A Novel Electrocardiographic T-Wave Measurement (Tp-Te Interval) as a Predictor of Heart Abnormalities in Hypertension: A New Opportunity for First-Line Electrocardiographic Evaluation

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The aim of the study was to evaluate the role of conventional and new markers of early cardiac organ damage (OD) on 12-lead electrocardiography (ECG) in 25 outpatients with newly diagnosed untreated essential hypertension compared with 15 normotensive, otherwise healthy individuals. Each participant underwent ECG, echocardiographic, and blood pressure (BP) measurements. Conventional and new ECG indexes for cardiac OD (Tp-Te interval, ventricular activation time, and P-wave analysis) were also measured. Clinic and 24-hour ambulatory BP levels as well as left ventricular mass indexes were significantly higher in hypertensive than in normotensive patients. No significant differences were found between the two groups for ECG and echocardiographic markers of OD. Only Tp-Te interval was higher in hypertensive than in normotensive individuals (3.06 mm vs 2.24 mm; $P<.0001$), even after adjustment for anthropometric and clinical parameters. Preliminary results of this study demonstrated prolonged Tp-Te interval in newly diagnosed, untreated hypertensive outpatients compared with normotensive individuals. *J Clin Hypertens (Greenwich).* 2015;17:441–449. © 2015 Wiley Periodicals, Inc.

Global cardiovascular risk assessment represents a fundamental step in the clinical management of hypertension.[1,2] Beyond proper measurement of clinic blood pressure (BP) levels, current European guidelines strongly recommend including a thorough assessment of markers of hypertension-related organ damage (OD) at cardiac, renal, and vascular levels.[3] Systematic search of OD has been demonstrated to be useful for the daily clinical management of hypertensive patients by: (1) ameliorating individual global cardiovascular risk stratification; (2) improving patients' own awareness of an asymptomatic disease; and (3) helping physicians choose the best diagnostic and therapeutic options.[1,2] Presence of OD, in fact, may suggest the use of select antihypertensive drug classes or molecules, which have been demonstrated to confer proven benefits in favoring prevention and promoting regression of markers of OD, beyond their BP-lowering efficacy.[4,5]

At the cardiac level, hypertension-related OD is characterized by an increased left ventricular mass (LVM), leading to the development of left ventricular hypertrophy (LVH) and increased risk of major cardiovascular events.[6–10] LVH can be detected on conventional 12-lead electrocardiography (ECG) using Sokolow-Lyon and Cornell indexes.[11,12] Even in the presence of high sensitivity; however, the diagnostic ability of ECG is blunted by its relatively low specificity, which may induce false-negative results. To overcome this intrinsic limitation and to improve early detection of LVH in a setting of clinical practice, even in the asymptomatic stages of hypertension, a larger use for echocardiography has been proposed over the years.[13,14] This method has the advantage of providing more accurate estimation of LVM and LV geometry with both high sensitivity and specificity for LVH detection. Even in this case, however, the relatively high cost of the procedure as well as the need for adequate user expertise have limited the applicability of echocardiographic estimation of LVH to the general population of hypertensive patients.[3] Other advanced diagnostic procedures, eg, computed tomography or magnetic resonance for LVM assessment, have limited applicability in the daily clinical practice of hypertension because of high cost and reduced availability in some hospital divisions and hypertension excellence centers.

The primary role of conventional 12-lead ECG has recently been reaffirmed in the first-line diagnostic workup of hypertension to estimate presence of cardiac OD.[15] In the past few years, several new ECG parameters have been proposed for improving detection of LV dysfunction and hypertrophy. These parameters, which include the time interval between the peak and the end of the T wave (Tp-Te interval),[16] ventricular activation time (VAT),[17] and the P-wave analysis,[18] have been demonstrated to be related to increased LVM, LV diastolic dysfunction, and risk of cardiac arrhythmias in several clinical settings other than hypertension. In particular, Tp-Te interval, defined as the time interval

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between complete epicardial and myocardial repolarization, has been viewed as a powerful and independent index of transmural dispersion of LV repolarization.[19,20] From a pathophysiological point of view, increased LVM is considered to be the main determinant of prolonged Tp-Te interval.[21] This has been related to increased risk of cardiac arrhythmias in several clinical conditions, including long-QT and Brugada syndromes,[22] as well as in the early stages of acute myocardial infarction[23] and ventricular tachyarrhythmias.[24] More recently, prolonged Tp-Te interval has been associated with impaired LV relaxation and diastolic dysfunction in unselected outpatients with or without hypertension.[25] The potential implication of this ECG marker in essential hypertension, however, remains to be defined.

