Atrial fibrillation (AF) is a known complication of right ventricular (RV) pacing, occurring in 3% to 15% per year, being more common in older subjects and in the absence of AV synchrony. As AF poses a significant medical and economic burden, appropriate risk prediction for AF might be helpful in improving the cost-effectiveness of diagnostic and therapeutic measures directed toward preventing this arrhythmia and its well-known consequences. However, risk factors for AF are multiple and many of them remain ill-defined, so additional risk profiling to stratify the risk of pacemaker-related AF may enable a more personalized approach to decision-making.

**Background** — Better prediction of cardiac pacing patients at risk of atrial fibrillation (AF) would enable more effective prophylaxis. We sought whether left atrial (LA) electromechanical conduction time (EMT) and myocardial mechanics were associated with incident AF in patients undergoing dual chamber pacemaker implantation, independent of left atrial volume (LAV).

**Methods and Results** — Clinical data were obtained prospectively in 146 enrollees (73±10 years) undergoing dual chamber pacemaker implantation in the Protect-Pace study. Echocardiograms and 2-dimensional strain analysis were obtained post implantation and at 2 years. Complete ascertainment of AF during follow-up was identified from interrogation of permanent pacemakers. Cox regression was used to identify correlates of AF. Incident AF (n=29, 20%) was associated with higher systolic blood pressure (P=0.01), lower left ventricular ejection fraction (P=0.03), lower LA strain at atrial contraction (LASac; P<0.001), higher LAV (P<0.003), and longer septal electromechanical conduction time (P<0.01). The associations of LAV and LASac with incident AF were independent of age, sex, systolic blood pressure, and left ventricular size and function. However, the combination of the 3 strongest predictors showed LASac (P=0.02) and systolic blood pressure (P=0.01) were independently associated with incident AF, but LAV was not (P=0.07). Using the optimal cut points from receiver operator characteristic curves (62 mL for LAV and 8.6% for LASac), we demonstrated that a significantly greater rate of AF was associated with both lower LASac at higher LAV and with lower LASac at lower LAV.

**Conclusions** — The risk of AF in patients receiving dual chamber pacing is independently associated with LA size and function, not left ventricular structural and functional characteristics or right ventricular lead location.

**Clinical Trial Registration** — URL: http://www.clinicaltrials.gov. Unique identifier: NCT00461734.

**Key Words:** atrial fibrillation ■ atrial strain ■ atrial volume ■ cardiac pacing ■ electromechanical conduction time
documented to predict a recurrence of AF after successful cardioversion or catheter ablation,8,9,16–18 but whether measurements of atrial deformation provide incremental benefit in the prediction of a first episode of AF needs to be established. Similarly, a newly proposed echo-Doppler–derived LA electromechanical conduction time (EMT), reflecting the ability of atrial tissue to propagate electric activation, has been reported to be predictive of recurrent or new-onset AF,19–21 but it lacks validity in a broader spectrum of patient populations, as well as a comprehensive comparative evaluation with other atrial indices. Accordingly, we sought in this study to investigate factors associated with a first episode of AF in patients undergoing dual chamber pacemaker implantation, with special focus on LA volume, LA strain, and EMT measurement.

Methods

Patient Selection

This study included a cohort of 146 patients (mean age, 73±10 years) participating in the PROTECT-PACE trial (The Protection of Left Ventricular Function During Right Ventricular Pacing, ClinicalTrials.gov number NCT00461734), who underwent dual chamber pacemaker implantation. The Protect-Pace study was designed to assess whether the position of RV lead (RV apex versus RV high septum) affects the development of left ventricular (LV) dysfunction. This study was approved by the Human Research Ethics Committees of participating centres in Australia and New Zealand, and the NRES Committee East Midlands—Nottingham in the United Kingdom and was conducted in compliance with the Declaration of Helsinki. All patients provided written informed consent.

Patients were eligible for this trial if they had a high grade AV block and preserved baseline function. The main exclusion criteria were myocardial infarction, bypass surgery, or valve replacement within 3 months before enrollment, mechanical right heart valve, complex congenital heart disease, hypertrophic obstructive cardiomyopathy, acute coronary syndrome, unstable angina, severe mitral regurgitation, and hemodynamically significant aortic stenosis, known paroxysmal AF or a documented episode of AF before enrollment; amiodarone therapy within the last 6 months before enrollment, indication for an implantable cardioverter defibrillator or cardiac resynchronisation therapy, and junctional ablation.

Evaluation and Follow-Up

Patients were assessed after pacemaker implantation (at baseline) and during follow-up visits, scheduled at 6 weeks, and 12, 18, and 24 months thereafter. At each visit, device interrogations were performed to retrieve data on the episodes of AF. Patients were categorized as having AF if >5 minutes of AF were recorded in any 1 day, which represents a minimum threshold previously demonstrated to be of clinical relevance.12,23 The AF burden was calculated by summing the daily time with AF and dividing by the follow-up duration.

