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Clinical and echocardiographic correlates of intra-atrial conduction delay

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Aims The total atrial conduction time (TACT) is an important electrophysiological parameter. We developed a new transthoracic echocardiographic tool (PA-TDI). The PA-TDI interval is a reflection of the TACT. In the present study, we evaluated the clinical and echocardiographic correlates of intra-atrial conduction delay.

Methods and results We studied 427 patients without class I anti-arrhythmic agents or amiodarone. All patients underwent an echocardiogram and the PA-TDI interval was measured. Patient characteristics were recorded. The mean PA-TDI was 157 ± 22 ms. Multivariate linear regression analysis revealed that atrial fibrillation (AF) in history ($B = 9.7$; 95%CI 5.7–13.8; $P < 0.001$), hypertension ($B = 5.5$; 95%CI 1.4–9.8; $P = 0.01$), clinically relevant valve disease ($B = 5.7$; 95%CI 0.5–10.8; $P = 0.03$), age ($B = 5$; 95%CI 3.3–6.6; $P < 0.001$), and body mass index (BMI; $B = 2.6$; 95%CI 0.3–4.9; $P = 0.026$) were independently associated with the PA-TDI interval. On the echocardiogram: the aortic diameter ($B = 0.7$; 95%CI 0.2–1.2; $P = 0.009$), left atrial dimension ($B = 0.9$; 95%CI 0.5–1.3; $P < 0.001$), mitral valve E-wave deceleration time ($B = 0.1$; 95%CI 0.1–0.1; $P < 0.001$), aortic incompetence ($B = 13$; 95%CI 3.3–22.6; $P = 0.008$), and mitral incompetence ($B = 11$; 95%CI 3.6–17.5; $P < 0.003$) were independently associated with the PA-TDI interval.

Conclusion This study is the largest to investigate the relation between the atrial conduction time, underlying heart diseases, and echocardiographic parameters. We found that the PA-TDI was independently prolonged in patients with a history of AF, hypertension, valve disease, higher age, and a higher BMI. Signs of diastolic dysfunction, valve incompetence, and enlarged atrium or aortic root on the echocardiogram were associated with a prolonged PA-TDI. This suggests that early and aggressive treatment of hypertension, diastolic dysfunction, and obesity could prevent intra-atrial conduction delay.

Keywords Atrial • Conduction • Tissue Doppler imaging • Echocardiography • Hypertension

Introduction

The total atrial conduction time (TACT) is an important electrophysiological parameter that can be determined during an electrophysiological study.[1] A delay of atrial conduction is strongly associated with underlying diseases affecting the atria directly or indirectly.[2–5] Delayed conduction is one of the requirements for the initiation of reentry and the development of atrial fibrillation (AF).[6] This implies that prevention or amelioration of atrial conduction delay may prevent the development of atrial arrhythmias such as AF. Indeed, previous studies suggest that the TACT may be a useful target of therapy.[7–10] We validated a novel non-invasive echocardiographic technique using atrial tissue Doppler imaging (PA-TDI or atrial electromechanical interval) that strongly correlates with TACT.[11] In previous studies, we showed that a prolonged PA-TDI is the most important predictor of new-onset AF.[11,12] Other investigators confirmed our findings in different populations.[13,14] A prolonged PA-TDI interval is also associated with recurrence of AF after catheter ablation.[15] Knowing the conditions that prolong the TACT is essential in order to

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develop therapies or strategies for prevention of AF. However, the clinical determinants of a prolonged TACT were never studied before in a large population. In this report, we used the echocardiographic PA-TDI to study the clinical and echocardiographic correlates of intra-atrial conduction delay in a large group of patients.

Methods

Study population

We studied 522 outpatient clinic patients referred to the Maastricht University Medical Centre for a standard transthoracic echocardiographic examination for various medical conditions (including AF in 273 patients). Patients were included between January 2003 and February 2007. Patients were enrolled if they were 18 years or older and had sinus rhythm during the echocardiogram. Exclusion criteria were previous pacemaker implantation, an implantable cardioverter–defibrillator and the use of class I anti-arrhythmic agents or amiodarone. The 249 patients without previous AF have been reported in a separate paper on the role of PA-TDI in the prediction of AF.[12]

