



Original Article

Atrial electromechanical delay in patients undergoing heart transplantation

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ABSTRACT

Background: We aimed to assess atrial electromechanical delay (AEMD) in patients who had undergone heart transplantation.

Methods: A total of 32 patients who underwent biatrial anastomosis heart transplantation (24 men, 8 women; mean age: 42 ± 11 years) and 30 healthy volunteers (20 men, 10 women; mean age: 36 ± 13 years) were included in the study. Atrial electromechanical coupling (PA), intra-AEMD, and inter-AEMD were measured.

Results: PA lateral (68 ± 7 vs. 51 ± 11 ms, $p < 0.01$), PA septal (50 ± 5 vs. 42 ± 8 ms, $p < 0.01$) and PA tricuspid (39 ± 6 vs. 36 ± 9 ms, $p < 0.01$), inter-AEMD (PA lateral–PA tricuspid) (27 ± 7 vs. 10 ± 4 ms, $p < 0.01$), left intra-AEMD (PA lateral–PA septal) (18 ± 7 vs. 10 ± 4 ms, $p < 0.01$), right intra-AEMD (PA septal–PA tricuspid) (13 ± 5 vs. 5 ± 3 ms, $p < 0.01$) values were higher in patients who underwent heart transplantation than in a control population.

Conclusion: Inter-AEMD and intra-AEMD were prolonged in patients who underwent heart transplantation as compared to a control population. This may explain the increased atrial fibrillation and other atrial arrhythmia incidences associated with the biatrial anastomosis heart transplantation technique and may contribute to the treatment of atrial fibrillation in this special patient group.

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1. Introduction

Owing to recent advances in transplant immunology and surgical improvements, heart transplantation appears to be a prevailing alternative for end-stage heart disorders. Early postoperative atrial rhythm disturbances occur in approximately 10–20% of heart transplant patients [1,2]. However, they become significantly less common during the late follow-up period after heart transplantation. While macro-reentrant atrial tachyarrhythmia arises from surgical anastomosis lines, focal atrial tachyarrhythmias can be seen in the late postoperative period [3].

The most common arrhythmias encountered after heart transplantation are ventricular or atrial premature complexes, sinus or junctional bradycardia, atrial fibrillation, and atrial flutter, which have varying clinical significance, depending on associated or causative conditions. Allograft rejection, transplant coronary

artery disease, altered anatomy, or autonomic nervous system changes have been suggested to be responsible for posttransplant arrhythmia [4]. Atrial electromechanical coupling (PA) and atrial electromechanical delay (AEMD) measured by Doppler tissue imaging (DTI) were found to be significantly longer in patients with paroxysmal atrial fibrillation (AF) [5–7]. AEMD has also been demonstrated to be longer in many diseases that affect heart tissue [8–14].

To date, DTI has not been used in patients undergoing heart transplantation for the detection of atrial conduction abnormalities and electromechanical coupling. The aim of our study was to investigate PA noninvasively in patients who underwent heart transplantation.

2. Materials and methods

2.1. Study population

A total of 32 patients who had undergone biatrial anastomosis heart transplantation and were operated between January 2005

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and December 2014 at Kartal Kosuyolu High Specialty Training and Research Hospital (24 men, 8 women; mean age: 42 ± 11 years) and 30 healthy volunteers (20 men, 10 women; mean age: 36 ± 13 years) were included in the study. Echocardiographic and biochemical data were collected at least six months after the surgery in the study group. Patients with moderate to severe left ventricular (LV) wall motion abnormality, moderate to severe vasculopathy and rejection, LV ejection fraction (LVEF) less than 50%, bundle branch block, atrioventricular conduction abnormalities on electrocardiogram (ECG), and patients with moderate to severe atrial conduction delay (first-degree AV block in ECG), pericarditis, thyroid dysfunction, anaemia, hypercholesterolaemia, electrolyte imbalance, renal failure, pulmonary disease, moderate to severe valvular dysfunction, or echocardiographic images that were technically insufficient were excluded from the study. The patients who had electrocardiographically documented AF episodes or who were cardioverted to sinus rhythm pharmacologically and/or electrically, and patients who were taking antihypertensive drugs causing prolongation in PR duration (such as beta blocking agents, verapamil, or diltiazem) were also excluded. All of the study patients were taking prescribed immunosuppressive medication. We did not perform a pharmacological denervation to avoid the influence of the autonomic nerve system. All of the patients were in sinus rhythm and none was taking medications such as antiarrhythmics, tricyclic antidepressants, antihistaminics, or antipsychotics. Written informed consent was obtained from each subject. The institutional ethics committee approved the study protocol. The demographic and baseline characteristics of patients in the study and control groups are provided in Table 1.

