ORIGINAL RESEARCH

Influence of aging and chronic heart failure on temporal dispersion of myocardial repolarization

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Background and purpose: QT and T_{peak}-T_{end} (Te) intervals are associated with sudden cardiac death in patients with chronic heart failure (CHF). We studied age-dependent influence on short-term temporal dispersion of these two variables in patients with postischemic CHF.

Method: We grouped 75 CHF and 53 healthy control subjects into three age subsets: $\leq$50 years, >50 years and $\leq$65 years, and >65 years. We then calculated the following indices: QT and Te variability index (QTVI and TeVI), the ratio between the short-term variability (STV) of QT or Te, and the STV of resting rate (RR) (QT/RR STV and Te/RR STV).

Results: In all different age subgroups, patients with CHF showed a higher level of QTVI than age-matched control subjects ($\leq$50 years: $P < 0.0001$; >50 years and $\leq$65 years: $P < 0.05$; >65 years: $P < 0.05$). Patients with CHF < 50 years old also had all repolarization variability indices higher than normal age-matched controls (TeVI, $P < 0.05$; QT/RR STV, $P < 0.05$; Te/RR STV, $P < 0.05$), whereas we did not find any difference between the two older classes of subjects. Both QTVI (r^2: 0.178, $P < 0.05$) and TeVI (r^2: 0.433, $P < 0.001$) were positively related to age in normal subjects, even if the first correlation was weaker than the second one.

Conclusion: Our data showed that QTVI could be used in all ages to evaluate repolarization temporal liability, whereas the other indices are deeply influenced by age. Probably, the age-dependent increase in QTVI was more influenced by a reduction of RR variability reported in older normal subjects.

Keywords: aging, QT variability, heart rate variability, chronic heart failure, sudden death

Introduction

Malignant ventricular arrhythmias are common complications of chronic heart failure (CHF) induced by myocardial infarction. Senescence[1,2] and CHF[3,4] strongly influence the cardiovascular autonomic control and myocardial repolarization phase.[5–9] Indeed, both these conditions are able to increase α-adrenoreceptor-mediated peripheral resistance[1] and to reduce β-adrenergic adrenoreceptor[10] and baroreflex function,[10,11] with a consistent decrease of heart rate variability.[12–16] The increase of temporal dispersion of the repolarization ventricular phase[17–25] and the reduction of heart rate variability[25–27] are risk factors for ventricular malignant arrhythmias and sudden cardiac death (SCD) and non-SCD. Aging[28–30] and CHF[31] are clear pathogenetic factors able to induce ventricular arrhythmogenesis. Neurohumoral activation,[4,6,32] electroanatomical remodeling,[33,34] chronic inflammatory condition,[35] and endothelial dysfunction[36–39] are well-recognized causes of ventricular arrhythmia in patients with CHF. Elderly patients with CHF show higher proneness for the malignant ventricular arrhythmias because these subjects have lower levels of functional reserve capable of

resisting arrhythmogenesis. Although the influence of CHF and aging on ventricular arrhythmias is well known, the underlying pathogenic mechanisms are not yet completely understood. Particularly, the impact of aging on markers of repolarization's temporal dispersion during CHF has not been clarified. In a recent large community-based study, an increased risk of SCD has been found related to a prolonged T_{peak}-T_{end} interval (Te).[40] In addition, in patients with CHF and SCD, a higher temporal dispersion was reported.[5]

All in all, we analyzed QT interval (from Q to end T wave electrocardiogram [ECG]) variability index (QTVI) and short-term variability (STV) of QT in CHF subjects with different ages, in order to individuate a possible age-dependent influence on these markers. Finally, we calculated the same indices of variability on the last part of the T wave (considering the peak and end of the T wave) to observe a peculiar age-related effect on this important part of repolarization.

Methods
Study subjects
For this study we selected 75 outpatients (63 men and 12 woman) who had stable CHF secondary to ischemic dilated cardiomyopathy, and 53 healthy control subjects (41 men and 12 women). We defined clinically stable patients as those who had not been hospitalized or had their therapy adjusted or had experienced any other acute coronary artery or noncoronary event during the past 3 months. All participants had undergone revascularization either cutaneously or by aortocoronary artery bypass at least 3 months before the study. None of the patients had malignancy, primary valve disease, atrial fibrillation, premature complexes (one premature complex per minute was permitted), or other arrhythmias likely to interfere with heart rate and QT analysis. None of the patients was New York Heart Association class IV. Before the study, none of the subjects had a documented history of cardiac arrest, ventricular tachycardia, or fibrillation. We suggested that all patients with ejection fraction ≤35% underwent an implant of implantable cardioverter/defibrillator device.

