery disease, atrial fibrillation, sick sinus syndrome, prior pacemaker implantation, clinically overt heart failure [New York Heart Association (NYHA) classes II–IV], pericarditis, valvular heart disease, or nonischemic cardiomyopathy. Patients receiving digitalis or any antiarrhythmic drugs as well as patients having other risk factors for coronary artery disease, were also excluded. Because of the strict inclusion and exclusion criteria, it was not possible to find suitable controls matched to patients among the Rafina Study participants (the total number of participants of this study is around 600). Hence, controls were not gender and age matched to patients. The study was approved by the local Ethics Committee and informed consent was obtained from all participants.

Twelve-Lead Surface Electrocardiogram

In all subjects, a 12-lead digital ECG was recorded in the supine resting position using a computer-based electrocardiograph (Cardioperfect, version 1.1, CardioControl NV, Amsterdam, Netherlands). All 12 leads of each ECG were recorded simultaneously for 20 s and sampled at a rate of 1200 Hz. During the recording, the subjects were breathing freely and were not allowed to speak. From each lead, the average complex was calculated by the MEANS (Modular ECG Analysis) system.[22,23] Individual averaged complexes were stored digitally. Standard criteria were used to diagnose ECG-documented LVH.[24]

QT Interval and QT Dispersion Measurements

QT interval and QT dispersion measurements were performed manually using the digitally stored ECGs displayed on a high-resolution computer screen. Each lead was separately magnified (160 mm/s and 60 mm/mV), and the QT interval was measured using the on-screen calipers from the onset of the QRS complex to the end of the T wave. The point of T-wave offset was defined as the return to baseline.[8] If a U wave followed the T wave without an isoelectric separation, the end of the T wave was taken as the nadir between the T and U waves. If the end of the T wave could not be reliably determined, or when the T wave was of very low amplitude (< 50 μV), QT measurements were not made and the lead was excluded from analysis.[15] QT dispersion was calculated as the difference in ms between the longest (QT maximum) and shortest (QT minimum) measured QT intervals. No attempt was made to correct for missing leads.[9]

Twelve-Lead Vectorcardiogram

To derive T-loop descriptors, orthogonal X, Y, and Z leads were reconstructed from the standard 12 ECG leads.[15,25,26] From the spatial T loop and its projection on the frontal (XY) plane, the following parameters were automatically calculated: the amplitude of the maximum T vector (T amplitude) and the angle between the maximum T vector and X axis (T angle).

Accuracy of the Measurements

Two independent investigators measured the QT intervals of all ECGs. The averages of the measurements of the two observers were used for comparisons. Intraobserver and interobserver mean percent error (absolute difference between two observations divided by the mean and expressed in percent) for QT maximum, QT minimum, and QT dispersion measurements were determined in 50 randomly selected study participants (25 patients and 25 controls). To define intraobserver errors of measurements, one of the two investigators measured the QT intervals of all 50 ECGs twice. Neither observer was aware of the subjects' assignment.

Statistical Analysis

Continuous variables are expressed as mean ± standard deviation. For comparisons between patients with and without LVH and controls, the Mann-Whitney test and the chi-square test were used where appropriate. The Kruskal-Wallis test was used for comparisons among multiple variables. Spearman's correlation coefficients were used to assess the association between different variables.

Using a previously reported algorithm,[27] univariate receiver operator characteristics were computed for the separation of patients from healthy controls based on QT maximum, QT minimum, QT dispersion, T amplitude, and T angle. The graphs of the characteristics were compared visually.

To determine the multivariate contribution of other factors to the values of different repolarization indices, linear regression equations were constructed:

$$Z = B_0 + B_1\text{Diagnosis} + B_2\text{Age} + B_3\text{Sex} + B_4\text{Heart rate},$$

where Z was one of the considered repolarization indices (QT maximum, QT minimum, QT dispersion, T amplitude, T angle) and diagnosis was the presence of hypertension among the entire study population and the presence of ECG-documented LVH among the hypertensive patients. For each repolarization index, the statistical significance of the regression coefficients B_1, B_2, B_3, and B_4 was evaluated. P values of < 0.05 were considered statistically significant.

Results

In the patient group, the history of hypertension extended for 10.6 ± 5.4 years. At the time of investigation, 26 (25%) patients received angiotensin-converting enzyme inhibitors, 20 (19%) calcium-channel blockers, 9 (9%) beta blockers, and 30 (29%) diuretics. Thirty-seven (35%) patients had an ECG-documented LVH. The demographic and ECG characteristics of patients and controls are listed in Table I.

