Electrophysiological and echocardiographic parameters predisposing to atrial fibrillation in patients with a structurally normal heart

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Abstract

Background: The electroanatomical substrate of dilated atria is characterised by increased non-uniform anisotropy and macroscopic slowing of conduction, which promote reentrant circuits.

Aim: To analyse the relationship between electrophysiological properties of atria and echocardiographic markers of dilatation and increased filling pressure.

Methods: The study group consisted of 79 patients without structural heart disease, aged 53±22 years, who were referred for electrophysiological study. In order to examine the atrial electrophysiological characteristics we studied interatrial conduction time (iaCT), double potentials and fragmented atrial activity during premature stimulation of the high right atrium (HRA). The analysed parameters included: duration of atrial activity, baseline iaCT (iaCTb) between HRA and distal coronary sinus (CS), iaCT during HRA pacing S1S1 600 ms (iaCTS1), maximum prolongation of iaCT during S2 and S3 delivery (iaCTS2, iaCTS3). We also calculated the decremental index (DI)=iaCT S3- iaCTS1/iaCTS1%. The following echocardiographic parameters were assessed: left atrial (LA) dimensions, surface (LAs), volume using ellipse formula (LAv), right surface (RAs), total atrial surface (TAs=LAs+RAs), and global myocardial index (GMI).

Results: Patients were divided into two groups. Group 1 consisted of 37 patients with evidence of slow atrial conduction (atrial fragmentation/iaCTb>80ms/DI>50%/double atrial potentials), whereas group 2 was composed of 42 patients without slow conduction properties. There were no significant differences concerning age, body mass index or LA parasternal dimensions between the groups. Thirty-seven patients, of whom 32 were from group 1, had documented episodes of paroxysmal atrial fibrillation. GMI, LAs, LAv and TAs values were significantly higher in patients from group 1 than in group 2 subjects. A statistically significant linear correlation between iaCTb and TAs ($r=0.52$ $p<0.0001$)/LAv ($r=0.38$ $p<0.0001$) was found. There was also a trend toward a correlation between DI and TAs.

Conclusion: This study supports the role of stretch and dilated atria in electrophysiological changes which occur in structurally normal hearts. The iaCT value may be indirectly and non-invasively evaluated using echocardiograhic measurements.

Key words: interatrial conduction, decremental conduction, atrial dilatation, atrial fibrillation

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Introduction

The relationship between atrial electrophysiological properties and atrial dilatation in patients with a structurally normal heart who are prone to atrial fibrillation (AF) has not been fully investigated. The electroanatomical substrate of dilated atria is characterised by increased non-uniform anisotropy and macroscopic slowing of conduction, promoting reentrant circuits. Acute and chronic atrial stretch, delayed atrial conduction, and dilated atria with increased atrial pressure are involved in the development of AF [1-3].

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The subclinical markers of chronic atrial stretch in patients with a structurally normal heart have not yet been extensively investigated in humans. The early electrophysiological modifications due to atrial dilatation and increased pressure have rarely been described. The global myocardial index (GMI) is a sensitive echocardiographic indicator of overall cardiac function, introduced in 1995 by Tei and co-workers [4], and has been shown to correlate significantly with left ventricular (LV) filling pressure [5].

The aim of the present study was to analyse the relationship between modifications of the electrophysiological properties of the atria and echocardiographic markers of dilatation and increased filling pressure.

Methods

Patients

Consecutive patients referred for electrophysiological evaluation were included in the study. Exclusion criteria were any structural heart disease, moderate or severe valvar regurgitation, coronary artery disease, and significant co-morbidities (creatinine >1.3 mg%, diabetes, abnormal liver function, etc).

Structural heart disease was excluded based on medical history, physical examination, 12-lead surface ECG, chest radiography, and transthoracic echocardiography (LV hypertrophy or dilatation, and right ventricular dilatation). Coronary artery disease was excluded based on a lack of symptoms, estimated risk of less than 10% at 10 years based on the Framingham score, and normal exercise test.