Clinical Data

Patient data were collected before discharge. The CHADS2 score, considering the presence of congestive heart failure, hypertension, diabetes, prior stroke or thromboembolism, and patient age, was calculated as previously described.21

Echocardiography

The readers performing echocardiographic analyses were blinded to the patients’ clinical data. Echocardiographic evaluation was performed at baseline (post implantation) and at 24 months using the same commercially available ultrasound machine (Vivid 7; GE Vingmed, Horten, Norway—135 patients [93%] and ie33; Phillips Medical Systems, Andover, MA—11 patients [7%]). The measurements of cardiac dimensions and wall thicknesses were performed from 2-dimensional (2D) images according to the recommendations of the American Society of Echocardiography. LV mass was computed by the Devereux-modified cube formula and indexed for body surface area to obtain the LV mass index. A modified Simpson’s biplane method was used to calculate LV end-diastolic and end-systolic volumes and LV ejection fraction. LA volume was determined using Simpson’s rule from apical 4-chamber and 2-chamber views at end-ventricular systole, just before mitral valve opening. LV diastolic and systolic volume indexes and LA volume index were obtained by adjusting LV and LA volumes to body surface area. The parameters of LV inflow, including peak early (E) and late diastolic flow velocity (A), were assessed by pulsed wave Doppler from the apical 4-chamber view with the sample volume placed at the tips of mitral leaflets. Peak early diastolic tissue velocity (e’) was assessed by pulse wave tissue Doppler at the septal and lateral portions of the mitral annulus. The ratio of mitral inflow early diastolic velocity/average e’ velocity from both sides of the mitral annulus (E/e’) was used for the approximation of LV filling pressure.

LV longitudinal deformation was evaluated by a semiautomated 2D speckle tracking technique (Echopac, GE Medical Systems, and QLAB, Philips Medical Systems) from the 3 apical views with typical temporal resolution of 60 to 70 frames per second. After manual tracing of the endocardial border and subsequent software processing, the operator confirmed adequate tissue tracking. Segments with inadequate tracking were readjusted manually and if this was ineffective they were excluded from the analysis. Global longitudinal strain, defined as the greatest negative value on the strain curve, was calculated as the average value from all LV segments.

LA Longitudinal Strain

Measurements were performed in the apical 4- and 2-chamber views using dedicated software (Image-Arena Version 4.6.1.5, TomTec Imaging Systems, Unterscheissheim, Germany) installed on an external computer workstation using the option of endocardially located region of interest, with the same frame rate as for LV strain imaging. We used the onset of the P wave as the zero reference point, as proposed previously,24 which enabled the identification of the peak negative strain (LA strain at atrial contraction, LASac) representing atrial contractile function, peak positive strain corresponding to LA conduit function, and their sum (total LA strain) representing LA reservoir function (Figure 1).

Initially, the endocardial border was traced manually and then the software determined 6 conventional segments and categorized the tracking and 2D speckle tracking technique (Echopac, GE Medical Systems, and QLAB, Philips Medical Systems) from the 3 apical views with typical temporal resolution of 60 to 70 frames per second. After manual tracing of the endocardial border and subsequent software processing, the operator confirmed adequate tissue tracking. Segments with inadequate tracking were readjusted manually and if this was ineffective they were excluded from the analysis. Global longitudinal strain, defined as the greatest negative value on the strain curve, was calculated as the average value from all LV segments.

LA Longitudinal Strain

Measurements were performed in the apical 4- and 2-chamber views using dedicated software (Image-Arena Version 4.6.1.5, TomTec Imaging Systems, Unterscheissheim, Germany) installed on an external computer workstation using the option of endocardially located region of interest, with the same frame rate as for LV strain imaging. We used the onset of the P wave as the zero reference point, as proposed previously,24 which enabled the identification of the peak negative strain (LA strain at atrial contraction, LASac) representing atrial contractile function, peak positive strain corresponding to LA conduit function, and their sum (total LA strain) representing LA reservoir function (Figure 1).

Initially, the endocardial border was traced manually and then the software determined 6 conventional segments and categorized the tracking and 2D speckle tracking technique (Echopac, GE Medical Systems, and QLAB, Philips Medical Systems) from the 3 apical views with typical temporal resolution of 60 to 70 frames per second. After manual tracing of the endocardial border and subsequent software processing, the operator confirmed adequate tissue tracking. Segments with inadequate tracking were readjusted manually and if this was ineffective they were excluded from the analysis. Global longitudinal strain, defined as the greatest negative value on the strain curve, was calculated as the average value from all LV segments.

LA Longitudinal Strain

Measurements were performed in the apical 4- and 2-chamber views using dedicated software (Image-Arena Version 4.6.1.5, TomTec Imaging Systems, Unterscheissheim, Germany) installed on an external computer workstation using the option of endocardially located region of interest, with the same frame rate as for LV strain imaging. We used the onset of the P wave as the zero reference point, as proposed previously,24 which enabled the identification of the peak negative strain (LA strain at atrial contraction, LASac) representing atrial contractile function, peak positive strain corresponding to LA conduit function, and their sum (total LA strain) representing LA reservoir function (Figure 1).

