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Original Article

Electrophysiological validation of total atrial conduction time measurement by tissue doppler echocardiography according to age and sex in healthy adults

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ABSTRACT

Background: We sought to validate total atrial conduction time (TACT) measurement via tissue Doppler imaging (TDI) by comparing the electrophysiological study (EPS) measurements of healthy subjects, according to age and sex.

Methods: Eighty patients with normal EPS results were included. TACT was measured by EPS and TDI. For validation, the results of TDI were compared with those of EPS. TACT was assessed by measuring the time interval between the beginning of the P-wave on the surface ECG, and the peak A-wave on TDI from the left atrial lateral wall, just over the mitral annulus. Electrophysiological TACT was defined as the time from the high right atrial electrogram to the distal coronary sinus atrial electrogram around the left lateral portion of the mitral ring.

Results: EPS and TDI measurements of the TACT were significantly and positively correlated among men and women in 20–30 years ($p=0.008$, $r=0.412$; $p>0.001$, $r=0.706$, respectively), and those in the 30–40 years group ($p=0.001$, $r=0.649$; $p=0.001$, $r=0.696$). In contrast, EPS and TDI measurements of TACT were not significantly different among men and women in the 20–30 years and those in the 30–40 years group ($p>0.05$, for both). On univariate regression analyses, TACT was independently associated with age ($\beta=0.342$, $=0.001$).

Conclusions: When assessed according to the age and sex of healthy participants, TDI and EPS measurements during TACT assessments were similar and correlated with each other. The measurement of TACT via TDI may be used accurately and confidently than the measurement via EPS in healthy individuals.

1. Introduction

Prolongation of total atrial conduction time (TACT) has been shown to increase the risk of atrial fibrillation in many studies [1–3]. Many different methods can be used to evaluate the TACT. Although 12-lead, signal-averaged, M-mode, and tissue Doppler echocardiography are usually used, intracardiac measurements using the electrophysiological study (EPS) remain the gold standard method. In recent years, 2-dimensional echocardiographic tissue Doppler has been used for measuring the ACT (atrial conduction time) in many clinical studies. Although it is not the gold standard, this non-invasive method is usually preferred for ACT measurements [1,2,4]. However, to the best of our knowledge, no study has directly compared the TDI TACT measurements with the currently accepted gold standard electrophysiological TACT measurements for validation, except one where conventional Doppler echocardiography was used instead of TDI in healthy subject [5]. Moreover, no validation study has been performed among different age and sex groups in subjects with normal EPS results. In this study, we aimed to compare the TACT measured by TDI and EPS according to age and sex among healthy individuals without cardiovascular and systemic diseases for the purpose of validation of TDI use in the evaluation of TACT.

2. Methods

2.1. Study population

Eighty healthy subjects with normal EPS results (40 women and 40 men; 2 different age groups [20–30 and 30–40 years]), who were referred to our EPS laboratory for various reasons, such as

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unexplained palpitation or syncope, were included in this study. Four groups, consisting of 20 subjects in each group, were organized according to age and gender (Group A: women, aged 20–30; Group B: women, aged 30–40; Group C: men, aged 20–30; Group D: men, aged 30–40). Only individuals with normal EPS results were included. Subjects with any kind of known systemic disease and history of drug use that may affect the conduction system were excluded. All subjects had normal cardiac anatomy, cardiac systolic and diastolic functions on echocardiography, and normal sinus rhythm on electrocardiography (ECG). The entire study population's demographic characteristics, biochemical parameters, lipid values, and ECGs were obtained. Patients with at least one of the following conditions were excluded from the study: hyperthyroidism, hypothyroidism, acute coronary syndrome, prior myocardial infarction and coronary artery disease, congestive heart failure, left ventricular (LV) hypertrophy, left and right atrial enlargement, prolonged QRS duration ($\geq$120 msn), reduced LV ejection fraction ($<$55%), atrial flutter or fibrillation, significant valvular heart disease, pacemaker implantation, frequent ventricular pre-excitation and atrio-ventricular conduction abnormalities, diabetes mellitus, arterial hypertension (resting blood pressure $\geq$140/90 or antihypertensive drug use), medications known to alter cardiac conduction, peripheral vascular diseases, congenital heart disease, pulmonary or neurological disease, pericarditis, peripheral neuropathy, alcohol abuse, renal or hepatic disease and poor echocardiographic imaging. Echocardiographic measurements were obtained after the completion of electrophysiological studies in the same day. The local ethics committee approved this study and all subjects gave their informed consent prior to participation.

