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Prediction of atrial arrhythmia in adult patients with congenital heart disease with tissue Doppler imaging

Submitted

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ABSTRACT

Aims: Atrial arrhythmia (AA) is common in adult patients with congenital heart disease (CHD). To enable prevention of AA or its complications, timely identification of adult CHD patients at risk for AA is crucial. Long total atrial activation times have been related to AA. Tissue Doppler imaging permits non-invasive evaluation of the total atrial conduction time (PA-TDI duration). The present study evaluated the role of PA-TDI duration in adult CHD patients to predict AA.

Methods and Results: A total of 223 adult CHD patients were followed-up for the occurrence of AA after PA-TDI duration assessment. The PA-TDI duration was defined as the time interval from the onset of the P-wave on the electrocardiogram to the peak of the A wave at the lateral atrial wall on TDI tracings. Among various clinical and echocardiographic parameters, the value of the PA-TDI duration to predict AA occurrence was investigated. Median follow-up was 39 months (inter-quartile range 21 to 57 months). A PA-TDI duration ≥ 126 ms predicted AA during follow-up (log rank p<0.001). At multivariate analysis, PA-TDI duration (hazard ratio (HR) 2.02, 95% confidence interval (CI) 1.07-3.83), prior history of AA (HR 4.85, 95% CI 2.71-8.69) and surgical procedures during follow-up (HR 2.33 95% CI 1.26-4.33) independently predicted the occurrence of AA.

Conclusion: The PA-TDI duration, prior history of AA and surgical procedures during follow-up are independent predictors of the occurrence of AA in adult CHD patients. PA-TDI duration is a useful tool to identify CHD patients at risk for AA during follow-up.
INTRODUCTION

Improvements in cardiac surgery have led to increased survival of patients with congenital heart disease (CHD). Consequently, the population of adult patients with CHD is growing and aging. During follow-up, atrial arrhythmia (AA) is a frequent clinical problem in this group of patients with a lifetime risk over 50% in patients with severe CHD. AA in adult patients with CHD is related to thrombo-embolic complications, heart failure and increased mortality. To enable prevention of AA or its complications, timely identification of adult CHD patients at risk for AA is essential. In CHD patients, longstanding altered atrial hemodynamics, increased atrial pressure and surgical atrial scarring promote atrial remodeling and electrical conduction abnormalities. These electrical disturbances include prolonged atrial conduction time, favoring the onset of AA. Recently, a novel echocardiographic tool using tissue Doppler imaging (TDI), has shown to be a fast, easy and reliable method to assess the total atrial conduction time. With color-coded TDI of the atria, the time interval from the onset of the P-wave on the electrocardiogram to the peak of the A’ wave on the TDI tracings of the lateral atrial wall can be measured (so-called PA-TDI duration). The PA-TDI duration reflects the total atrial conduction time, and has been shown to be a predictor of AA in patients with cardiac disease. However, the value of the PA-TDI duration to predict AA in CHD patients has not been evaluated. The current study investigated the clinical and echocardiographic predictors of AA in adult CHD patients. Specifically, the value of PA-TDI duration to predict the occurrence of AA in adult CHD patients was assessed.

METHODS

Patient population and data collection

The present population included adult patients with CHD, who were followed-up for the occurrence of AA from the first available TDI echocardiogram in sinus rhythm (baseline) until November 2010. Patients without sinus rhythm at baseline or without further clinical follow-up visits were excluded from the analysis. AA was defined as atrial tachycardia, atrial flutter, or atrial fibrillation on surface electrocardiogram (ECG), 24 or 48 hours Holter ECG or implantable cardioverter-defibrillator device recordings.

Clinical and echocardiographic data were retrieved from the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Center) and the echocardiographic database, respectively. All adult CHD patients underwent a complete clinical evaluation at baseline. The CHD diagnosis was specified to be ‘severe CHD’ or ‘not severe CHD’, as described previously. In addition, the use of beta-blockers, anti-arrhythmic medication or angiotensin-converting enzyme (ACE) inhibitors at baseline was recorded. Furthermore, the presence of hypertension at baseline (systolic pressure >140 mmHg and/or diastolic pressure >90 mmHg) and any surgical procedures during follow-up were documented. In addition, baseline echocardiographic variables included dimensions

