Improving risk stratification after acute myocardial infarction : focus on emerging applications of echocardiography

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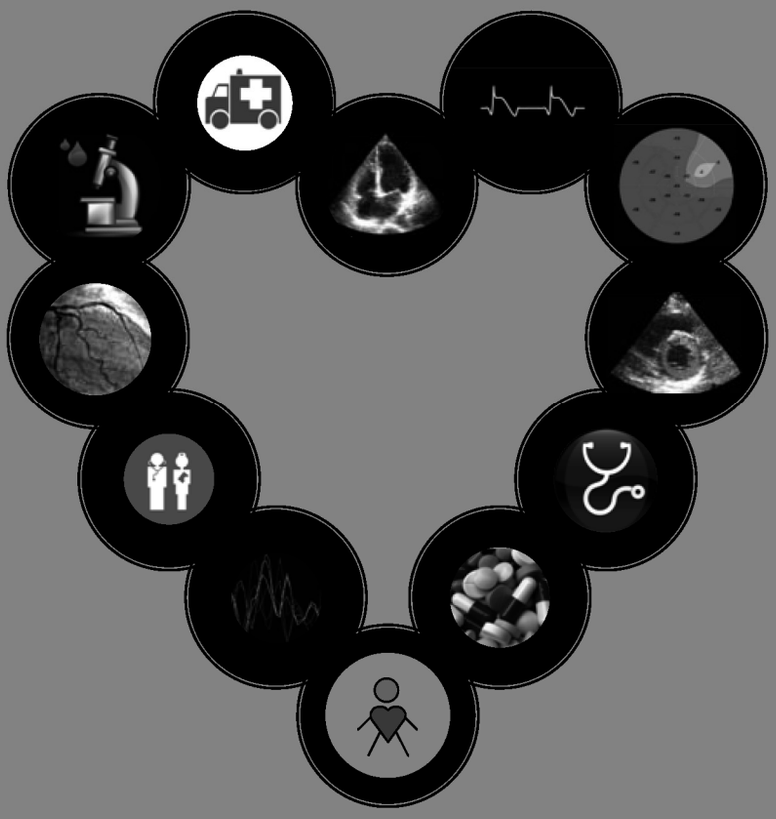

Chapter 12

Predictive Value of Total Atrial Conduction Time Estimated with Tissue Doppler Imaging for the Development of New-Onset Atrial Fibrillation after Acute Myocardial Infarction

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Abstract

Objectives

Patients who develop new-onset atrial fibrillation (AF) after acute myocardial infarction (AMI) show an increased risk of adverse events and mortality during follow-up. Recently, a novel non-invasive echocardiographic method has been validated for the estimation of the total atrial activation time using tissue Doppler imaging of the atria (PA-TDI duration). PA-TDI duration has shown to be independently predictive of new-onset AF. However, whether PA-TDI duration provides predictive value for new-onset AF in patients after AMI has not been evaluated.

Methods and results

Consecutive patients admitted with an AMI and treated with primary percutaneous coronary intervention underwent echocardiography within 48 hours of admission. All patients were followed at the outpatient clinic for at least 1 year. During follow-up, 12-lead electrocardiograms and Holter recordings were performed regularly and the development of new-onset AF was noted. Baseline echocardiography was performed to assess left ventricular and left atrial function. Left atrial performance was quantified with left atrial volumes, function and PA-TDI duration. A total of 613 patients were evaluated. Left atrial maximal volume (HR 1.07, 95%CI 1.04 – 1.11), total left atrial ejection fraction (HR 0.96, 95%CI 0.93 – 0.99) and PA-TDI duration (HR 1.05, 95%CI 1.04 – 1.06) were univariate predictors of new-onset AF. After multivariate analysis, left atrial maximal volume and PA-TDI duration independently predicted new-onset AF. Furthermore, PA-TDI duration provided incremental prognostic value to traditional clinical and echocardiographic parameters for the prediction of new-onset AF.

Conclusions

PA-TDI duration is a simple measurement which provides important value for the prediction of new-onset AF in patients after AMI.