Initially, the endocardial border was traced manually and then the software determined 6 conventional segments and categorized the tracking

Figure 1. Example of assessment of left atrial strain.
The incremental value of study parameters for the prediction of AF was assessed by sequential Cox analysis using nested models. The first step consisted of CHADS2 score, and then septal EMT, LA volume, change in LA (ΔLA) volume, and LA strain at atrial contraction were successively included in the next steps. The change in overall log-likelihood ratio \( \chi^2 \) was used to assess the increase in predictive power after the addition of subsequent parameter. The c-statistic was used to evaluate model performance. A receiver operator characteristic analysis was used to examine the ability of particular variables to predict AF as well as to assist the determination of the discriminatory cutoff point for LA volume, LA strain at atrial contraction, and septal EMT. Differences in the area under the receiver operator characteristic curves were analyzed using the z-test. Using binary parameters categorized on the basis of the optimal cutoff values from receiver operator characteristic analysis, reclassification was evaluated to assess the incremental benefit of adding LA volume or LA strain at atrial contraction to the model based on septal EMT or adding LA strain at atrial contraction to the model based on LA volume. Changes in particular parameters during follow-up were calculated by subtracting the baseline value from the follow-up value and were expressed in the units of their measurements. The reproducibility of echocardiographic measurements was evaluated by the Bland–Altman method (mean difference and 95% confidence interval). Statistical analysis was performed using standard statistical computer software (Statistica for Windows 10; StatSoft Inc, Tulsa, OK and R software ver.3.0.2 [http://cran.r-project.org/]). A \( P \) value of 0.05 was deemed to be statistically significant.

Results

Clinical Characteristics

During a 2-year follow-up, episodes of AF were noted in 29 patients (20%), of whom 2 developed permanent AF. The median AF burden was 3 minutes/d, the maximal duration of AF episodes varied from 7 to 1440 minutes/d, and the median number of days with AF was 23. No patient from

### Table 1. Clinical Characteristics of Patients With and Without AF During Follow-Up

<table>
<thead>
<tr>
<th></th>
<th>No AF During Follow-Up (n=117)</th>
<th>AF During Follow-Up (n=29)</th>
<th>Effect Size of Each Variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>72.7±10.4</td>
<td>74.8±10.4</td>
<td>β</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>77 (65)</td>
<td>22 (76)</td>
<td>SE</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.5±5.2</td>
<td>27.9±5.6</td>
<td>( \Delta ) change in LA</td>
</tr>
<tr>
<td>HR, 1/min*</td>
<td>68±10</td>
<td>69±11</td>
<td>Factor (95% CI)</td>
</tr>
<tr>
<td>SBP, mm Hg*</td>
<td>143±26</td>
<td>158±34</td>
<td>P Value</td>
</tr>
<tr>
<td>DBP, mm Hg*</td>
<td>70±15</td>
<td>72±15</td>
<td></td>
</tr>
<tr>
<td>DM, n (%)</td>
<td>26 (22)</td>
<td>6 (20)</td>
<td></td>
</tr>
<tr>
<td>HT, n (%)</td>
<td>64 (54)</td>
<td>20 (69)</td>
<td></td>
</tr>
<tr>
<td>CAD, n (%)</td>
<td>31 (26)</td>
<td>7 (24)</td>
<td></td>
</tr>
<tr>
<td>CABG, n (%)</td>
<td>6 (5)</td>
<td>3 (10)</td>
<td></td>
</tr>
<tr>
<td>CHADS2 score</td>
<td>1.3±1.0</td>
<td>1.6±0.9</td>
<td></td>
</tr>
<tr>
<td>Antiarrhythmic drugs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>class I, n (%)†</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td></td>
</tr>
<tr>
<td>Antiarrhythmic drugs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>class III, n (%)†</td>
<td>0 (0)</td>
<td>3 (10)</td>
<td></td>
</tr>
<tr>
<td>β-blockers, n (%)</td>
<td>24 (20)</td>
<td>8 (28)</td>
<td></td>
</tr>
<tr>
<td>Apical lead position, n (%)</td>
<td>62 (53)</td>
<td>16 (55)</td>
<td></td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; DBP, diastolic blood pressure; DM, diabetes mellitus; HR, heart rate; HT, hypertension; and SBP, systolic blood pressure.

*At baseline (post implantation).
†Introduced to treatment after the occurrence of AF.