To detect possible statistical differences related to age we divided each of the two study groups into three age subsets: ≤50 years, >50 years and ≤65 years, and >65 years.

Study protocol and offline data analysis
After a 10-minute rest lying down, each subject underwent a 5-minute, single ECG lead recording during controlled breathing (15 breaths per minute, 0.25 Hz). All digitized signal recordings were analyzed by a single physician (GP) blinded to the subjects' circumstances.

We measured the following intervals from the respective time series of ECG recordings: resting rate (RR), QT (from the Q wave to the T wave end), and Te (from the T peak to T wave end). We therefore calculated mean and variance values of each of these intervals and then used the original formula proposed by Berger et al[41] to calculate three different QT variability indices:

$$QTVI = \log_{10}\{[[QT_{variance}]/[QT_{mean}]^2]/[[RR_{variance}]/[RR_{mean}]^2]\}$$

$$TeVI = \log_{10}\{[[T_{Evariance}]/[T_{Emean}]^2]/[[RR_{variance}]/[RR_{mean}]^2]\}$$

Software for data acquisition and storage and for spectral analysis were designed and produced by our research group and are described in detail elsewhere.[7–9,42–45]

Finally, we used all ECG recordings to measure the STV of the aforementioned intervals. This variable was calculated following the standard method, namely by using the first 60 consecutive beats (STV_{60})[6,46,47] and also by using the total number of beats in the whole 5-minute recording (STV_T). The formula used was:

$$STV_{60} = \Sigma\,[D_{n+1} - D_n]\,(60 \times \sqrt{2})$$

$$STV_T = \Sigma\,[D_{n+1} - D_n]\,(\text{total beats number} \times \sqrt{2})$$

where D was the duration of RR or QTe, or Te interval. Consequently, we were able to obtain the following six STV indices: RR STV_{60}, QT STV_{60}, Te STV_{60}, RR STV_T, QTe STV_T, and Te STV_T.

Finally, we calculated the following ratio between the different STVs:

QT/RR STV_{60} = QT STV_{60}/RR STV_{60};
Te/RR STV_{60} = Te STV_{60}/RR STV_{60}

QT/RR STV_T = QT STV_T/RR STV_T;
Te/RR STV_T = Te STV_T/RR STV_T

Moreover, from the same 5-minute ECG segment, the corrected QT and Te intervals were obtained according to the formulas proposed by Bazett ($QT/RR^{0.5}$; QT; $Te/RR^{0.5}$), Friedericia ($QT/RR^{0.33}$; $Te/RR^{0.33}$), Lilly ($QT/RR^{0.4}$; $T_e/RR^{0.4}$), and Framingham ($QT_+\,[0.154*\{1000\text{-}RR\}]$; Te+ $[0.154*\{1000 - RR\}]$).

Statistical analysis
Unless otherwise indicated, all data are expressed as means ± standard deviation. Data with skewed distribution are given as median and interquartile range (75th percentile–25th percentile).

Categorical variables were analyzed with the χ^2 test. One-way analysis of variance and the Bonferroni test were used to compare data for the normally distributed variables. Kruskal–Wallis and Mann–Whitney tests were used to compare non-normally distributed variables (as evaluated by the Kolmogorov–Smirnov test). To detect possible statistical differences related to age, we divided each of the two study groups into three age subsets: ≤50 years, >50 years and ≤65 years, and ≥65 years.

Stepwise multiple regression analysis was used to determine possible relationships between the studied variables. P-values ≤ 0.05 were considered statistically significant. All data were evaluated with the database SPSS-PC+ (SPSS-PC+ Inc, Chicago, IL, USA).

Results

We examined 128 subjects, 75 with CHF and 53 healthy controls. The clinical characteristics of subjects enrolled in the study are shown in Table 1.

Age, body mass index, and sex distribution did not differ significantly between the two groups, whereas heart rate, diastolic arterial pressure, left ventricular ejection fraction, and QT interval differed significantly (Table 1). Both subgroups had a similar mean intergroup age (Table 2).