2.2. Conventional echocardiography

All subjects were evaluated by transthoracic M mode, two dimensional (2D), pulsed-wave (PW), continuous wave (CW), color flow, and tissue Doppler imaging (TDI). Echocardiographic examinations were performed using the GE- Vivid-3 system (GE Vingmed, Horten, Norway) with a 2–4 MHz transducer at a depth of 16 cm. During echocardiography, continuous single-lead ECG recording was obtained. Images were obtained in the left lateral decubitus position. The 2D and conventional Doppler examinations were obtained in the parasternal and apical views, according to the guidelines of the American Society of Echocardiography [6]. LV diameters and wall thickness were measured by M-mode echocardiography. LV ejection fraction was calculated using the apical two-and four-chamber views by Simpson's method, according to American Society of Echocardiography guidelines [6]. The mitral valve inflow patterns [E-wave, A-wave, E-wave deceleration time (Dt), E/A ratios, and isovolumic relaxation times (IVRT)] were measured using PW Doppler.

2.3. Tissue Doppler echocardiography

TDI was performed using transducer frequencies of 3.5–4.0 MHz, adjusting the spectral pulsed Doppler signal filters until the Nyquist limit of 15–20 cm/s was reached, and using the minimal optimal gain. Myocardial TDI velocities (Peak systolic [Sm], early diastolic [Em] and late diastolic velocities [Am]) were measured via spectral pulsed Doppler of the LV-free wall from the apical four-chamber view [6]. The ultrasound beam was positioned, as parallel as possible, to the myocardial segment in order to acquire the optimal imaging angle. A novel echocardiographic consideration based on TDI was introduced in order to assess the total atrial conduction time [4]. The total atrial conduction time was assessed by measuring the time interval between the beginning of the P wave on the surface ECG and the point of the peak A wave on TDI from the LA lateral wall just over the mitral annulus [2,4]. All measurements were repeated three times and average values were received for each of the parameters. The measurements were also corrected for the heart rate using the following formula: Corrected ACT=ACT $\times$ 800/R-R [5,7]. Two experienced investigators, who were unaware of the subject's clinical status, performed all measurements. If a difference of $>$5% in any of the variables measured by both investigators was found, the patient was not included, whereas if the difference was $<$5%, the measurements were averaged.

2.4. Electrophysiology study

All patients underwent an EPS after at least 6–8 h fasting. The measurements related to the ACT were performed on subjects with normal EPS results using four multi-electrode mapping catheters (Medtronic, Inc., USA). Intracardiac recordings were received via a computer with EP Tracer (CardioTek, Maastricht, the Netherlands) software. Surface ECG and intracardiac electrograms (EGMs) were recorded simultaneously, and the conduction times were measured at a rate of 300 mm/s. The first quadripolar catheter was placed on the high right atrial (HRA) region. A second decapolar catheter was positioned into the coronary sinus (CS) around the left lateral portion of the mitral ring. Additionally, another catheter was placed on the His bundle (HB) region. Electrophysiological total atrial conduction time was defined as the time from the atrial HRA electrogram to the distal CS atrial electrogram around the left lateral portion of the mitral ring. The measurements were also corrected for the heart rate as the TDI measurements using the mentioned formula [5,7].