2.2. Echocardiography

In all subjects, two-dimensional, pulsed wave Doppler, colour flow Doppler, m-mode echocardiographic examinations (Vivid 7 pro, GE, Horten, Norway, 2–4 MHz phased array transducer) were performed by a cardiologist who was blinded to the clinical details and results of the study. During echocardiography, a one-lead surface ECG (D III) was recorded continuously. Echocardiographic measurements were obtained according to the criteria of the American Society of Echocardiography [15]. Four consecutive cycles were averaged for every parameter. Left atrial dimension LV end-systolic dimension, LV end-diastolic dimension, LVEF, interventricular septal thickness, and posterior wall thickness were measured.

Table 1
Demographic and clinical properties of patients with heart transplantation and controls.

	Transplant group (n=32)	Control group (n=30)	p Value
Age, years	41.6 ± 11	37.4 ± 14	0.21
Sex, n (%) male	24 (75%)	20 (33%)	0.48
Systolic blood pressure, mmHg	129.25 ± 9.46	126.15 ± 9.13	0.21
Diastolic blood pressure, mmHg	76.16 ± 8.69	74.85 ± 6.51	0.12
Heart rate, bpm	77.3 ± 13	72.6 ± 14	0.19
Underlying heart disease before heart transplantation			
✓Idiopathic dilated CMP, n (%)	20 (62.5%)	NA	–
✓Ischemic CMP, n (%)	4 (12.5%)		
✓Peripartum CMP, n (%)	3 (9.4%)		
✓Restrictive CMP, n (%)	2 (6.2%)		
✓Myocarditis, n (%)	3 (9.4%)		

Notes: bpm: beats per minute, CMP: cardiomyopathy, NA: not applicable.

2.3. Atrial electromechanical coupling

DTI was performed by transducer frequencies of 3.5–4.0 MHz, adjusting the spectral pulsed Doppler signal filters until a nyquist limit of 15–20 cm/s was reached while using the minimal optimal gain. The monitor sweep speed was set at 50–100 mm/s to optimise the spectral display of myocardial velocities. In apical four-chamber view, the pulsed Doppler sample volume was accordingly set at the level of LV lateral mitral annulus, septal mitral annulus, and right ventricular tricuspid annulus. The sampling window was positioned as parallel as possible to the myocardial segment of interest to provide the optimal angle of imaging. The time interval (in milliseconds) from the onset of the P wave on the surface electrocardiogram to the beginning of the late diastolic wave (Am wave), which is called atrial electromechanical coupling, was obtained from the lateral mitral annulus, septal mitral annulus, and right ventricular tricuspid annulus and named as PA lateral, PA septum, and PA tricuspid, respectively (Fig. 1). Values were averaged over four consecutive beats. These values were corrected for heart rate by dividing by the square root of the R–R interval [16]. The difference between PA lateral and PA tricuspid, i.e., PA lateral–PA tricuspid, was defined as the inter-AEMD. The difference between PA septum and PA tricuspid, i.e., PA septum–PA tricuspid, was defined as right intra-AEMD. The difference between PA lateral and PA septum, i.e., PA lateral–PA septum, was defined as left intra-AEMD [6]. In AEMD measurements, intraobserver variability was assessed in 10 subjects selected at random from the study group by repeating the measurements under the same conditions. Interobserver variability was tested by a second observer while the measurements were performed offline from video recordings. The intraobserver and interobserver variability for DTI calculated from 10 consecutive patients was 4.2% and 4.7% for PA lateral, 4.9% and 4.1% for PA septum, and 5.9% and 4.8% for PA tricuspid, respectively.

