

Comparison of Prolonged Atrial Electromechanical Delays with Different Definitions in the Discrimination of Patients with Non-Valvular Paroxysmal Atrial Fibrillation

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Background and Objectives: Previous studies have evaluated atrial electromechanical delays (AEMDs) with a number of different definitions to discriminate patients with paroxysmal atrial fibrillation (PAF) from controls without PAF. However, their discriminative values for PAF have not previously been directly compared.

Subjects and Methods: A total of 65 PAF patients and 130 control subjects matched for age, sex, history of hypertension, and diabetes mellitus were selected. The AEMDi and AEMDp were defined as the time intervals from the initiation of the P wave on the surface electrocardiogram to the initiation and peak of the late diastolic transmitral inflow on pulsed wave Doppler images, respectively. The AEMDim and AEMDpm were defined as the time intervals from the initiation of the P wave on the surface electrocardiogram to the initiation and peak of the late diastolic lateral mitral annular motion on tissue Doppler images, respectively.

Results: There were no significant differences in the clinical characteristics between the two groups. All 4 AEMDs were consistently longer in the PAF group, and proven effective to differentiate the PAF patients from the controls. The AEMDi measurement had a larger area under the curve (AUC) than the other AEMDs, left atrial volume index, and P wave amplitude. However, the AEMDp, AEMDim, and AEMDpm measurements had AUCs similar to those of the left atrial volume index and P wave amplitude.

Conclusion: The findings suggest that the AEMDi is better than the other AEMDs for the discrimination of PAF patients from the controls. (*Korean Circ J* 2015;45(6):479-485)

KEY WORDS: Atrial fibrillation; Electrocardiography; Echocardiography.

Introduction

Atrial electromechanical delays (AEMDs) are defined as the time intervals between the atrial electrical depolarization and the

initiation or peak of atrial mechanical contraction. It has been shown that prolonged AEMDs can be used as markers to discriminate patients with paroxysmal atrial fibrillation (PAF) from controls without PAF or to predict the occurrence of PAF in case-control or observational studies.¹⁻¹⁰⁾ The clinical evidence supports the notion that prolonged AEMDs reflect left atrial electrical remodeling, which is essential for the maintenance of atrial fibrillation (AF).⁷⁾ However, studies on this aspect have evaluated the single AEMD using specific, yet independent definitions. The discriminative and predictive values of the AEMDs with such different definitions have not previously been compared with each other, and the potential influences of major clinical variables on AEMDs have not been sufficiently excluded in previous studies. In this study, we conducted a retrospective analysis to more accurately evaluate the discriminative values of AEMDs while excluding the influences of major clinical variables, and compared the discriminative

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values of predefined AEMDs when differentiating between the PAF patients and the controls.

Subjects and Methods

Study population

Patients were screened who were first diagnosed with PAF between 2010 and 2013 with available electrocardiographic and echocardiographic records; furthermore, those patients selected had clear P waves on surface electrocardiogram (ECG) channel, pulsed wave Doppler images (PWDI) of trans-mitral inflow, and tissue Doppler images (TDI) of mitral annular motion. Those patients excluded from this study had ambiguous ECG or Doppler study images, or abnormal rhythms other than normal sinus rhythm at the time of echocardiographic measurements. In addition, those patients were also excluded who reported current medication with drugs influencing intracardiac conduction (beta-blocker, non-dihydropyridine calcium channel blocker, class Ic or III antiarrhythmic drugs) in the prior week (3 months for amiodarone) before echocardiographic measurements. However, the patients with the following were permitted to participate in the study: use of dihydropyridine calcium channel blockers, alpha-blockers, or diuretics. Other exclusion criteria were: a history of previous cardiac surgery, reduced ejection fraction (<50%), enlarged left ventricle size (end diastolic dimension >55 mm), valvular heart disease (\geq American College of Cardiology/American Heart Association grade 2), any cardiomyopathy, coronary artery disease requiring interventional treatment, uncontrolled thyroid disease, advanced chronic kidney disease (estimated glomerular filtration rate <30 mL/min/1.73 m²) or liver disease (bilirubin >2.0 mg/dL), malignancy, chronic inflammatory or systemic connective tissue diseases, and the presence of moderate electrolyte imbalances.