Introduction

Atrial fibrillation (AF) is a common arrhythmia after acute myocardial infarction (AMI) and a major predictor of outcome.[1 2] Patients who develop AF after AMI show an increased risk of in-hospital adverse events and mortality during follow-up.[1-7] Therefore, risk stratification based on clinical and echocardiographic parameters to define patients who are at risk of AF following AMI has been studied extensively.[8-10] Recently, a novel non-invasive echocardiographic method has been developed which predicts new-onset AF. This novel technique measures the total atrial conduction time using transthoracic tissue Doppler imaging of the atria (PA-TDI duration) and has been validated against P-wave duration on signal-averaged electrocardiogram, which is the gold standard for non-invasive determination of total atrial conduction time.[11 12] Importantly, PA-TDI duration has been demonstrated to be a simple, fast and reliable method to obtain total atrial conduction time.[13] An increased PA-TDI duration reflects both conduction slowing and atrial dilatation and may therefore reflect an increased vulnerability for the development of AF. Previously, De Vos et al. have demonstrated that PA-TDI duration was independently predictive of new-onset AF in a general population of 249 patients from a cardiology outpatient clinic.[14] However, whether PA-TDI duration provides predictive and incremental value in addition to known risk factors for new-onset AF in patients after AMI has not been evaluated. Accordingly, the aim of the current study was to evaluate the predictive value of PA-TDI duration for new-onset AF in patients after AMI, together with other established clinical and echocardiographic predictors of new-onset AF after AMI.

Methods

Since February 2004 consecutive patients admitted with an AMI treated with primary percutaneous coronary intervention were included in an ongoing registry. All patients were treated according to the institutional AMI protocol. This protocol, designed to improve care around AMI, includes structurized medical therapy and standardized follow-up at the outpatient clinic, as described previously.[15] In addition, 2-dimensional echocardiography was performed within 48 hours of admission. All patients visited the outpatient clinic at 1, 3, 6 and 12 months after the index infarction and 12-lead electrocardiograms were performed during these visits. In addition, Holter recordings were performed at 3 and 6

months follow-up and the development of new-onset AF was noted. Patients with a history of AF were excluded from the present analysis because the aim was to identify predictors of new-onset AF after AMI. AF was determined based on electrocardiographic findings consistent with the diagnosis of AF on 12-lead electrocardiograms and Holter recordings during hospitalization and follow-up at the outpatient clinic. All patients were followed prospectively for at least 1 year.

Patients were imaged in the left lateral decubitus position using a commercially available system (Vivid 7, General Electric - Vingmed, Horton, Norway). Data acquisition was performed using a 3.5-MHz transducer, at a depth of 16 cm in the parasternal and apical views. Standard M-mode and 2-dimensional images were obtained during breath hold and saved in cine-loop format from 3 consecutive beats. Analysis was performed offline (EchoPac version 108.1.5, General Electric - Vingmed) by 2 experienced observers. The LV end-systolic volume and end-diastolic volume were traced and the LV ejection fraction was calculated using the biplane Simpson's method.[16] The LV was divided into 16 segments and each segment was analyzed individually and scored based on its motion and systolic thickening (1 = normokinesis, 2 = hypokinesis, 3 = akinesis, 4 = dyskinesis). Subsequently, the wall motion score index (WMSI) was calculated as the sum of the segment scores divided by the number of segments scored.[16] Severity of mitral regurgitation was graded semiquantitatively from the jet area of color-flow Doppler data and by measuring the width of the vena contracta. Mitral regurgitation was characterized as: mild = jet area/left atrial (LA) area <20% and vena contracta width <0.3 cm, moderate = jet area/LA area 20% to 40% and vena contracta width 0.3 to 0.69 cm, and severe = jet area/LA area >40% and vena contracta width ≥0.7 cm.[17] Pulsed-wave Doppler of the mitral valve inflow was obtained by positioning the Doppler sample volume between the tips of the mitral leaflets. Peak early (E) and late (A) diastolic velocities and E-wave deceleration time were measured. The E/E' ratio was obtained by dividing E by E', which was measured using color-coded tissue Doppler imaging at the septal side of the mitral annulus in the apical 4-chamber view.[18]