### Statistical Analysis

Data are presented as mean±SD or as median (interquartile range). Comparisons of clinical and echocardiographic features in patients with and without AF were made using univariable Cox regression. Sensitivity and specificity were computed according to the standard formulas. The time to the first occurrence of AF was compared with the use of Kaplan–Meier curves. A series of Cox proportional hazards models was performed to elucidate the association of LAV and LASac with incident AF, independent of other univariable associations of AF. Relative risks were expressed as hazard ratios with 95% confidence intervals. The proportional hazards assumption was confirmed by a plot of Schoenfeld residuals over time.

The incremental value of study parameters for the prediction of AF was assessed by sequential Cox analysis using nested models. The first step consisted of CHADS2 score, and then septal EMT, LA volume, change in LA (ΔLA) volume, and LA strain at atrial contraction were successively included in the next steps. The change in overall log-likelihood ratio \( \chi^2 \) was used to assess the increase in predictive power after the addition of subsequent parameter. The c-statistic was used to evaluate model performance. A receiver operator characteristic analysis was used to examine the ability of particular variables to predict AF as well as to assist the determination of the discriminatory cutoff point for LA volume, LA strain at atrial contraction, and septal EMT. Differences in the area under the receiver operator characteristic curves were analyzed using the z-test. Using binary parameters categorized on the basis of the optimal cutoff values from receiver operator characteristic analysis, reclassification was evaluated to assess the incremental benefit of adding LA volume or LA strain at atrial contraction to the model based on septal EMT or adding LA strain at atrial contraction to the model based on LA volume. Changes in particular parameters during follow-up were calculated by subtracting the baseline value from the follow-up value and were expressed in the units of their measurements. The reproducibility of echocardiographic measurements was evaluated by the Bland–Altman method (mean difference and 95% confidence interval). Statistical analysis was performed using standard statistical computer software (Statistica for Windows 10; StatSoft Inc, Tulsa, OK and R software ver.3.0.2 [http://cran.r-project.org/]). A \( P \) value of 0.05 was deemed to be statistically significant.

### Left Atrial Electromechanical Conduction Time

The time intervals from the onset of the P wave from the ECG signal (lead II) provided by the echocardiographic machine to the peak of the late diastolic wave (a′ wave), defined as EMT, were obtained in the apical 4-chamber view with the pulsed-wave sample volume placed at the level of the septal and lateral mitral annulus. The monitor sweep speed was optimized to perform timing measurement and the P wave was magnified to confirm the onset as appropriate, but measurements were possible in 127 patients (86%).

All LA strain and EMT parameters were averaged over 3 consecutive cardiac cycles.

### Sensitivity and Specificity

Sensitivity and specificity were computed according to the standard formulas. The time to the first occurrence of AF was compared with the use of Kaplan–Meier curves. A series of Cox proportional hazards models was performed to elucidate the association of LAV and LASac with incident AF, independent of other univariable associations of AF. Relative risks were expressed as hazard ratios with 95% confidence intervals. The proportional hazards assumption was confirmed by a plot of Schoenfeld residuals over time.

The incremental value of study parameters for the prediction of AF was assessed by sequential Cox analysis using nested models. The first step consisted of CHADS2 score, and then septal EMT, LA volume, change in LA (ΔLA) volume, and LA strain at atrial contraction were successively included in the next steps. The change in overall log-likelihood ratio \( \chi^2 \) was used to assess the increase in predictive power after the addition of subsequent parameter. The c-statistic was used to evaluate model performance. A receiver operator characteristic analysis was used to examine the ability of particular variables to predict AF as well as to assist the determination of the discriminatory cutoff point for LA volume, LA strain at atrial contraction, and septal EMT. Differences in the area under the receiver operator characteristic curves were analyzed using the z-test. Using binary parameters categorized on the basis of the optimal cutoff values from receiver operator characteristic analysis, reclassification was evaluated to assess the incremental benefit of adding LA volume or LA strain at atrial contraction to the model based on septal EMT or adding LA strain at atrial contraction to the model based on LA volume. Changes in particular parameters during follow-up were calculated by subtracting the baseline value from the follow-up value and were expressed in the units of their measurements. The reproducibility of echocardiographic measurements was evaluated by the Bland–Altman method (mean difference and 95% confidence interval). Statistical analysis was performed using standard statistical computer software (Statistica for Windows 10; StatSoft Inc, Tulsa, OK and R software ver.3.0.2 [http://cran.r-project.org/]). A \( P \) value of 0.05 was deemed to be statistically significant.
either group was receiving agents class I or III at enrollment. There was more frequent use of class I and III antiarrhythmic drugs during follow-up in the AF group; these were prescribed after the onset of AF. β-blockers were used as a continuation of pre-enrollment antihypertensive therapy in all but 2 cases (both in the AF group). The median RV-paced burden in the no AF group (100% [99%–100%]) and AF group (100% [97%–100%]) were similar ($P=0.41$). Groups with and without AF did not differ in terms of age, sex, body mass index, heart rate, diastolic blood pressure, frequency of comorbidities, CHADS2 score or RV lead location (apical versus septal). Patients with AF demonstrated higher systolic blood pressure measured after implantation (Table 1).

