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T-wave axis deviation and left ventricular hypertrophy interaction in diabetes and hypertension☆

Deodato Assanelli, MD,[a] Augusto Di Castelnuovo, MSc, PhD,[b] Livia Rago, MD,[b] Fabio Badilini, PhD, FACC,[c] Giovanni Vinetti, MD,[a] Francesco Gianfagna, MD, PhD,[b] Massimo Salvetti, MD,[a] Francesco Zito, MD,[b] Maria Benedetta Donati, MD, PhD,[d] Giovanni de Gaetano, MD, PhD,[d] Licia Iacoviello, MD, PhD[d,e,*] on behalf of the *Moli-sani Project* Investigators

[a]*Department of Sports–Internal Medicine, University of Brescia, Brescia, Italy*

[b]*Laboratory of Genetic and Environmental Epidemiology. Research Laboratories, "John Paul II" Centre for High Technology Research and Education in Biomedical Sciences, Catholic University, Campobasso, Italy*

[c]*AMPS LLC, New York, NY, USA*

[d]*Department of Epidemiology and Prevention. IRCCS Istituto Neurologico Mediterraneo Neuromed, Pozzilli (IS), Italy*

[e]*Laboratory of Cardiovascular and Neurovascular Epidemiology. Casa di Cura Montevergine, Mercogliano (AV), Italy*

Abstract Electrocardiographic signs of left ventricular hypertrophy (ECG-LVH) and T-wave axis (TA) deviation are independent predictors of fatal and non fatal events. We assessed the prevalence of ECG-LVH, TA abnormalities and their combination according to the presence or absence of diabetes and/or hypertension in a large sample of the adult general Italian population. Data from 10,184 women (54 ± 11 years) and 8775 men (54 ± 11 years) were analyzed from the Moli-sani cohort, a database of randomly recruited adults (age > 35) from the general population of Molise, a central region of Italy that includes collection of standard 12-lead resting ECG. Subjects with previous myocardial infarction, angina, cerebrovascular disease or left bundle brunch block or missing values for TA or ECG-LVH have been excluded. TA was measured from the standard 12-lead ECG and it was defined as the rotation of the T wave in the frontal plane as computed by a proprietary algorithm (CalECG/Bravo, AMPS-LLC, NY). ECG-LVH was defined as Sokolow Lyon voltage (SLv) > 35 mm or Cornell voltage duration Product (CP) > = 2440 mm*ms. Among subjects with ECG-LVH, prevalence of hypertension was 59.0% and 49.7%, respectively for men and women, whereas that of diabetes was 10.7% and 5.7%. In hypertensives, TA was normal in 72.3% of subjects, borderline in 24.8% and abnormal in 2.9%. In diabetics, TA was normal in 70.4% of subjects, borderline in 26.5% and abnormal in 3.1%. In both hypertensive and diabetic subjects, the prevalence of ECG-LVH, was significantly greater in subjects with borderline or abnormal TA. Hypertension was an independent predictor of abnormal TA (odd ratio: 1.38, $P = .025$). These results suggest that hypertension might play a relevant role in the pathogenesis of TA deviation.

Keywords: Left ventricular hypertrophy T-wave axes; Coronary artery disease; Diabetes; Hypertension

Introduction

T-wave axis (TA) deviation from surface ECG is considered an easy-to-measure and strong marker of cardiovascular risk which has been shown to be able to independently predict fatal and nonfatal events.[1–3] While TA deviation is an accepted global measure of repolarisation abnormalities that is able to increase the electrical vulnerability of the heart,[4] the underlying physiopathology of this abnormality is not known.

Arterial hypertension (HTN) is a major cardiovascular risk factor and it is more common in patients with diabetes mellitus (DM), when compared with the general population. Left ventricular hypertrophy (LVH) is common in hypertensive patients, and it increases the risk of myocardial infarction, stroke, and death. Several criteria for electrocardiographic signs of LVH (ECG-LVH) have been proposed

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* Corresponding author. Department of Epidemiology and Prevention. IRCCS Istituto Neurologico Mediterraneo Neuromed, Via dell'Elettronica. 86077 Pozzilli (IS), Italy.