Data for the healthy control group was extracted from the echocardiography registry of Dong-A University Medical Center, Busan, Korea, and there was a screening of subjects who underwent echocardiography during health care examinations from 2010 to 2013. The excluded subjects from this study had documented atrial tachycardia, flutter, or fibrillation. The matched healthy controls were selected in a 1:2 ratio for those patients with available medical records, age, sex, a history of hypertension, and diabetes mellitus. Age discrepancies of less than 5 years were allowed for patient-control age matching. The identical inclusion and exclusion criteria for the PAF patient selection were used for the selection of the control subjects. The present study protocol was reviewed and approved by the internal review board of Dong-A University Hospital, Busan, Korea.

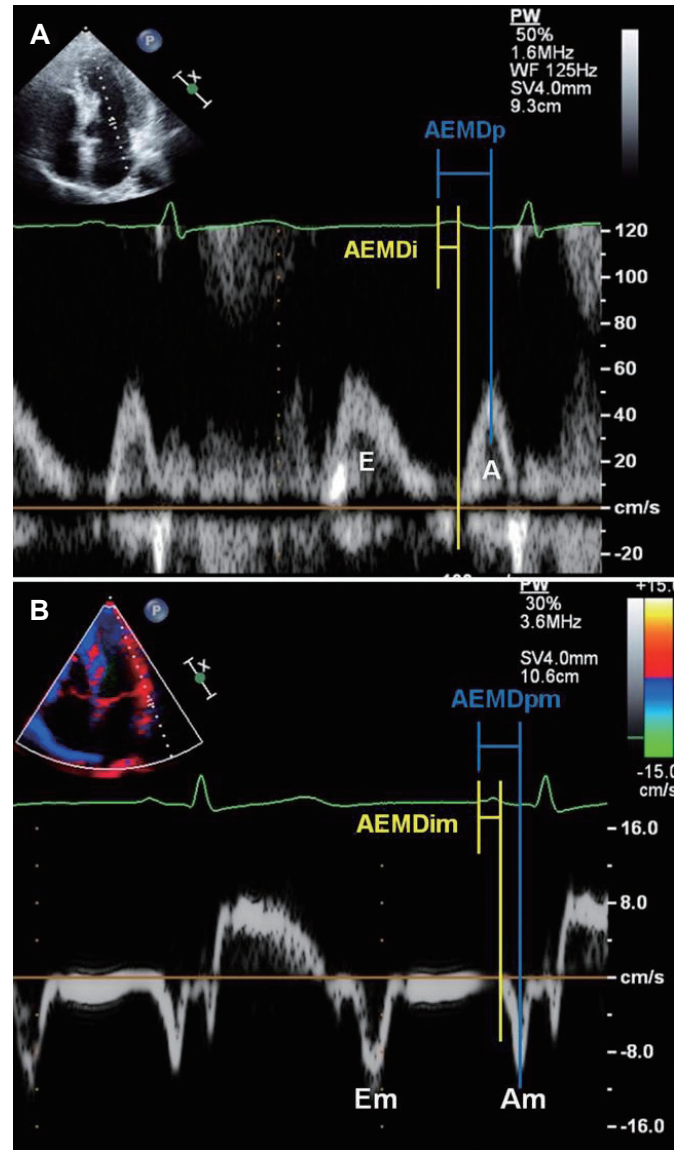


Fig. 1. Echocardiographic measurements of AEMDs. (A) The time intervals, from the P wave initiation on the surface electrocardiogram channel to the initiation and peak of the late diastolic transmitral inflow on pulse wave Doppler images, were defined as the AEMDi and AEMDp. (B) The time intervals, from the P wave initiation on the surface electrocardiogram channel to the initiation and peak of the late diastolic lateral mitral annular motion on tissue Doppler images, were defined as the AEMDim and AEMDpm. AEMD: atrial electromechanical delay.

