T- wave axis deviation is associated with biomarkers of low-grade inflammation

Findings from the MOLI-SANI study

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Summary

T-wave axis deviation (TDev) may help identifying subjects at risk for major cardiac events and mortality, but the pathogenesis of TDev is not well established; in particular, the possible association between TDev and inflammation is unexplored and unknown. We aimed at investigating the association between low-grade inflammation and TDev abnormalities by conducting a cross-sectional analysis on 17,507 subjects apparently free from coronary heart and haematological diseases enrolled in the MOLI-SANI study. TDev was measured from a standard 12-lead resting electrocardiogram. High sensitivity (Hs) C-reactive protein (CRP), leukocyte (WBC) and platelet counts, neutrophil or granulocyte to lymphocyte ratios were used as markers of inflammation. In multivariable model subjects reporting high CRP levels had higher odds of having borderline and abnormal TDev (OR=1.70; 95 %CI: 1.53–1.90 and OR=1.72; 95 %CI: 1.23–2.41, respectively); the association was still significant, although reduced, after controlling for body mass index (OR=1.17; 95 %CI: 1.05–1.32, for borderline and OR=1.46; 95 %CI: 1.03–2.08, for abnormal). Similarly, higher neutrophil or granulocyte to lymphocyte ratios were associated with increased odds of having abnormal TDev. Neither platelet nor leukocyte counts were associated with abnormal TDev. The relationship between CRP with TDev abnormalities was significantly stronger in men, in non- obese or normotensive individuals, and in those without metabolic syndrome. In conclusion, C-reactive protein and some cellular biomarkers of inflammation such as granulocyte or neutrophil to lymphocyte ratios were independently associated with abnormal TDev, especially in subjects at low CVD risk. These results suggest that a low-grade inflammation likely contributes to the pathogenesis of T- wave axis deviation.

Keywords

T-wave axis deviation, low-grade inflammation, hypertension, obesity, metabolic syndrome

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Introduction

TDev is a marker of ventricular repolarisation, and may help identifying subjects at high risk for arrhythmias and/or major cardiac events. It has been associated with increased risk of coronary heart disease and total mortality, independently of other cardiovascular risk factors, particularly in the elderly population (1, 2). In spite of being an accepted global measure of repolarisation abnormalities, the underlying physiopathology of TDev is not fully understood (3, 4). It has been recently speculated that obesity and hypertension could have a relevant role in the pathogenesis of T-wave axis deviation (3, 5). In addition, latest studies showed that abnormal T-wave axis shift is also independently associated with metabolic syndrome (5, 6), suggesting to perform a careful electrocardiographic recording among persons with metabolic syndrome for early detection of abnormal T-wave axis in clinical practice to prevent severe and often fatal arrhythmias.

The association between TDev and inflammation is unexplored and unknown. Chronic low-grade inflammation has been hypothesised as an underlying pathophysiological mechanism linking behavioural factors and obesity to chronic disease risk (7). High sensitivity (hs) C-reactive protein (CRP) is a plasmatic protein synthesized by the liver and, beyond being considered a reliable biomarker for inflammation (8), has an independent predictive value

for future coronary events and mortality independently of other conventional risk factors (9, 10). Both increased white blood cells (WBC) and platelet counts have been recognised as markers of inflammation and have been associated with higher risk for cerebrovascular and coronary heart disease. Specifically, platelet count has been associated with vascular (11) and non-vascular death, including cancer (12) while WBC count is a predictor of fatal and non-fatal ischaemic vascular disease independent of other traditional CVD risk factors (13, 14) and is a broadly used marker of systemic inflammation (15). Both WBC and platelet counts were also inversely associated with a Mediterranean dietary pattern endowed with anti-inflammatory properties (16). The neutrophil to lymphocyte ratio has been recently proposed as a reliable prognostic marker for cardiovascular disease (17).

Our starting hypothesis was that in an apparently normal population a low-grade inflammation could be associated with TDev independently of other risk factors for cardiovascular disease.

We therefore investigated the association between several inflammatory biomarkers with TDev in a large sample of an Italian population apparently free from major coronary heart or haematological diseases in the hope to better understanding of the complex relationship among low-grade chronic inflammation, TDev and cardiovascular risk factors.