E-mail address: licia.iacoviello@moli-sani.org

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and the most used are the Sokolow–Lyon index[5] and the Cornell product.[6]

Diabetes is a primary factor in determining cardiovascular diseases mainly by both micro and macrovascular damage. Several articles have recently evaluated ECG abnormalities in patients with diabetes in the absence of coronary artery disease (CAD). These abnormalities have been advocated as a specific pattern of diabetes: nonspecific abnormalities,[7] abnormal repolarization,[8] increase of QRS duration[9,10] and strain pattern[11]; when DM is associated with HTN, a prolonged QTc interval,[12] an impaired heart rate variability,[13] and an increased Cornell voltage–duration product have been shown. Despite this, a consensus on the results obtained has not been reached.

To our knowledge, an association between TA deviation and diabetes has never been investigated. In addition, the interaction between HTN and DM for ECG abnormalities is not clear, even if the combination is very common. Interaction between ECG-LVH and TA abnormalities pathophysiology has been, to date, deeply studied only in animal models and seems to indicate an inhomogeneous repolarization.[14]

The goal of this study is to evaluate the role of hypertension alone, diabetes alone and the combination between the two in determining the occurrence of ECG abnormalities such as TA deviation and ECG-LVH from 12-lead digital ECG in a large cohort of adults from the adult general Italian population.

Methods

The cohort of the Moli-sani Study was randomly recruited in the Molise region from city hall registries by a multistage sampling.[15] First, townships were sampled in major areas by cluster sampling; then, within each township, participants aged ≥35 years were selected by simple random sampling. Exclusion criteria were pregnancy at the time of recruitment, disturbances in understanding or willingness, current polytraumas or coma, or refusal to sign the informed consent. Thirty percent of subjects refused to participate; these were generally older and had a higher prevalence of CVD and cancer.

Between March 2005 and April 2010, 24,325 subjects were recruited in two centers: the Catholic University of Campobasso (n = 19,217; 79%) and San Timoteo Hospital of Termoli (n = 5,108; 21%), by research personnel, accurately trained. The recruitment strategies were carefully defined and standardised across the two recruiting centres. Structured digitalized questionnaires were administered to collect personal and clinical information. The Moli-sani study complies with the Declaration of Helsinki and was approved by the Catholic University ethical committee. All participants enrolled provided written informed consent.

The set of clinical data collected included a standard 12-lead resting electrocardiogram (ECG) which was acquired with a Cardiette® ar2100-view electrocardiograph (Cardioline). Digital ECG waveforms were stored in a public domain format (the standard communication protocol ECG, also known as SCP-ECG standard) and subsequently exported and processed by a dedicated on-screen computer application[16] which embeds a proprietary measuring tool and the University of Glasgow 12-Lead ECG diagnostic algorithm.[17]

Subjects with complete bundle brunch blocks (QRS duration ≥ 120 ms) were excluded since this condition might provoke T-wave changes to altered ventricular depolarization sequence. After excluding subjects with incomplete questionnaire, history of cardiovascular disease, T-axis value missing, ECG-LVH value missing, diabetes or hypertension values missing, 18,959 subjects (80%), 10,184 women (54 ± 11 years) and 8775 men (54 ± 11 years) were analyzed.

Frontal T-wave axis measurement

TA deviation was measured from the standard 12-lead SCP-ECG saved records. The ECGs were then processed by the "University of Glasgow 12-Lead ECG Analysis Algorithm"[17] that produces the value of rotation of the T-wave in the frontal axis.

T-wave axis was categorized as normal ($15° \le TA \le 75°$), borderline ($75° < TA \le 105°$ or $-15° \le TA < 15°$), and abnormal ($-180° \le TA < -15°$ or $105° < TA \le 180°$), according to Kors et al.[2]

Electrocardiographic signs of left ventricular hypertrophy

ECG-LVH was identified using criteria on the basis of the Cornell Product (CP): [(RaVL + SV3) × QRS duration > 2440 mm × ms in men and (RaVL + SV3 + 6 mm) × QRS duration > 2440 mm × ms in women], and the Sokolow–Lyon voltage combination (SLv): SV1 + (RV5 or RV6) > 35 mm.