Measurements of echocardiographic parameters

Echocardiography was performed using an iE33 ultrasound system and 2.5 MHz transducers (Philips Ultrasound, Andover, MA, USA). The standard M-mode, 2D, and Doppler echocardiography were routinely performed, in accordance with the recommendations of the American Society of Echocardiography.¹¹⁾¹²⁾ The ECG was recorded continuously during echocardiographic studies at a sweep speed of 100 mm/sec and the amplitude gain was set to 70%. The

PWDI sample volume for late diastolic trans-mitral inflow velocity measurement was placed on the center of the mitral valve at the level of the mitral annulus, in the apical 4-chamber view. The sampling window was positioned as parallel as possible to the longitudinal axis of the left ventricle. The TDI echocardiography was performed using a transducer frequency of 3.5 to 4.0 MHz, adjusting the spectral pulsed Doppler signal filters to obtain the Nyquist limit of 15 cm/s to 20 cm/s with the optimal gain settings. The TDI sample volume for late diastolic mitral annular motion was placed at the lateral mitral annulus. All measurements were repeated 3 times and their average values were used for the analysis.

The AEMDs were defined as the time interval (milliseconds, ms) from the atrial electrical depolarization to the initiation or peak of atrial mechanical contraction seen in the echocardiographic studies. The time intervals, from the initiation of P wave on surface ECG to the initiation and peak of late diastolic transmitral inflow on PWDI, were defined as AEMDi and AEMDp, respectively (Fig. 1A). The time intervals, from the initiation of P wave on surface ECG to the initiation and peak of late diastolic lateral mitral annular motion on TDI, were defined as AEMDim and AEMDpm, respectively (Fig. 1B). There was also a measurement of other conventional echocardiographic parameters: left ventricular ejection fraction, left ventricular end diastolic dimension, left ventricular mass index, left atrial volume index (LAVI), peak trans-mitral inflow (mitral E and A) velocities on PWDI during diastole, as well as early diastolic lateral mitral annular motion velocity (mitral e') on TDI. All echocardiographic measurements were performed by a well-trained and experienced sonographer who was blinded to each patient's clinical information, furthermore, the data acquired were further confirmed by an echocardiologist.

Measurements of electrocardiographic parameters

Electrocardiographic parameters, including P wave duration, P wave amplitude, QRS duration, PR interval, and RR interval, were calculated in limb lead II using a digital caliper of TraceMaster Viewer (Philips Electronics, Andover, MA, USA). The presence of bundle branch block, pathologic q waves, abnormal ST-segment elevation or depression, and T-wave inversion suggesting structural heart disease were evaluated using a standard 12-lead ECG acquired before the echocardiographic measurements. All electrocardiographic measurements were performed by a general cardiologist who was blinded to each patient's clinical information, and the data acquired were further confirmed by an electrophysiologist.

Statistical analysis

The data are presented as the mean values±standard deviation for continuous variables and as numbers with percentages for categorical variables. The differences between normally distributed

continuous values were assessed by independent sample t-tests, whereas the proportional differences between categorical values were assessed by a chi-square test. The relationships between AEMD values and electrocardiographic or echocardiographic parameters were assessed by Pearson's correlation and linear regression analysis. The discriminative values of the AEMDs for PAF were identified using their receiver operating characteristic (ROC) curves. All statistical comparisons were two-sided and p-values <0.05 were regarded as statistically significant. Case-control matching and all statistical analyses were conducted using Statistical Package for the Social Sciences version 20.0 (SPSS Inc., Chicago, IL, USA). A comparison between ROC curves was performed using MedCalc (MedCalc Software Company, Brunswick, ME, USA).

Results

Baseline characteristics

Among the 304 documented PAF patients screened for the study, the following categories were excluded: 73 for underlying structural heart diseases or other significant medical conditions, 51 for E/A summation or ambiguous initiation of A wave, and 11 for ambiguous initiation of P waves; and 42 patients had AF, and 62 were taking drugs that could potentially influence intracardiac conduction at the time of echocardiographic measurements. Thus, in total, 65 patients were selected for the analysis. Furthermore, 130 matched healthy controls were then chosen, matched for age, sex, history of hypertension, and diabetes mellitus. The mean age of the study population was 57±16 years and 117 subjects (60%) were male. There was no significant difference in the baseline clinical characteristics between the PAF and control groups (Table 1).