Methods

Study population

Cross-sectional analysis was performed in a sample of subjects recruited in the MOLI-SANI study, a population based, cohort of 24, 325 men and women (aged ≥ 35 years) living in the Molise region, a southern-central area of Italy that was randomly enrolled from city hall registries by a multistage sampling (18). The MOLI-SANI study was approved by the Ethics Committee of the Catholic University of Rome, Italy. All participants signed an informed consent.

Subjects (n=690) with QRS > 120 ms or with bundle branch blocks (n=1250) according to the Glasgow algorithm (19) were excluded since this conditions might provoke T-wave changes to altered ventricular depolarisation sequence. Individuals with incomplete anamnestic questionnaire (n=235), history of coronary heart disease (n=1,140), left ventricular hypertrophy (n=1141), inferior or anterior myocardial infarction by ECG (n= 1,033 and n=38 respectively), T-wave axis value missing (n=195), hs-CRP values missing (n=28) or hs-CRP≥ 10 mg/l (n=974) (to avoid introducing confounding due to an acute inflammatory condition), those with missing information on body mass index (n=17), WBC (n=659), platelets (n=659), granulocytes (n=783) or lymphocytes (n=780), individuals with WBC (n=466) or platelets (n=468) counts with values over or under the 99% percentile of the corresponding distribution and those with major haematological diseases (n=526) or hepatitis (n=710) were also excluded. The final study sample included 17,507 subjects (46.3% men).

Inflammatory biomarkers and T-wave axis assessment

High sensitivity C-reactive protein was measured on fresh serum by a latex particle-enhanced immunoturbidimetric assay (IL Coagulation Systems on ACL9000). Inter- and intra-day CV were 5.5% and 4.17%, respectively. Depending on hs-CRP levels, participants were classified as at low (CRP < 1.0 mg/l), medium (CRP 1.0 to 3.0 mg/l), or high cardiovascular risk (> 3.0 mg/l), according to the American Heart Association (20).

High or low platelet groups included individuals with counts above or below the median (> or ≤ 245×10^9/l), respectively. Similarly, high or low WBC categories were defined as those with counts above or below the median (> or ≤ 5.9×10^9/l), respectively.

Percent neutrophil or percent granulocyte to percent lymphocyte ratios were measured as markers of inflammation (17). High or low neutrophil or granulocyte to lymphocyte ratios categories were defined as those having counts above or below the median (> or =1.73 and >or =1.84, respectively).

TDev was measured from a standard 12-lead resting electrocardiogram. ECG was recorded using a Cardiette®ar2100-view electrocardiograph digitally acquiring and storing ECG in SCP format. The ECG were then processed by the Glasgow 12-Lead ECG Analysis Algorithm X that produces the value of rotation of the T-wave in the frontal axis. T-wave axis deviation was categorized in normal (15° to 75°; n=13,954), borderline (-15° to 15° or 75° to 105°; n=3,618) or abnormal (-180° to –15° or 105° to 180°; n= 312) (3).

Definition of common risk factors

Hypertension was defined as systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm/ Hg, or when using pharmacological treatment for hypertension. Diabetes was defined as glucose level ≥ 126 mg/dl or by current antidiabetic treatment. Hypercholesterolaemia was defined as a total cholesterol level ≥ 240 mg/dl or by use of lipid- lowering treatment. Metabolic syndrome was defined according to Adult Treatment Panel III criteria (21): at least three of these criteria:

- elevated waist circumference (> 102 cm in men > 88 cm in women);
- elevated triglycerides (> 150 mg/dl) or drug treatment for elevated triglycerides;
- reduced HDL-C < 40 mg/dl (1.03 mmol/l) in men, < 50 mg/dl (1.3 mmol/l) in women, or drug treatment for reduced HDL-C, elevated blood pressure (> 130 mm Hg systolic blood pressure or > 85 mm Hg diastolic blood pressure), or antihypertensive drug treatment in a patient with a history of hypertension;
- elevated fasting glucose (> 100 mg/dl) or drug treatment for elevated glucose.