### Table 1. Patient characteristics at baseline and during follow-up

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Univariate analysis</th>
<th>p-value</th>
<th>Multivariate analysis</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR 95% CI</td>
<td></td>
<td>HR 95% CI</td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>51 ± 13</td>
<td>48 ± 12</td>
<td>0.245</td>
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</tr>
<tr>
<td>Male/female, n(%)</td>
<td>30/27 (53/47)</td>
<td>79/87 (48/52)</td>
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<tr>
<td>Severe CHD*, n (%)</td>
<td>30 (53)</td>
<td>57 (34)</td>
<td>0.015</td>
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</tr>
<tr>
<td>Prior history of AA, n (%)</td>
<td>35 (61)</td>
<td>26 (16)</td>
<td>&lt;0.001</td>
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</tr>
<tr>
<td>Medication, n (%)</td>
<td>Beta-blocker</td>
<td>31 (54)</td>
<td>25 (15)</td>
<td>&lt;0.001</td>
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<td></td>
<td>Anti-arrhythmic</td>
<td>5 (9)</td>
<td>10 (6)</td>
<td>0.475</td>
</tr>
<tr>
<td></td>
<td>ACE inhibitor</td>
<td>21 (36)</td>
<td>32 (19)</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>Hypertension, n (%)</td>
<td>5 (9)</td>
<td>23 (14)</td>
<td>0.318</td>
</tr>
<tr>
<td>Surgical procedure during follow-up, n (%)</td>
<td>14 (25)</td>
<td>15 (9)</td>
<td>0.003</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. Univariate and multivariate predictors of atrial arrhythmia in patients with congenital heart disease

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Univariate analysis</th>
<th>p-value</th>
<th>Multivariate analysis</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR 95% CI</td>
<td></td>
<td>HR 95% CI</td>
<td></td>
</tr>
<tr>
<td>Severity of CHD</td>
<td>1.61</td>
<td>0.96 - 2.71</td>
<td>0.074</td>
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<td>History of AA</td>
<td>6.38</td>
<td>3.69 - 11.03</td>
<td>&lt;0.001</td>
<td>4.85</td>
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<tr>
<td>Gender</td>
<td>0.84</td>
<td>0.50 - 1.41</td>
<td>0.510</td>
<td></td>
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<tr>
<td>Hypertension</td>
<td>0.74</td>
<td>0.29 - 1.84</td>
<td>0.512</td>
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<tr>
<td>Surgical procedure</td>
<td>2.91</td>
<td>1.58 - 5.34</td>
<td>0.001</td>
<td>2.33</td>
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<td>Systemic ventricle EDV</td>
<td>1.00</td>
<td>0.99 - 1.01</td>
<td>0.554</td>
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<tr>
<td>Systemic ventricle ESV</td>
<td>1.00</td>
<td>0.99 - 1.01</td>
<td>0.316</td>
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<tr>
<td>Systemic ventricle EF</td>
<td>0.99</td>
<td>0.96 - 1.01</td>
<td>0.247</td>
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<tr>
<td>PA-TDI dichotomized</td>
<td>3.66</td>
<td>2.03 - 6.61</td>
<td>&lt;0.001</td>
<td>2.02</td>
</tr>
</tbody>
</table>

Abbreviations: AA: atrial arrhythmia, CHD: congenital heart disease, CI: confidence interval, EDV: end-diastolic volume, ESV: end-systolic volume, EF: ejection fraction, HR: hazard ratio, PA-TDI: total atrial activation time, as assessed with tissue Doppler imaging.
entered as variables in the multivariate analysis using the enter method. None of the significant univariate predictors had a linear correlation coefficient >0.7 and therefore, multicollinearity between the parameters was unlikely. Hazard ratios and 95% confidence intervals (CI) were calculated for each independent variable. Data were analyzed using the SPSS 17.0 software (SPSS Inc, Chicago, Illinois). A p-value of <0.05 was considered statistically significant.

RESULTS

Patient population
A total of 223 adult CHD patients were included (mean age 49 ± 12 years, 49% male). During a median follow-up duration of 39 months (inter-quartile range 21 to 57 months), a total of 57 (26%) patients presented with AA. Table 1 displays the clinical and echocardiographic characteristics of both groups of adult CHD patients (AA during follow-up vs. no AA during follow-up). The proportion of patients with severe CHD was significantly larger in the group of patients with AA compared to the group of patients without AA (53% vs. 34%, p=0.015). A total of 61% of patients with AA during follow-up had a prior history of AA. No differences between the two groups were observed for the presence of hypertension. Surgical procedures were performed during follow-up in 29 patients (5 atrioventricular valve repairs or replacements, 17 pulmonary or aortic valve replacements, 5 atrial septum defect closures, 2 other procedures). In the group with AA during follow-up, surgical procedures were more frequently performed (25% vs. 9%, p=0.003).
On echocardiography, no significant differences in dimensions and ejection fraction of the systemic ventricle were observed between the two groups (Table 1). Interestingly, the PA-TDI duration was significantly longer in the group with AA during follow-up as compared with the group with no AA during follow-up (152 ± 33 ms vs. 121 ± 24 ms, p<0.001).