Comparison of differently defined atrial electromechanical delays

The AEMDi, AEMDp, AEMDim, and AEMDpm measurements were consistently longer in the PAF group (Table 2), and the LAVI and P wave amplitude values were higher. However, there were no significant differences in the other electrocardiographic and echocardiographic parameters. All 4 AEMDs were proven to be effective to discriminate the PAF patients from controls (Table 3). Among the AEMDs, in discriminating the PAF patients from the controls, a prolonged AEMDi had a larger AUC than the other AEMDs, LAVI, and P wave amplitude. However, the AEMDp, AEMDim, and AEMDpm measurements had AUCs similar to those of LAVI and P wave amplitude. The AEMDi value of 64 ms had a sensitivity of 75% and specificity of 86% for the discrimination of patients with PAF from the controls. There were weak correlations between the AEMDi and LAVI ($r=0.311$, $p<0.001$), and the P wave amplitude

Table 1. Clinical characteristics of the study population

	PAF (n=65)	Control (n=130)	p
Age (years)	57±16	57±16	0.941
Male sex	39 (61)	78 (61)	1.000
Body mass index (kg/m ²)	25±3	24±3	0.073
Hypertension	27 (42)	54 (42)	1.000
Antihypertensive agent			
Dihydropyridine CCB	12 (19)	17 (13)	0.318
Other agents	18 (28)	34 (27)	0.818
Diabetes mellitus	7 (11)	14 (11)	1.000
HbA1c (%)	6.0±1.0	5.6±0.7	0.107
CHADS ₂ score	0.7±0.8	0.6±0.8	0.510
Systolic BP (mmHg)	123±13	124±15	0.778
Diastolic BP (mmHg)	73±8	77±18	0.089
Total cholesterol (mg/dL)	184±37	188±44	0.481
Estimated GFR (mL/min/1.73 m ²)	89±22	89±21	0.815

Data are presented as mean±standard deviation and n (%). PAF: paroxysmal atrial fibrillation, CCB: calcium channel blocker, HbA1c: hemoglobin A1c, BP: blood pressure, GFR: glomerular filtration rate

($r=0.088$, $p=0.227$). The prolonged AEMDi was not explained by LAVI ($r^2=0.011$, $p=0.140$) or P wave amplitude ($r^2=0.08$, $p=0.227$) in linear regression analyses.

Discussion

Previous studies have attempted to predict the occurrence of PAF using various electrocardiographic or echocardiographic parameters, including P wave morphology on surface ECG, P wave-triggered signal-averaged ECG, and left atrial size and function.^{5,13-16} Several AEMDs using a number of different definitions have also been tested to discriminate PAF patients from healthy controls, or predict the occurrence of PAF using M-mode TDI,¹ AEMDp,^{5,7} AEMDim^{2,4,8}, and AEMDpm.^{3,6,9,10} The AEMDp has been shown to be effective for discriminating patients with PAF from controls with sensitivity of 78%–81% and specificity of 71%–78%.^{5,7} The AEMDim and AEMDpm have also been shown to be effective in predicting the occurrence of new onset AF or the recurrence of AF after coronary artery bypass surgery, radiofrequency catheter ablation, and electrical cardioversion.⁶⁻¹⁰ In this study, we measured the 4 AEMDs, each of which has been tested in other studies, except for AEMDi, with different definitions to determine which AEMD is the best discriminator for PAF. For measurements of the AEMDs using TDI, the TDI sample volume was placed at the lateral mitral annulus, because previous studies have shown good discriminative or predictive values for PAF when late diastolic atrial motion velocity is measured at this location.^{2-4,6,8-10} The AEMDs are known to be