On the basis of these considerations, the primary aim of this study is to evaluate the role of these new ECG indexes as markers of early cardiac abnormalities in outpatients with newly diagnosed, untreated essential hypertension compared with normotensive individuals.

METHODS

Study Population

Adult outpatients were consecutively recruited among those admitted to the adult outpatient service of the hypertension unit at Sant'Andrea Hospital in Rome, Italy, for hypertension assessment (including home, clinic, and 24-hour ambulatory BP measurements).

To be included in the study protocol, participants had to meet the following inclusion criteria: (1) adult individuals younger than 55 years; (2) recently diagnosed (naive), untreated hypertension; and (3) signature of informed consent for study participation. Exclusion criteria were at least one of the following: (1) history of treated hypertension; (2) any history of supraventricular or ventricular arrhythmia, including atrial fibrillation; (3) history of any previous cardiovascular disease, including coronary artery disease, congestive heart failure, severe valvular heart disease; (4) hyperthyroidism, electrolyte imbalance, chronic kidney dysfunction (estimated glomerular filtration rate <60 mL/min by the Cockroft-Gault formula); and (5) any neurological or psychiatric disease that may at least, in part, affect the signature of informed consent.

Diagnosis of hypertension was made in the presence of clinic BP levels above the normal values (average of three BP measurements), performed according to the recommendations of the latest set of European guidelines.[26] On the other hand, normotension was defined in the presence of clinic BP levels below the normal values (140/90 mm Hg).[26]

Once included in the study protocol, participants were classified into two groups, including hypertensive patients (cases) and otherwise healthy normotensive individuals (controls) on the basis of the presence or absence of hypertension, as defined by current European guidelines.[3]

The study conformed to the Declaration of Helsinki and its subsequent modifications. The confidentiality of the data of each patient included in the present study was carefully and strictly protected. Informed consent was obtained in all patients and the study was approved by the local ethical committee.

BP Measurements

Clinic BP measurements were performed in the hypertension clinic during the morning section (from 8 AM to 10 AM). Sequential BP measurements were performed in a quiet room, after 10 minutes of rest, on the same arm and with the participant in the sitting position, by using an automated oscillometric device (Omron 705 IT, Lake Forest, IL). The average of three consecutive BP measurements and heart rate was considered as clinic systolic/diastolic BP levels.

Ambulatory BP monitoring was performed by an oscillometric Spacelabs 90207 (Spacelabs Inc, Redmond, WA) device. The device was set in the hypertension clinic after completion of the clinic BP measurements, and the monitoring was started at about 9 AM. Automatic BP readings were obtained every 15 minutes during the daytime period (from 6 AM to 10 PM) and every 30 minutes during the nighttime period (from 10 PM to 6 AM) over 24 hours. Each patient was instructed not to alter her/his usual 24-hour schedule during the monitoring period, but was asked to avoid unusual physical activities and to maintain the arm still during BP measurements. Average values for the 24-hour, daytime, and nighttime systolic and diastolic BP levels were reported. In addition, standard deviation from the average values, as well as number of BP measurements above the normal BP thresholds were reported for each time period (24-hour, daytime, and nighttime) in each participant. Ambulatory BP monitoring examinations were included in the calculation of the 24-hour, daytime, and nighttime average values, if there were at least two valid readings per hour for at least 21 hours.

ECG Analysis

All study patients had to be in sinus rhythm on the day of examination. A 12-lead surface ECG was performed for all patients in the supine position using a Mortara Eli 350 ECG device (Milwaukee, WI). The 12-lead ECG was recorded at a paper speed of 25 mm/s and 1 mV/cm standardization. All ECGs were scanned at 600 dpi and conventional and new ECG parameters were measured on a high-resolution computer screen.