3. Statistical analysis

All analyses were performed using the SPSS (SPSS Inc., Chicago, IL, USA) software package. All data were presented as the mean $\pm$ standard deviation. Total atrial conduction time measurements by the two methods were compared using the paired *t* tests. The comparison of echocardiographic data between the two groups were performed using one-way analysis of variance (ANOVA) with post hoc analysis by Tukey's Honestly Significant Difference (HSD) or independent sample *t*-tests, and Kruskal–Wallis tests or Mann–Whitney *U* test for normally and abnormally distributed data, respectively. Correlations between variables were tested by means of Pearson's bivariate correlation testing. We used a univariate logistic regression analysis to quantify the association of variables with TACT. Variables that were found to be statistically significant in the univariate analysis and other potential confounders were used in a multiple logistic regression model using the forward stepwise method, in order to determine the independent prognostic factors. Analyses of the differences in the TDI and EPS measurements were performed according to the Bland–Altman technique. A value of $p<0.05$ was considered statistically significant.

4. Results

4.1. Clinical and echocardiographic assessment

The clinical cardiovascular examination, chest radiography, cardiac systolic and diastolic functions, cardiac volumes, and ejection fractions were normal in all subjects. Baseline demographic and laboratory characteristics of all subjects are shown in Table 1. Additionally, the echocardiographic characteristics of all subjects are shown in Table 2. There were no complications related to the EPS procedures.

4.2. Total atrial conduction time measurement

Measurements were recorded successfully in all subjects. The EPS and TDI measurements of TACT were similar in male and female subjects (68.4 ± 4.4 vs. 68.6 ± 4.6 ms, $p > 0.05$ and 71.4 ± 4.9 vs. 71.5 ± 5.3 ms, $p > 0.05$, respectively) in the 20–30 years group. Additionally, the TACT measurements using both methods were similar among male and female subjects (78.7 ± 7.4 vs. 77.9 ± 7.1 ms, $p > 0.05$ and 77.3 ± 7.3 vs. 76.9 ± 7.1 ms, $p > 0.05$, respectively) in the 30–40 years group. The results of the EPS and TDI measurements of TACT in all groups are shown in Table 3. The EPS and TDI measurements of TACT were significantly and positively correlated in male and female subjects ($p = 0.008$, $r = 0.412$; $p < 0.001$, $r = 706$, respectively) in the 20–30 years group. Additionally, TACT measurements using both methods were significantly and positively correlated among male and female subjects ($p = 0.001$, $r = 0.649$; $p = 0.001$, $r = 0.696$; Fig. 1) in the 30–40 years group.

The measurement score of TACT with EPS and TDI among female subjects aged 20–30 were statistically borderline, and significantly lower compared to females subjects aged 30–40 ($p = 0.045$). However no significantly statistical differences were found between the two different male age groups ($p = 0.098$).

In all of groups, TACT with TDI was longer than TACT with EPS (mean TACT) (1.89 ± 0.54 ms). In the subgroup analyses, TACT with TDI was longer than TACT with EPS for all groups. However, statistically non-significant results were observed between certain groups (20–30 years old, males: 2.09 ± 0.31 vs. females: 1.94 ± 0.21; 30–40 years old, males: 0.31 ± 0.04, females: 0.28 ± 0.07; $p > 0.05$). There was a positive and significant correlation between mean TACT and TACT with EPS ($r = 0.321$, $p = 0.041$). Additionally, statistically significant positive correlations were observed between mean TACT and age. However, statistically non-significant correlations were observed between mean TACT and sex groups ($r = 0.521$, $p = 0.002$; $r = 0.131$, $r = 0.216$; respectively).

Among all the factors included in the univariate analyses (i.e., sex, age, systolic blood pressure, diastolic blood pressure, heart rate, body mass index, ejection fraction, left ventricular diastolic diameter, left ventricular systolic diameter, left atrial diameter, right atrial diameter, fractional shortening) only age was determined to have a prognostic significance with TACT (β coefficients = 0.342, $p = 0.001$). In the multivariate regression analyses, a non-significant association between age and TACT was observed (β coefficients = 0.163, $p = 0.132$).

The comparison of TACT obtained by TDI and EPS was tested by the Bland–Altman method that revealed the compliance and large limits of agreement (Fig. 2).