influenced by cardiac and non-cardiac factors. Previous studies have revealed a significant prolongation of AEMDs in various cardiac and non-cardiac conditions including hypertension,¹⁷ valvular heart disease,¹⁷ cardiomyopathy,¹⁸ atrial septal defect,¹⁹ type I diabetes mellitus,²⁰ obstructive sleep apnea,²¹ connective tissue diseases affecting the atrial myocardium,^{22,23} acute alcohol consumption,²⁴ hypothyroidism,²⁵ and other conditions. In this study, we attempted to evaluate the true discriminative value of prolonged AEMD for PAF by excluding patients and controls with potential confounding factors, including structural heart disease, cardioactive drugs, electrolyte imbalances, and other significant medical conditions. Strict patient-control matching, for age, sex, history of hypertension and diabetes mellitus, was also incorporated to minimize potential influences.

Similar to previous study results, all the 4 AEMDs of different definitions were proven to be effective to discriminate the PAF patients from the controls (Table 3). Among the 4 AEMDs, the AEMDi was superior to other AEMDs with the highest AUC value. The AEMDi value of 64 ms had a sensitivity of 75% and a specificity of 86%, which were comparable to previous study results. It is not certain why the AEMDi is superior to the other AEMDs. The AEMDi was not evaluated in previous studies, possibly because of technical issues. In clinical practice, it is often impossible to measure the AEMDi because of technical issues. However, if the AEMDi is technically measurable, the prolonged AEMDi may be a better discriminator than the other AEMDs for PAF.

Although AEMDp, AEMDim, and AEMDpm have been shown to be

Table 2. Electrocardiographic and echocardiographic parameters of the study population

	PAF (n=65)	Control (n=130)	p
PR interval (ms)	172±25	167±22	0.172
RR interval (ms)	984±177	961±124	0.364
AEMDs			
AEMDi (ms)	73±16	53±10	<0.001
AEMDp (ms)	146±22	134±18	0.001
AEMDim (ms)	80±22	63±17	<0.001
AEMDpm (ms)	141±23	125±19	<0.001
P wave duration (ms)	62±22	69±20	0.403
P wave amplitude (µV)	96±41	68±35	<0.001
Width of QRS complex (ms)	94±13	95±15	0.604
Bundle branch block	6 (9)	12 (9)	1.000
Ejection fraction (%)	63±4	64±3	0.610
LA volume index (mL/m ²)	35±11	29±10	<0.001
LV end diastolic dimension (mm)	49±4	48±4	0.156
LV mass index (g/m ²)	88±17	85±19	0.339
LV hypertrophy*	3 (5)	8 (6)	0.661
Mitral E velocity (cm/sec)	72±20	67±14	0.131
Mitral A velocity (cm/sec)	69±20	71±18	0.485
Mitral E/A ratio	1.1±0.5	1.0±0.4	0.106
Mitral e' velocity (cm/sec)	10±7	9±3	0.106
E/e' ratio >15	4 (6)	8 (6)	0.989

Data are presented as mean±standard deviation and n (%). PAF: paroxysmal atrial fibrillation, AEMD: atrial electromechanical delay, LA: left atrium, LV: left ventricle. *Left ventricular hypertrophy was defined as the echocardiographically measured left ventricular mass index greater than 115 g/m² for males and 95 g/m² for females

Table 3. The values of area under the curve for electrocardiographic and echocardiographic parameters

	AUC values	95% CI	p	p*
AEMDi (ms)	0.851±0.033	0.787–0.916	<0.001	-
AEMDp (ms)	0.678±0.042	0.595–0.762	<0.001	0.0012
AEMDim (ms)	0.743±0.039	0.666–0.819	<0.001	0.0345
AEMDpm (ms)	0.718±0.040	0.369–0.796	<0.001	0.0103
LAVI (mL/m ²)	0.703±0.039	0.627–0.779	<0.001	0.0038
P-amplitude (µV)	0.703±0.038	0.628–0.778	<0.001	0.0033