Echocardiographic examination

The echocardiographic examination consisted of a standard two-dimensional echocardiogram, including M-mode and Doppler echocardiography (Sonos 5500, Philips Medical Systems, Andover, MA, USA) during continuous electrocardiogram (ECG) monitoring according to the recommendations as described in the American Society of Echocardiography guidelines. Left atrial volume was obtained from the single-plane area-length of the apical four-chamber view, just prior to mitral valve opening, and with the patient in the left-lateral decubitus position. Additionally, we determined the PA-TDI interval.[11] In the apical four-chamber view, the pulsed-wave tissue Doppler sample was placed on the lateral wall of the left atrium just above the mitral annulus. The PA-TDI interval, defined as the time-interval from initiation of the electrocardiographic P-wave recorded by the echo machine (lead II) to the peak of the A'-wave of the atrial tissue Doppler tracing (*Figure 1*), was measured in three cardiac cycles and averaged.

The investigator who performed the echocardiographic measurements (including PA-TDI interval) was an independent observer blinded for other patient characteristics.

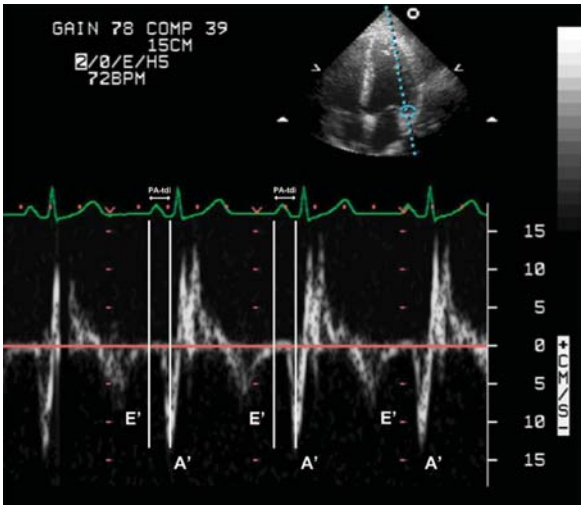

Figure 1 Example of PA-TDI measurement. PA-TDI is defined as the time interval between the onset of electrocardiographic P wave in lead II and the top of the A'-wave on the atrial tissue Doppler velocity curve from the left atrial wall.

Data collection

Patient characteristics, including medication, (arrhythmia) history, and ECGs at the time of echocardiography were collected. Data were derived from the patient charts and electronic medical records. A diagnosis of AF in history was defined as a documented episode of AF lasting 30 s or more. 'Valve disease' was defined as clinically relevant valve disease at discretion of the treating physician. The study complies with the Declaration of Helsinki. Patient informed consent was obtained and the Institutional Review Board approved the study.

Table 1 Baseline characteristics in relation to the mean PA-TDI duration in our population—univariate analysis

	PA-TDI <157 ms (*n* = 222)	PA-TDI ≥157 ms (*n* = 205)	*P* value
Age (years)[a]	60 ± 13	67 ± 11	<0.001
Female, *n* (%)	121 (45)	97 (47)	0.147
Body mass index (kg/m2)[a]	27 ± 4	28 ± 4	0.081
Underlying risk factors and cardiovascular disease			
AF in history, *n* (%)	74 (33)	114 (55)	<0.001
Hypertension, *n* (%)	122 (55)	132 (64)	0.049
Coronary artery disease, *n* (%)	22 (10)	34 (17)	0.045
Diabetes mellitus, *n* (%)	29 (13)	22 (11)	0.551
Valve disease, *n* (%)	30 (14)	50 (24)	0.004
Heart failure, *n* (%)	14 (6)	20 (10)	0.213
Thyroid disease, *n* (%)	15 (7)	12 (6)	0.843
Chronic obstructive pulmonary disease, *n* (%)	14 (6)	15 (7)	0.704
Medication			
Oral anticoagulation, *n* (%)	39 (18)	85 (42)	<0.001
Aspirin, *n* (%)	70 (32)	42 (21)	0.011
Beta-blocker, *n* (%)	63 (28)	104 (51)	<0.001
Sotalol, *n* (%)	28 (13)	40 (20)	0.064
Verapamil, *n* (%)	18 (8)	19 (9)	0.732
Digitalis, *n* (%)	10 (5)	14 (7)	0.401
Nitrates, *n* (%)	8 (4)	22 (11)	0.004
Angiotensin-converting enzyme inhibitor, *n* (%)	37 (17)	61 (30)	0.002
Angiotensin-II receptor blocker, *n* (%)	49 (22)	44 (22)	0.907
Diuretics, *n* (%)	33 (15)	56 (27)	0.002
Statins, *n* (%)	64 (29)	54 (26)	0.589
Alpha-blocker, *n* (%)	7 (3)	5 (3)	0.774
Dihydropyridin calcium channel blocker, *n* (%)	27 (12)	36 (18)	0.133

[a]Average (standard deviation).