5. Discussion

Atrial fibrillation is widely recognized as the most common sustained arrhythmia. The risk of AF development may be determined by evaluating the patients' age, sex, underlying heart disease, other medical illnesses, and echocardiographic findings. However, better predictors of AF are needed for early and effective preventive measures. TACT is a promising parameter for the prediction of AF. Previous studies have identified TACT as an important predictor of AF. Additionally, it is independently associated with AF incidence [1,2,8]. A recent study also showed that the TACT is an independent predictor of AF recurrence and can be used to predict the maintenance of SR after external electrical CV [9]. In this study, we aimed to evaluate the validation of the TDI technique for the measurement of TACT, particularly in healthy individuals.

In this study, the EPS and TDI measurements of TACT were found to be similar in all age and sex groups 2. Additionally, the EPS-derived measurements of TACT were positively correlated with the TDI-derived measurements among the healthy subjects of all age- and sex-matched groups. These results showed us that the TDI method might be used accurately and confidently, instead of the EPS, for the evaluation of TACT in persons without cardiovascular and systemic diseases. Echocardiographic evaluation with TDI is currently the most commonly used method for the measurement of TACT because of the invasive nature and high cost of the EPS procedure [1,2]. The validation of the measurement of ACT by means of a non-invasive method such as TDI is very important for the new trials on atrial fibrillation and supraventricular arrhythmias.

In a similar validation study, Fuenmayor et al. [5] found a correlation between the echocardiography-derived atrial conduction times and the electrophysiological measured atrial conduction times in 21 patients with supraventricular tachycardia, in accord with our trial. However, the measurements by means of echocardiography and EPS in that study were found to be significantly

Table 1
Comparison of the patient characteristics according to age and sex groups.

	Group I (Women, 20–30 years)	Group II (Men, 20–30 years)	Group III (Women, 30–40 years)	Group IV (Men, 30–40 years)
Age	24.0 ± 2.3	24.9 ± 2.9	33.8 ± 2.4	36.2 ± 3.5
BMI	24.8 ± 2.1	24.1 ± 2.3	25.3 ± 2.9	25.5 ± 2.9
Heart rate	87.5 ± 9.4	86.6 ± 9.7	84.6 ± 8.1	79.6 ± 9.1
SBP, mmHg	115.1 ± 10.1	116.3 ± 10.9	118.1 ± 10.8	119.3 ± 11.4
DBP, mmHg	66.5 ± 8.1	67.3 ± 6.5	68.1 ± 8.5	69.3 ± 7.8
Glucose, mg/dL	84.8 ± 7.1	83.7 ± 6.9	85.4 ± 7.2	84.7 ± 7.9
Creatinine, mg/dL	0.72 ± 0.14	0.79 ± 0.13	0.73 ± 0.13	0.81 ± 0.15
Total cholesterol, mg/dL	165.1 ± 36.4	162.2 ± 34.9	170.1 ± 38.2	169.3 ± 38.7
LDL, mg/dL	101.1 ± 28.6	102.3 ± 27.8	103.4 ± 29.9	104.1 ± 30.4
HDL, mg/dL	45.2 ± 10.4	38.3 ± 11.0	45.1 ± 9.7	39.1 ± 10.2
Triglyceride, mg/dL	135.1 ± 48.1	138.9 ± 41.9	136.9 ± 49.2	137.1 ± 42.0
Hemoglobin, mg/dL	12.9 ± 1.4	13.8 ± 1.8	12.2 ± 1.2	13.7 ± 1.7

BMI = body mass index; DBP = diastolic blood pressure; HDL = high density lipoprotein; LDL = low density lipoprotein; SBP = systolic blood pressure; values are mean ± SD.

Table 2
Comparison of the echocardiographic characteristics according to age and sex groups.