Conventional ECG parameters for LVH were defined according to standard criteria by using Sokolow-Lyon, Cornell voltage, and Cornell product indexes, as recommended by current hypertension guidelines.[3]

In addition, the following novel ECG parameters were calculated for each patient included in the study: (1) T_{peak}-T_{end} (Tp-Te) interval, defined as the distance between the peak and the end of the T wave and expressed as millimeters (mm);[16] (2) VAT, defined as the

time interval between the onset of the Q wave and the peak of the R wave (QR interval) and expressed as mm;[17] (3) P-wave analysis,[18] including average P-wave duration in each ECG lead, maximum P-wave duration in any measurable leads (P maximum), minimum P-wave duration in any measurable leads (P minimum), P-wave dispersion (PWD), defined as the difference between the maximum P-wave duration and the minimum P-wave duration, and P-wave area (PWA), defined as the product of the P-wave amplitude per half of the duration in DII.

The onset of the P and T waves was defined as the point of the first visible upward departure of the trace from the bottom of the baseline for the positive waves and as the point of first downward departure from the top of the baseline for negative waves. The return to the baseline of the bottom of the trace in positive waves and of the top of the trace in negative waves were considered the end of the P and T waves, respectively. Duration of P and T waves was assessed by two investigators blinded to patient clinical information. All these parameters were calculated using Adobe Photoshop CS6 (average of three measurements; San Jose, CA). ECG with measurable P and T waves in fewer than nine of 12 ECG leads was excluded from the study.

Echocardiography

All participants underwent Doppler echocardiographic examination performed by an Acuson Sequoia C512 (Siemens Medical Solution, Mountain View, CA) with a multi-frequency transducer (2.5–4 MHz). Images were implemented using standardized acquisition methods. LV dimensions were measured at end diastole and end systole, just below the mitral leaflets, through the standard left parasternal window. LV ejection fraction was calculated according to the Simpson method. Left atrial size was calculated as the anteroposterior diameter and measured as the distance from the leading edge of the posterior aortic wall to the leading edge of the posterior left atrial wall at end systole. LV mass (LVM) was calculated and then normalized by body surface area and height$^{2.7}$. Echocardiographic LVH was defined according to standard criteria.

The following echocardiographic indexes of LV systolic function were considered: (A) Conventional Doppler analysis: (1) LV ejection fraction and (2) LV fractional shortening; (B) TDI analysis: (1) systolic myocardial peak flow velocity (Sm) wave amplitude; (2) isovolumetric contraction time; and (3) myocardial performance index. At the same time, the following indexes of diastolic function were considered: (A) Conventional Doppler analysis: (1) early diastolic peak flow velocity (E); (2) late diastolic peak flow velocity (A); and (3) ratio of early to late peak (E/A ratio); (B) TDI analysis of the lateral wall of the left ventricle: (1) early diastolic myocardial peak flow velocity (Em); (2) late diastolic myocardial peak flow velocity (Am); (3) ratio of early to late myocardial peak (Em/Am ratio); and (4) isovolumetric relaxation time. Finally, the ratio of early diastolic peak flow velocity (E) at conventional Doppler and early diastolic myocardial peak flow velocity (Em) at TDI was also considered a marker of diastolic dysfunction.

Statistical Analysis

All data were entered into Microsoft Access for Windows (Microsoft Office, Microsoft Corp, Redmond, WA). Baseline characteristics of patients are presented as number and percentage for dichotomous variables and mean±standard deviation of the mean for continuous variables. Normal distribution of data was assessed using histograms and Kolmogorov-Smirnov test. All variables were normally distributed, with the exceptions of BP levels and LVM, which were log-transformed. Differences between continuous variables were assessed using Student *t* test. Categorical variables were compared among groups by chi-square test. To evaluate the association among clinical variables, hazard ratios (HRs) and 95% confidence intervals (CIs) were derived from logistic regression analysis. A multivariable model was fitted with baseline covariates associated with the primary endpoint at the <.05 significance level. All tests were two-sided, and a *P* value of <.05 was considered statistically significant. All calculations were generated using SPSS version 15.0 (SPSS Inc, Chicago, IL).

RESULTS

Study Population

From March to May 2014 we consecutively enrolled 50 young individuals who were referred to our hypertension unit for home, clinic, and 24-hour ambulatory BP evaluation. On the basis of the presence or absence of hypertension, and according to inclusion and exclusion criteria, patients were classified into two groups, including 32 (64%) hypertensive patients and 18 (36%) otherwise normotensive individuals.

General characteristics of the study population are reported in Table I. There were no differences between the groups with regard to anthropometric characteristics, lipid and glucose profile, and renal parameters, with the only exception of BMI, which was higher in hypertensive than in normotensive outpatients (27.0±2.6 vs 24.7±5.2; *P*=.043).