Subjects were also classified as never-smokers, current smokers or ex-smokers (quitting from at least 1 year). Education was used as proxy of socioeconomic status and was defined as low (secondary school or lower) or high (high school or higher). Physical activity was assessed by a structured questionnaire (24 questions on work-

ing time, leisure time and sport participation) and expressed as daily energy expenditure in metabolic equivalent task-hours (MET-h). Body mass index (BMI) was calculated as kg/m^2 and then grouped into three categories as normal (≤25), overweight (>25 <30) or obese (≥30). For sensitivity analysis BMI was considered as normal or overweight (<30) or obese (≥30).

Statistical analysis

For inferential analysis, hs-CRP levels were transformed into natural logarithms to reduce their positive skewness, but hs-CRP means were reported untransformed for clarity. Values for continuous variables are presented as means ± standard deviation (SD). Analysis of variance was used to identify potential predictors tested for association with abnormalities of TDev and included socio-demographic variables (age, sex, smoking habit, educational status and physical activity), BMI, QT dispersion, QRS duration, heart rate, hypertension and diabetes. Using multivariable logistic regression analysis, odds ratio (ORs) with corresponding 95% confidence intervals (95%CI) were calculated to quantify the association of biomarkers of inflammation (considered either as continuous or categorical variables) with status of borderline or abnormal TDev in comparison with the normal condition. Terms of interaction between TDev and BMI, hypertension, sex, age (≤65 or >65 years) or metabolic syndrome were included in the multivariable model to test for modification of the inflammatory markers and TDev association. Data for neutrophil to lymphocyte ratio were available only for a sample of 12,908 subjects.

The 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

►Table 1 shows the main characteristic of the population by categories of TDev. Borderline or abnormal TDev was observed in 19.4% and 1.6% of subjects, respectively. Compared to persons with normal TDev, those in the borderline or abnormal group were older, had lower education and higher prevalence of obesity, hypertension, diabetes and metabolic syndrome. Other ECG indicators were also higher in the abnormal TDev group (►Table 1).

The association between biomarkers of low-grade inflammation (considered either as continuous or categorical variables) and TDev are reported in ►Table 2. All inflammatory markers

Table 1: Subjects characteristics by frontal T-wave axis deviation categories.

	All	Frontal T-wave axis			P-value
		Normal	Borderline	Abnormal	
Number of subjects (%)	17507	13816 (78.9)	3420 (19.4)	271 (1.6)	-
Sex (men)	8110 (46.3)	6145 (44.5)	1838 (53.7)	127 (46.9)	<0.0001
Age (years)	54.1 (11.3)	53.9 (11.2)	54.7 (11.2)	59.1 (13.0)	<0.0001
Smokers *					0.019
Never	8763 (50.1)	6839 (49.5)	1783 (52.1)	141 (52.0)	
Current	4175 (23.9)	3507 (25.4)	614 (18.0)	54 (19.9)	
Former	4550 (26.0)	3453 (25.0)	1021 (29.9)	76 (28.0)	
High school or higher	8517 (48.7)	7015 (50.8)	1397 (40.9)	105 (38.8)	<0.0001
Physical activity (MET-h/day)	43.3 (8.9)	43.1 (8.7)	44.1 (9.6)	42.8 (6.7)	<0.0001
BMI (Kg/m^2)					<0.0001
Normal (=25)	5090 (29.1)	4617 (33.4)	416 (12.2)	57 (21.0)	
Overweight (25–30)	7556 (43.2)	5925 (42.9)	1531 (44.8)	100 (36.9)	
Obese (=30)	4861 (27.8)	3274 (23.7)	1473 (43.1)	114 (42.1)	
Hypertension	9081 (51.9)	6858 (49.6)	2039 (59.6)	184 (67.9)	<0.0001
Diabetes	1370 (7.8)	1000 (7.2)	323 (9.4)	47 (17.3)	<0.0001
Metabolic syndrome	4241 (24.4)	3075 (22.4)	1068 (31.5)	98 (36.3)	<0.0001
Hypercholesterolaemia	5307 (30.3)	4140 (30.0)	1086 (31.8)	81 (29.9)	0.06
Heart rate (bpm)	66.9 (9.9)	67.0 (9.9)	66.5 (9.9)	68.6 (12.1)	0.0061
QRS duration (ms)	88.3 (8.2)	88.0 (8.1)	89.4 (8.1)	89.3 (10.3)	<0.0001
QT Dispersion (ms)	47.5 (23.5)	47.3 (23.2)	46.9 (23.3)	66.2 (32.4)	<0.0001