The younger CHF group showed a reduction of RR variance in comparison with the age-matched healthy controls, whereas only the older CHF group reported a longer RR_{mean} than controls (Table 3). Only elderly subjects had a significantly larger QT_{mean} ($P < 0.05$), QT variance ($P < 0.05$), and Te_{mean} ($P < 0.05$) than age-matched healthy controls. Furthermore, the middle-aged group showed a $QT_{variance}$ ($P < 0.05$) significantly higher than age-matched controls (Table 3). In all subsets, independently from age, the CHF group showed a significantly higher QTVI ($P < 0.001$) than age-matched controls, but only the younger CHF group had all other QT variability values significantly higher (TeVI: $P < 0.05$, QT/RR STV_{60}: $P < 0.05$, Te/RR STV_{60}: $P < 0.05$, QT/RR STV_T: $P < 0.05$, and Te/RR STV_T: $P < 0.05$) in comparison with age-matched controls (Table 4). In the middle-aged and elderly CHF groups we did not find any differences for the other repolarization variables (Table 4).

We did not find any difference between the three CHF groups in respect of the RR and QT variables (Tables 3 and 4). $RR_{variance}$ ($P < 0.001$) was significantly higher in younger and middle-aged control subjects than older subjects (Table 3), and this variable was also significantly higher in younger controls compared with healthy middle-aged subjects. Te ($P < 0.05$) was higher in younger and middle-aged control subjects than older subjects (Table 3). On the other hand, $Te_{variance}$ ($P < 0.05$) was higher in the two younger groups than the older normal subjects.

In the control group, all temporal dispersion variables (QTVI, TeVI, QT/RR STV_{60}, Te/RR STV_{60}, QT/RR STV_T, Te/RR STV_T) were significantly lower in the younger group in comparison with the older subjects ($P < 0.05$) (Table 4). QTVI, TeVI, QT/RR STV_T, and Te/RR STV_T were lower in the middle-aged subjects than in the older ones. Only QTVI results were significantly lower in the younger control group compared with the middle-aged group (Table 4).

Table 1 General characteristics of study sample

Characteristics	Chronic heart failure	Healthy controls	P values
	N = 75	N = 53	
Age, years	64 ± 13	60 ± 15	0.452
Male/female	63/12	41/12	0.275
BMI, kg/m²	26 ± 4	26 ± 3	0.155
HR, beats/min	66 ± 11	68 ± 10	0.329
Systolic blood pressure, mmHg	123 ± 26	122 ± 17	0.700
Diastolic blood pressure, mmHg	66 ± 15	75 ± 11	0.002
Left ventricular ejection fraction, %	40 ± 10	57 ± 4	0.0001
QT, ms	375 ± 58	353 ± 26	0.007
QT_{Bazett}, ms	389 ± 51	372 ± 20	0.017
$QT_{Fridericia}$, ms	384 ± 51	366 ± 19	0.008
QT_{Lilly}, ms	386 ± 51	361 ± 19	0.011
$QT_{Framingham}$, ms	385 ± 51	368 ± 18	0.012
NYHA class, I/II/III	10/46/19	0	0.0001
Serum K⁺ mmEq/L	4.2	4.1	0.842
β-blockers	35	0	0.0001
Furosemide	33	0	0.0001
ACEi/Sartans	56	5	0.0001
Spironolactone	22	0	0.0001
Digoxin	13	0	0.0001
Amiodarone	11	0	0.017

Note: Data are expressed as means ± standard deviation.
Abbreviations: BMI, body mass index; HR, heart rate; NYHA, New York Heart Association; ACEi, angiotensin converting enzyme; ms, milliseconds; mmEq/L milliequivalents per liter.

Table 2 Mean age of subjects in the three age-subgroups

Age subgroups	Chronic heart failure	Healthy controls	P values
	N = 75	N = 53	
≤50 years	46 ± 4 (n = 19)	44 ± 3 (n = 17)	0.371
>50 ≤ 65 years	58 ± 3 (n = 21)	57 ± 4 (n = 18)	0.342
≥65 years	75 ± 6 (n = 35)	77 ± 4 (n = 18)	0.317

Note: Data are expressed as means ± standard deviation.