### Cardiac Structure and Function

AF was associated with higher baseline LV end-diastolic dimension, LV mass index, LV end-diastolic and end-systolic volume and end-systolic volume index, LA volume, LA volume index, LA dimension, and septal EMT and
lower LV ejection fraction, total LA strain, and LA strain at atrial contraction when compared with their peers without AF (Table 2). The only change in echocardiographic parameter during follow-up that differed between both groups was LA volume (significantly larger increase in LA volume in patients with AF, Table 3). LA volume outperformed other parameters (including LA volume index) in our analyses.

**Correlates of AF**

In a series of Cox proportional hazards models, LAV (Table 4) and LASac (Table 5) were shown to be associated with incident AF independent of other clinical and imaging variables. A model combining the LA parameters (Table 6) showed systolic blood pressure and LASac to be independently associated with AF. There was no significant interaction between any of these variables.

**Association of LA Characteristics With AF**

The ability of LA volume, LA strain at atrial contraction, septal EMT, and change in LA volume during follow-up to predict AF was estimated using receiver operator characteristic curves (Figure 2). The optimal cut point for LA strain at atrial contraction was 8.6% (sensitivity, 52%; specificity,
83%), for LA volume 62 mL (sensitivity, 69%; specificity, 61%), for septal EMT 105 ms (sensitivity, 83%; specificity, 42%), and for ΔLA volume 8.5 mL (sensitivity, 50%; specificity, 76%). Comparison of the area under the curves did not reveal significant differences between particular variables in the prediction of AF (LA strain at atrial contraction versus LA volume, P=0.02, versus septal EMT, P=0.42, and versus ΔLA volume, P=0.24; LA volume versus septal EMT, P=0.72, and versus ΔLA volume, P=0.45; septal EMT versus ΔLA volume, P=0.68).

### Incremental Value of LA Characteristics for Predicting AF

In the sequential logistic analysis, each subsequent parameter added to a previous model improved the predictive power for AF, namely adding septal EMT improved the model based on clinical risk factors included in the CHADS2 score; adding LA volume improved the model based on CHADS2 and EMT; adding ΔLA volume improved the model including CHADS2, EMT, and LA volume; and finally adding LA strain at atrial contraction improved the model based on CHADS2, EMT, LA volume, and ΔLA volume (Figure 3). Changing the order of entering the covariates so that septal EMT was added to the model, including CHADS2 and LA volume, revealed no significant incremental benefit from adding EMT (P=0.07).

### Influence of LA Size, Function, and Electromechanical Properties on the Occurrence of AF

The study population was divided into 4 groups using the optimal cut points for LA volume (62 mL) and LA strain at atrial contraction (8.6%): small LA volume with high and low LA strain and high LA volume with high and low LA strain. The incidence of AF in these groups was lowest when both were normal. AF was more frequent in groups with low LA strain at atrial contraction (ie, >8.6%) had a negative predictive value for AF of 88%, contributing to the discrimination process both below and above the optimal cut point for LA volume (negative predictive value in the group with LA volume below 62 mL was 93% and in the group with LA volume above 62 mL was 80%).

An analogous stratification was accomplished with the use of the optimal cut points for LA volume (62 mL) and for septal EMT (105 ms). The frequency of AF was highest with high LA volume and high EMT, and lowest with low LA volume and low EMT, with a significant difference noted only between groups with high both and low both components (P<0.02). Nonprolonged septal EMT (ie, <105 ms) was characterized by negative predictive value for AF of 91% (92% in the group with higher and 91% in the group with lower LA volume). Kaplan–Meier estimates of time to the first episode of AF showed that a greater rate of AF was associated with lower LA strain at atrial contraction and longer septal EMT (Figure 4).

### Reproducibility

The intra- and interobserver variability of LA measurements was assessed in 15 randomly selected examinations, analyzed twice by 2 observers (W.K. and M.S.) blinded to the patients’ clinical data on 2 separate days, and was for LA strain at atrial contraction −0.2% (−2.4; 2.0) and 1.6% (−3.3; 0.1), for positive LA strain −0.1% (−1.9; 1.6) and 1.1% (−0.1; 2.4), for total LA strain −0.4% (−3.1; 2.4) and −0.5% (−2.9; 1.9), for LA volume 1.5 mL (−1.7; 4.7) and 2.1 mL (−3.9; 8.1), and for EMT 2 ms (−10; 13) and −1 ms (−13; 10), respectively.