LA volumes were calculated according to the biplane Simpson's method. LA volumes were measured at 3 time points during the cardiac cycle: (1) maximal volume (LA max) at end-systole, just before mitral valve opening; (2) minimal volume (LA min) at end-diastole, just before mitral valve closure; and (3) volume before atrial active contraction (LA preA)

obtained from the last frame before mitral valve reopening or at time of the P wave on the surface electrocardiogram. All LA volumes were indexed to the body surface area as recommended.[16] The LA function was derived from the LA volumes and expressed with the following formulas: (1) Total atrial emptying fraction: LA total ejection fraction = [(LA max – LA min)/LA max] *100; (2) active atrial emptying fraction: LA active ejection fraction = [(LA preA – LA min)/LA preA] *100, which is considered an index of LA active contraction; (3) passive atrial emptying fraction: LA passive ejection fraction = [(LA max – LA preA)/LA max] *100, which is considered an index of LA conduit function; and (4) atrial expansion index: LA expansion index = [(LA max – LA min)/LA min] *100, which is considered an index of LA reservoir function.[19]

In addition, the total atrial conduction time was determined with a validated non-invasive echocardiographic method.[13] Using color-coded tissue Doppler imaging, the sample volume was placed on the lateral wall of the LA just above the mitral annulus in the apical 4-chamber view. The PA-TDI duration, defined as the time-interval from the initiation of the electrocardiographic P wave on surface electrocardiogram to the peak of the A'-wave of the atrial tissue Doppler tracing, was measured in 3 cardiac cycles and averaged (Figure 1). The measurement of PA-TDI duration was feasible in 89% of the patients.

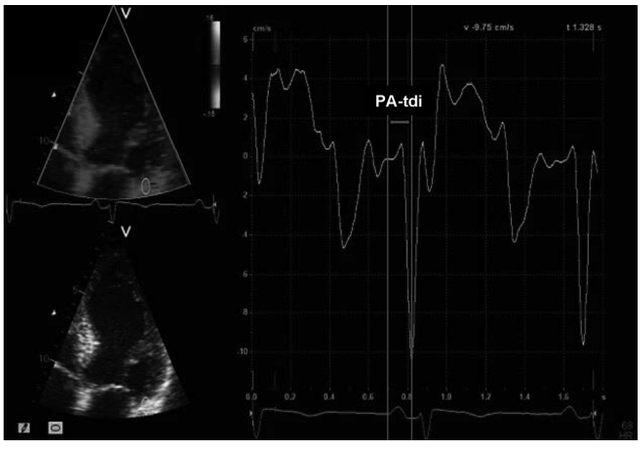

Figure 1.

An example of a PA-TDI duration measurement: the sample volume was placed on the lateral wall of the left atrium just above the mitral annulus in the apical 4-chamber view. The PA-TDI duration was defined as the time-interval from the initiation of the electrocardiographic P wave on surface electrocardiogram to the peak of the A'-wave of the atrial tissue Doppler velocity tracing.

Continuous data are presented as mean ± standard deviation and categorical data are presented as frequencies and percentages. Differences in baseline characteristics between patients who developed new-onset AF versus patients without AF during follow-up were evaluated using the unpaired Student's *t* test and chi-square test, where appropriate. Twenty patients were randomly selected to test the intra- and interobserver variability for the PA-TDI duration measurements by Bland-Altman analysis.[20] Univariable and multivariable Cox proportional hazards regression analyses were performed to relate clinical characteristics and echocardiographic parameters to the development of new-onset AF. The number of covariables had to be limited because of the relatively small number of endpoint events. Therefore, separate clinical and echocardiographic multivariate models were constructed. Variables with a p value ≤0.25 in univariable analysis were considered as potential predictors of endpoint events. The separate clinical and echocardiographic multivariate models were based on this selection, and were constructed by backward deletion of the least significant variable, until all variables had a p value ≤0.10. To avoid co-linearity, peak creatine phosphokinase level, LA min, LA preA and LA passive ejection fraction were excluded from multivariate analysis. The final multivariate model was constructed by combining the clinical and echocardiographic models. Thereafter, the incremental value of PA-TDI duration to the known risk-factors for adverse outcome, related to clinical information and echocardiographic parameters, was established. For this purpose, those characteristics were first entered into the Cox proportional hazard model in a stepwise fashion. Subsequently, PA-TDI duration was entered individually. Global chi-square values, including the significance level for each step in relation to the previous value, were calculated. Time to first episode of AF in relation to PA-TDI duration was analyzed with the Kaplan-Meier method and compared with the log-rank test. Therefore, PA-TDI was dichotomized based on the median (110 ms). To determine the optimal cut-off value of PA-TDI duration for the prediction of new-onset AF, receiver operating characteristic (ROC) curve analysis was applied. The optimum was defined as the value for which the sum of sensitivity and specificity was maximized and sensitivity, specificity, positive and negative predictive values were calculated for the cut-off value. Statistical analysis was performed with SPSS 16.0 (SPSS, Inc., Chicago, Illinois). All statistical tests were 2-sided, and a p value <0.05 was considered to be statistically significant.