P-value adjusted for age and sex. Continuous variables (age, physical activity, heart rate, QT duration and QT dispersion) are presented as means ± SD. Categorical variables are presented as numbers and percentages. *numbers do not add up to 100% due to missing values.

were significantly higher in the abnormal TDev group, in multivariable models including sex, age, or further adjusted for smoking, physical activity, education, hypertension, diabetes, QT dispersion, QRS duration and heart rate (►Table 2, Model 1 and Model 2). However, the association between TDev and WBC disappeared after further adjustment for BMI (Model 3, ►Table 2).

►Table 3 shows the ORs of having borderline (in comparison with normal) TDev according to categories of inflammatory biomarkers. Subjects with high hs-CRP or platelet count above the median value showed greater odds of having borderline T-wave axis deviation in the fully adjusted model controlled for BMI (►Table 3, Model 2). The ORs of having abnormal TDev are reported in ►Table 4. High hs-CRP, granulocyte or neutrophil to lymphocyte ratios above the median value were significantly associated with greater odds of having abnormal TDev; the associations were significantly reduced, but still significant (except for neutrophil/lymphocyte ratio), when BMI was included as a covariate in the model (Model 3, ►Table 4). WBC or platelet counts were not associated with abnormal TDev (Models 2–3, ►Table 4).

Sensitivity analysis is reported in ►Table 5. The association between hs-CRP levels and TDev categories was more apparent for men, not obese subjects, normotensive individuals and those without the metabolic syndrome (►Table 5). Interaction terms were significant ($p<0.05$) for sex, BMI, hypertension and metabolic syndrome subgroups (►Table 5).

Discussion

Our findings show that T-wave axis deviation is significantly associated with plasmatic and cellular biomarkers of low-grade inflammation in a large sample of the Italian population apparently free from major coronary heart and haematological disease or acute inflammatory status. In particular, T-wave abnormalities were found to be related to increased levels of hs-CRP, a reliable circulating inflammatory marker associated with cardiovascular risk (8–10). Besides hs-CRP, we tested the association of TDev with cellular biomarkers of inflammation, such as WBC and platelets: T-wave abnormalities were positively associated with WBC, neutrophil or granulocyte to lymphocyte ratios but not with platelet count even if the latter showed a modest predictive role for increased borderline TDev. Elevated leukocyte levels have been proven to be reliable predictors of CVD risk (13–15), while scarce evidence is available on the likely role of platelet count in the CVD

Table 2: Inflammatory markers by frontal T-wave axis deviation categories.