	Group I (Women, 20–30 years)	Group II (Men, 20–30 years)	Group III (Women, 30–40 years)	Group IV (Men, 30–40 years)	*p* Value
EF (%)	64.0 ± 5.3	64.9 ± 7.9	63.8 ± 6.4	64.2 ± 6.5	> 0.05
LA diameter (mm)	31.1 ± 0.9	32.3 ± 1.4	33.1 ± 1.7	32.2 ± 0.9	> 0.05
RA diameter (mm)	21.5 ± 3.4	20.2 ± 3.7	22.4 ± 4.1	23.6 ± 4.1	> 0.05
LVED diameter (mm)	44.5 ± 2.1	45.6 ± 1.5	46.1 ± 1.8	45.8 ± 1.1	> 0.05
LVES diameter (mm)	28.5 ± 2.3	28.7 ± 1.3	30.9 ± 1.0	30.3 ± 1.1	> 0.05
LV FS (%)	37.1 ± 2.5	38.2 ± 3.1	38.1 ± 1.7	38.3 ± 1.4	> 0.05

EF = ejection fraction, LA = left atrium, RA = right atrium, LVED = left ventricular end-diastolic, LVES = left ventricular end-systolic, FS = fractional shortening, Values are mean ± SD.

Table 3
Comparison of total atrial and interatrial conduction times (TACT), as measured by TDI and EPS, according to age and sex groups.

20–30 years	Total atrial conduction time	TACT	30–40 years	Total atrial conduction time	TACT
Women	66.00	64.00	**Women**	79.00	76.00
	65.00	66.00		66.00	63.00
	68.00	68.20		64.00	68.00
	72.00	66.80		73.00	77.00
	63.00	71.90		78.00	77.00
	72.00	66.80		82.00	81.00
	60.00	64.20		83.00	83.00
	70.00	71.30		86.00	85.00
	66.00	66.80		84.00	80.00
	70.00	64.90		82.00	78.00
	66.00	71.00		88.00	79.00
	72.00	72.00		75.00	78.00
	63.00	63.00		77.00	74.00
	72.00	65.00		64.00	62.00
	80.00	84.00		83.00	82.00
	70.00	69.00		82.00	75.00
	66.00	67.00		86.00	77.00
	68.00	69.00		81.00	87.00
	72.00	73.00		82.00	88.00
	68.00	70.00		82.00	84.00
Mean ± SD	$68.4 \pm 4.4^{*}$	$68.6 \pm 4.6^{*}$	**Mean ± SD**	$78.7 \pm 7.4^{**}$	$77.9 \pm 7.1^{**}$
Men	72.00	67.00	**Men**	64.00	57.50
	68.00	70.00		67.00	61.20
	74.00	71.00		74.00	81.00
	74.00	79.40		68.00	73.00
	79.00	77.00		75.00	67.00
	82.00	84.30		77.00	71.00
	68.00	65.00		74.00	82.00
	72.00	74.00		71.00	73.00
	66.00	68.00		78.00	80.00
	68.00	67.00		82.00	81.00
	66.00	68.00		86.00	86.00
	65.00	66.00		85.00	85.50
	68.00	67.00		78.00	77.00
	72.00	72.00		83.00	83.00
	71.00	70.00		86.00	85.00
	67.00	68.00		84.00	80.00
	72.00	70.00		88.00	83.00
	72.00	71.00		82.00	84.00
	76.00	78.00		77.00	79.00
	79.00	78.00		71.00	73.00
Mean ± SD	$71.4 \pm 4.9^{\&}$	$71.5 \pm 5.3^{\&}$	**Mean ± SD**	$77.3 \pm 7.3^{\&\&}$	$76.9 \pm 7.1^{\&\&}$

All $*$, $**$, $^{\&}$ and $^{\&\&}$ demonstrate the absence of statistical significance, $p > 0.05$.

different. The main reason for this may be the different echocardiographic techniques and subject populations. Namely, we used the TDI, which is the newer and the most often used technique, and received the signal from LA lateral wall just over the mitral annulus. However, Fuenmayor et al. used conventional Doppler echocardiography and performed the measurement from the beginning of P wave to the mitral valve A wave. Additionally, we believe that most important reason for the differences in results is the fact that the subjects in the present study were without arrhythmia while the other study population consisted of patients with supraventricular tachycardia. Another superiority of the present study is the large study population.