Results

A total of 726 patients were included. Nine (1.2%) patients died during hospitalization before echocardiographic assessment could be performed, and in 22 (3.0%) patients echocardiographic assessment was not available within 48 hours of admission due to logistic reasons. An additional 35 (4.8%) patients were excluded, because 1-year follow-up was not completed. From the remaining 660 patients, 47 patients were excluded with prior AF or AF during baseline echocardiography. The final patient population therefore comprised 613 patients. Tables 1 and 2 summarize the baseline clinical and echocardiographic characteristics of the patient population. Mean age was 60 ± 12 years and most patients were men (480 patients, 78%). Mean LV ejection fraction, E/E' ratio and LA max were 46 ± 8%, 13 ± 5 and 21 ± 8 ml/m^2, respectively. Overall, mean PA-TDI duration was 110 ± 18 ms. During a mean follow-up duration of 21 ± 13 months, 38 patients (7%) developed new-onset AF.

Bland-Altman analysis demonstrated a good intra-observer and inter-observer agreement with a small non-significant bias for PA-TDI duration. Mean differences ± 2 standard deviations for PA-TDI duration were 1.8 ± 10 ms for intra-observer agreement and 1.7 ± 10 ms for inter-observer agreement.

Differences in baseline characteristics between patients who developed new-onset AF and patients without AF during follow-up are shown in Tables 1 and 2.

Table 3 shows the significant univariate predictors for development of new-onset AF. Additionally to LA volumes and function measurements, PA-TDI duration significantly predicted the development of new-onset AF in patients after AMI. After multivariable analysis, moderate or severe mitral regurgitation, LA max and PA-TDI duration appeared to be independent predictors of the development of new-onset AF (Table 4).

Global chi-square scores were calculated to assess the incremental prognostic value of PA-TDI duration for the prediction of the development of new-onset AF in patients after AMI. Moderate or severe mitral regurgitation and LA max volume quantified by 2-dimensional echocardiography provided incremental prognostic value to baseline clinical information (age, peak cardiac troponin T level and PR interval).

Table 1: Baseline clinical characteristics of the total study population and of patients with and without development of new-onset atrial fibrillation

	All Patients (N = 613)	*New-onset atrial fibrillation (N = 38)*	*No atrial fibrillation (N = 575)*	*P*
Age (years)	60 ± 12	66 ± 9	60 ± 12	<0.001
Male gender	480 (78%)	27 (71%)	453 (79%)	0.26
Body surface area (m^2)	1.9 ± 0.2	1.9 ± 0.2	2.0 ± 0.2	0.38
Current smoking	313 (51%)	14 (37%)	299 (52%)	0.07
Diabetes	60 (10%)	3 (8%)	57 (10%)	0.69
Family history of CAD	255 (42%)	14 (37%)	241 (42%)	0.53
Hyperlipidemia	124 (20%)	8 (22%)	116 (20%)	0.84
Hypertension	178 (29%)	12 (32%)	166 (29%)	0.72
Prior myocardial infarction	44 (7%)	3 (8%)	41 (7%)	0.86
LAD culprit vessel	295 (48%)	13 (34%)	282 (49%)	0.08
Multivessel disease	290 (48%)	22 (58%)	268 (47%)	0.19
TIMI flow	2.9 ± 0.3	2.9 ± 0.4	2.9 ± 0.3	0.22
Peak CPK level (U/l)	2463 ± 2125	3382 ± 2427	2403 ± 2092	0.006
Peak cTnT level (µg/l)	6.8 ± 6.5	9.3 ± 8.6	6.7 ± 6.3	0.02
Heart rate (bpm)	71 ± 13	72 ± 14	71 ± 13	0.84
PR interval (ms)	167 ± 28	187 ± 38	166 ± 27	0.002
ACE inhibitor / ARB	576 (98%)	38 (100%)	538 (98%)	0.32
Antiplatelet	590 (100%)	38 (100%)	552 (100%)	1.00
Beta-blocker	540 (92%)	34 (90%)	506 (92%)	0.64
Statin	581 (99%)	38 (100%)	543 (98%)	0.43