Definition of risk factors

Blood pressure was measured by an automatic device (OMRON-HEM-705CP) three times on the non-dominant arm and the average of the last two values was taken as the BP.[18] Measurements were made in a quiet room with comfortable temperature with participants lying down for at least 5 min. Hypertension was defined as systolic BP ≥ 140 mm Hg and/or diastolic BP ≥90 mm Hg, or active pharmacological treatment for hypertension. Overall, 47% of the hypertensive subjects were under pharmacological treatment.

Diabetes was defined as fasting glucose level > 126 mg/dL or current treatment with antidiabetic drugs. Overall, 49% of the diabetic subjects were under pharmacological treatment.

Subjects were classified as non-smokers if they had smoked less than 100 cigarettes life-long or they had never smoked cigarettes, ex-smokers if they had smoked cigarettes in the past and had stopped smoking for at least 1 year, and current smokers those who reported having smoked at least 100 cigarettes in their lifetime and still smoked or had quit smoking within the preceding year.

Physical activity was assessed by a structured questionnaire (24 questions on working time, leisure time and sport participation) and expressed as daily energy expenditure in metabolic equivalent task-hours (MET-h).

Statistical analysis

Values for continuous variables are expressed as means ± Standard Deviation. All the analyses were conducted separately by sexes. The potential covariates used to test for association with abnormalities of T-axis (two levels:

Table 1
T wave axis and traditional cardiovascular risk factors.

Characteristics	WOMEN (N = 10,184)			MEN (N = 8775)		
	T-axis					
	Normal or Borderline (N = 10,010)	Abnormal (N = 174)	p	Normal or Borderline (N = 8616)	Abnormal (N = 117)	p
Age, years (sd)	55 (11)	60 (13)	<0.0001	54 (11)	59 (12)	<0.0001
Smokers n, (%)	6543 (65)	123 (71)	0.079	2908 (34)	55 (35)	0.62
Never	2072 (21)	24 (14)		2292 (27)	37 (23)	
Current	1380 (14)	27 (15)		3410 (39)	67 (42)	
Former						
Physical activity, MET-h/day (sd)	42.7 (7.6)	42.1 (7.3)	0.30	44.0 (10.0)	43.5 (8.0)	0.54
BMI, kg/m^2 (sd)	27.9 (5.3)	29.4 (6.1)	<0.0001	28.2 (4.0)	29.4 (4.2)	<0.0001
Hypertension n, (%)	4975 (49.7)	123 (70.7)	<0.0001	5086 (59.0)	117 (73.6)	0.0002
Diabetes n, (%)	568 (5.7)	22 (12.6)	<0.0001	919 (10.7)	26 (16.4)	0.022
Hyperlipidaemia n, (%)	3204 (32.2)	60 (34.7)	0.49	2397 (27.8)	37 (31.6)	0.026

normal or borderline vs. abnormal) included age, sex, physical activity and BMI. Generalized linear models (PROC GENMOD in SAS) were used for testing the association of T wave axis classification with potential predictors. Using multivariable logistic regression analysis, odds ratio (ORs) with corresponding 95% confidence intervals (95% CI) were calculated to quantify the association of T-axis (two levels, normal or borderline versus abnormal, dependent variable) with diabetes, hypertension, their combination, and appropriate terms for interaction. Data analysis was generated using SAS/STAT software, Version 9.1.3 of the SAS System for Windows© 2009. SAS Institute Inc. and SAS are registered trademarks of SAS Institute Inc., Cary, NC, USA.

Results

T wave axis deviation and traditional cardiovascular risk factors

In Table 1, the prevalence and the magnitude of several risk factors (including hypertension and diabetes) in relation to TA are given, separately for males and females. With univariate analysis, HTN and DM were significantly related to abnormal TA ($p < 0.0001$), while smoke, physical activity and hyperlipidemia were much less related. However, in men TA was associated with a higher prevalence of hyperlipidemia ($p = 0.026$). BMI and age were also higher in subjects with abnormal TA, both in men and in women ($p < 0.0001$).