Controls were significantly younger and had lower blood pressure than hypertensive patients with and without LVH (Table I). QT dispersion values were similar between hypertensive patients without LVH and controls (p = 0.62), but significantly higher in hypertensive patients with LVH (p = 0.04). QT maximum and QT minimum values were not significantly different among the three groups. T amplitude and T angle were significantly different among the three groups, with the lower values of both indices measured in hypertensive patients with documented LVH (Table I). T amplitude was significantly higher in controls than in hypertensive patients without ECG-documented LVH (p = 0.002). No significant differences were noticed among the three groups concerning heart rate, body mass index, and plasma potassium levels. A trend toward a significant difference in gender was noted (Table I).

Associations between Repolarization Indices and Clinical Variables

For the total of the study participants, QT maximum was found to be significantly dependent on age, gender, and heart rate; QT minimum was significantly dependent on heart rate and gender; and QT dispersion was not significantly dependent on any of the three. Neither QT maximum nor QT minimum nor QT dispersion was significantly dependent on the presence of hypertension in the complete study population. T amplitude was significantly dependent on the presence of hypertension in the complete study population, while T angle was dependent on heart rate (Table II).

Among the patients, QT maximum was significantly dependent on heart rate, gender, and the presence of LVH; QT minimum was dependent on heart rate and gender, and QT dispersion was significantly dependent only on the presence of LVH. T amplitude was highly significantly dependent on the presence of LVH and T angle was dependent on heart rate (Table III).

Comparison among the Different Repolarization Indices for the Identification of Hypertensive Patients

Figure 1 shows receiver operator characteristics of separation of hypertensive patients from controls based on the different repolarization indices. The curve of T amplitude is clearly shifted higher than that of other indices (QT maximum, QT minimum, QT dispersion), although only moderate sensitivity and specificity values were achieved.

Correlations among Different Variables

QT maximum correlated significantly with QT minimum, T amplitude, and heart rate in patients, and with QT minimum,

TABLE I Demographic, electrocardiographic, and vectorcardiographic characteristics of hypertensive patients and controls

	Hypertensives with LVH (n = 37)	Hypertensives without LVH (n = 68)	Controls (n = 110)	p Value
Age (years)	64.8 ± 11.7	63 ± 12.6	49.7 ± 14.3	< 0.001
Men % (no.)	62 (23)	37 (25)	30 (33)	0.06
BMI (kg/m^2)	27.9 ± 4.5	27.9 ± 5.3	26.9 ± 6	0.26
Heart rate (beats/min)	70.9 ± 14.6	70.4 ± 11.1	71.9 ± 10.9	0.62
SBP (mmHg)	158.7 ± 19	158.1 ± 23	131.4 ± 17.2	< 0.001
DBP (mmHg)	91.4 ± 12	93.9 ± 15.2	83.2 ± 9.6	< 0.001
QT maximum (ms)	400.5 ± 41.2	396.5 ± 29.8	388.5 ± 27.1	0.14
QT minimum (ms)	352.9 ± 40	356.1 ± 31.1	349.1 ± 26.5	0.35
QT dispersion (ms)	47.6 ± 18.7	40.4 ± 13.9	39.3 ± 14	0.04
T amplitude (μV)	242.4 ± 161.2	319.1 ± 109	370.6 ± 115.8	< 0.001
T angle (degrees)	14.9 ± 70.2	31 ± 9.3	33.2 ± 9.5	0.05
K+ (mEq/lt)	4.9 ± 0.6	5.1 ± 0.6	4.9 ± 0.5	0.3

Abbreviations: BMI = body mass index, DBP = diastolic blood pressure, LVH = left ventricular hypertrophy, SBP = systolic blood pressure. See text for the definition of the individual indices.

TABLE II Regression coefficients and significance of various independent variables (history of hypertension, age, gender, and heart rate) entered in the linear regression models

Dependent	Hypertension		Age		Gender		Heart rate	
variable	RC	p Value	RC	p Value	RC	p Value	RC	p Value
QT maximum	−4.453	0.15	0.303	0.004	13.591	<0.001	−1.911	<0.001
QT minimum	−2.372	0.47	0.198	0.07	13.235	<0.001	−1.84	<0.001
QT dispersion	−2.08	0.37	0.105	0.17	0.356	0.86	−0.071	0.42
T amplitude	69.271	<0.001	−1.026	0.1	−23.499	0.18	−1.272	0.08
T angle	6.522	0.16	−0.092	0.55	4.072	0.34	−0.411	0.02

Abbreviation: RC = regression coefficient. See text for the definition of the individual indices.