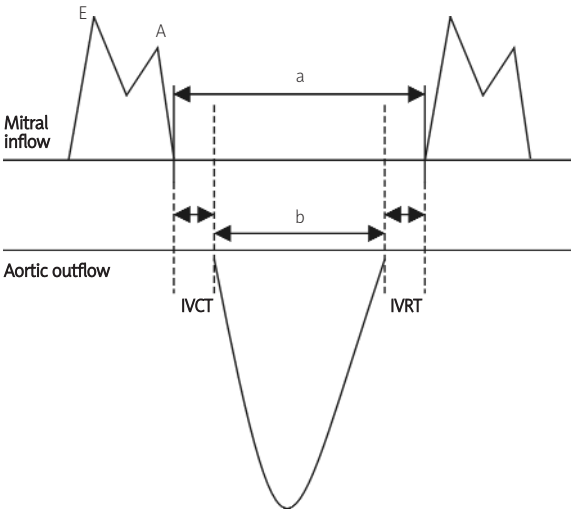

Figure 1. Echocardiographic Doppler measurement of GMI: GMI=a-b/b, where a – interval between cessation and onser of mitral flow, b – aortic ejection time, ICT – isovolumetric contraction time, IRT – isovolumetric relaxation time (4)

All patients provided written informed consent, and the study protocol was approved by the locally appointed Ethics Committee.

Echocardiography

Images were taken less than 24 hours before the electrophysiological study, with patients in the left lateral decubital position, using a SONOS 5500 echo machine (Hewlett Packard, Andover, Massachusetts, USA). An electrocardiogram (lead D1) was simultaneously recorded in each patient. The echocardiographic examination was done using standard views and techniques [6]. The Doppler tracings were recorded over more than 3 cardiac cycles at a sweep speed of 50 or 100 mm/sec, and stored on an optical disc. Standard echocardiographic measurements, including interventricular septum thickness (IVS), LV end-diastolic diameter (LVEDD), and ejection fraction (EF) (Simpson's method), were evaluated.

Atrial dimensions and function were assessed. Left atrial diameter (LAd) was measured by M-mode in the parasternal long-axis view, and LA transversal (LAt) as well as longitudinal (LAl) diameters were measured in the apical 4-chamber view, at ventricular end-systole. Left atrial (LAs) and right atrial (RAs) areas were measured by two-dimensional planimetry in the apical 4-chamber view, and total atrial area (TAs) was calculated. Left atrial volume was calculated using the ellipse formula (7): $\pi/6$ (LAdxLAlxLAt), where LAd is LA diameter in the parasternal view, and LAl and LAt are longitudinal and transversal LA diameters, respectively, in the apical 4-chamber view.

The global myocardial index was calculated using time intervals measured from mitral inflow and LF outflow tracings recorded by pulsed-wave Doppler (Figure 1). The *a* interval was measured from the cessation to the onset of mitral inflow and was the sum of isovolumic contraction time, ejection time, and isovolumic relaxation time. The ejection time *b* was measured from the duration of the aortic velocity profile. The sum of isovolumic contraction and relaxation time was obtained by subtracting b from a. Global myocardial index was calculated using the formula (a-b)/b (Figure 1).

All measurements were obtained from three consecutive cardiac cycles and presented as an average of these measurements.

Electrophysiological study

All antiarrhythmic drugs were discontinued prior to the electrophysiological evaluation for at least five half-life

times of each drug. Patients were studied in the fasting, nonsedated state. The electrophysiological study was performed using Bard Electrophysiology LabSystem DUO (Software version 2.73N). In all patients a minimum of 3 catheters was inserted: 1. two 6F-quadripolar catheters, 5 mm interelectrode spacing, inserted percutaneously using the right femoral vein approach, and positioned in the right lateral atrial wall and His bundle region; 2. a 5F-decapolar catheter, 2 mm interelectrode spacing, inserted percutaneously using the jugular vein, and positioned into the coronary sinus (CS) with the proximal bipole at the level of the CS ostium. The IaCT was assessed in normal sinus rhythm as the time interval between the high right atrium and distal part of the CS.

Programmed stimulation was performed using a square wave at 2.5 diastolic threshold and 2-ms duration. The stimulation protocol included the single and second extrastimulus method at the basic cycle length and at the cycle length of 600 ms. The distal electrode pairs of the high right atrium (HRA) catheter were used for bipolar stimulation until the atrial ERP was reached. The extrastimulus was delivered after 8 paced beats late in diastole, and the coupling interval was shortened by steps of 10 ms until the effective atrial refractory period was reached. Atrial fibrillation (AF) was considered inducible if the standard deviation of FF intervals was >10 ms during its most regular phases.