In another similar study, Deniz et al. determine the correlation of inter- and intraatrial conduction times between the electrophysiological and tissue Doppler echocardiographic measurements, and evaluated the appropriateness of tissue Doppler echocardiography for this measurement [10]. The study population included patients who underwent electrophysiological studies for clinical arrhythmias. They found a weak correlation between the measurement of the interatrial conduction times with the electrophysiological and tissue Doppler techniques. A mode-366rate correlation was found in the intraleft atrial conduction times. They concluded that tissue Doppler echocardiography might be used for the measurement of interatrial and intra-left atrial conduction times [10]. The validation of the ACT in the different age and sex groups, is one the most important differences of our study. Additionally, the present study population was free of arrhythmia while the other study population consisted of different types of patients with supraventricular tachycardia. The result of the present study showed the closed correlation between the measurements of interatrial conduction times with the electrophysiological and tissue Doppler techniques just in healthy person without cardiovascular and systemic diseases. For that reason, we believed that the generalizations of our study result not be appropriate for the subject with arrhythmias and systemic diseases.

In the present study, the TACT measurement scores by EPS and TDI among women aged 20–30 were statistically and borderline significantly lower than in those aged 30–40. Similarly, men aged 20–30 years had lower scores than those aged 30–40. However, non-significant statistical differences were observed between the two groups. We believe that this is because of the small sample size. Similarly, the present study results clearly show decreased atrial conduction due to aging [11–14]. Kistler et al. showed that aging is associated with a decrease in the regional conduction, anatomically determined conduction delay at the crista, and