### Table 4. Independence of LA Volume in a Series of 3-Variable Cox Proportional Hazards Regression Models of Features Associated With the Occurrence of Atrial Fibrillation

<table>
<thead>
<tr>
<th>Variables Other Than LA Volume</th>
<th>Effect Size Associated With LA Volume</th>
<th>Model Fit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (P=0.36), sex (P=0.96)</td>
<td>1.02 (1.01–1.04)</td>
<td>0.003 267 0.31</td>
</tr>
<tr>
<td>LV end-diastolic dimension</td>
<td>1.02 (1.00–1.03)</td>
<td>0.045 259 0.48</td>
</tr>
<tr>
<td>LV ejection fraction (P=0.25), systolic blood pressure (P=0.009)</td>
<td>1.02 (1.00–1.03)</td>
<td>0.04 260 0.46</td>
</tr>
</tbody>
</table>

AIC indicates Akaike’s information criterion; CI, confidence interval; LA, left atrial; and LV, left ventricular.

### Table 5. Independence of Strain at LA Contraction in a Series of 3-Variable Cox Proportional Hazards Regression Models of Features Associated With the Occurrence of Atrial Fibrillation

<table>
<thead>
<tr>
<th>Variables Other Than LA Strain</th>
<th>Effect Size Associated With LA Strain</th>
<th>Model Fit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (P=0.82), sex (P=0.99)</td>
<td>0.88 (0.81–0.95)</td>
<td>0.001 274 0.39</td>
</tr>
<tr>
<td>LV end-diastolic dimension</td>
<td>0.90 (0.84–0.97)</td>
<td>0.006 267 0.53</td>
</tr>
<tr>
<td>LV ejection fraction (P=0.30), systolic blood pressure (P=0.02)</td>
<td>0.90 (0.83–0.97)</td>
<td>0.005 268 0.51</td>
</tr>
</tbody>
</table>

AIC indicates Akaike’s information criterion; CI, confidence interval; LA, left atrial; and LV, left ventricular.
Discussion
This study shows that the risk of AF in patients receiving dual chamber pacing is independently associated with abnormalities of LA size and function, rather than LV structural and functional characteristics or RV lead location. The addition of LA strain and EMT measurement to the evaluation of LA volume and clinical factors may be helpful to stratify the risk of first episode of AF in this population.
Chronically paced patients are at increased risk of developing AF. Specifically, AF is associated with cumulative

Figure 2. Receiver operating characteristic curves defining the usefulness of left atrial (LA) strain at atrial contraction, LA volume, and change in LA volume ($\Delta$LA volume) during follow-up, and septal EMT for prediction of atrial fibrillation. Values with optimal sensitivity and specificity (optimal cut points) are displayed as solid circles. Optimal cut points were 8.6% for LA strain at atrial contraction (sensitivity, 52%; specificity, 83%), 62 mL for LA volume (sensitivity, 69%; specificity 61%), 8.5 mL for follow-up $\Delta$LA volume (sensitivity, 50%; specificity, 76%), and 105 ms for septal EMT (sensitivity, 83%; specificity, 42%). AUC indicates area under the curve; and EMT, electromechanical conduction time.

Figure 3. Incremental value of left atrial (LA) characteristics for prediction of atrial fibrillation. CI indicates confidence interval; EMT, electromechanical conduction time; LASac, LA strain at atrial contraction; LAV, LA volume; and $\Delta$LAV, change in LA volume.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
<th>Model 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHADS2</td>
<td>$\chi^2$ 1.8 OR (95%CI)</td>
<td>$\chi^2$ 8.2 OR (95%CI)</td>
<td>$\chi^2$ 12.4 OR (95%CI)</td>
<td>$\chi^2$ 20.0 OR (95%CI)</td>
<td>$\chi^2$ 24.8 OR (95%CI)</td>
</tr>
<tr>
<td>CHADS2 + Septal EMT</td>
<td>$\chi^2$ 13.1 (0.88-1.54)</td>
<td>$\chi^2$ 13.8 (0.91-2.09)</td>
<td>$\chi^2$ 13.3 (0.86-2.04)</td>
<td>$\chi^2$ 1.9 (0.88-2.17)</td>
<td>$\chi^2$ 2.0 (0.81-2.05)</td>
</tr>
<tr>
<td>CHADS2 + Septal EMT + LAV</td>
<td>$\chi^2$ 13.1 (0.88-1.54)</td>
<td>$\chi^2$ 13.8 (0.91-2.09)</td>
<td>$\chi^2$ 13.3 (0.86-2.04)</td>
<td>$\chi^2$ 13.1 (0.88-2.17)</td>
<td>$\chi^2$ 2.0 (0.81-2.05)</td>
</tr>
<tr>
<td>CHADS2 + Septal EMT + $\Delta$LAV</td>
<td>$\chi^2$ 13.1 (0.88-1.54)</td>
<td>$\chi^2$ 13.8 (0.91-2.09)</td>
<td>$\chi^2$ 13.3 (0.86-2.04)</td>
<td>$\chi^2$ 13.1 (0.88-2.17)</td>
<td>$\chi^2$ 2.0 (0.81-2.05)</td>
</tr>
<tr>
<td>CHADS2 + Septal EMT + LAV + $\Delta$LAV</td>
<td>$\chi^2$ 13.1 (0.88-1.54)</td>
<td>$\chi^2$ 13.8 (0.91-2.09)</td>
<td>$\chi^2$ 13.3 (0.86-2.04)</td>
<td>$\chi^2$ 13.1 (0.88-2.17)</td>
<td>$\chi^2$ 2.0 (0.81-2.05)</td>
</tr>
</tbody>
</table>