Table 2 Echocardiographic parameters in relation to the mean PA-TDI duration in our population—univariate analysis

	PA-TDI <157 ms (n = 222)	PA-TDI ≥157 ms (n = 205)	P value
Dimensions			
Aorta diameter (mm)	33.6 ± 4	35.1 ± 4	<0.001
Left atrial dimension (mm)	39 ± 5	42 ± 5	<0.001
Left atrial volume (cc)	51 ± 20	57 ± 25	0.012
Right atrial volume (cc)	42 ± 14	46 ± 16	0.049
Left ventricular end diastolic dimension (mm)	48 ± 5	50 ± 5	<0.001
Left ventricular end systolic dimension (mm)	32 ± 6	34 ± 6	0.002
Inter-ventricular septum width (mm)	9.1 ± 1.1	9.9 ± 5.8	0.025
Posterior wall width (mm)	8.7 ± 0.9	9.1 ± 1.1	0.002
Left ventricular mass (g)	185 ± 44	209 ± 54	<0.001
Left ventricular end diastolic volume (cc)	109 ± 28	120 ± 35	0.001
Left ventricular end systolic volume (cc)	42 ± 21	49 ± 27	0.006
Caval vein (mm)	17 ± 4	17 ± 4	0.256
Right ventricular systolic pressure (mmHg)	30 ± 6	32 ± 8	0.182
Left ventricular function			
Left ventricular ejection fraction (%)	61 ± 9	60 ± 9	0.072
Mitral valve Doppler			
Maximal E-wave velocity (cm/s)	75 ± 17	73 ± 20	0.292
E-wave deceleration slope (m/s^2)	396 ± 145	355 ± 157	0.006
E-wave deceleration time (ms)	196 ± 44	218 ± 62	<0.001
Maximal A-wave velocity (cm/s)	76 ± 20	75 ± 21	0.462
E/A ratio	1.04 ± 0.4	1.06 ± 0.6	0.603
Valve disease			
Aortic incompetence (>grade 1)	4 (2%)	18 (9%)	0.002
Mitral incompetence (>grade 1)	9 (4%)	28 (14%)	<0.001
Tricuspid incompetence (>grade 1)	14 (6%)	17 (8%)	0.460
Mitral valve stenosis	0	2 (1%)	0.230
Aortic stenosis	8 (4%)	8 (4%)	1.000

Table 3 Multivariate linear regression analysis: clinical and echocardiographic parameters that independently prolong the PA-TDI interval and correlation coefficients of all continuous variables resulting from the correlation with PA-TDI

	B (ms)	95%CI for (B)	P value	R^2	P value
Demographic and clinical parameters					
AF in history	9.7	5.7–13.8	<0.001		
Hypertension	5.5	1.4–9.8	0.010		
Valve disease	5.7	0.5–10.8	0.030		
Age (per 10 years)	5	3.3–6.6	<0.001	0.34	<0.001
BMI (per 5 kg/m^2)	2.6	0.3–4.9	0.026	0.13	0.008
Echocardiographic parameters					
Aorta diameter (per mm)	0.7	0.2–1.2	0.009	0.22	<0.001
Left atrial dimension (per mm)	0.9	0.5–1.3	<0.001	0.34	<0.001
Aortic incompetence (>grade 1)	13	3.3–22.6	0.008		
Mitral incompetence (>grade 1)	11	3.6–17.5	0.003		
Mitral valve E-wave deceleration time (per ms)	0.076	0.039–0.113	<0.001	0.25	<0.001