Fragmented atrial activity was defined as disorganised atrial activity with multiple negative deflections resulting in a prolonged duration of the activation complex greater than or equal to 150% of the duration atrial activity of basic beats. Atrial double potentials was defined as two potentials separated by an interval of >20 ms and by an isoelectric line.

The following parameters were assessed in all patients:

- baseline iaCT (iaCTb) between HRA and distal CS;
- iaCT during HRA pacing S1S1 600ms (iaCTS1) as the time interval between spike and distal CS;
- maximum prolongation of iaCT during HRA S2 and S3 delivery (iaCTS2, iaCTS3);
- maximum percentage prolongation of iaCT/decremental index (DI)=iaCTS3- iaCTS1/iaCTS1%.

Slow atrial conduction was identified in a patient if at least one of the following findings was proved: 1. iaCTb>100 ms; 2. atrial fragmentation; 3. reproducible double atrial potentials recorded in the CS electrodes or 4. DI >50%.

Statistical analysis

Statistical analysis was performed using the software package Stat View 5.0 version (SAS Institute, USA). All results are expressed as mean ± SD. Subgroup data were compared using an independent samples t-test for continuous variables. Correlations of the results of various measurements recorded were tested using simple regression analysis. A p <0.05 (two-tailed test) was considered significant.

Results

Patients were divided in two groups: group 1 with evidence of slow atrial conduction, and group 2 without slow conduction properties. Representative intracardiac electrograms are presented in Figure 2.

Group 1 comprised 37 patients (26 males) aged 51±10 years, and group 2 comprised 42 patients (23 males) aged 49±16 years. There were no significant differences concerning age, body mass index and LA parasternal dimensions between groups 1 and 2. Clinical characteristics and basic electrophysiological as well as echocardiographic findings are presented in Table I.

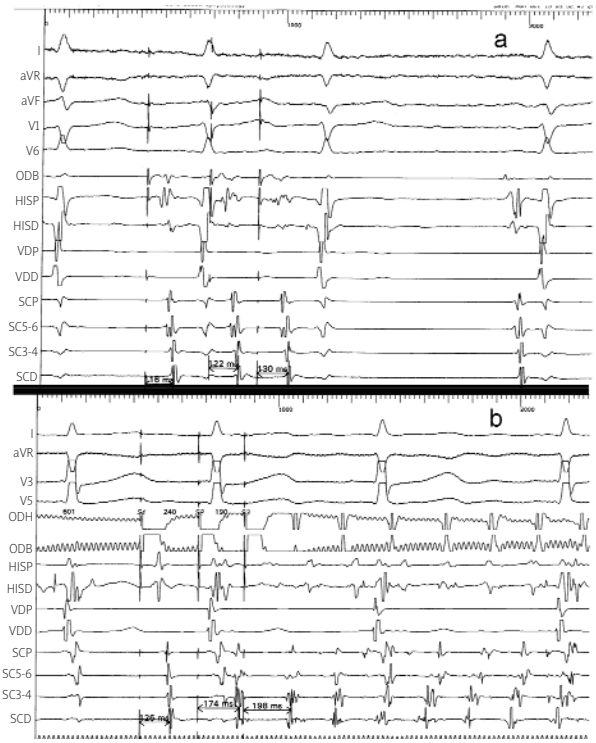

Figure 2. Representative examples of patients from gr 2 (a) and gr 1 (b). No significant increase in iaCT in patient a (116-122-130 ms). Note the progressive increase in iaCT patient b (126-174-198 ms). ODB – bazal right atrium, HISP – proximal His catheter electrodes, HISD – distal His catheter electrodes, SCD – distal coronary sinus, SCP – proximal coronary sinus

Table I. Clinical, baseline echocardiographic and electrophysiological data

	Group 1	Group 2	P
Age [years]	51±10	49±16	NS
BW [kg]	81.2±16	82.5±15	NS
BMI [kg/m^2]	28.3±7	27.5±7	NS
HR [min-1]	79.4±11	77.5±8	NS
SBP [mmHg]	133±16	129±13	NS
DBP [mmHg]	80± 9	78±11	NS
LVEF [%]	63±11	60±9	NS
IVS [cm]	1.05±0.11	1.09±0.08	NS
LVEDD [cm]	4.75±0.5	4.65±0.6	NS
LAd [cm]	4.07±0.3	3.88±0.4	NS
iaCTb [ms]	73±21	62±17	0.014
DI [%]	43±25	23±16	0.0001