BP Profile

As expected, systolic and diastolic BP levels were significantly higher in hypertensive outpatients and normotensive individuals, both at clinic (153.8±12.2/101.0±13.6 mm Hg vs 125.1±13.0/84.1±10.3 mm Hg; *P*<.001) and 24-hour ambulatory (140.8±8.4/89.2±5.5 mm Hg vs 120.0±14.9/74.4±8.6 mm Hg; *P*<.001) BP measurements. Also, daytime (146.1±8.8/94.3±6.8 mm Hg vs 122.4±13.1/77.9±8.8 mm Hg; *P*<.001) and nighttime (128.6±11.5/77.9±7.3 vs 110.5±14.4/66.4±8.8 mm Hg; *P*<.001) BP levels were significantly higher in the former than

TABLE I. General Characteristics of the Study Population and Conventional ECG Parameters for Cardiac Organ Damage

Parameters	Overall (N=50)	Normotensive (n=18)	Hypertensive (n=32)	*P* Value
Clinical characteristics				
Age, y	42.8±9.1	41.2±9.6	43.8±8.8	.458
Height, cm	172.0±9.1	171.9±9.8	172.1±8.9	.934
Weight, kg	78.0±16.6	73.8±21.0	80.3±13.3	.072
BMI, kg/m^2	26.1±4.0	24.7±5.3	27.0±2.6	.043
TC, mg/dL	220.3±56.8	224.5±53.9	220.3±56.8	.562
HDL-C, mg/dL	50.0±13.0	51.6±13.5	50.0±13.0	.618
LDL-C, mg/dL	138.6±28.5	136.9±28.4	138.6±28.5	.745
TG, mg/dL	122.9±69.9	121.7±70.1	122.9±69.9	.663
Fasting glucose, mg/dL	88.1±6.8	89.0±6.3	88.1±6.8	.379
BUN, mg/dL	31.8±10.7	31.3±10.5	31.8±10.7	.187
Serum creatinine, mg/dL	0.90±0.16	0.92±0.17	0.90±0.16	.692
BP profile				
Clinic systolic BP, mm Hg	144.0±18.5	125.1±13.0	153.8±12.2	<.001
Clinic diastolic BP, mm Hg	95.2±14.8	84.1±10.3	101.0±13.6	<.001
Heart rate, beats per min	80.3±14.1	78.2±15.4	81.3±13.7	.511
24-h systolic BP, mm Hg	133.7±14.7	120.0±14.9	140.8±8.4	<.001
24-h diastolic BP, mm Hg	84.2±9.7	74.4±8.6	89.2±5.5	<.001
24-h heart rate, beats per min	74.9±8.0	73.9±8.8	75.4±7.7	.568
Daytime systolic BP, mm Hg	138.0±15.3	122.4±13.1	146.1±8.8	<.001
Daytime diastolic BP, mm Hg	88.7±10.8	77.9±8.8	94.3±6.8	<.001
Daytime heart rate, beats per min	78.0±8.4	76.1±8.2	78.9±8.5	.306
Nighttime systolic BP, mm Hg	122.4±15.1	110.5±14.4	128.6±11.5	<.001
Nighttime diastolic BP, mm Hg	74.0±9.5	66.4±8.8	77.9±7.3	<.001
Nighttime heart rate, beats per min	67.3±9.2	67.0±9.0	67.4±9.5	.890
Conventional ECG parameters				
PR interval, ms	152.6±20.1	149.1±20.6	154.4±19.9	.389
QRS duration, ms	99.4±18.5	97.5±18.2	100.4±18.8	.606
QT interval, ms	373.3±32.1	375.0±32.0	372.4±32.6	.791
QTc interval, ms	397.7±24.7	396.9±21.9	398.2±26.4	.866
Sokolow-Lyon index, mV	24.8±6.9	26.6±7.6	23.8±6.3	.178
Cornell voltage index, mV	15.3±6.4	13.9±5.6	16.1±6.7	.248
Cornell product index, mV × ms	1553.6±755.9	1365.1±630.9	1657.0±807.3	.204
Positive Sokolow-Lyon index, No.	4 (8.3)	3 (17.6)	1 (3.2)	.084
Positive Cornell voltage index, No.	11 (22.9)	4 (23.5)	7 (22.6)	.940
Positive Cornell product index, No.	6 (12.5)	1 (5.9)	5 (16.1)	.305

Abbreviations: BMI, body mass index; BP, blood pressure; BUN, blood urea nitrogen; ECG, electrocardiographic; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.

in the latter group. No significant differences were found with regard to clinic and 24-hour ambulatory heart rate between the two study groups.