	Frontal T-wave axis			P-values		
	Normal	Borderline	Abnormal	P(1)	P(2)	P(3)
hs-C-Reactive Protein* (mg/l)	1.29 (1.27–1.31)	1.61 (1.56–1.66)	1.65 (1.48–1.83)	<0.0001	<0.0001	0.0012
hs-C-Reactive Protein (n,%)				<0.0001	<0.0001	0.0024
Normal (<1)	5421 (39.2)	961 (28.1)	71 (26.2)			
Medium (1–3)	5725 (41.4)	1637 (47.9)	114 (42.1)			
High (>3)	2670 (19.3)	822 (24.0)	86 (31.7)			
White blood cell count ($\times10^9$/l)	6.13 (1.43)	6.18 (1.37)	6.30 (1.39)	0.037	0.0009	0.51
WBC count (n,%)				0.038	0.0044	0.62
Below median(≤5.90)	7007 (50.)	1627 (47.6)	124 (45.8)			
Above median (>5.90)	6809 (49.3)	1793 (52.4)	147 (54.2)			
Granulocyte/lymphocyte ratio	1.98 (0.93)	1.90 (0.66)	2.11 (0.87)	<0.0001	<0.0001	0.0007
Granulocyte/lymphocyte ratio (n,%)				<0.0001	0.0005	0.0022
Below median (≤1.84)	6867 (49.7)	1800 (52.6)	109 (40.2)			
Above median (>1.84)	6949 (50.3)	1620 (47.4)	162 (59.8)			
Neutrophil/lymphocyte ratio	1.86 (0.73)	1.79 (0.66)	2.05 (0.99)	<0.0001	<0.0001	0.0001
Neutrophil/lymphocyte ratio (n,%)				0.0039	0.024	0.11
Below median(≤1.73)	4957 (49.2)	1386 (52.2)	72 (42.1)			
Above median (>1.73)	5126 (50.8)	1268 (47.8)	99 (57.9)			
Platelet count ($\times10^9$/l)	248.6 (56.0)	250.5 (54.0)	250.8 (58.0)	0.17	0.17	0.16
Platelet count (n,%)				0.010	0.011	0.014
Below median(≤245)	6937 (50.2)	1691 (49.4)	139 (51.3)			
Above median (>245)	6879 (49.8)	1729 (50.6)	132 (48.7)			

*Geometric hs-CRP means with corresponding 95 % confidence intervals, adjusted for age and sex. Means (± SD) are adjusted for age and sex. Categorical variables are presented as numbers and percentages. Continuous variables are means and standard deviation. (1) Adjusted for age and sex. (2) Adjusted for age, sex, smoking habit, physical activity, education, hypertension, diabetes, heart rate, QT dispersion and QRS duration. (3) As in model (2), further adjusted for BMI (normal, overweight, obese). Analyses with NLR were performed on 12,908 subjects.

Table 3: Odds ratio of having borderline frontal T-wave axis deviation according to inflammatory biomarkers.

	Borderline (n=3,420) vs Normal (n=13,816)		
	OR (95 %CI) [1]	OR (95 %CI) [2]	OR (95 %CI) [3]
hs-C-reactive protein (mg/l)			
Normal (<1)	(reference)	(reference)	(reference)
Medium (≥1≤3)	1.59 (1.46–1.74)	1.54 (1.41–1.69)	1.23 (1.12–1.35)
High (>3)	1.75 (1.58–1.95)	1.70 (1.53–1.90)	1.17 (1.05–1.32)
Leukocyte count (×10^9/l)			
Below median (≤5.92)	(reference)	(reference)	(reference)
Above median (>5.92)	1.08 (1.00–1.17)	1.14 (1.05–1.23)	1.02 (0.94–1.11)
Granulocyte/lymphocyte ratio			
Below median (≤1.84)	(reference)	(reference)	(reference)
Above median (>1.84)	0.89 (0.83–0.96)	0.92 (0.85–0.99)	0.96 (0.88–1.03)
Neutrophil/lymphocyte ratio			
Below median (≤1.73)	(reference)	(reference)	(reference)
Above median (>1.73)	0.89 (0.82–0.97)	0.91 (0.83–0.99)	0.96 (0.87–1.05)
Platelet count (×10^9/l)			
Below median (≤245)	(reference)	(reference)	(reference)
Above median (>245)	1.13 (1.04–1.22)	1.13 (1.04–1.22)	1.13 (1.05–1.23)

(1) Model adjusted for age and sex. (2) As model 1 further adjusted for smoking habit, physical activity, education, diabetes, hypertension, heart rate, QT dispersion and QRS duration. (3) As model 2 further adjusted for BMI. Analyses with neutrophil to lymphocyte ratio were performed on 12,908 subjects.

Table 4: Odds ratio of having abnormal frontal T-wave axis deviation according to inflammatory biomarkers.