Abbreviations: BW – body weight, BMI – body mass index; HR – heart rate, SBP – systolic blood pressure, DBP – diastolic blood pressure, LVEF – left ventricular ejection fraction, IVS – interventricular septum, LVEDD – left ventricular end diastolic diameter, Lad – parasternal left atrial diameter, iaCTb – baseline interatrial conduction time, DI – decremental index

Thirty-seven patients, of whom 32 belonged to group 1, had documented/inducible episodes of paroxysmal AF. Of these 37 patients, 23 subjects (all from group 1) had documented episodes of AF (in 16 of them AF was reproducibly and easily inducible using programmed stimulation), and the remaining 14 had inducible AF >10 sec duration during the electrophysiological study but no previous evidence of this arrhythmia. Other underlying conditions were atrioventricular nodal reentrant tachycardia (n=23), neurally-mediated syncope (n=6), paroxysmal junctional tachycardia (n=11) and idiopathic ventricular tachycardia (n=2).

Baseline iaCT and DI were significantly prolonged in patients with rather than without AF (iaCTb: 73.4±26 ms *vs* 58.8±16 ms, p=0.012, DI: 51.2±21.5% *vs* 20.4±13.6%, p <0.0001). The mean atrial refractory period was shorter in patients from group 1 (210±10 ms *vs* 230±20 ms, p=0.01)

The values of LAl (5.5±0.7 cm *vs* 4.4±0.3 cm), GMI (0.48±0.1 *vs* 0.37±0.07), LAs (19.2±2.8 cm^2 *vs* 16.2±2.2 cm^2), LAv (49.9±9.8 ml *vs* 36.3±8.2 ml) and TAs (38.9±6.8 cm^2 *vs* 28.4±5.4 cm^2), were significantly greater in group 1 than in group 2 (p <0.001 for all comparisons).

The simple regression analysis demonstrated (Figure 3) a statistically significant linear correlation between iaCTb and LA surface (r=0.72, r^2=0.52, p <0.0001), total atrial surface (r=0.68, r^2=0.51, p <0.0001) and LAl volume (r=0.62, r^2=0.38, p <0.0001). A moderate significant correlation was found between iaCTb and the right atrial surface (r=0.35, r^2=0.12, p <0.01) as well as between iaCTb and GMI (r=0.39, r^2=0.15, p <0.01).

A significant but weak correlation was calculated for DI *vs* TAS (r=0.57, r^2=0.32, p <0.01). No significant correlation was found with other echocardiographic parameters.

Discussion

We demonstrated that patients without structural heart disease but with markers of slow atrial conduction had indirect markers of atrial stretch. These are macroscopic subclinical structural modifications of atria dilatation and evidence of increased LV pressure.

Several studies have shown that atrial dilatation and increased pressure play an important role in paroxysmal AF, but the question of whether the increase of intraatrial pressure is the cause or consequence remains debatable and has not yet been answered [8-10]. The role of atrial conduction delay in inducing onset conditions of AF has also been demonstrated in other studies [11, 12]. To the best of our knowledge, no previous study has investigated comparative and complete assessment of atrial dimensions in patients with atrial decremental conduction properties but a structurally normal heart. However, atrial stretch has been studied in patients with atrial septal defect and heart failure [13, 14], but the patients included in those studies already presented structural heart disease and diseased atria.

The results of our study suggest that subclinical atrial dilatation may well be the cause and substrate of decremental conduction properties which may lead to inducible episodes of AF. The parasternal LA dimension was not different in study subgroups and may not be the best choice in the evaluation of atrial stretch. However, the longitudinal diameter of LA, which was found to be different between the two analysed groups, may be a better parameter of atrial dilatation. We believe that this can be explained by the fact that atrial dilatation cannot be correctly measured at the junction of the aortic root and mitral annulus, which is a fixed point. In fact, atrial dilatation may develop mainly in the anteroposterior plane at the base of the atrium in the direction of the pulmonary veins.

Pritchett and co-workers [7] validated the LA volume measurement using the ellipse formula, which may be the best alternative for characterising subclinical LA enlargement. In our experience, LAs, RAs and TAs values may also be valuable. Our study was conducted using all these parameters; slow atrial conduction was found in patients with atrial dilatation but without obvious structural heart disease. The degree of decremental conduction (DI) tended to correlate positively with the degree of atrial dilatation.