Conventional ECG Parameters

Conventional ECG parameters for cardiac OD are reported in Table I. No significant differences were found between the two study groups with regard to general ECG parameters, including PR, QT, and QTc intervals, as well as QRS duration. At the same time, no significant differences were found with regard to conventional ECG indexes of cardiac OD in hypertensive outpatients compared with normotensive individuals, including Sokolow-Lyon (26.6±7.6 mV vs 23.8±6.3; *P*=.178), Cornell voltage (16.1±6.7 vs 13.9±5.6 mV; *P*=.248), and Cornell product (1657.0±807.3 vs 1365.1±630.9 mV × ms; *P*=.204) indexes.

ECG criteria for LVH were met by three (15.8%) normotensive individuals and one (3.2%) hypertensive outpatient according to Sokolow-Lyon criterion (*P*=.084), by four (21.0%) normotensive individuals and seven (22.6%) hypertensive outpatients according to Cornell voltage criterion (*P*=.940), and by one (5.2%) normotensive individual and five (16.1%) hypertensive outpatients according to Cornell product criterion (*P*=.305).

Novel ECG Parameters

New ECG parameters for cardiac OD are reported in Table II. No significant differences were found between

TABLE II. Novel ECG Parameters for Cardiac Organ Damage

Parameters	Overall (N=50)	Normotensive (n=18)	Hypertensive (n=32)	*P* Value
Tp-Te, mm	2.7015±0.577	2.2234±0.32531	2.9554±0.52002	<.001
VAT, mm	0.9930±0.1836	0.9786±.1973843	1.0008±0.178492	.693
P-wave duration				
DI	2.2123±0.5331	2.1368±0.6221	2.2525±0.4853	.475
DII	2.6377±0.3987	2.5759±0.3839	2.6706±0.4085	.435
DIII	2.1921±0.5995	2.3756±0.3977	2.0945±0.6683	.119
aVR	2.4751±0.3936	2.3654±0.3652	2.5333±0.4012	.157
aVL	1.7968±0.5116	1.9925±0.3987	1.6929±0.5395	.050
aVF	2.4179±0.5493	2.3195±0.5618	2.4702±0.5442	.336
V1	2.0581±0.5057	2.0049±0.4399	2.0863±0.5419	.597
V2	1.8437±0.4073	1.7631±0.3924	1.8866±0.4147	.317
V3	2.1528±0.4752	2.0175±0.4226	2.2247±0.4921	.148
V4	2.4795±0.4540	2.3338±0.5178	2.5569±0.4036	.102
V5	2.5048±0.5067	2.4618±0.5272	2.5276±0.5026	.670
V6	2.5105±0.5149	2.4758±0.5549	2.5290±0.5006	.734
Maximum duration	2.9699±0.4043	2.8653±0.3903	3.0254±0.4066	.190
Minimum duration	1.3784±0.3249	1.4485±0.3374	1.3412±0.3172	.276
Average duration	2.2285±0.2892	2.2332±0.2824	2.2260±0.2971	.934
P-wave dispersion	1.5027±0.4387	1.4126±0.4288	1.5505±0.4431	.300
P-wave area	2.0900±0.7746	2.1524±0.8706	2.0568±0.7311	.685
P-wave amplitude (DIII)	1.5652±0.5401	1.6455±0.6326	1.5226±0.4896	.454

Abbreviations: ECG, electrocardographic; VAT, ventricular activation time.

the two study groups with regard to VAT and P-wave analysis (which includes P-wave duration measured in all leads, maximum, minimum, and average duration, as well as dispersion, area, and amplitude). On the contrary, Tp-Te was significantly higher in hypertensive outpatients compared with normotensive individuals, both as absolute values (2.9554±0.52002 mm vs 2.2234±0.32531 mm; *P*<.001) (Figure 1). In addition, receiver operating characteristic analysis revealed an area under the curve of 0.886 (range, 0.795–0.977) for log Tp-Te interval, 0.528 (range, 0.357–0.698) for log VAT, and 0.494 (range, 0.318–0.670) for log P duration (Figure 2).