	Abnormal (n=271) vs Normal (n=13,816)		
	OR (95 %CI) [1]	OR (95 %CI) [2]	OR (95 %CI) [3]
hs-C-reactive protein (mg/l)			
Normal (<1)	(reference)	(reference)	(reference)
Medium (≥1≤3)	1.34 (0.99–1.81)	1.25 (0.92–1.70)	1.14 (0.83–1.56)
High (>3)	2.01 (1.45–2.78)	1.72 (1.23–2.41)	1.46 (1.03–2.08)
Leukocyte count (×10^9/l)			
Below median (≤5.9)	(reference)	(reference)	(reference)
Above median (>5.9)	1.24 (0.97–1.58)	1.16 (0.90–1.50)	1.10 (0.85–1.42)
Granulocyte/lymphocyte ratio			
Below median (≤1.84)	(reference)	(reference)	(reference)
Above median (>1.84)	1.44 (1.13–1.84)	1.44 (1.12–1.85)	1.47 (1.14–1.89)
Neutrophil/lymphocyte ratio			
Below median (≤1.73)	(reference)	(reference)	(reference)
Above median (>1.73)	1.32 (0.97–1.79)	1.28 (0.93–1.74)	1.30 (0.95–1.78)
Platelet count (×10^9/l)			
Below median (≤245)	(reference)	(reference)	(reference)
Above median (>245)	1.08 (0.84–1.38)	1.08 (0.84–1.38)	1.08 (0.84–1.39)

(1) Model adjusted for age and sex. (2) As model 1 further adjusted for smoking habit, physical activity, education, diabetes, hypertension, heart rate, QT dispersion and QRS duration. (3) As model 2 further adjusted for BMI. Analyses with neutrophil to lymphocyte ratio were performed on 12,908 subjects.

Table 5: Mean values (95 % confidence interval) of hs-C-reactive protein according to T-wave axis deviation.

	N of subjects	Frontal T-wave axis			P-value	β	P for interaction
		Normal	Borderline	Abnormal			
All subjects	17507	1.29 (1.27–1.31)	1.61 (1.56–1.66)	1.65 (1.48–1.83)	0.0012	0.05	-
Sex							
Women	9397	1.30 (1.28–1.33)	1.72 (1.65–1.81)	1.63 (1.40–1.90)	0.0074	0.06	0.0059
Men	8110	1.29 (1.26–1.32)	1.50 (1.44–1.56)	1.68 (1.54–1.95)	0.0024	0.05	
Age							
≤65 years	14260	1.21 (1.19–1.23)	1.55 (1.50–1.61)	1.57 (1.38–1.80)	0.0061	0.052	0.17
>65 years	3247	1.75 (1.69–1.81)	1.87 (1.75–1.99)	2.15 (1.80–2.56)	0.30	0.037	
BMI							
<30	12646	1.10 (1.08–1.11)	1.27 (1.22–1.33)	1.29 (1.12–1.49)	<.0001	0.13	<.0001
≥30	4861	2.20 (2.15–2.26)	2.20 (2.11–2.29)	2.50 (2.17–2.88)	0.18	0.029	
Hypertension							
No	8314	1.06 (1.03–1.08)	1.41 (1.34–1.48)	1.41 (1.14–1.73)	0.0032	0.08	0.0057
Yes	9081	1.58 (1.55–1.62)	1.79 (1.73–1.86)	1.88 (1.66–2.13)	0.26	0.03	
Metabolic syndrome*							
No	13173	1.15 (1.13–1.17)	1.44 (1.39–1.49)	1.53 (1.33–1.75)	0.0002	0.07	0.010
Yes	4241	1.97 (1.92–2.03)	2.06 (1.97–2.17)	2.10 (1.79–2.47)	0.84	0.014	

Geometric hs-CRP means with corresponding 95 % confidence intervals adjusted for age and sex. P values are obtained from a model adjusted for sex, age, smoking habit, physical activity, education, diabetes, hypertension, BMI, heart rate, QT dispersion and QRS duration. β is the coefficient of the multivariable linear regression of hs-CRP vs TDev categories. *Numbers do not add up to 100 % due to missing values.

risk assessment (12). However, platelets may have a role in inflammation due to the production and release of prostaglandins and other substances causing either vasodilation or vasoconstriction (22–24). More recently we found that platelet count is associated with increased predicted CVD risk in men (16). The neutrophil or granulocyte to lymphocyte ratio was also used as a potential marker of inflammation since neutrophils (together with monocytes) are the first WBC involved in the inflammatory response (25) . So far, the prognostic value of the T-wave axis has not been widely investigated; yet data from epidemiological settings showed that T-wave axis is a predictor of cardiovascular morbidity and mortality (2), either in subjects with no previous coronary heart disease (1) or in patients with previous cardiac events (26). Moreover, we showed that abnormal T-wave axis deviation was associated with an increased risk of CVD in 10 years in men (5).