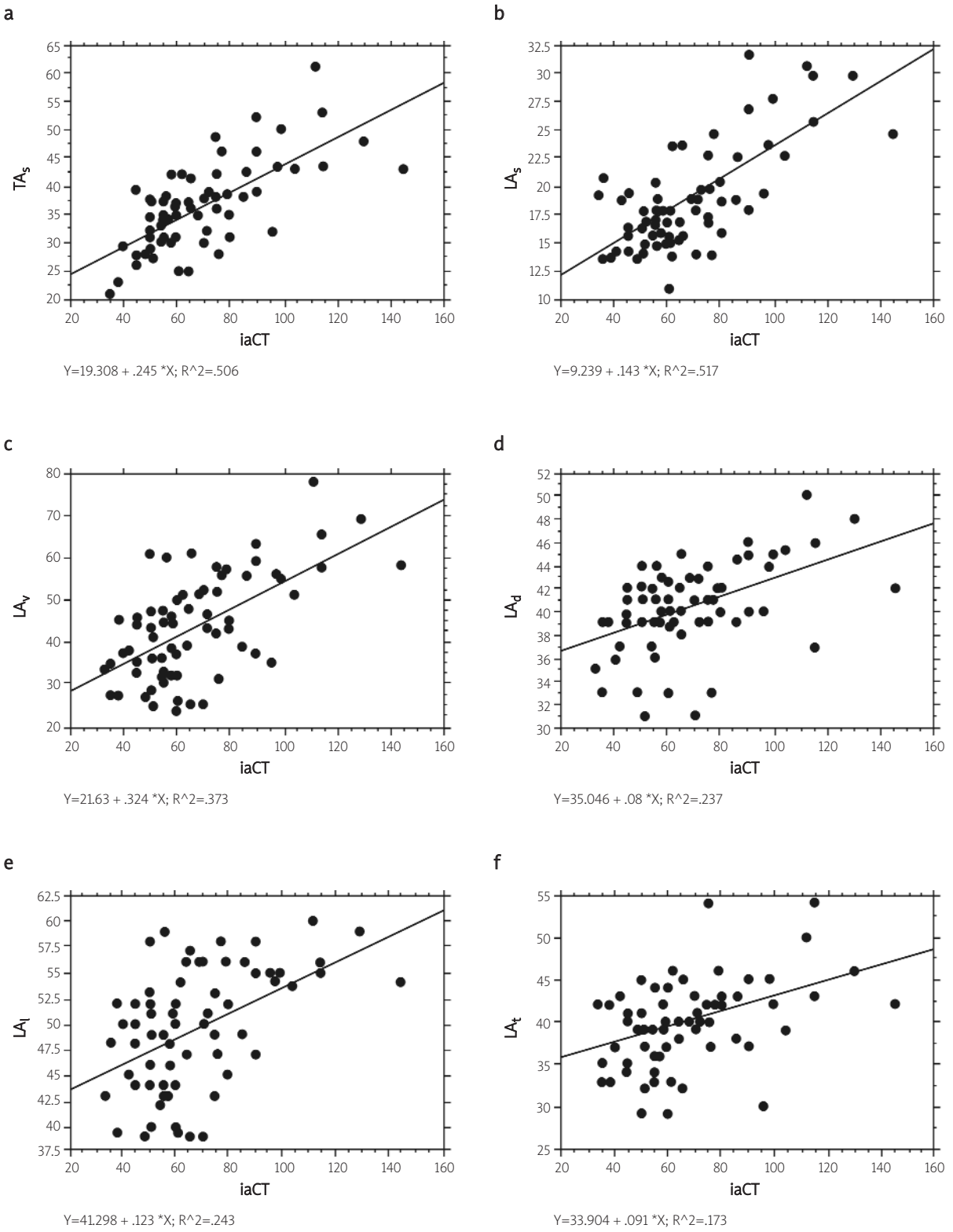

Figure 3. Significant correlation between iaCT and TAs (a)/LAs (b)/and LAv (c); no significant correlation with the rest of echocardiographic parameters (d-i)