**Prediction of AA during follow-up**

The ROC curve analysis to identify the optimal PA-TDI cut-off value to predict AA yielded a cut-off value of 126 ms (area under the curve 0.76). Subsequently, this cut-off value for PA-TDI duration was used to dichotomize the population, and the time-to-event data with respect to the occurrence of AA was evaluated with Kaplan-Meier survival analysis.

The Kaplan-Meier curves showed a significantly higher cumulative event rate in the group of adult CHD patients with longer PA-TDI duration (≥126 ms) as compared with adult CHD patients with a shorter PA-TDI duration (<126 ms) (Chi-square: 21.10, log rank p<0.001) (Figure 2). The cumulative event rates in the group with a PA-TDI duration ≥126 ms were 20%, 26%, 36% and 43% at 12, 24, 36 and 48 months, respectively. In contrast, in the group of patients with a PA-TDI duration <126 ms, these event rates were 5%, 6%, 8% and 8%, for the respective time frames.

Table 2 shows the hazard ratios for the univariate predictors for the occurrence of AA during follow-up. Prior history of AA, surgical procedure during follow-up and PA-TDI duration were significant univariate predictors. Finally, at multivariate analysis, prior history of AA (hazard ratio: 4.85, 95% CI: 2.71 to 8.69, p<0.001) surgical procedure during follow-up (hazard ratio: 2.33, 95% CI: 1.26 to 4.33, p=0.007) and the PA-TDI duration (hazard ratio: 2.02, 95% CI: 1.07 to 3.83, p=0.031) were independent predictors of the occurrence of AA during follow-up.

**DISCUSSION**

The present evaluation demonstrates that in adult CHD patients, long total atrial activation time as assessed with echocardiographic techniques (PA-TDI duration) is associated with increased risk of AA occurrence during follow-up. Particularly, the risk of AA occurrence during follow-up was twofold in adult CHD patients with a PA-TDI duration ≥126 ms compared with adult CHD patients with a PA-TDI duration <126 ms.

**Atrial arrhythmia in CHD patients**

AA is common during long-term follow-up in adult CHD patients. In a recent population-based study, Bouchardy et al. reported a lifetime risk of AA of 63% in patients with severe CHD and of 47% in patients without severe CHD. AA is an important clinical burden in adult CHD patients as it is associated with the occurrence of stroke, heart failure, cardiac interventions and increased mortality. Particularly, in patients with severe CHD, the occurrence of AA may further impair a compromised hemodynamic condition. Previous studies have identified various clinical predictors of AA in adult patients with CHD, such as CHD diagnosis and type and number of surgical repairs.

In the current study, prior history of AA and surgical procedures during follow-up were related to AA. Furthermore, the present evaluation showed that the assessment of PA-TDI duration with echocardiography provided an additional parameter to further improve the stratification of CHD patients for AA occurrence.

**PA-TDI duration in CHD patients**

In CHD patients, the principal pathophysiological substrate for AA is provided by electrical re-entry through atrial areas with delayed electrical conduction. These areas result from surgical atrial scar tissue (e.g. after Fontan and Mustard/Senning procedure, closure of atrial septal defect, or atriotomy in tetralogy of Fallot correction) or atrial fibrosis in patients with longstanding pressure or volume overload of the atria. These sites of delayed electrical conduction prolong the time required for atrial electrical activation. Prolonged total atrial conduction time is a reliable predictor of AA. Currently, the gold standard for assessing total atrial conduction time is the P-wave duration as assessed with signal-averaged electrocardiograms. However, this is a time-consuming technique and therefore not suitable for routine clinical use. The novel echocardiographic modality of TDI enables assessment of the total atrial activation time by measuring the PA-TDI duration, a readily and feasible noninvasive method to identify patients with a prolonged atrial conduction...
time. Recently, Merckx and co-workers validated PA-TDI duration against the P-wave duration on signal-averaged electrocardiograms. The authors observed a strong correlation between the two techniques (r=0.91). In addition, subsequent studies demonstrated the value of PA-TDI to predict AA in various groups of patients with heart disease with or without prior AA. In the current study, the PA-TDI duration independently predicted the occurrence of AA during follow-up of CHD patients. This finding may have important implications. Timely identification of CHD patients at risk for AA provides an opportunity for preventive measures for AA occurrence (such as anti-tachycardia pacing or surgical treatment of an underlying hemodynamic problem) or for indication of anticoagulant therapy to prevent complications of AA (such as stroke). Future studies are warranted to identify the cut-off values of PA-TDI duration for risk stratification of AA in the various diagnostic subgroups with CHD.

CONCLUSION

In conclusion, the PA-TDI duration, prior history of AA and surgical procedures during follow-up were independently associated with the occurrence of AA in adult CHD patients. PA-TDI duration is a useful tool for the identification of CHD patients at risk for AA during clinical follow-up.
REFERENCE LIST