Echocardiographic Parameters

Echocardiographic parameters for cardiac OD are reported in Table III. Absolute LVM (158.7±41.3 vs 130.9±35.9 g; *P*=.009), as well as LVM indexed by body surface area (81.9±18.0 vs 69.5±12.8 g/m^2; *P*=.003), by height (91.4±21.3 vs 75.5±18.3 g/cm; *P*=.005), and by height$^{2.7}$ (36.6±7.8 vs 29.7±6.1 g/cm$^{2.7}$; *P*=.001) were significantly higher in hypertensive

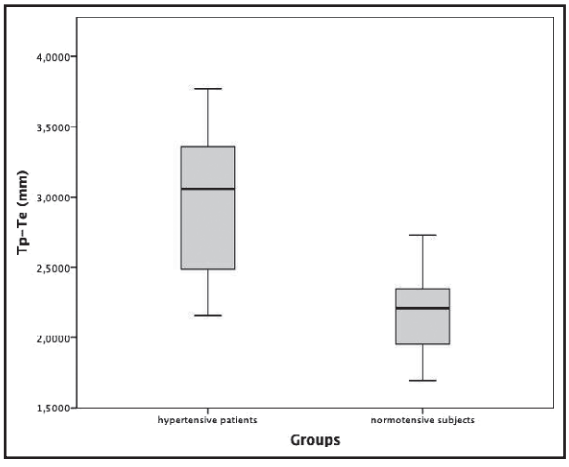

FIGURE 1. Box plot reporting Tp-Te intervals in hypertensive patients (group A) and normotensive individuals (group B).

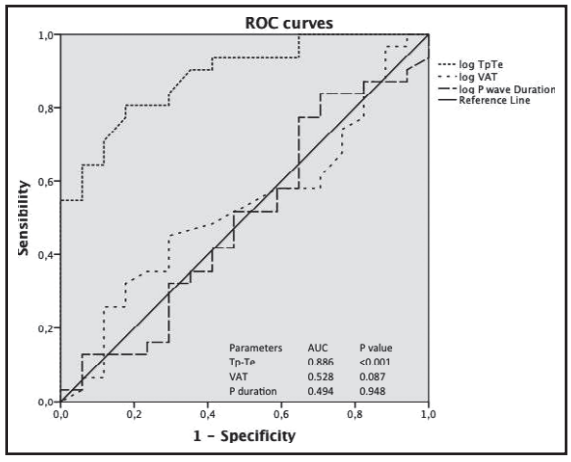

FIGURE 2. Receiver operating characteristics (ROC) curves illustrating ability of Tp-Te interval, ventricular activation time (VAT), and average *P* duration to predict presence of hypertension.

TABLE III. Echocardiographic Parameters of the Study Population

Parameters	Overall (N=50)	Normotensive (n=18)	Hypertensive (n=32)	*P* Value
LV mass, g	148.2±41.3	130.9±35.9	158.7±41.3	.009
LV mass/BSA, g/m^2	77.2±17.2	69.5±12.8	81.9±18.0	.003
LV mass/height, g/cm	85.4±21.5	75.5±18.3	91.4±21.3	.005
LV mass/height$^{2.7}$, g/cm$^{2.7}$	34.0±7.9	29.7±6.1	36.6±7.8	.001
Systolic parameters				
LVEF, %	69.5±7.1	70.7±5.6	68.8±7.8	.220
LVFS, %	40.0±5.7	40.6±4.5	39.7±6.4	.408
LV Sm wave	0.148±0.041	0.152±0.044	0.145±0.039	.658
Conventional diastolic parameters				
E wave	74.4±16.7	71.9±13.3	76.2±19.0	.430
A wave	63.9±13.7	58.4±9.4	67.9±15.1	.026
E/A ratio	1.4±1.5	1.8±2.3	1.2±0.5	.330
DT, ms	209.3±56.3	194.9±34.5	219.5±66.8	.160
Left atrium area, cm^2	16.6±3.6	16.5±4.3	16.6±3.1	.095
TDI diastolic parameters				
LV Em wave	0.185±0.049	0.195±0.058	0.177±0.041	.311
LV Am wave	0.162±0.051	0.144±0.036	0.176±0.056	.045
LV Em/Am ratio	1.223±0.390	1.420±0.406	1.082±0.317	.013
LV E/Em ratio	4.17±0.96	3.81±1.06	4.40±0.84	.149

Abbreviations: BSA, body surface area; DT, deceleration time; LV, left ventricular; LVEF, left ventricular ejection fraction; LVFS, left ventricular fractional shortening.

outpatients compared with normotensive individuals. Of note, although these parameters were significantly different between the two groups, they were all within the normal thresholds. In particular, in the hypertensive group, seven (22.6%) patients showed concentric remodeling and 24 (77.4%) showed normal LV geometry.