Variable | Model 1 | Model 2 | Model 3 | Model 4 | Model 5 |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>CHADS2</td>
<td>$p=0.19$</td>
<td>$p=0.13$</td>
<td>$p=0.19$</td>
<td>$p=0.15$</td>
<td>$p=0.28$</td>
</tr>
<tr>
<td>Septal EMT</td>
<td>$p=0.14$</td>
<td>$p=0.083$</td>
<td>$p=0.070$</td>
<td>$p=0.12$</td>
<td>$p=0.12$</td>
</tr>
<tr>
<td>LAV</td>
<td>$p=0.049$</td>
<td>$p=0.009$</td>
<td>$p=0.009$</td>
<td>$p=0.009$</td>
<td>$p=0.019$</td>
</tr>
<tr>
<td>$\Delta$LAV</td>
<td>$p=0.008$</td>
<td>$p=0.008$</td>
<td>$p=0.008$</td>
<td>$p=0.008$</td>
<td>$p=0.008$</td>
</tr>
<tr>
<td>LASac</td>
<td>$p=0.90$</td>
<td>$p=0.90$</td>
<td>$p=0.90$</td>
<td>$p=0.90$</td>
<td>$p=0.90$</td>
</tr>
</tbody>
</table>

AUC 0.71; SE 0.056
AUC 0.67; SE 0.052
AUC 0.64; SE 0.059
AUC 0.60; SE 0.066

Atrial Fibrillation With Cardiac Pacing
Kosmala et al

7

Discussion
This study shows that the risk of AF in patients receiving dual chamber pacing is independently associated with abnormalities of LA size and function, rather than LV structural and functional characteristics or RV lead location. The addition of LA strain and EMT measurement to the evaluation of LA volume and clinical factors may be helpful to stratify the risk of first episode of AF in this population.
Chronically paced patients are at increased risk of developing AF. Specifically, AF is associated with cumulative
The usefulness of LA size quantification by volumetric measurements has been validated in various studies,12,13 which underpins readiness of this parameter to be exploited in AF risk stratification. A similar implementation of LA function and electromechanical conduction measurements is more challenging as it is constrained by a lower specificity and relatively poor correlation of LA functional and electrophysiological indexes with other corresponding cardiac parameters, as well as by problems with an accurate interpretation because of the interplay between atrial and ventricular performance.

In this study, we demonstrated that the likelihood of the occurrence of AF in pacemaker-dependent patients is associated with higher LA volume and lower LA strain at atrial contraction. In addition, changes in LA electromechanical characteristics including prolonged septal EMT also contributed to a better prediction of risk for AF; however, their input was less apparent in our analysis.

The findings build on earlier work showing LA functional assessment may extend the prognostic value of LA remodeling in AF in prediction of AF recurrence.8,9,18,29 LA strain precisely depicts LA function during particular phases of cardiac cycle and may reflect the amount of LA fibrosis—a potent contributor to AF.30 However, the magnitude of strain during atrial contraction, which was a predictor of AF in our study, is associated not only with intrinsic atrial contractility, but also depends on venous return and LV end-diastolic pressure. Atrial conduction abnormalities, associated with decreased electric connections and deposition of connective tissue between the myocytes, can lead to the decrease in atrial conduction velocity and shorten the wavelength of the reentrant wave fronts, resulting in a higher number of daughter wavelets promoting AF.19,31,32 Therefore, prolonged EMT reflects LA structural and electric remodeling and contributes to the prediction of AF.

Although high negative predictive values of LA strain at atrial contraction and septal EMT were noted both for higher and lower values of LA volume, measurement of these parameters seems to be particularly relevant in patients with more severe LA enlargement, as the incidence of AF in this group is much higher than in patients with smaller atrial size. Moreover, the potential differences in the performance of EMT as a predictor of AF between different LA volume strata (as suggested by our results) need further assessment in larger studies.

The importance of LA remodeling and its independence on other cardiac and extracardiac factors in the prediction of AF, as shown by this study, may reinforce the need for LA size, function, and electromechanical properties to be considered when estimating AF risk. However, although our observations are concordant with the hypothesis that the increase in LA size or deterioration of function are contributors to the development of AF, this arrhythmia promotes the progression of LA dilatation, which in turn may cause more AF. A study design involving multiple sequential measurements of AF burden and LA size and function could address this question. From the standpoint of risk prediction, however, it seems more feasible to image the LA rather than monitor for AF, at least in the absence of a pacemaker.