P values are given for the comparison of patients who developed new-onset atrial fibrillation versus patients who did not develop new-onset atrial fibrillation.
ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; CAD: coronary artery disease; CPK: creatine phosphokinase; cTnT: cardiac troponin T; LAD: left anterior descending coronary artery; TIMI: thrombolysis in myocardial infarction.

Furthermore, PA-TDI duration provided significant additional value to clincial and echocardiographic parameters for the prediction of new-onset AF (Figure 2). Kaplan-Meier

curves for PA-TDI duration dichotomized by the median (110 ms) and the development of new-onset AF are shown in Figure 3.

Table 2: Echocardiographic baseline characteristics of the total study population and of patients with and without development of new-onset atrial fibrillation

	All Patients (N = 613)	***New-onset atrial fibrillation (N = 38)***	***No atrial fibrillation (N = 575)***	***P***
LV end-systolic volume (ml)	57 ± 22	57 ± 23	57 ± 22	0.84
LV end-diastolic volume (ml)	104 ± 34	104 ± 35	104 ± 34	0.98
LV ejection fraction (%)	46 ± 8	45 ± 8	46 ±8	0.74
Wall motion score index	1.48 ± 0.27	1.54 ± 0.22	1.47 ± 0.28	0.13
E/A ratio	0.96 ± 0.35	1.04 ± 0.47	0.95 ± 0.34	0.24
Deceleration time (ms)	213 ± 74	202 ± 73	214 ± 74	0.34
E/E' ratio	13 ± 5	15 ± 8	13 ± 5	0.16
Moderate or severe MR	42 (7%)	7 (18%)	35 (6%)	0.004
LA max (ml/m^2)	21 ± 8	26 ± 11	21 ± 8	0.004
LA min (ml/m^2)	9 ± 5	13 ± 7	9 ± 5	0.002
LA preA (ml/m^2)	15 ± 6	19 ± 8	15 ± 6	0.002
LA total ejection fraction (%)	58 ± 10	53 ± 13	58 ± 10	0.04
LA passive ejection fraction (%)	30 ± 12	26 ± 14	30 ± 12	0.03
LA active ejection fraction (%)	39 ± 12	37 ± 16	39 ± 12	0.30
LA expansion index (%)	153 ± 68	141 ± 102	154 ± 65	0.47
PA-TDI duration (ms)	110 ± 18	138 ± 29	109 ± 16	<0.001

P values are given for the comparison of patients who developed new-onset atrial fibrillation versus patients who did not develop new-onset atrial fibrillation. E/A: mitral inflow peak early velocity (E) / mitral inflow peak late velocity (A); E/E': mitral inflow peak early velocity (E) / mitral annular peak early velocity (E'); LA: left atrium; LV: left ventricular and MR: mitral regurgitation.

Univariate and multivariate analysis performed for PA-TDI duration dichotomized based on the median demonstrated HRs of 7.7 (95% CI 2.7 – 22, p <0.001) and 6.3 (95% CI 2.2 – 18, p = 0.001), respectively. ROC curve analysis demonstrated that a cut-off value of 127 ms for PA-TDI duration yielded a sensitivity of 89% and a specificity of 74% for the

prediction of new-onset AF (area under the curve of 0.84). The positive and negative predictive values were 30% and 98%, respectively. Of note, the low positive predictive value of 30% may be due to the relatively low prevalence of new-onset AF after AMI.[21]

Table 3. Prediction of development of new-onset atrial fibrillation by univariable analysis

