Mechano-Electrical Interaction Late After Fontan Operation
Relation Between P-Wave Duration and Dispersion, Right Atrial Size, and Atrial Arrhythmias

Tom Wong, MRCP; Periklis A. Davlouros, MD; Wei Li, MD, PhD; Catherine Millington-Sanders, MBBS; Darrel P. Francis, MRCP; Michael A. Gatzoulis, MD, PhD, FESC

Background—The growing population with Fontan operation surviving into adulthood has significant morbidity and mortality rates from recurrent atrial tachyarrhythmias. We hypothesized that the structural characteristics and electrical behavior of atria may differ in these patients compared with those without arrhythmias.

Methods and Results—We studied 33 consecutive patients (age, 25.4±9.5 years) with Fontan circulation, of whom 19 had a history of documented sustained atrial tachyarrhythmias. We analyzed their clinical and investigational data, including echocardiographic assessment of atrial dimensions and surface 12-lead ECG measurement of the P-wave duration and its dispersion between leads. Twenty age- and sex-matched healthy control subjects were also studied. First, patients who had the Fontan procedure overall had longer P-wave duration (144±33 versus 100±7 ms, \(P<0.001\)) and greater P-wave dispersion (74±33 versus 34±9 ms, \(P<0.001\)) than control subjects. Among the patients who had the Fontan procedure, those with atrial tachyarrhythmias had longer P-wave duration (159±28 versus 123±28 ms, \(P<0.001\)) and greater P-wave dispersion (91±30 versus 50±19 ms, \(P<0.001\)) than those without. Second, the patients with atrial tachyarrhythmias who had the Fontan procedure had larger right atrial dimension than those without arrhythmias (6.4±1.4 versus 5.0±1.0 cm, \(P=0.01\)). Third, both P-wave duration and dispersion were significantly correlated to right atrial dimension within the Fontan group (\(r=0.55, P=0.002\), and \(r=0.56, P=0.002\), respectively).

Conclusions—Patients with atrial tachyarrhythmias late after Fontan operation have longer P-wave duration and P-wave dispersion and larger right atrial dimension than those without the arrhythmias; these abnormalities are interrelated. This observation represents an atrial mechano-electrical remodeling phenomenon in parallel to an increase in arrhythmia propensity in this vulnerable population and warrants further investigation. (Circulation. 2004;109:2319-2325.)

Key Words: Fontan procedure ■ arrhythmia ■ atrium

The ever-growing population of Fontan patients surviving into adulthood is highly susceptible to disabling symptoms and even fatal complications from recurrent atrial tachyarrhythmias (atrial fibrillation [AF] and intra-atrial re-entry tachycardia [IART]).1–9 Despite the exquisite vulnerability of this cohort to the consequences of late atrial tachyarrhythmias, little is known about structural electrical characteristics and their interplay among patients who have the arrhythmias and those who do not.

Structural remodeling of the right atrium is ubiquitous in long-term survivors after the Fontan procedure. By analogy to patients without congenital heart disease, this may have led to electrical remodeling and heterogeneity, which in turn could provide a substrate for sustained atrial tachyarrhythmias.10–16 We hypothesized Fontan patients demonstrating atrial tachyarrhythmias may differ from those who do not in structural characteristics (particularly atrial size) and in electrical behavior (represented by P-wave characteristics on the 12-lead ECG).

Methods

Patients

This study is a retrospective analysis of all patients with previous Fontan type operation(s) for univentricular physiology attending the Royal Brompton Adult Congenital Heart Disease Programme in 2000. Patients were identified from the program’s database; those in permanent atrial arrhythmia and or with pacemakers were excluded from the study. The control group consisted of age- and sex-matched healthy subjects with a structurally normal heart and without a history of arrhythmia, randomly sampled from our database.

Data Acquisition

Background demographics, surgical details, and clinical characteristics were obtained from the hospital records. Standard ECG and...
transthoracic echocardiograms (ECHO) during sinus rhythm performed at the clinic were analyzed by 2 blinded, experienced investigators.

**ECG Markers**

All surface ECGs were recorded at paper speed of 25 mm/s and 1 mV/cm standardization. Measurements were obtained manually from the printout with electronic calipers (Jensen digital caliper, 66 to 220, Central Tools, Inc) and the aid of a magnifying glass. P-wave duration was defined as the interval between the onset (the junction between the isoelectric line and the beginning of P-wave deflection) and the offset (the junction between the end of the P-wave deflection and the isoelectric line) of the P-wave (Figure 1). P-wave duration was measurable in at least 8 ECG leads in all patients. P-wave dispersion was defined as the difference between the maximum and the minimum P-wave duration in any of the measurable leads. Intraobserver and interobserver variability was assessed in a random sample of 15 ECG (10 from patients who had the Fontan procedure and 5 from control subjects) by a second investigator. P-wave amplitude, PQ interval, and QRS duration were also measured in the standard way.