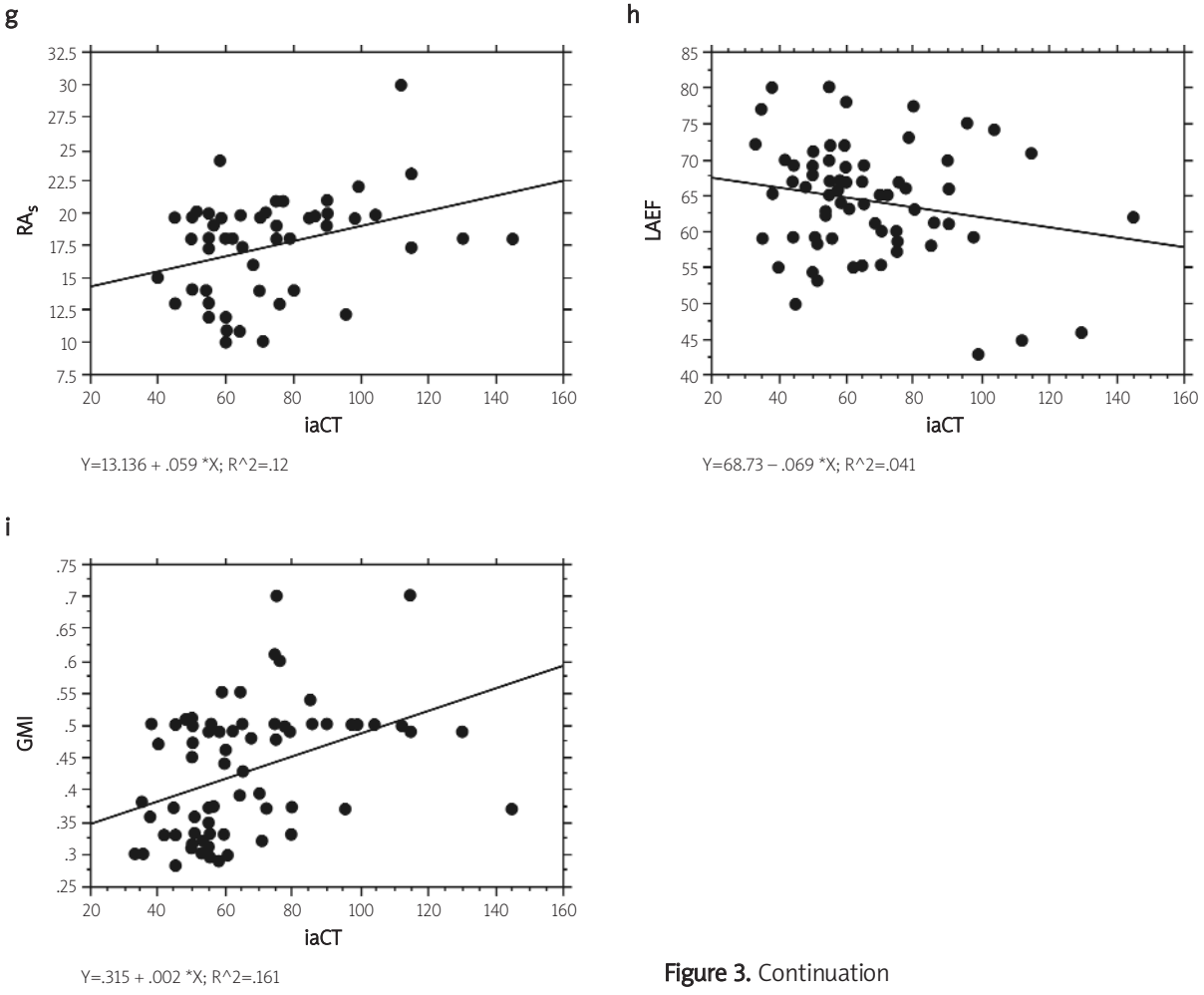

Figure 3. Continuation

The clinical and therapeutic implications of atrial stretch remain controversial. In a canine model of heart failure, angiotensin-converting enzyme inhibition has been shown to reduce the extent of atrial fibrosis, reduce conduction abnormalities, and reduce AF duration [15, 16]. There is indirect proof in the human model that improving filling conditions by earlier intervention can delay or abort the initiation of AF in patients with elevated LA pressure, acute atrial stretch and mitral stenosis [17]. Thus, we might speculate that earlier detection of subclinic atrial dilatation and stretch may play a role in the management of patients without obvious electrophysiological and arrhythmogenic atrial remodelling who are prone to AF.