T wave axis deviation and ECG left ventricular hypertrophy

Table 2 explores the associations between ECG-LVH and TA abnormality. When considering the entire population, prevalence of normal, borderline or abnormal TA was 77.4%, 20.8% and 1.8%, respectively. Among subjects with normal, borderline or abnormal TA, prevalence of ECG-LVH (defined by either SLv or CP) was 2.6%, 4.8% and 11.4%, respectively (p for trend <0.0001). The increasing trend of ECG-LVH prevalence in subjects with normal, borderline or abnormal TA was particularly evident in hypertensive patients (5.2%, 7.4% and 14.5%, respectively, p for trend <0.0001), and was also significant in diabetic patients (4.1%, 7.1% and 12.5%, respectively, p for trend = 0.0082). Apart for the subgroup of diabetics, CP enhanced a stronger relationship with TA, thus suggesting this to be a better marker of ECG-LVH than SLv.

Hypertension and/or diabetes and T wave axis deviation

In Table 3, the odd ratios (OR) for having abnormal TA of HTN alone, DM alone, or their combination (HTN + DM) are shown. Hypertension alone resulted as the major factor determining abnormal TA, with an OR of 1.38 ($p = 0.025$). Similar results are reached for HTN in non-diabetic subjects

Table 2
T wave axis and ECG signs of left ventricular hypertrophy.

	T-axis			
	Normal	Borderline	Abnormal	p for trend
ALL (N = 18959)	N = 14,680 (77.4%)	N = 3946 (20.8%)	N = 333 (1.8%)	
Sokolow +	45 (0.3%)	13 (0.3%)	3 (0.9%)	0.24
Cornell Product +	344 (2.3%)	181 (4.6%)	35 (10.5%)	<0.0001
Sokolow + or Cornell Product +	383 (2.6%)	188 (4.8%)	38 (11.4%)	<0.0001
Hypertensive patients (N = 6880)	N = 4974 (72.3%)	N = 1706 (24.8%)	N = 200 (2.9%)	
Sokolow +	24 (0.5%)	7 (0.4%)	3 (1.5%)	0.17
Cornell Product +	236 (4.7%)	124 (7.3%)	26 (13.0%)	<0.0001
Sokolow + or Cornell Product +	256 (5.2%)	127 (7.4%)	29 (14.5%)	<0.0001
Diabetic patients (N = 1535)	N = 1080 (70.4%)	N = 407 (26.5%)	N = 48 (3.1%)	
Sokolow +	0 (0.0%)	3 (0.7%)	1 (2.1%)	0.0069
Cornell Product +	44 (4.1%)	27 (6.6%)	5 (10.4%)	0.035
Sokolow + or Cornell Product +	44 (4.1%)	29 (7.1%)	6 (12.5%)	0.0082

Table 3
Odds ratios (OR) and 95% confidence interval (95% CI) for having abnormal TA of hypertension alone, diabetes mellitus alone, or their association.

Sub-samples (All =18 959)	T-axis		
	N	Normal or Borderline (N = 18 626)	Abnormal (N = 333)
a) HTN NO and DM NO	8376	8287 (98.9%)	89 (1.1%)
b) HT YES and DM NO	9048	8852 (97.8%)	196 (2.2%)
c) HTN NO and DM YES	282	278 (98.6%)	4 (1.4%)
d) HTN YES and DM YES	1253	1209 (96.5%)	44 (3.5%)
Sub-samples comparison	OR (95% CI) for abnormal TA	p	
HTN (b + d *versus* a + c)	1.38 (1.04–1.83)	0.025	
HTN, in non-DM patients (b *versus* a)	1.37 (1.03–1.82)	0.033	
HTN, in DM patients (d *versus* c)	2.03 (0.71– 5.86)	0.19	
DM (c + d *versus* a + b)	0.98 (0.35–2.69)	0.96	
DM, in non-HTN patients (c *versus* a)	1.15 (0.41–3.22)	0.79	
DM, in HTN patients (d *versus* b)	1.34 (0.95–1.88)	0.094	