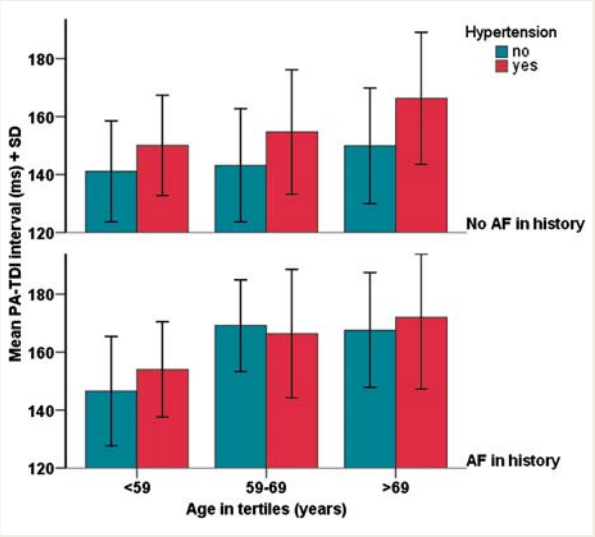

Figure 2 Clinical parameters affecting the PA-TDI interval. Mean PA-TDI interval + standard deviation according to age in tertiles and hypertensive patients (red bars) versus non-hypertensive patients (turquoise bars). The upper panel shows patients without a history of atrial fibrillation and the lower panel patients with a history of atrial fibrillation.

Statistical analysis

Continuous variables are presented as mean and standard deviation, categorical variables as observed number of patients and percentages. We used an independent *t*-test after performing Levene's test for equality of variances to compare all continuous variables. Categorical variables were tested with Fisher's exact test. *Tables 1* and *2* show the *P* values resulting from multiple uncorrected *t*-tests for continuous variables and Fisher's exact tests for categorical variables. This allowed us to identify parameters to feed into the linear regression analysis. Therefore, these tables are not presenting the ultimate results of the analysis. All parameters with a *P* value <0.1 resulting from the univariate comparisons in *Tables 1* and *2* were included in the linear regression models presented in *Table 3*. We did not include medication in the multivariate analysis presented in *Table 3* since it is a reflection of the underlying diseases already included in the model. Model reduction was performed by stepwise exclusion of variables from the model with a *P* value <0.1. For all continuous variables in the final regression analysis model, we determined their correlation with PA-TDI using Pearson's correlation test. Statistical analysis was performed with SPSS statistical software (SPSS Inc. release 16.0) and statistical significance was assumed for $P < 0.05$. All tests performed were two sided.

Results

From the initial population of 522 patients, 95 patients were excluded because of use of conduction slowing class I anti-arrhythmic agents or amiodarone leaving a final study population of 427. The mean PA-TDI was 157 ± 22 ms. The shortest PA-TDI interval we measured was 103 ms and longest was 230 ms. Baseline characteristics of all patients in relation to the mean PA-TDI interval in our population are shown in *Table 1*. Patients with a prolonged PA-TDI duration (>157 ms) were older and more often suffered from AF, hypertension, coronary artery disease, clinically relevant valve disease, and more often used oral anticoagulation, beta-blockers, nitrates, angiotensin-converting enzyme (ACE)-inhibitors and diuretics. Patients with a shorter PA-TDI interval used more aspirin. *Figure 2* shows the mean PA-TDI interval according to age in tertiles and hypertension in patients with and without AF.

A history of AF was present in 188 (44%) patients. Atrial fibrillation was paroxysmal and self-terminating in 162 (88%) patients and persistent and previously terminated by electrical or chemical cardioversion in 21 (12%) patients.

Echocardiographic differences according to PA-TDI duration are shown in *Table 2*. Patients with a longer PA-TDI interval have an increased aortic width, increased atrial dimensions, and a larger and thicker left ventricle. The E-wave deceleration slope is decreased and the E-wave deceleration time is increased in the patients with a longer PA-TDI interval. Patients with a prolonged PA-TDI interval had more aortic valve incompetence and mitral valve incompetence. *Figure 3* shows the mean PA-TDI interval according to mitral valve E-wave deceleration time and left atrial dimension.

Multivariable linear regression analysis revealed that AF in history, hypertension, clinically relevant valve disease, age, and BMI were independently associated with the PA-TDI interval (*Table 3*). When excluding patients with AF in history, hypertension ($B = 10$, $P < 0.001$), age ($B = 5$ per 10 years increase of age, $P < 0.001$), and BMI ($B = 4$ per 5 points increase of BMI, $P < 0.011$) remained significantly associated with a prolonged PA-TDI interval.