	Univariable analysis		
	HR	***95%CI***	***P***
Age	1.05	1.02 – 1.08	0.001
Peak CPK level (U/l)	1.00	1.00 – 1.00	0.005
Peak cTnT level (µg/l)	1.06	1.02 – 1.10	0.005
PR interval (ms)	1.02	1.01 – 1.03	<0.001
E/E' ratio	1.05	1.00 – 1.10	0.04
Moderate or severe mitral regurgitation	3.83	1.68 – 8.73	0.001
LA max (ml/m^2)	1.07	1.04 – 1.11	<0.001
LA min (ml/m^2)	1.11	1.06 – 1.17	<0.001
LA preA (ml/m^2)	1.10	1.05 – 1.14	<0.001
LA total ejection fraction (%)	0.96	0.93 – 0.99	0.007
LA passive ejection fraction (%)	0.97	0.94 – 0.99	0.04
PA-TDI duration (ms)	1.05	1.04 – 1.06	<0.001

CPK: creatine phosphokinase; cTnT: cardiac troponin T; E/E': mitral inflow peak early velocity (E) / mitral annular peak early velocity (E'); LA: left atrium.

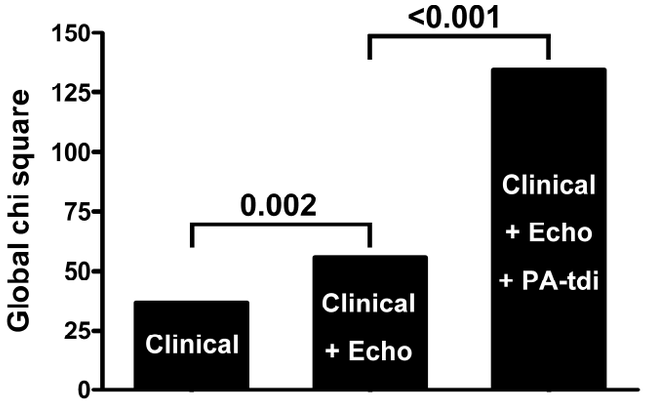

Figure 2.

Bar graph illustrating the incremental predictive value of PA-TDI duration for the development of new-onset atrial fibrillation (depicted by chi-square value on the y axis). The addition of echocardiographic parameters (moderate or severe mitral regurgitation and left atrial maximal volume) to clinical information (age, peak cardiac troponin T level and PR interval) increased the chi-square value significantly from 37 to 55 (p = 0.002). Moreover, the addition of PA-TDI duration to the clinical and echocardiographic risk factors improved the model even further by increasing the chi-square value from 55 to 134 (p <0.0001).

Table 4. Prediction of development of new-onset atrial fibrillation by multivariable analysis

	Multivariable analysis		
	HR	***95%CI***	***P***
Age (years)	1.02	0.98 – 1.06	0.36
Peak cTnT level (µg/l)	1.03	0.99 – 1.07	0.15
PR interval (ms)	1.01	0.99 – 1.02	0.11
Moderate or severe mitral regurgitation	4.66	1.76 – 12	0.002
LA max (ml/m^2)	1.03	1.00 – 1.07	0.03
PA-TDI duration (ms)	1.04	1.03 – 1.05	<0.001

cTnT: cardiac troponin T; LA: left atrium; LAD: left anterior descending coronary artery.

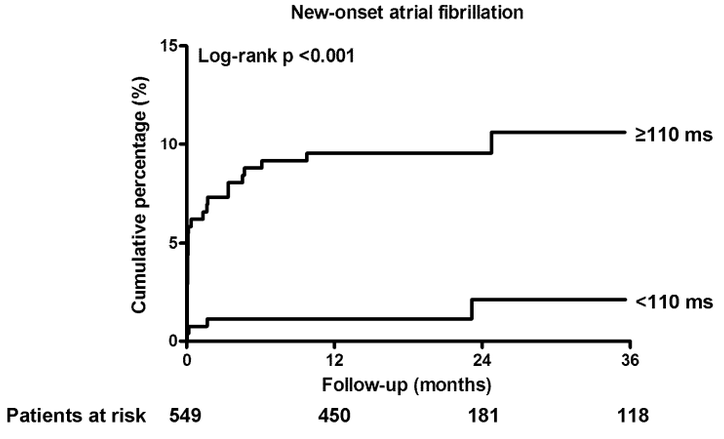

Figure 3.