Data are presented as mean±standard deviation. AUC: area under the curve, CI: confidence interval, AEMD: atrial electromechanical delay, LAVI: left atrial volume index, P-amplitude: P wave amplitude. *p for AEMDi vs. other parameters. There were no significant differences between AEMDp, AEMDim, AEMDpm, LAVI, and P wave amplitude

discriminators or predictors for PAF in previous studies, most of the studies did not postulate whether AEMDs were superior to conventional risk factors for PAF, such as left atrial chamber size. The results, of this study, show that the AEMDp, AEMDim, and AEMDpm measurements were no better than the LAVI and P wave amplitude approaches. Only the AEMDi was a better discriminator. It is not certain why the AEMDi is superior to the LAVI and P wave

amplitude. The prolonged AEMDi may actually reflect left atrial remodeling, which is a complex process consisting of anatomic and electrophysiologic changes. Previous electrophysiologic studies already reported that prolonged AEMDs can reflect mechanical and electrophysiologic remodeling of the left atrium.⁷⁾¹⁰⁾ Intra-atrial conduction delay, resulting from left atrial remodeling, may prolong the coupling interval between atrial electrical depolarization and

mechanical contraction. The difference in AUCs between AEMDi and LAVI or P wave amplitude may reflect, at least in part, the proportion of left atrial anatomic and electrophysiologic remodeling that cannot be measured by left atrial chamber size or P wave morphology alone. That hypothesis may be supported by results of this study, which showed a weak relationship between the AEMDi and LAVI or P wave amplitude.

We note several limitations in the present study. First, this is a relatively small case-controlled study involving a limited number of PAF patients. Because subjects with unsuitable echocardiographic images or potential confounding factors were excluded with strict patient-control matching performed for major clinical variables, the study results should be interpreted cautiously, bearing in mind the risk of patient selection bias. Second, the burden of PAF itself was not considered. The frequency and duration of PAF episodes could not be quantified using a predefined electrocardiographic evaluation schedule and patients with at least a single episode of documented PAF were included for analysis according to the initial study plan. The probable burden of PAF could vary among the patients, and hence the degree of left atrial remodeling could be heterogeneous. The cut-off values for AEMDi should be adjusted accordingly in further studies. Third, the recovery time from atrial stunning after spontaneous cardioversion was not taken into consideration. The echocardiographic measurements were performed during normal sinus rhythm after spontaneous cardioversion, however, the time interval could not be evaluated from the electrocardiographic diagnosis to the echocardiographic measurement. Thus, this study cannot exclude the possibility of incorrect measurements of AEMDs because of early echocardiographic measurements before complete recovery from atrial stunning. Fourth, although medical records were meticulously reviewed, this study cannot exclude the possibility that subjects in the healthy control group could have had asymptomatic atrial arrhythmias or other medical confounders. Fifth, although the AEMDi was better discriminator, it is not always possible to measure the AEMDi in clinical practice, possibly because of technical issues. In addition, many patients with suspected PAF will already be receiving cardioactive drugs or have coexistent medical conditions, which potentially influence the AEMDi at the time of echocardiographic measurements. Therefore, considering those problems, the AEMDi values should be interpreted carefully,

Although modern diagnostic technology is developing rapidly, PAF diagnosis still relies on electrocardiographic studies. However, electrocardiographic diagnosis can be challenging. Hence, the measurements of AEMDs during normal sinus rhythm may give more exact information for the presence of left atrial remodeling, in addition to conventional electrocardiographic and echocardiographic parameters such as the LAVI and P wave amplitude. Prolonged AEMD

analysis, in combination with typical history and suspicious electrocardiographic abnormalities, may help clinicians in making presumptive diagnoses and give guidance to perform regular electrocardiographic follow-up in order to confirm the diagnosis.

Conclusion

In conclusion, all the 4 AEMDs were proven to be effective to discriminate PAF patients from controls who were matched for age, sex, history of hypertension, and diabetes mellitus. Among the 4 AEMDs, the prolonged AEMDi was better discriminator than the other AEMDs, LAVI, and P wave amplitude. However, the AEMDp, AEMDim, and AEMDpm measurements were no better than the LAVI and P wave amplitude in discrimination of the PAF patients from the controls.

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