**Transthoracic Echocardiography**

All patients underwent comprehensive echocardiographic assessment at the time of ECG acquisition, including 2-dimensional imaging, Doppler, color flow mapping, and M-mode, according to our clinic protocol. Right and left atrial sizes were measured transversely from the apical view and were analyzed off-line. In patients with a total cavopulmonary connection (all intracardiac), the size of the native right atria (but not the intra-atrial baffle) was included in the analysis. Because of the heterogeneity of cardiac anatomy, we quantified ventricular function subjectively from multiple 2-dimensional echocardiographic views by grading it from I to IV: I, normal, ejection fraction (EF) >60%; II, mild dysfunction, EF 40% to 59%; III, moderate dysfunction, EF 20% to 39%; and IV, severe dysfunction, EF <20%. Atrioventricular valve regurgitation was also graded on a scale from I (absent) to IV (severe). 17

**Data Analysis**

Data are expressed as frequency for nominal variables and as mean±SD for continuous variables. Differences between the two groups were assessed by an unpaired Student’s t test for variables with normal distribution. One-way ANOVA with Bonferroni post hoc tests was used to compare continuous variables in more than 2 groups. Pearson’s correlation was used for determining possible association between continuous variables. Data analysis was performed with SPSS for windows (version 10).

**Results**

**Patients**

Our study population comprised 33 consecutive patients with Fontan modifications fulfilling the inclusion criteria (Table 1). Their mean age was 25.4±9.5 years (range, 11 to 47 years), and 13 were male. Their underlying anatomic diagnoses were tricuspid atresia in 20, double-inlet ventricle in 9, isomeric atrial appendages in 2, and pulmonary stenosis with intact interventricular septum in 2. The index Fontan modification was performed at a mean age of 13.0±8.2 years (range, 1 to 29 years); patients had subsequently been followed up for 12.0±5.5 years (range, 2 to 25 years). Seven patients had undergone redo Fontan operation, and 1 patient had undergone a second Fontan revision. Six patients had redo surgery because of Fontan circuit obstruction, of whom 1 patient had further Fontan conversion to a total cavopulmonary connection 7 years later for restenosis and paroxysmal atrial tachyarrhythmias. The seventh patient had redo surgery because of cyanotic right-sided pulmonary AV malformation; the original classic Glenn anastomosis was converted to bidirectional Glenn combined with revision of atrioventricular connection to an intra-atrial tunnel-type Fontan. Twenty-five patients had an atrio pulmonary connection, 2 an atrioventricular connection, and 7 a total cavopulmonary connection (including 1 who had previously undergone atrio pulmonary connection).

Patients were divided into 2 subgroups, on the basis of their history of arrhythmia. The arrhythmia group con-
sisted of the 19 patients who had had at least 1 episode of sustained atrial tachyarrhythmia by 2000. Sustained tachyarrhythmia was defined as AF and/or IART that was clinically apparent and documented by ECG, Holter recording, or ECG strip before electrical cardioversion. Among these 19 patients, 16 had undergone atriopulmonary connection, 1 atrioventricular connection, and 3 total cavopulmonary connection.

The no-arrhythmia group consisted of the 14 patients who had not had such events. Among these 14, 9 had undergone atriopulmonary connection, 1 atrioventricular connection, and 4 total cavopulmonary connection. There was no significant association between the type of operation and the presence of arrhythmia.

Twenty healthy control subjects, matched for age and sex, were also studied. Ten patients from the arrhythmia group had a history of AF, 12 had IART, and 3 had both AF and IART. All 19 patients in the arrhythmia group were taking class III antiarrhythmic drugs: 14 were taking amiodarone and 5 were taking sotalol. In addition, 6 patients in this group were taking more than 1 antiarrhythmic drug: 5 were taking digoxin, 1 was taking propranolol, 1 was taking disopyramide, and 1 was taking propafenone. No patients in the no-arrhythmia group and no control subjects were receiving antiarrhythmic therapy. No patient from this cohort had undergone either surgical or percutaneous catheter ablation for arrhythmia.