TABLE III Regression coefficients and significance of various independent variables (presence of left ventricular hypertrophy, age, gender, and heart rate) entered in the linear regression models

Dependent	LVH		Age		Gender		Heart rate	
variable	RC	p Value	RC	p Value	RC	p Value	RC	p Value
QT maximum	9.551	0.03	0.241	0.16	19.315	<0.001	−2.062	<0.001
QT minimum	2.789	0.58	0.203	0.29	21.374	<0.001	−1.885	<0.001
QT dispersion	6.762	0.04	0.038	0.76	−2.059	0.52	−0.178	0.16
T amplitude	−84.948	0.003	−0.243	0.81	−34.947	0.19	−0.289	0.78
T angle	−15.376	0.08	−0.117	0.73	0.727	0.93	−0.702	0.04

Abbreviations: LVH = left ventricular hypertrophy, RC = regression coefficient. See text for the definition of the individual indices.

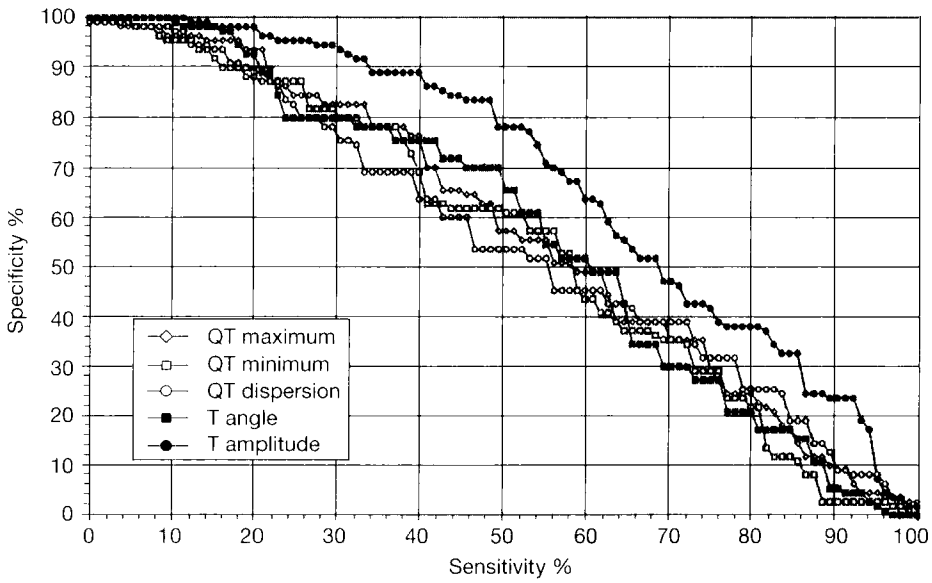

FIG. 1 Receiver-operator characteristic (ROC) curves of different repolarization indices distinguishing hypertensive patients from controls. The ROC curve of T amplitude shifted higher in comparison with those of other indices.

age, and heart rate in controls. QT minimum was significantly related with QT dispersion and heart rate in both study groups. T amplitude correlated significantly with T angle and age in controls (Table IV).

Accuracy of the Measurements

The intraobserver relative errors for QT maximum, QT minimum, and QT dispersion were 2 ± 1.5, 1.9 ± 1.8, and 24.6 ± 18.8%, respectively. The interobserver relative errors for the same indices were 4.5 ± 3.8, 2.9 ± 2.8, and 32.8 ± 21.9%, respectively.

Discussion

The principal finding of this study is that the T-loop descriptors (particularly the amplitude of the maximum vector) are

TABLE IV Correlation coefficients between clinical, electrocardiographic, and vectorcardiographic variables in normal subjects (regular numbers) and in hypertensive patients (bold numbers)

	QT maximum	QT minimum	QT dispersion	T amplitude	T angle	Age	HR
QT maximum		**0.873b**	**0.181**	**−0.197[a]**	**0.171**	**0.178**	**−0.761[b]**
QT minimum	0.896[b]		**−0.243[a]**	**−0.156**	**0.164**	**0.114**	**−0.701[b]**
QT dispersion	0.135	−0.288[b]		**−0.058**	**−0.075**	**0.026**	**−0.095**
T amplitude	0.035	0.092	−0.092		**−0.033**	**−0.056**	**0.019**
T angle	−0.001	−0.015	−0.037	−0.372[b]		**0.064**	**−0.142**
Age	0.265[b]	0.185	0.138	−0.192[a]	−0.082		**−0.143**
HR	−0.721[b]	−0.740[b]	0.058	−0.179	0.024	−0.074	

[a] $p<0.05$.