2.4. Statistical analysis

SPSS 15.0 statistical program (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. All data are presented as mean ± standard deviation. Values between different groups were compared using the independent-samples *t*-test. The chi-square test was used to assess differences between categorical variables. The relationship between parameters was determined using the Pearson coefficient of correlation. *P* values < 0.05 were considered significant.

3. Results

The two groups were similar regarding age, sex, systolic blood pressure, diastolic blood pressure, and heart rate (bpm) (Table 1). LV end-diastolic dimension, LV end-systolic dimension, posterior wall thickness, and LV ejection fraction (%) were not statistically different between the groups (Table 2). Left atrial dimension and interventricular septal thickness were higher and deceleration time was lower in patients who underwent heart transplantation than in the control population (Table 2). Biochemical and complete blood count parameters were not statistically different between the groups. Two-dimensional conventional Doppler and the PA parameters of different sites measured by DTI are shown in Table 2. PA lateral (68 ± 7 vs. 51 ± 11 ms, $p < 0.01$), PA septal (50 ± 5 vs. 42 ± 8 ms, $p < 0.01$) and PA tricuspid (39 ± 6 vs. 36 ± 9 ms, $p < 0.01$) values were higher in patients who underwent heart transplantation than in a control population (Table 2). Furthermore, inter-AEMD, right AEMD and left intra-AEMD were prolonged in patients who underwent heart transplantation as compared to the control population. Inter-AEMD (27 ± 7 vs.

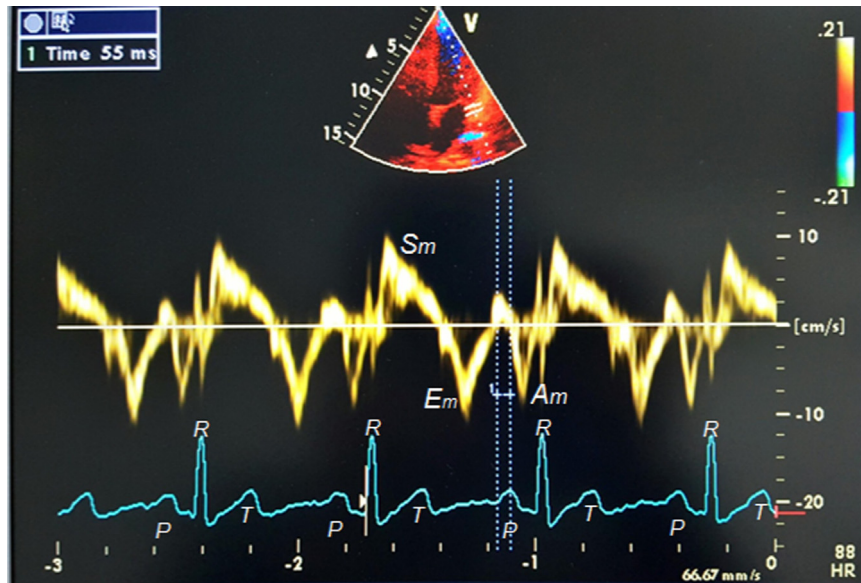


Fig. 1. Measurement of atrial electromechanical coupling (PA). The time interval (in milliseconds) from the onset of the P wave on surface electrocardiogram to the beginning of the late diastolic wave (Am wave), which is called atrial electromechanical coupling (PA), was obtained from the lateral mitral annulus, named as PA lateral. ms: millisecond.

Table 2
Atrial electromechanical coupling (PA) and echocardiographic parameters in patients with heart transplantation and controls.