Table 3 RR interval and QT dynamics data according to age and presence of chronic heart failure

Variables	Group 1 (≤50 years)		P	Group 2 (>50 ≤ 65 years)		P	Group 3 (≥65 years)		P
	CHF (N = 19)	Controls (N = 17)		CHF (N = 21)	Controls (N = 18)		CHF (N = 35)	Controls (N = 18)	
RR mean, ms	899 ± 154	945 ± 142	0.354	918 ± 140	906 ± 127	0.785	966 (164)	873 (126)	0.040
RR variance, ms^2	574 (1124)	1627 (2244)*,#	0.0001	805 (1309)	885 ± 990§	0.349	611 (820)	580 (1340)	0.992
QT mean, ms	363 ± 42	359 ± 30	0.801	371 ± 57	355 ± 31	0.294	385 ± 66	347 ± 18	0.008
QT variance, ms^2	36 (84)	18 (14)	0.066	43 (76)	19 (10)	0.011	38 (67)	14 (52)	0.004
Te mean, ms	85 ± 29	86 ± 13#	0.847	81 ± 18	87 ± 22†	0.402	91 ± 43	70 ± 13	0.019
Te variance, ms^2	23 (80)	20 (16)#	0.397	38 (85)	17 (33)†	0.349	33 (80)	39 (35)	0.696

Notes: Data are expressed as median and interquartile range (75th–25th). *$P < 0.05$ Group 1 vs Group 2; #$P < 0.05$ Group 1 vs Group 3; †$P < 0.05$ Group 2 vs Group 3; §$P < 0.001$ Group 2 vs Group 3.
Abbreviations: CHF, chronic heart failure; TeVI, T_{peak}-T_{end} variability index; RR mean or variance, waves interval; ms, milliseconds; QT interval mean or variance.

The stepwise multiple regression analysis found a significant relation with QTVI and ejection fraction (R: 0.364; R^2: 0.132, β: –0.364, P: 0.001) in CHF subjects. Instead, QTVI ($P < 0.05$), TeVI ($P < 0.001$), QT/RR STV$_{60}$ ($P < 0.05$), Te/RR STV$_{60}$ ($P < 0.05$), QT/RR STV$_T$ ($P < 0.001$), and Te/RR STV$_T$ ($P < 0.001$) showed a significant positive relation with aging in control groups (Figures 1 and 2). We also found a negative significant correlation between all measures of RR variability and age (Figure 3) in the same subjects. Except for Te$_{variance}$/(T$_{mean}^2$) (Figure 4), we did not find any significant correlation between age and repolarization variables without RR normalization in the control group.

Discussion

Our main and original finding was that only QTVI values remained significantly higher in patients with CHF regardless of their age, whereas all other indices of temporal myocardial repolarization dispersion were significantly higher only in those patients with CHF belonging to the youngest category, namely those characterized with an age ≤50 years. Our second, somewhat confirmatory, finding was the significant

positive correlation between QTVI and left ventricular ejection fraction in patients with CHF,[10] whereas, in healthy control subjects, all repolarization variability parameters showed a significant relation only with age. Thus, although QTVI suffers a certain age influence, this index seems to be the only useful variable to measure temporal dispersion of myocardial repolarization independently from age of the patients with CHF.

An increase in temporal myocardial repolarization dispersion, as assessed by several QT interval-derived indices, has been proven to be significantly associated with an increased SCD risk in patients with structural heart disease.[17–21,41–44] However, it is well known that, particularly in patients with CHF, aging represents an additional feature able to magnify this risk, most likely through a further increase in myocardial repolarization lability. Indeed, aging typically leads to a prolongation of action potential duration due to different mechanisms, such as an increased number and overactivity of cardiac L-type Ca^{2+} channels with a consequent slow inactivation of calcium influx and a reduction in outward potassium current.[48,49] As a result, with aging, the QT length and variability tends to increase. Nonetheless, it should be

Table 4 QT variability indices according to age and presence of chronic heart failure