[b] $p<0.01$.

Abbreviation: HR = heart rate. See text for the definition of the individual indices.

significantly different between hypertensive patients and healthy controls. Among the repolarization descriptors considered, T amplitude was the only index capable to identify the hypertensive patients even in the absence of ECG criteria for LVH and with only subtle and nonquantifiable differences in the T-wave shape (Fig. 2).

Repolarization Abnormalities in Hypertension

Systemic hypertension affects up to 25% of the adult population and is a potent cardiovascular risk factor.[17] Left ventricular hypertrophy in hypertensive patients is widely recognized as a risk factor for ventricular arrhythmias and sudden cardiac death, although the factors predisposing to the electrical instability and arrhythmic sudden death are not well established.[28,29] It has been reported that myocardial hypertrophy alters the ionic channels of the early repolarization phase.[30,31] Abnormalities in the potassium channels in hypertrophied myocytes have been shown to contribute to the action potential prolongation.[31] Furthermore, the deposition of fibrous tissue results in an increased anisotropy and stretching of the myocardial fibers and may also account for the alterations in ventricular repolarization found in the hypertrophic heart.[32]

QT Dispersion in Systemic Hypertension

QT dispersion has been proposed to reflect abnormal ventricular repolarization.[7] High QT dispersion values have been reported in patients with systemic hypertension and particularly in those with echocardiographic evidence of LVH.[16–20] Furthermore, QT dispersion has been reported to decrease after the appropriate treatment of high blood pressure.[19–21] However, the relationship observed between QT dispersion and LVH was fairly weak in some studies,[16,17] and QT dispersion has not been shown to have any prognostic value in the assessment of risk of ventricular arrhythmias in hypertensive patients.[18] These conflicting results in combination with the poor reproducibility of QT dispersion measurements may limit its use as an estimate of repolarization inhomogeneity.

In this study, QT dispersion was significantly although only marginally increased merely in the patients with ECG documented LVH (Table I). No significant differences were noticed between patients without LVH and controls. QT maximum and QT minimum did not differ among the three groups. QT dispersion was not significantly associated with age, gender, or heart rate, which is discordant with some other studies.[19,33,34] QT maximum and QT minimum were significantly associated with gender and heart rate, as previously reported.[33,34]

T Loop Abnormalities in Hypertension

The QT interval duration is not the only important aspect of ventricular repolarization. The shape of the T wave and the presence of notches and/or other morphologic aberrations are believed to be major markers of abnormal repolarization.[35] Principal component analysis has been used in previous studies to quantify the complexity of the T wave;[13,14] however, subtle changes in the shape of a monophasic T wave are not detectable by this method. Furthermore, principal component analysis requires an adequate mean T-wave amplitude (> 100 μV).[13] Hence, low-amplitude T waves may not only lead to an incorrect definition of the T-wave end, but also influence the correct quantification of the T-wave complexity by principal component analysis.

The T loop features have gained interest lately and QT dispersion has been reported to be an attribute of T-loop morphology.[15] Previous studies have reported a widened QRS-T angle in patients with eccentric LVH.[36]

In this study, the T-loop characteristics and particularly the amplitude of the maximum vector were found to be significantly different between hypertensive patients and healthy controls. T amplitude was found to be significantly lower in patients with LVH than in hypertensive patients without LVH and controls. The high T-amplitude values found in normal subjects are in agreement with those previously reported.[37,38] T amplitude showed a better discriminative ability than do conventional ECG markers of ventricular repolarization, although we observed only moderate sensitivity and specificity values. Hence, T amplitude assessment may serve as an early auxiliary marker of repolarization heterogeneity in hypertension. Future studies should clarify the ability of T loop morphology analysis to offer a more precise and reproducible measure of ventricular repolarization.