No significant differences were found between the two study groups with regard to indexes of LV systolic function, including LV ejection fraction, fractional shortening, and Sm wave amplitude at TDI analysis.

With regard to indexes of LV diastolic dysfunction, no significant differences were found between the two groups, with the only exception of A-wave amplitude, which was slightly but significantly higher in hypertensive outpatients compared with normotensive individuals both at conventional Doppler (68±15 vs 58±9; *P*=.026) and TDI (0.176±0.056 vs 0.144±0.036; *P*=.045) analyses.

Correlations and Multivariate Analysis

Increased Tp-Te interval was significantly related to both clinic (*r*=0.380; *P*=.012) and 24-hour (*r*=0.448; *P*=.03) BP levels. In addition, significant positive correlations were found between Tp-Te interval and LVM (*r*=0.313; *P*=.29) and LVM indexed by height$^{2.7}$ (*r*=0.345; *P*=.015). However, Tp-Te interval did not show any significant correlation with BMI (*r*=0.251; *P*=.082), as well as with different parameters of LV diastolic dysfunction, including E/A ratio (*r*=0.068; *P*=.694), Em/Am ratio (*r*=−0.265; *P*=.119), and E/Em ratio (*r*=0.136; *P*=.428). Finally, when the Cox regression model was fitted with all covariates predictive of hypertension at the 0.1 significance level at univariate analysis, several parameters, including Tp-Te and BMI, LVM indexed by height$^{2.7}$ and Em/Am ratio independently predicted the presence of hypertension, with Tp-Te interval emerging as the only predictor of hypertension at multivariate analysis (Table IV).

DISCUSSION

First, our study demonstrated that recently diagnosed, untreated hypertensive outpatients had higher values of Tp-Te interval than those observed in normotensive individuals. This was associated with significantly higher, although normal, values of LVM and diastolic function in untreated hypertensive outpatients compared with normotensive individuals. These findings may be of potential clinical relevance on the basis of the following considerations.

ECG assessment of cardiac OD has been recently reaffirmed by the most recent sets of European guidelines[26] as a fundamental step in both diagnostic and therapeutic processes during the clinical course of the very complex, although asymptomatic disease, that is hypertension. Several characteristics of this technique has prompted its first-line application in order to identify those hypertensive patients with LV remodeling or dysfunction. Among these, the large diffusion in almost all clinical settings, the relatively low cost of the procedure in various countries, the objective (semiautomatic) interpretation of the data needed for the diagnostic criteria, and the high sensitivity, even in the presence of its relatively low specificity, have substantially contributed to its predominant positioning compared with echocardiographic assessment of cardiac

TABLE IV. Univariate and Multivariate Analyses

Variable	Univariate Analysis (95% CI)	*P* Value	Multivariate Analysis (95% CI)	*P* Value
Male sex (categorical)	0.529 (0.164–1.711)	.288	–	
Age	1.034 (0.970–1.101)	.308	–	
BMI	1.204 (1.001–1.447)	.049	2.059 (0.867–4.889)	.102
Heart rate	1.021 (0.972–1.071)	.407	–	
QRS	1.015 (0.979–1.053)	.412	–	
QT	1.003 (0.985–1.021)	.748	–	
QTc	1.003 (0.980–1.027)	.773	–	
Tp-Te[a]	1.497 (1.176–1.905)	.001	1.835 (1.064–3.167)	.029
VAT[b]	1.070 (0.770–1.488)	.686	–	
Average *P* duration	1.185 (0.156–8.979)	.869	–	
LV mass indexed 2.7	1.160 (1.042–1.292)	.007	1.366 (0.951–1.964)	.092
E/A ratio	0.490 (0.111–2.156)	.345	–	
Em/Am ratio	0.052 (0.004–0.628)	.020	0.064 (0.000–11–942)	.303

Abbreviations: BMI, body mass index; LV, left ventricular. [a]Hazard ratio is expressed as relative risk for each 0.1-mm increase of Tp-Te interval. [b]Hazard ratio is expressed as relative risk for each 0.1-mm increase of ventricular activation time (VAT).