Limitations of the study

We did not assess and compare separately intraatrial to interaatrial conduction or the relation with atria dilatation as the sample size population was small. This can be achieved in a study involving a larger number of patients and in a more homogeneous population. Our study included patients who were not healthy volunteers but had various types of arrhythmias, although without structural heart disease.

Conclusions

This study supports the role of stretch and dilated atria in electrophysiological changes which occur in structurally normal hearts; the severity of the atrial conduction abnormalities is closely related to stretch. Interatrial conduction time may be indirectly and noninvasively evaluated using echocardiograhic measurements.

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Związek pomiędzy elektrofizjologicznymi i echokardiograficznymi parametrami sprzyjającymi migotaniu przedsionków u chorych bez organicznej choroby serca

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Streszczenie

Wstęp: Elektroanatomiczne parametry sprzyjające występowaniu migotania przedsionków (AF) u chorych z powiększonym lewym przedsionkiem (LA) polegają na anizotropii i zwolnieniu przewodzenia, co stanowi podłoże nawrotnych arytmii.

Cel: Zbadanie związku pomiędzy elektrofizjologicznymi właściwościami przedsionków a powiększeniem przedsionka i zwiększonym ciśnieniem napełniania.

Metodyka: Grupę badaną stanowiło 79 chorych bez organicznej choroby serca w średnim wieku 53±22 lata, którzy zostali zakwalifikowani do wykonania inwazyjnego badania elektrofizjologicznego. Podczas stymulacji programowanej prawego przedsionka (HRA) oceniano takie parametry elektrofizjologiczne jak czas przewodzenia międzyprzedsionkowego (iaCT) i występowanie podwójnych potencjałów oraz fragmentację potencjałów przedsionkowych. W szczególności oceniano czas pobudzenia przedsionków, podstawowy iaCT (iaCTb) pomiędzy HRA a dystalnym odcinkiem zatoki wieńcowej (CS), iaCT podczas stymulacji HRA o długości cyklu S1-S1 600 ms (iaCTS1) i maksymalne wydłużenie iaCT po bodźcach przedwczesnych S2 i S3 (iaCTS2, iaCTS3). Obliczono także indeks zwolnienia przewodzenia (ang. *decremental index*) (DI)=iaCTS3-iaCTS1/iaCTS1%. Parametry hemodynamiczne, oceniane przy pomocy echokardiografii, obejmowały ocenę wielkości LA, powierzchni LA (LAs), objętości LA przy użyciu wzoru elipsowego (LAv), powierzchni RA (RAs), całkowitej powierzchni przedsionków (TAs=LAs+RAs) oraz globalnego indeksu sercowego (GMI).

Wyniki: Chorych podzielono na dwie grupy w zależności od zmierzonych parametrów elektrofizjologicznych. Grupę 1 stanowiło 37 chorych ze zwolnionym przewodzeniem (fragmentacja potencjałów przedsionkowych, iaCTb >80 ms, DI >50% lub obecność podwójnych potencjałów), podczas, gdy grupę 2 stanowiło 42 chorych bez zaburzeń przewodzenia w przedsionkach. Obie grupy nie różniły się istotnie pod względem wieku, indeksu masy ciała lub wymiarami LA. U 37 chorych (w tym 32 pacjentów z grupy 1) występowały w przeszłości udokumentowane napady AF. Wartości GMI, LAs, LAv i TAs były istotnie większe w grupie 1 niż w grupie 2. Wykazano istotną liniową korelację pomiędzy iaCTb i TAs ($r=0.52$, $p<0.0001$) oraz LAv ($r=0.38$, $p<0.0001$). Występował także trend w kierunku korelacji pomiędzy DI i TAs.

Wnioski: Wyniki badania potwierdzają wpływ rozciągnięcia i powiększenia mięśnia przedsionków w powstawaniu zmian na właściwości elektrofizjologiczne przedsionków u chorych bez istotnej organicznej choroby serca. Czas trwania przewodzenia międzyprzedsionkowego (iaCT) może być nieinwazyjnie oceniany przy pomocy wskaźników echokardiograficznych.

Słowa kluczowe: przewodzenie międzyprzedsionkowe, zwolnienie przewodzenia, powiększenie przedsionków

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