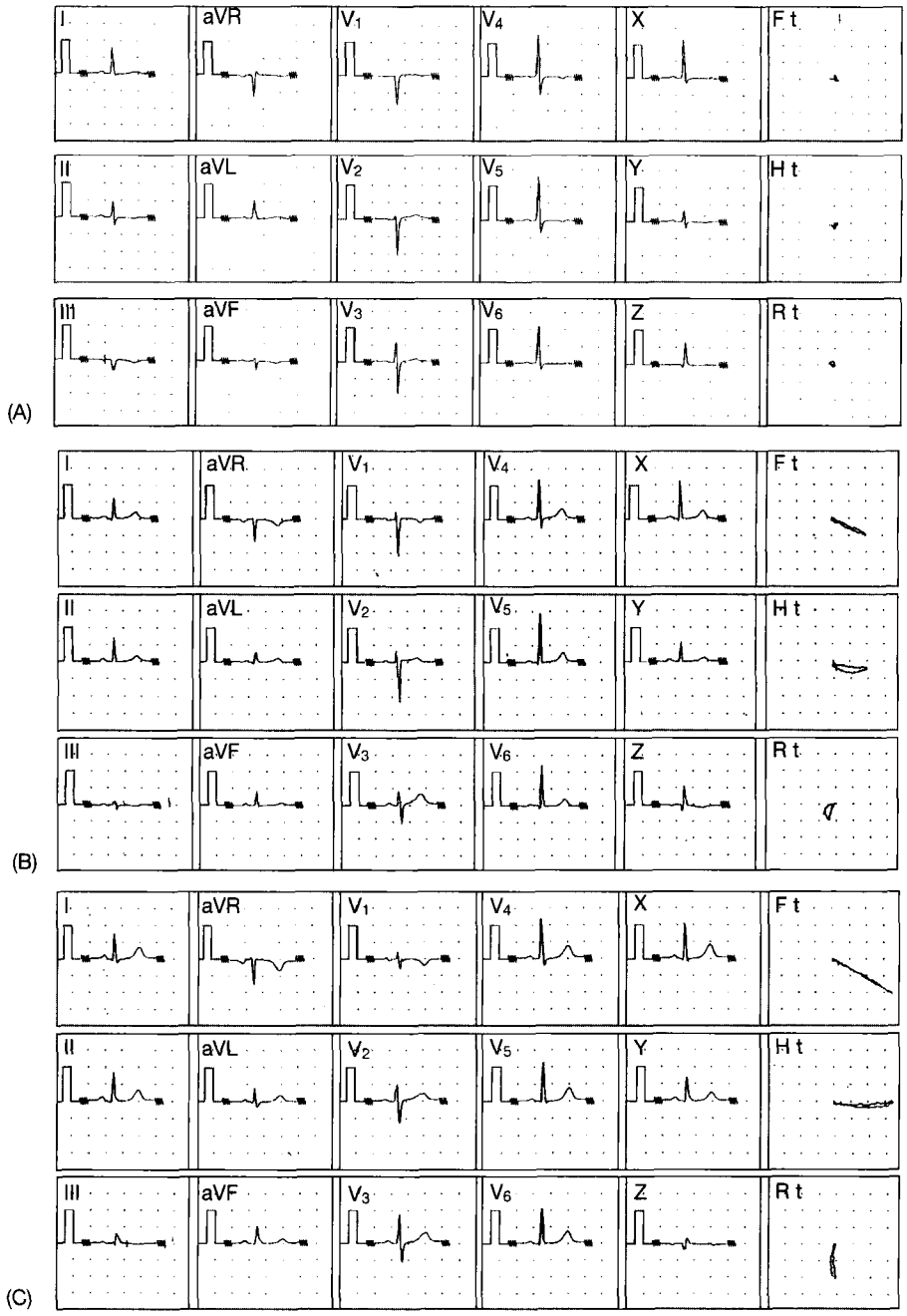

FIG. 2 Twelve-lead electrocardiogram, reconstructed X, Y, and Z leads, and T loop projections in the (XY), (XZ), and (YZ) planes from (A) a hypertensive patient with left ventricular hypertrophy, (B) a patient without left ventricular hypertrophy, and (C) a healthy subject.

Limitations

The relationships between T-loop morphology and the pathophysiology of specific repolarization abnormalities are not established. However, this study may suggest that T loop parameters have a discriminative value and are able to quantify ventricular repolarization. Moreover, they can be measured easily and are not affected by observation biases.

Only ECG documentation of LVH was obtained in this study population. Additional studies using echocardiographically determined LVH may prove to be more informative. Finally, neither coronary angiography nor other imaging techniques were applied to our study patients to rule out the presence of significant but not clinically apparent coronary artery disease.

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