Variables	Group 1 (≤50 years)		P	Group 2 (>50 ≤ 65 years)		P	Group 3 (≥65 years)		P
	CHF (N = 19)	Controls (N = 17)		CHF (N = 21)	Controls (N = 18)		CHF (N = 35)	Controls (N = 18)	
QTVI	−0.40 (1.00)	−1.22 (0.35)*,#	0.0001	−0.54 (0.88)	−1.09 (0.28)†	0.001	−0.38 (0.90)	−0.77 (0.62)	0.033
TeVI	0.96 (1.00)	0.20 (0.66)¥	0.003	0.72 (1.02)	0.47 (0.69)§	0.133	0.77 (1.38)	1.12 (0.72)	0.551
QT/RR STV$_{60}$	0.49 (0.58)	0.17 (0.63)#	0.002	0. 38 (0.75)	0.27 (0.46)	0.438	0.53 (0.70)	0.37 (0.51)	0.393
Te/RR STV$_{60}$	0.54 (1.28)	0.26 (0.28)#	0.030	0.31 (0.65)	0.33 (0.52)	0.982	0.48 (0.81)	0.58 (0.79)	0.794
QT/RR STV$_T$	0.59 (0.38)	0.18 (0.20)¥	0.001	0.40 (0.33)	0.31 (0.21)†	0.256	0.44 (0.62)	0.47 (0.71)	0.460
Te/RR STV$_T$	0.53 (1.09)	0.25 (0.26)¥	0.022	0.37 (0.36)	0.33 (0.34)†	0.707	0.46 (0.76)	0.81 (1.11)	0.223

Notes: Data are expressed as median and interquartile range (75th–25th). *$P < 0.05$ Group 1 vs Group 2; #$P < 0.05$ Group 1 vs Group 3; ¥$P < 0.001$ Group 1 vs Group 3; †$P < 0.05$ Group 2 vs Group 3; §$P < 0.001$ Group 2 vs Group 3.
Abbreviations: QTVI, QT variability index; TeVI, T_{peak}-T_{end} variability index; STV, short term variability.
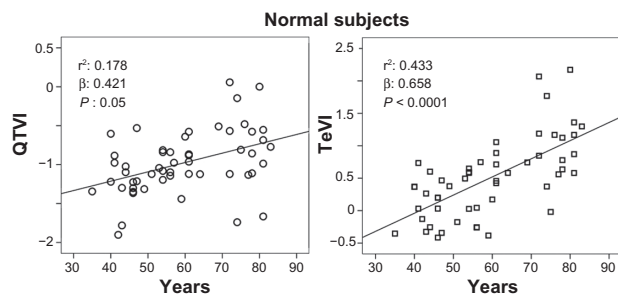
Figure 1 Relationship between QT variability index (QTVI) or T_{peak}-T_{end} variability index (TeVI) and age in healthy control subjects.
Abbreviation: QT, from the Q wave to the T wave end.

emphasized that CHF leads to a prolongation and dispersion of action potential duration that is quantitatively more pronounced in respect of pure aging. Specifically, functional downregulation of potassium current and an alteration in depolarizing sodium and calcium currents are responsible for electrical remodeling, with a consequent increase in QT temporal dispersion in CHF.[50] Our data, besides confirming that QT variability-derived indices are significantly higher in patients with CHF compared with healthy controls, suggest that aging might represent a confounding factor for a number of them but not for QTVI. Initially, our data also

suggested through which mechanisms QTVI remains a solid marker of myocardial repolarization lability despite aging. Indeed, in patients with CHF aged ≤50 years, QTVI suffers because of extremely low RR variance values, whereas, considering those patients with CHF aged >50 years, QTVI was much worse, as indicated by a marked increase in QT variance. Thus, it could be hypothesized that in relatively young patients with CHF, an increased QTVI might mirror a sinus node dysfunction due to a prevalent autonomic nervous system control derangement, whereas, with aging, QTVI mainly reflects an altered myocardial repolarization phase. A possible reason underlying a major role of sinus node dysfunction in worsening QTVI of young patients with CHF could be represented by the well-known age-related decline in heart rate variability.[11–16]