Our study population was carefully selected in order to exclude those with an acute inflammatory condition. The link between TDev and a low-grade inflammation was independent of common cardiovascular risk factors, or main ECG markers such as QT dispersion , QRS duration or heart rate and the relationship was more evident for abnormal rather than borderline TDev. The association between ECG parameters and blood markers reflecting endothelial function and inflammation was already observed in a sample of coronary artery disease patients (27). In their study on Cystadin C and T-wave axis deviation, Faramawi et al. (4) speculated on the possible undiagnosed or subclinical coronary inflammation and myocardial ischaemia in heart disease- free individuals with chronic kidney disease that favours the expression of abnormal ventricular repolarisation represented by frontal T-wave axis deviation.

Since obesity is a favourable condition for a chronic low-grade inflammation to emerge (28–30) and is associated with T-wave abnormalities, we carefully addressed the accounting of BMI. Indeed, when the relationship between TDev and biomarkers of inflammation analysed in a model adjusted for age, sex, smoking habit, physical activity, education, diabetes, hypertension, heart rate, QT dispersion and QRS duration was further adjusted for body mass index, it was consistently attenuated. However, obesity only partially explained the association between TDev and inflammation, that remained statistically significant. Noticeably, the association between TDev and hs-CRP was more evident for normal or overweight subjects rather than for obese people, thus indicating a persisting link between this ECG marker and inflammation independently of pro-inflammatory conditions such as visceral adipose tissue.

Further analyses undertaken within groups at different CVD risk showed that the association between TDev and inflammation was more evident for those without major CVD risk factors, such as for normotensive or persons without metabolic syndrome. These findings stress the concept that abnormal T wave axis deviation is independent of other known CVD risk factors; additionally, we could speculate that T-wave axis abnormalities may allow

early identification of subclinical cardiac damage likely attributable to a chronic inflammation status. This hypothesis finds further support in previous evidence emphasising a positive association between TDev and risk of major coronary heart diseases (1, 2).

Strengths and limitations of this study

A major limitation of this study is its cross-sectional nature which does not allow any inference of possible causality. Prospective studies are needed and the present data can only give a clue but are not definitive. Additionally, the likelihood of residual confounding cannot be entirely excluded, although our analyses have been adjusted for a very large panel of potential confounders. Another limitation relies in the fact that abnormal TDev was only observed in 1.6% of subjects and the majority of cases was borderline.

Strengths rely in the large number of subjects included in the analyses and by testing both plasmatic a and cellular biomarkers of low-grade inflammation.

Conclusions

In conclusion, this study provides an interesting accounting of the pathogenesis of TDev by ascribing a role to subclinical inflammation as detected by increased levels of biomarkers of inflammation, such as hs-CRP or granulocyte or neutrophil to lymphocyte ratios.Additionally, T-wave axis deviation is an easy to measure and a not expensive tool, with the potential to better capture the complex association between low-grade inflammation and CVD risk, that may represent an advantage in future large epidemiological settings.

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Author contributions

LI, MB, DA designed the present research; LR, ADeC, MP, CC, SC, MV, FB managed data collection; MB, ADiC analyzed the data; MB, LI wrote the paper; GdG, MBD, LI originally inspired the research, obtained the financial support and critically reviewed the manuscript. All Authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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What is known about this topic?

- T-wave axis deviation (TDev) is a marker of ventricular repolarisation associated with increased risk of coronary heart disease and total mortality, independently of other cardiovascular risk factors, in the elderly population.
- The underlying physiopathology of TDev is not fully understood.

What does this paper add?

- This study provides an interesting accounting of the pathogenesis of TDev by ascribing a role to subclinical inflammation as detected by increased levels of biomarkers of inflammation.

Conflicts of interest
None declared.

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