Kaplan-Meier estimates of the percentage of patients with development of new-onset atrial fibrillation in relation to PA-TDI duration dichotomized based on the median.

Discussion

The major findings of the present study can be summarized as follows. (1) The incidence of new-onset AF after AMI during mean follow-up of 21 months was 7% despite optimal contemporary treatments. (2) After adjusting for the strongest clinical and echocardiographic predictors, moderate or severe mitral regurgitation, LA max and PA-TDI duration were independent predictors of the development of new-onset AF in patients after AMI. (3) PA-TDI duration provided incremental value for the prediction of new-onset AF to known clinical and echocardiographic risk factors. (4) Multivariable analysis performed for PA-TDI duration dichotomized based on the median demonstrated a HR of 6.3 (95% CI 2.2 – 18, p = 0.001) for the development of new-onset AF.

Recently, Schmitt et al. reported in a clinical review evaluating the incidence, clinical features and prognostic implications of AF in AMI, that AF has adverse prognostic implications for in-hospital and long-term mortality in patients hospitalized for AMI.[1] Importantly, the presence of new-onset AF after AMI carried an increased risk of developing in-hospital re-infarction, cardiogenic shock, heart failure and cardiac arrest. In addition, new-onset AF after AMI was associated with an increased risk of in-hospital, 30 days, 1 year and 3 years mortality, whereas pre-existing AF was not associated with this increased risk.[5 22 23]

To enable the prevention of AF, risk stratification based on large observational studies have shown that several clinical and echocardiographic parameters are associated with the development of new-onset AF.[8-10] Tsang et al. described in a large population of 840 elderly patients the value of diastolic function assessed with deceleration time, E/A ratio and LA volume for the prediction of new-onset AF.[24] The authors demonstrated the incremental value of diastolic function to clinical risk factors alone for the prediction of new-onset AF. In the present study, comparable observations were made and diastolic function was assessed extensively with standard parameters and LA volumes and LA function measurements. However, after multivariable analysis, only moderate or severe mitral regurgitation, LA max and PA-TDI duration remained significant predictors of new-onset AF. In addition, PA-TDI duration provided incremental value to a model with clinical and echocardiographic parameters for the prediction of new-onset AF. Of note, a relatively large percentage of the patients with new-onset AF developed the arrhythmia early after the

myocardial infarction. Therefore, although PA-TDI duration may detect LA dysfunction earlier than the traditional measurements of LA function, the clinical relevance of PA-TDI duration for the prediction of new-onset AF has to be further investigated.

Several techniques have been examined to quantify total atrial activation time. Currently, the gold standard is the time-consuming measurement of P-wave duration on signal-averaged electrocardiogram. PA-TDI duration was recently validated as a novel non-invasive technique which correlated well with P-wave duration on signal-averaged electrocardiogram.[13] Because PA-TDI duration is a simple, fast and reliable method, it is suitable for routine use in clinical practice. De Vos et al. demonstrated that PA-TDI duration predicts the development of new-onset AF in a general patient population from a cardiology outpatient clinic.[14] The present study showed that PA-TDI duration also predicts new-onset AF in patients after AMI and PA-TDI duration was superior to LA volumes and function for the prediction of new-onset AF. PA-TDI duration may be able to identify structural remodeling of the LA in an early stage and reflect the vulnerability of the LA for the development of new-onset AF.

Even though the patient population in the current study is large, a relatively small number of patients developed new-onset AF during long-term follow-up. However, the percentage of patients that developed new-onset AF after AMI in the present study is in line with previous studies.

Conclusions

Moderate or severe mitral regurgitation, LA max and PA-TDI duration were independent predictors of the development of new-onset AF in patients after AMI. In addition, PA-TDI duration provided incremental value for the prediction of new-onset AF to known clinical and echocardiographic risk factors. PA-TDI duration is a simple, fast and reliable method to obtain total atrial activation time which can be implemented in the risk stratification for new-onset AF in clinical practice.

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