Interaction effect [Hypertension*Diabetes]: p = 0.52.
HTN = hypertension, DM = diabetes.

only (OR for abnormal TA 1.37, p = 0.033). In patients with DM, the presence of HTN produced an OR for abnormal TA of 2.03, but the result did not reach statistical significance (p = 0.19). DM alone was not related with increased prevalence of abnormal TA, but the HTN subgroup showed a tendency with an OR of 1.34 for abnormal TA, which however did not reach statistical significance (p = 0.094). Finally, no interaction between HTN and DM has been demonstrated (p = 0.52).

Discussion

This study assessed the relationship between TA, ECG-LVH and demographic and hemodynamic variables in a large Mediterranean general population (n > 18,000).

Our findings confirm the close association between HTN and abnormal TA, as previously demonstrated in other Caucasian and non-Caucasian cohorts.[1–3] Prevalence of abnormal TA was greater in patients with DM (3.1% vs. 1.8%, as shown in Table 2), and subgroup univariate analysis confirmed this difference in both males and females: however this difference was not statistically different after adjusting for the possible confounders (Table 3). Conversely, the differences in the prevalence of abnormal TA between hypertensive and normotensive subjects remained significant, even after adjusting for potential confounders, including age, sex, physical activity and BMI (Table 3).

Interestingly, our data indicate that TA deviation is associated with ECG-LVH (Table 2). In fact, the prevalence of ECG-LVH progressively increased from 2.6% to 4.8% to 11.4% in subjects with normal, borderline, or abnormal TA, respectively (p < 0.0001). As for abnormal TA, the prevalence of ECG-LVH was significantly greater in hypertensives compared to normotensives, a difference that remained highly significant after adjustment for possible confounders. These results suggest that hypertension might play a relevant role in the pathogenesis of TA deviation and that LVH could be one of the key factors for its development.

The pathophysiology of interaction between TA and LVH has been deeply investigated only in animal models of catecholamine-induced LVH,[14] where frontal TAs were divergent and showed wide inter-animal variation and the normal epicardial to endocardial sequence of repolarization appears to be reversed. In men, to our knowledge, the meaning of this interaction is unknown.

Despite this, assessment of TA deviation has been shown to be predictive of cardiovascular events independently of LVH, thus suggesting that the information carried by the two alterations is partially independent and that other mechanisms could be involved. We do believe that it would be worth investigating the real meaning of strong risk markers as TA deviation and ECG-LVH on highly prevalent diseases as DM and HTN.

Results concerning the relationship between TA and DM seemed deceiving because, despite an increased OR for the combination of HTN and DM, the interaction term did not reach statistical significance (as shown in Table 3). This finding may be related to small number of subjects with abnormal T wave axis (n = 333) and of subjects with DM but without HTN (n = 282).

It is plausible that the cardiac effects of DM act either by increasing the HTN occurrence and its complications or/and by inducing a premature and diffuse CAD capable to impair cardiac and neural function. In this scenario, only stress ECG or stress image examination (Echo-stress or scintigraphy) could be able to recognize early CAD occurrence in individual subjects. As compared to patients with HTN, it is possible that patients with DM + HTN are more likely to have a higher prevalence of preclinical CAD. A more focused study design could allow to explore this CAD occurrence in patients with diabetes with and without HTN, and provide more definitive answers. An alternative interpretation, already postulated in the literature[9,11,14] but never demonstrated, states that patients with both HTN and DM are more likely to have a silent cardiomyopathy with left ventricle diastolic and systolic dilatation; for patients with these patterns, serial echocardiographic evaluation, in parallel with 12-lead ECG, will allow a conclusive diagnosis. To date, with the available results we are only able to confirm that TA deviation in patients with DM seems equally related to HTN and, when present, to the consequent LVH. In conclusion, while TA is clearly an

important indicator of cardiovascular events in both DM and HTN, further research is needed in order to better clarify the mechanisms underlying TA deviation, the determinants of its evolution over time and the possible favorable effect of antihypertensive and anti-diabetic treatments.

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