Limitations
Important limitations of LA strain evaluation, particularly its low signal-to-noise ratio, the challenges of tracking the thin-walled myocardium and intersoftware differences in speckle tracking algorithms, are important in the interpretation of these measurements.33 These drawbacks, together with the necessity of expertise and skilled operators, may restrict the use of this
technique. Measurement of EMT depends on the quality of ECG (onset of P wave), as well as echo imaging. However, there was a low exclusion rate because of poor ECG (<4%), and the reproducibility of EMT was satisfactory. Furthermore, there was limited available information on pharmacological treatment and on blood pressure control during follow-up—specifically, angiotensin-converting enzyme inhibitors may influence the development of AF, although there is no reason to expect that these agents would have been used differentially between groups. We used CHADS2 score, originally developed for the assessment of the risk of stroke in patients with nonhemodynamic AF, for the evaluation of clinical risk for the occurrence of AF, based on previous reports that demonstrated the usefulness of CHADS2 score in the prediction of AF. Finally, because of the lack of external validation, the estimated thresholds for LA volume, LA strain, and EMT in stratifying AF risk should be used with caution.

Conclusion
AF is relatively common in patients with permanent pacemakers, but there is no primary prevention strategy for AF complications. The combination of LA volume measurement with LA strain and electromechanical conduction assessment seems to identify low and high risk groups for AF.

Sources of Funding
The parent trial (ProtectPACE) was funded by Medtronic.

Disclosures
None.

References
Atrial fibrillation (AF) is a known complication of right ventricular pacing, and as it poses a significant medical and economic burden, appropriate risk-prediction for AF is necessary to improve the cost-effectiveness of diagnostic and therapeutic measures directed toward preventing this arrhythmia and its well-known consequences. Left atrial (LA) remodeling, including changes in LA size, function, and electric properties, provides a substrate for AF; however, LA assessment has not been recommended for routine use in risk evaluation because of insufficient validation in a broader spectrum of patient populations. Notwithstanding this, recent data indicate that atrial indices might provide incremental benefit in the AF risk stratification procedures. Accordingly, we aimed to investigate the predictive significance of LA characteristics, including LA volume, LA strain, and LA electromechanical conduction time, in the development of AF in patients undergoing dual chamber pacemaker implantation. We showed that the risk of AF in the above population was independently associated with abnormalities of LA size and function, rather than LV structural and functional characteristics or right ventricular lead location. Thus, the addition of LA strain and electromechanical conduction time measurement to the evaluation of LA volume and clinical factors might be helpful to stratify the risk of the occurrence of AF. Further research should verify the validity of these findings in other subsets of patients, including those without permanent pacemakers.
Incremental Value of Left Atrial Structural and Functional Characteristics for Prediction of Atrial Fibrillation in Patients Receiving Cardiac Pacing

Wojciech Kosmala, Makoto Saito, Gerry Kaye, Kazuaki Negishi, Nick Linker, Michael Gammage and Thomas H. Marwick
on behalf of the Protect-Pace Investigators

*Circ Cardiovasc Imaging*. 2015;8:
doi: 10.1161/CIRCIMAGING.114.002942

*Circulation: Cardiovascular Imaging* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-9651. Online ISSN: 1942-0080

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circimaging.ahajournals.org/content/8/4/e002942

Data Supplement (unedited) at:
http://circimaging.ahajournals.org/content/suppl/2015/04/10/CIRCIMAGING.114.002942.DC1
Supplemental Material

Recruiting Centres

Princess Alexandra Hospital, Woolloongabba, Queensland, Australia (Dr. Gerald Kaye)
Royal Brisbane and Womens Hospital, Brisbane, Australia (Dr. Paul Martin)
Leeds General Infirmary, Leeds, UK (Dr. Chris Pepper)
Colchester General Hospital, Colchester, UK (Dr. Kare Tang)
Christchurch Hospital, Christchurch, New Zealand (Dr. Ian Crozier)
Blackpool Victoria Hospital, Blackpool, UK (Dr. Graham Goode)
Royal Adelaide Hospital, Adelaide, Australia (Dr. Glenn Young)
New Cross Hospital, Wolverhampton, UK (Dr. Sanjiv Petkar)
Princess Royal Hospital, Orpington, Kent, UK (Dr. Ed Langford)
The James Cook University Hospital, Middlesbrough, UK (Dr. Nicholas John Linker)
Royal Bournemouth Hospital, Bournemouth, UK (Dr. Adrian Rozkovec)
St Thomas Hospital, London, UK (Dr. Aldo Rinaldi)
University Hospital of Wales, Cardiff, UK (Dr. Zaheer Yousef)
Auckland City Hospital, Auckland, New Zealand (Dr. Nigel Lever)
The Prince Charles Hospital, Brisbane, Australia (Dr. Russell Denman)
Calvary Wakefield Hospital, Adelaide, Australia (Dr. Glen Young)
Norfolk and Norwich University Hospital, Norfolk, UK (Dr. Ian Williams)
Flinders Medical Centre, Adelaide, Australia (Dr Andrew McGavigan)