Evidence indicates that an increased Te interval[40] is related to SCD, and also recent research from our group showed an increased temporal dispersion of the last part of repolarization (TeVI) in patients with CHF[5] and SCD, as well as in an animal model with pacing-induced heart failure (TeVI, Te/STV_T).[6] However, the pathophysiologic meaning of this ECG interval still remains controversial.
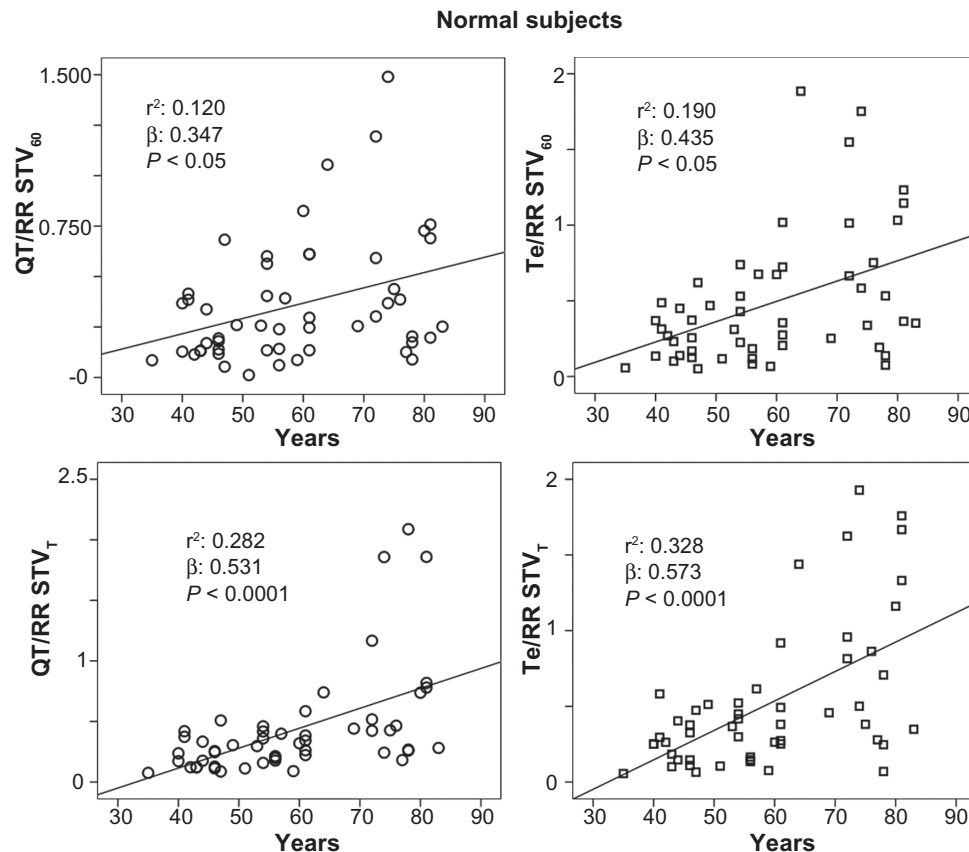

Figure 2 Relationship between age and ratio of short-term QT or T_{peak}-T_{end} (Te) variability (STV) and resting rate (RR) variability indices, calculated on 60 consecutive beats ($QT/RR STV_{60}$, Te/RRv STV_{60}) or on 5-minute electrocardiogram recordings ($QT/RR STV_T$, Te/RRv STV_T) in healthy control subjects.
Abbreviations: QT, from the Q wave to the T wave end; v, variance.
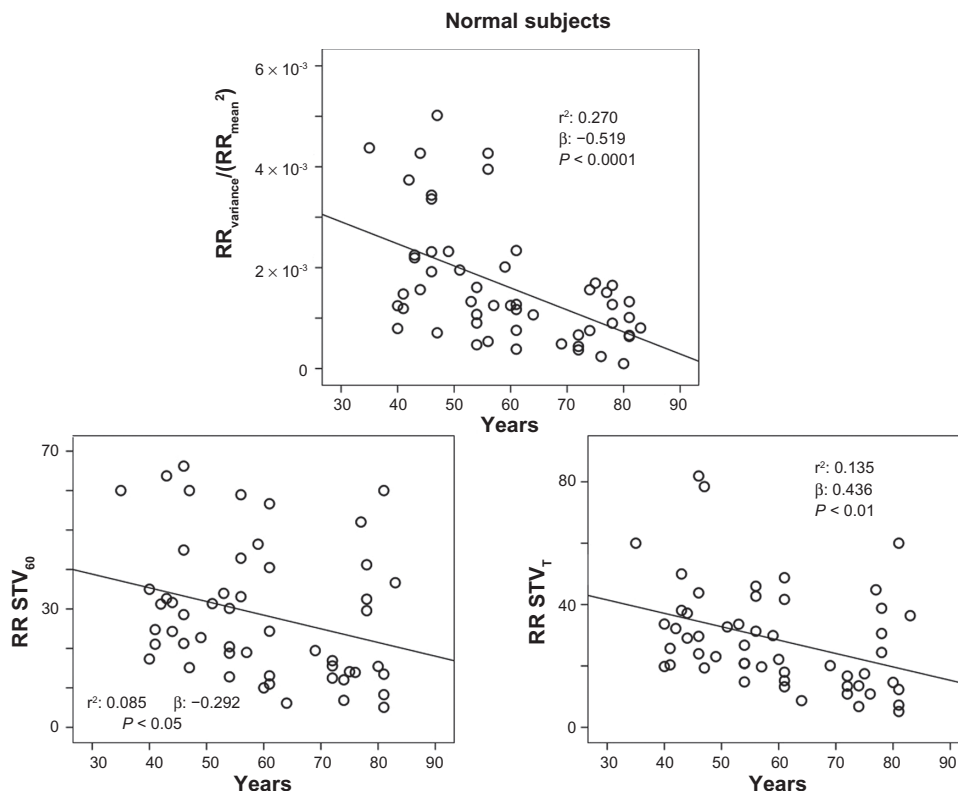
Normal subjects