OD. ECG detection of LVH has, in fact, been demonstrated to be independently correlated to an increased risk of major cardiovascular events in hypertensive patients with different cardiovascular risk profiles.[27] Nonetheless, ECG regression of LVH under pharmacologic treatment has been demonstrated to confer a significant reduction of such increased risk of major cardiovascular complications.[28] In fact, evidence from large, randomized clinical trials have, indeed, has demonstrated the beneficial effects of LVH regression in terms of reduced incidence of major cardiovascular complications in hypertension, mostly stroke.[29–32] As such, ECG detection, as well as regression of cardiac OD, namely LVH, can be viewed as an intermediate endpoint that may help physicians during the long-term clinical management of hypertension.[33,34]

Over the past years, several novel ECG criteria for LVH have been tested for the diagnostic workup of hypertensive outpatients in order to try to overcome some intrinsic limitations of this approach and to ameliorate its relatively low specificity.[35] The applicability of these new diagnostic criteria, however, was at least, in part, limited to frankly hypertensive populations (ie, patients with established diagnosis of hypertension under pharmacologic treatment), and it has not been tested in untreated, recently diagnosed hypertensive patients.

More recently, additional ECG indexes, including VAT, P-wave analysis, and Tp-Te interval, have been proposed for improving ECG detection of LVH and LV dysfunction. In particular, available evidence has demonstrated significant, positive, and independent correlations between increased LVM and prolonged Tp-Te interval, which has been viewed as an index of impaired transmural dispersion of LV repolarization.[19–21] These findings, however, have been obtained in various clinical conditions other than hypertension,[19–21] a condition in which both LVH and LV dysfunction are extremely frequent and independently related to worse prognosis.

At the same time, clinical studies specifically designed for hypertensive populations have reported significant correlations between increased LVM and prolonged LV repolarization, mostly defined as QTc interval,[36–38] without addressing the potential role of new ECG indexes of cardiac OD. The results of these studies, however, are similar to those reported in our analysis. Indeed, they demonstrated that prolonged LV repolarization throughout the 24-hour period was significantly related to nondipping status and increased LVM, which may lead to prolongation of QTc, potentially facilitating ventricular arrhythmias in nondipper hypertensive patients compared with dipper hypertensive or normotensive individuals.

On the basis of these considerations, the main findings of our analysis demonstrated for the first time that prolonged Tp-Te interval was associated with both increased LVM and BP levels in a relatively small sample of newly diagnosed, untreated hypertensive outpatients compared with normotensive individuals. Although preliminary, these results may have potential clinical relevance, since they suggest the use of a new, easy and low-cost diagnostic tool that may improve global cardiovascular risk stratification and proper assessment of cardiac impairment in the early, asymptomatic stages of hypertension, in which conventional markers of cardiac OD may not help physicians in the clinical decision process.

Potential Limitations

Our study has some limitations that should be acknowledged. First of all, the relatively small sample size may limit the applicability of Tp-Te measurement in a setting of clinical practice. The design of the study did not allow us to speculate on potential prognostic and therapeutic implications of Tp-Te in the long-term

clinical management of hypertensive outpatients. In addition, the data on the reproducibility of these ECG parameters over time are still lacking and should be tested before considering them for routine ECG testing. The cutoff age has been arbitrarily chosen according to the median age of the outpatient population referred to our hypertension unit. Finally, the need for additional software to calculate these novel ECG parameters may also limit the applicability of these indexes in a setting of daily clinical practice. Larger and more extended studies in hypertensive outpatients are needed to better clarify the potential clinical usefulness and prognostic value of these new indexes parameters.

CONCLUSIONS

Preliminary results of our study demonstrated that Tp-Te interval may be considered an early marker of cardiac abnormalities at 12-lead ECG. Prolonged Tp-Te interval was also related to an increased independent risk of having hypertension, even after adjusting for anthropometric and clinical parameters. Further studies are required to confirm our findings in patients with different degrees of hypertension and LV geometries, and to better clarify the potential role of this parameter in the diagnostic workup of hypertension and global cardiovascular risk stratification.

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