Regarding the echocardiographic parameters: the aortic diameter, left atrial dimension, mitral valve E-wave deceleration time, aortic incompetence, and mitral incompetence were independently associated with the PA-TDI interval in our population (*Table 3*). When excluding patients with a history of AF, the clinical parameters hypertension, age and BMI remained independently associated with the PA-TDI interval. The echocardiographic parameters aorta diameter, left atrial dimension, aortic incompetence, and mitral valve E-wave deceleration time remained independently associated with PA-TDI interval when performing multivariate linear regression analysis in patients without a history of AF.

Discussion

The present study is the largest to investigate the relationship between PA-TDI, underlying cardiovascular diseases and echocardiographic parameters. We used the PA-TDI interval—a relatively new echocardiographic parameter[11]—to estimate the TACT.

Clinical correlates of intra-atrial conduction delay

In this study, PA-TDI was independently prolonged in patients with a history of AF, hypertension, clinically relevant valve disease, higher age, and a higher BMI. We found that after

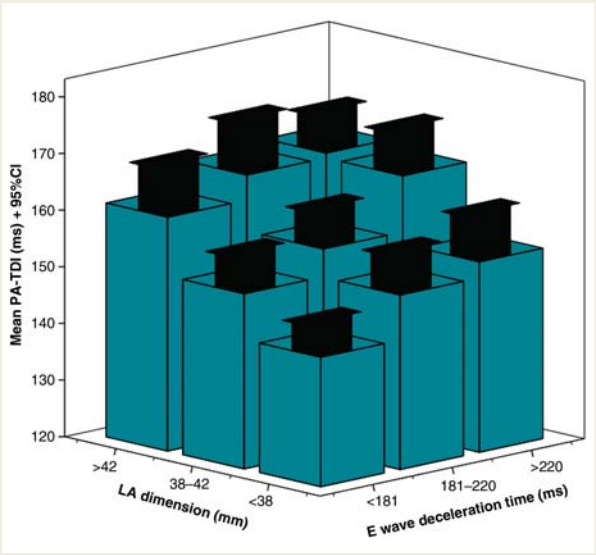

Figure 3 Echocardiographic parameters affecting the PA-TDI interval. Mean PA-TDI interval and 95% confidence intervals according to mitral valve E-wave deceleration time and left atrial dimension, both in tertiles.

correcting for possible confounders, a history of AF increases PA-TDI by ~10 ms, a history of hypertension by 5 ms and clinically relevant valve disease by 6 ms. Each additional 10 years of age increases PA-TDI with ~5 ms and each additional 5 kg/m^2 of BMI increases PA-TDI with 3 ms. The strong association between prolonged atrial conduction time and AF is not surprising since on one hand long conduction times are a prerequisite for the development of AF and on the other hand, AF itself may induce remodelling and hence contribute to lengthening of conduction through the atria.[6,16] As has been suggested previously, prevention of AF may ameliorate atrial structural remodelling and prevent further AF episodes. Since it is unlikely that available therapies reduce atrial conduction time, preventive therapy might focus especially on suppression of AF in the subset with still normal conduction. Ageing is a recognized determinant of atrial size and fibrosis but unfortunately non-modifiable with respect to prevention of conduction abnormalities. Hypertension and valve disease are associated with diastolic dysfunction inducing intermittent pressure rises and dilatation of the atria and hence atrial fibrosis.[17,18] In turn, this prolongs the TACT because of 'detour conduction' in larger atria. Although BMI relates to hypertension we showed an independent impact on TACT. From our data we cannot tell whether high BMI effected an increase in TACT through obstructive sleep apnea which was recently described as being associated with atrial conduction slowing.[2] On the other hand, the pericardial fat that overlies the cardiac surface including the inter- and intra-atrial conduction system might be responsible for atrial conduction delays. Recent studies demonstrate a relation between pericardial fat and atrial conduction delay.[19] Reducing body weight may ameliorate the atrial conduction time. Indeed, the effect of a high BMI on atrial conduction is likely to be reversible since obesity studies demonstrate that substantial weight loss is associated with improvement in atrial repolarization abnormalities on the ECG in obese subjects.[20] Patients with a prolonged PA-TDI interval more often used oral anticoagulation, beta-blockers, nitrates, ACE-inhibitors, and diuretics. It is difficult to interpret the relation between PA-TDI and the use of medication in the present study. The univariate analysis showed that in patients with a long PA-TDI interval AF, hypertension, and coronary artery disease occurred more frequently. Oral anticoagulation is typically prescribed in patients with AF, beta-blockers in patients with coronary artery but also in patients with hypertension and AF, nitrates are frequently applied in patients with coronary artery disease, and ACE-inhibitors and diuretics are usually prescribed in patients with hypertension. Therefore, one could hypothesize that the differences found in medication use according to the length of the PA-TDI interval are the result of underlying heart disease. On the other hand, one could imagine that some medication directly influences the PA-TDI interval. Unfortunately, the present study does not provide an answer to this question.