	Transplant group (n=32)	Control group (n=30)	p Value
LV end diastolic diameter, mm	44.2 ± 5.2	46.4 ± 2.6	0.47
LV end systolic diameter, mm	27.7 ± 3.9	28.5 ± 2.4	0.34
Interventricular septum thickness, mm	11.1 ± 1.8	9.9 ± 1.4	< 0.01 ^a
Posterior wall thickness, mm	11.1 ± 1.8	10.1 ± 1.6	0.29
LV mass index, g/m ²	98 ± 27	79 ± 14	< 0.01 ^a
LV ejection fraction, (%)	63.1 ± 3.4	65.7 ± 8.8	0.11
Left atrial diameter, mm	40.8 ± 7.9	32.1 ± 2.1	< 0.01 ^a
Mitral E, cm/s	94 ± 17	89 ± 10	0.21
Mitral A, cm/s	148 ± 35	197 ± 27	< 0.01 ^a
Deceleration time, ms	148.78 ± 35.93	194.08 ± 27.39	< 0.001 ^a
Intraventricular relaxation time, ms	93.74 ± 17.15	89.13 ± 9.95	0.21
PA lateral, ms	68 ± 7	51 ± 11	< 0.01 ^a
PA septal, ms	50 ± 5	42 ± 8	< 0.01 ^a
PA tricuspid, ms	39 ± 6	36 ± 9	< 0.01 [*]

Notes: LV: left ventricle, PA: atrial electromechanical coupling.

* Difference is statistically significant.

^a Difference is statistically not significant.

10 ± 4 ms, $p < 0.01$), left intra-AEMD (18 ± 7 vs. 10 ± 4 ms, $p < 0.01$), right intra-AEMD (13 ± 5 vs. 5 ± 3 ms, $p < 0.01$) (Fig. 2).

4. Discussion

Prolongation of intra-AEMD and inter-AEMD and the inhomogeneous propagation of sinus impulses are well-known electrophysiologic characteristics of the atria prone to fibrillation [5–7,17–24]. Fibrosis in the left atrium and left ventricle accounts for the development of LV diastolic dysfunction and AF [24–37]. Increases in intra- and inter-AEMD have been identified in patients who are prone to develop AF, such as those with mitral stenosis, familial Mediterranean fever, type II diabetes, scleroderma, paroxysmal AF, and

essential hypertension [5–7,20,21]. The anisotropy and dispersion of refractory periods resulting from the decrease in electrical connections and deposition of connective tissue between the myocytes may lead to atrial conduction abnormalities, resulting in intra- and inter-AEMD that can prepare a convenient substrate for AF [38–40]. However, because the number of wavelets at any time depends on the refractory period, mass, and conduction velocity in different parts of the atria, the shortened refractory period and delayed conduction may increase the quantity of daughter wavelets according to the multiple wavelet hypothesis.

Deniz et al. determined the correlation of AEMD with the electrophysiologic (EPS) and DTI measurements, and evaluated the appropriateness of the usage of DTI in patients with clinical arrhythmias [41]. However, Erdem et al. validated the correlation of AEMD with TDI and EPS measurements in healthy subjects. They suggested that DTI measurements of AEMD may be used accurately and confidently instead of the EPS and were significantly advantageous because of their low cost and non-invasiveness [42].

To our knowledge, there is no prior study of AEMD in patients undergoing heart transplantation. In this study, we found that intra- and inter-AEMD were higher in patients who underwent heart transplantation than in a control population. All patients included our study were operated on by using the orthotopic biatrial technique. In this technique, the incision that originates from the inferior vena cava is extended to the right atrial appendix. Then, the incision is lengthened to the left atrial ceiling in the vicinity of the transverse sinus. The septal suture line is revealed by extending the right atrial incision line towards the septum and septal leaflet of the tricuspid valve, and is connected to the incision in the left atrial wall. In the bicaval technique, the heart is extracted relatively intact and much fewer incisions are applied to the atrial tissue. Extensive incision lines applied to atrial tissue may create electrophysiological instability by disturbing action potential propagation velocity and homogeneous distribution, thus creating a tendency to AF after using the biatrial technique. Owing to more extensive surgery lines, a temporary pacemaker requirement, left bundle branch block, and atrioventricular block were also observed statistically more significantly often compared to bicaval anastomosis [43–46]. In a study comparing the atrial arrhythmia incidence after both techniques, 31 bicaval and 35