Figure 3 Relationship between age and the resting rate (RR) variability indices (ratio denominator of QTVI, TeVi, and short-term variability [STV], see Methods section), calculated on 5-minute electrocardiogram recordings ($RR_{variance}/RR_{mean}^2$ and RR STV_T) or on 60 consecutive QRSs (RR STV_{60}) in healthy control subjects.
Abbreviations: TeVI, Tend Variability index; Q-T, waves interval.

Some authors believe that Te is a reliable noninvasive marker of transmural repolarization gradient, whereas others affirm that this period reflects the total spatial ventricular repolarization dispersion.[41,46,51] Notably, clinical and experimental evidence indicates that Te should be considered as a marker of IK_s function, especially during sympathetic activation.[52,53] Indeed, an enhancement in IK_s was reported after a β-adrenergic stimulation, the latter leading to an elevation of intracellular cyclic adenosine monophosphate (cAMP) and an activation of protein kinase A.[54] Supporting

this datum, it was reported that subjects with concealed type 1 long QT reported a significant increase of Te interval during an infusion of epinephrine,[55] again favoring a close link between adrenergic burst and IK_s activity. Our current data seem to identify a possible role of Te-derived indices only when considering those patients with CHF aged <50 years. However, a real comparison is impossible given the different population enrolled and the lack of a follow-up. A possible explanation, albeit merely speculative, could be that aging per se, due to a downregulation of β-adrenoreceptor expression and function, could affect Te-derived indices, leading to an age-related loss of their diagnostic utility in patients with CHF. Accordingly, we can hypothesize that, between all indices of myocardial repolarization dispersion, QTVI might remain the only one that could be used to point out an increased SCD risk regardless of patients' age, whereas Te indices should be useful just in middle-aged patients.

Conclusion

Our data demonstrate a deep influence of age on the short-term variability of repolarization phases, and tend to suggest that only QTVI is able to characterize temporal myocardial repolarization lability in patients with CHF regardless of aging.
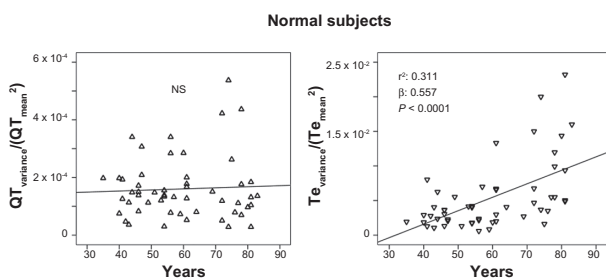
Normal subjects

Figure 4 Relationship between age and Te variance/Te mean² (ratio numerator of T_{peak}-T_{end} variability index, see Methods section).
Notes: No significant relation was reported between age and $QT_{variance}/QT_{mean}^2$ (ratio numerator of TeVI, see Methods section) in healthy control subjects.
Abbreviations: TeVI, Tend Variability index; Q-T, waves interval.

Disclosure

The authors report no conflicts of interest in this work.

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