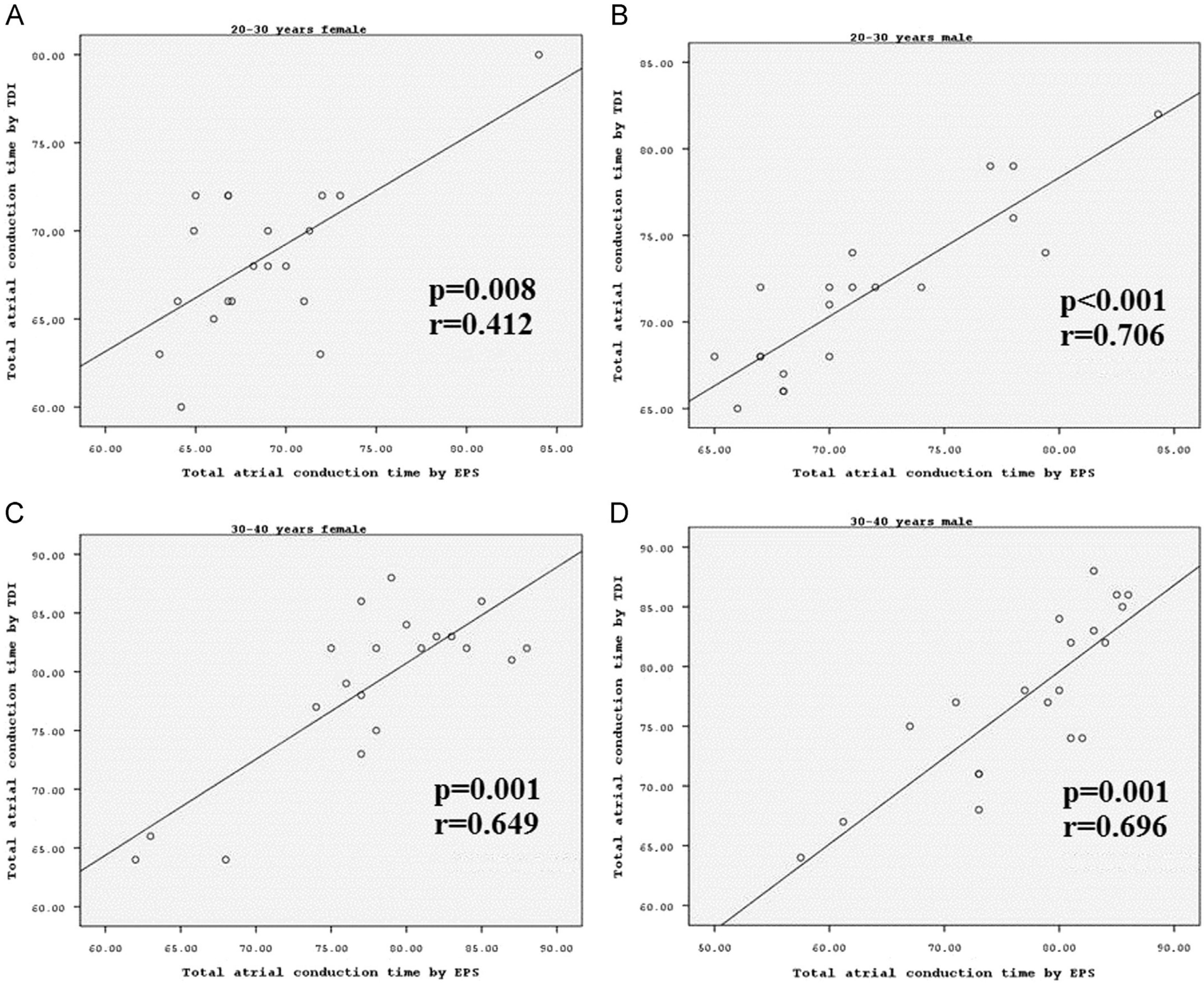

Fig. 1. TACT values, as measured by TDI and EPS, and their correlations.

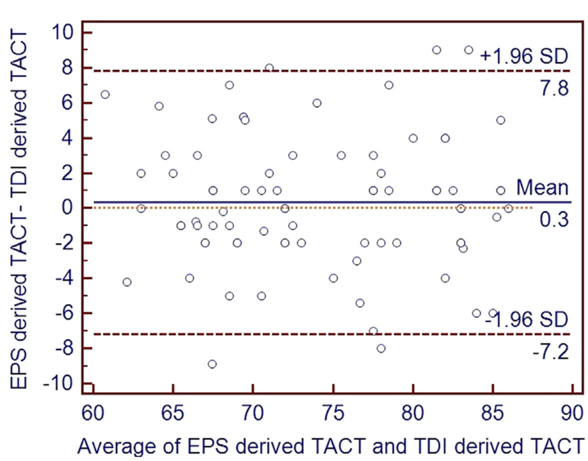

Fig. 2. Blan–Altman plot showing the compliance and the large limits of agreement.

structural changes that include areas of low voltage [11]. In an animal study, Hayashi et al. concluded that heterogeneous atrial interstitial fibrosis and atrial cell hypertrophy might contribute to decreased atrial conduction due to aging [12]. The incidence of atrial fibrillation (AF) increases with age. Anyukhovsky et al. concluded that dispersion of atrial repolarization increases with aging, creating a substrate for initiation of AF [13]. Additionally, Babaev et al. confirmed that age-related atrial conduction delay is also present in healthy subjects [14]. To the best of our knowledge, the present study is the first that has shown decreased atrial conduction due to aging by EPS and TDI in the literature.

5.1. Limitations of the study

First, the main limitation of our study was its relatively small group of patients. Since a small sample size results in low statistical power for equivalency testing, negative results may be simply because of chance. Second, the study had a single-center design. Future prospective studies at larger multicenter are required to confirm our results. The third limitation is that we cannot apply the present study results to the general population, especially to patients with arrhythmias, cardiovascular and systemic diseases, because of the broad exclusion criteria. As a methodological point of TDI and EPS measurements, the surface ECG might be improved in order to identify the exact onset of P-wave.

6. Conclusion

To the best of our knowledge, this is the first study that aimed to demonstrated the validation of TDI and EPS in the measurement of the TACT among different age and sex groups in healthy subjects without cardiovascular and systemic diseases. TDI measurements were found to be similar and strongly correlated with the measurements performed by EPS in the assessment of TACT among healthy subjects. TDI measurements of TACT are significantly advantageous because of the low cost and non-invasiveness. Thus, the measurement of TACT via TDI may be used accurately and confidently instead of the EPS among healthy subjects without cardiovascular and systemic diseases.

Conflict of interest

All authors declare no conflicts of interest related to this study.

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