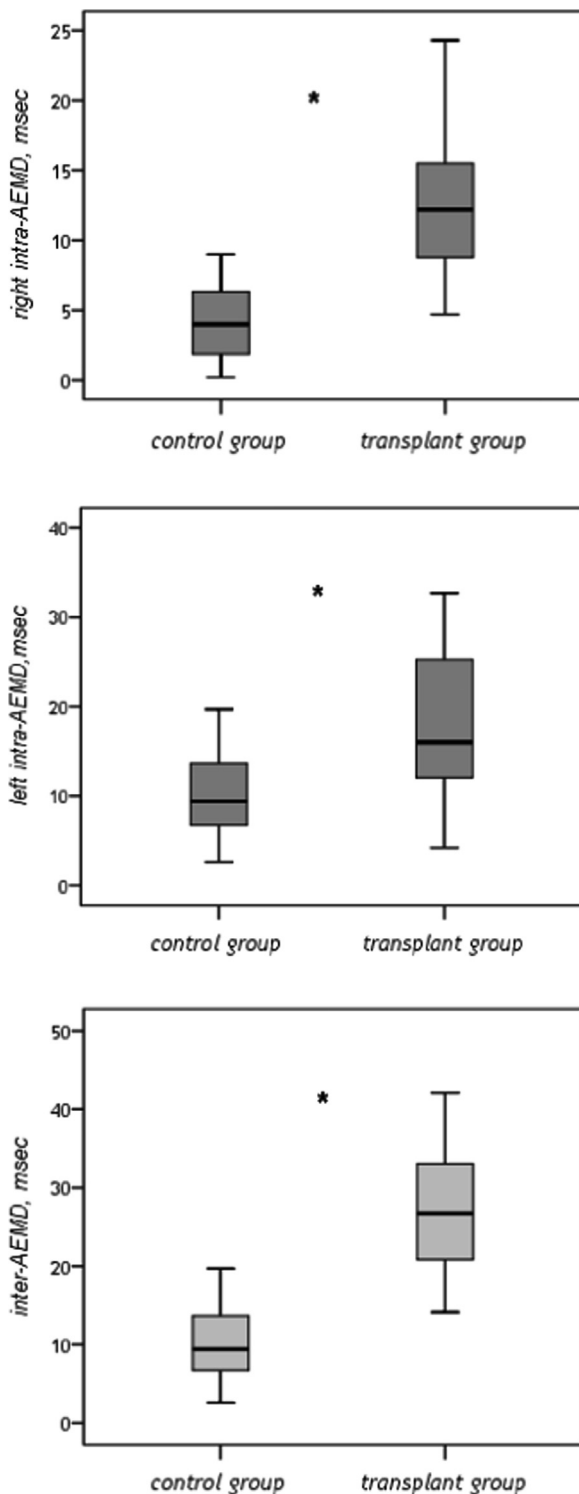


Fig. 2. Distribution plot of the atrial electromechanical delay (AEMD) between patients who underwent heart transplantation and controls. * Difference is statistically significant (* $p < 0.01$).

biatrial operated patients were examined and the AF incidence were found to be significantly higher in the biatrial group (21 vs. 3 patients, $p < 0.01$) [47]. Therefore, it can be suggested that bicaval anastomosis may be a better choice for avoiding future arrhythmias in patients undergoing heart transplantation.

In our study, inter-AEMD, right intra-AEMD, and left intra-AEMD durations were found to be significantly prolonged in

patients who underwent heart transplantation as compared to a control population.

It is thought that extensive surgery lines applied to the atrial tissue might create electrophysiologically insulated areas and inhomogeneously delayed conduction of action potential throughout the atrial tissue and might explain the higher incidence of AF observed in patients who underwent heart transplantation.

5. Conclusion

Inter-AEMD and intra-AEMD were prolonged in patients who underwent heart transplantation as compared to a control population. This may explain increased atrial fibrillation and other atrial arrhythmia incidences associated with the biatrial anastomosis heart transplantation technique and may contribute to the treatment of AF in this special patient group.

Limitations

Only patients who had undergone biatrial anastomosis heart transplantation were included in the study, so the results cannot be extrapolated to patients who had undergone bicaval surgery. Studies comparing these two techniques head to head might be useful to address this limitation. Effects of post-transplantation medications on the results cannot be fully negated because of the inconvenience of discontinuing immunosuppressive agents.

Conflict of interest

All authors declare no conflict of interest related to this study. They certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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