Echocardiographic correlates of intra-atrial conduction delay

We also investigated that echocardiographic parameters were associated with PA-TDI. We found that increased left atrium (LA) dimension, increased aortic diameter, aortic, and mitral valve incompetence and a longer E-wave deceleration time are independently associated with a prolonged PA-TDI interval. The latter probably reflects mild diastolic dysfunction since it might be a sign of an impaired relaxation of the left ventricle. However, other parameters necessary to confirm this finding such as the pulmonary vein flow and E/e'' were not available in all patients. However, smaller studies using the signal averaged ECG to assess atrial conduction also demonstrate increased left atrial pressure and impaired LV relaxation in patients with delayed atrial conduction.[21] The increased aortic diameter could be a reflection of the presence of aortic incompetence. However, our data show an independent relation between aortic diameter and PA-TDI. Another explanation could be inadequate management of hypertension. Since hypertension in history is also one of the clinical parameters, which was independently associated with a delay of the PA-TDI interval in this study, lowering the blood pressure is probably crucial to prevent prolongation of the TACT. An increased LA dimension could be the reflection of intermittent left atrial pressure rises typically seen in diastolic left ventricular dysfunction.[22]

Future perspectives

Since recent studies suggest that a prolonged PA-TDI is associated with the development of new-onset AF and poor outcome of rhythm control,[10,12–15] one could hypothesize that reducing the duration of PA-TDI (or preventing its lengthening) improves primary and secondary prevention of AF. Our study suggests that early and aggressive treatment of hypertension, diastolic dysfunction, and obesity could prevent an increased PA-TDI. This was also suggested in smaller clinical studies.[23] In addition, recent

laboratory studies affirm that upstream therapy might enhance atrial conduction by reducing atrial fibrosis.[7,23] PA-TDI could be used to select appropriate candidates for upstream therapy and evaluating its effect.

Limitations

The PA-TDI interval overestimates the total atrial activation time since it includes both the time required for the propagation of impulses from the sinus node area to the left atrium and the time required for the electromechanical coupling in the left atrium. Furthermore, there seems to be a minor delay in ECG processing on all echo machines. In our study, this delay amounts to a maximum of 5 ms (unpublished technical information by Philips Medical Systems, Andover, MA, USA). Fortunately, this delay is consistent and therefore unlikely to have affected our results.

Some of the parameters in *Table 2* showed only a small difference but still a significant univariate *P* value, which may relate to the large sample size. Obviously, these differences may be of limited clinical relevance because they were at times smaller than the error in individual measurements. However, it should be noted that *Tables 1* and *2* concerned univariate analyses used to identify parameters to feed the regression analysis. All our patients were included in a cardiology outpatient clinic. As a result, the population we studied may not be representative of the general population. On the other hand, PA-TDI is intended for patients with cardiovascular diseases. The investigator who included the patients (R.G.T.) is a general cardiologist with a special interest in electrophysiology. For that reason, many patients included in the present study had a history of AF. However, we verified our main findings in a group of patients excluding those with a history of AF and found similar results.

Conclusions

The present study is the largest clinical study to investigate the relation between the atrial conduction times, underlying heart diseases, and echocardiographic parameters. We found that PA-TDI was prolonged in patients with a history of AF, hypertension, clinically relevant valve disease, higher age, and a higher BMI. On the echocardiogram, a larger left atrium, a larger aortic diameter, a longer E-wave deceleration time, and aortic and mitral incompetence were also associated with a prolonged PA-TDI interval. Since recent studies suggest that atrial conduction delay is associated with the development of new-onset AF and poor outcome of rhythm control, one could hypothesize that reducing atrial conduction time (or preventing its lengthening) improves primary and secondary prevention of AF. Based on our results, one could hypothesize that early and aggressive treatment of hypertension, diastolic dysfunction, and obesity could prevent atrial conduction delay.

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Conflict of interest: none declared.

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