### ECG Characteristics

#### Maximum P-Wave Duration

Maximum P-wave duration (ie, measured in the lead that gives the longest value) was longer in the overall Fontan group compared with the control group (144±33 versus 100±7 ms, *P*<0.001). Among the patients who had the Fontan procedure, the arrhythmia group had longer maximum P-wave duration than the no-arrhythmia group (159±28 versus 123±28 ms, *P*<0.001, Figure 2A). Maximum P-wave duration did not differ in patients who had atriopulmonary or atrioventricular connection compared with those with total cavopulmonary connection (149±29 versus 122±40 ms, respectively, *P*<0.05). Maximum P-wave duration was not related to age (*r* =0.27, *P* =0.13) or time since Fontan operation (*r* =0.27, *P* =0.13).

Receiver operating characteristic (ROC) analysis showed that the accuracy of maximum P-wave duration in identifying patients with a history of sustained atrial tachyarrhythmia, who had the Fontan procedure, was 82%. A maximum P-wave duration of >134 ms had a sensitivity of 84% and specificity of 64% in distinguishing the patients with arrhythmia.

#### P-Wave Duration in Lead II

P-wave duration measured in lead II (a commonly used convention) was prolonged in the patients who had the Fontan procedure compared with control subjects (120±42 versus 93±8 ms, *P* =0.007). However, it was not different between the two Fontan subgroups (arrhythmia group, 126±48 ms versus no-arrhythmia group, 106±23 ms, *P* =0.16).

### TABLE 1. Clinical and Surgical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Arrhythmia Group (n=19)</th>
<th>No-Arrhythmia Group (n=14)</th>
<th><em>P</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>26.9±9.0</td>
<td>24.7±10.5</td>
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</tr>
<tr>
<td>Male/female, n</td>
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<td>5/9</td>
<td></td>
</tr>
<tr>
<td>Diagnosis</td>
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<td></td>
<td></td>
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<tr>
<td>Tricuspid atresia</td>
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<td>7</td>
<td></td>
</tr>
<tr>
<td>Double-inlet ventricle</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Isomeric atrial appendages</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Pulmonary stenosis with intact interventricular septum</td>
<td>0</td>
<td>2</td>
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<tr>
<td>Previous interventions</td>
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<td>Blalock-Taussig shunt(s)</td>
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<tr>
<td>Other arteriopulmonary shunt(s)</td>
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<td></td>
</tr>
<tr>
<td>Pulmonary artery banding</td>
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<td>1</td>
<td></td>
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<tr>
<td>Glenn</td>
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<td>1</td>
<td></td>
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<tr>
<td>Fontan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atriopulmonary connection</td>
<td>16</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Atrioventricular anastomosis</td>
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<td>1</td>
<td></td>
</tr>
<tr>
<td>Total cavopulmonary connection</td>
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<td>4</td>
<td></td>
</tr>
<tr>
<td>Fontan revision</td>
<td>4</td>
<td>3</td>
<td></td>
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<tr>
<td>Time of Fontan operation, y</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Age at 1st Fontan</td>
<td>14.6±8.7</td>
<td>10.9±7.6</td>
<td>NS</td>
</tr>
<tr>
<td>Age at Fontan revision</td>
<td>20.5±6.0</td>
<td>26.7±12.3</td>
<td>NS</td>
</tr>
<tr>
<td>Time since 1st Fontan</td>
<td>10.7±5.5</td>
<td>13.7±5.6</td>
<td>NS</td>
</tr>
<tr>
<td>Time since last Fontan revision</td>
<td>7.3±4.8</td>
<td>5.7±5.1</td>
<td>NS</td>
</tr>
</tbody>
</table>
were 11.5, 10.5, and 14.8 ms, respectively, and the corre-
mum, minimum P-wave durations and P-wave dispersion
respectively. The interobserver standard deviation for maxi-
num, minimum P-wave durations and P-wave dispersion
were 10.2, 6.6, and 10.9 ms, respectively, and the correspond-
ment P-wave duration in the 12 leads) was greater in the
arrhythmia group than in the no-arrhythmia group (91 ± 30
versus 50 ± 19 ms, P < 0.001, Figure 2B). P-wave dispersion
did not differ between patients who had atiopulmonary or
atrioventricular connection and those had total cavopulmo-
nary connection (77 ± 32 versus 60 ± 33 ms, P = 0.59). As with
P-wave duration, P-wave dispersion was not related to age
(r = 0.14, P = 0.42) nor to time since Fontan operation
(r = 0.27, P = 0.13).
Among the patients who had the Fontan procedure, ROC
analysis showed that the accuracy of P-wave dispersion in
identifying the arrhythmia group was 87%. A P-wave disper-
sion of > 66 ms had sensitivity of 79% and specificity of 79%
in distinguishing the patients with arrhythmia.

Other Measurements and Reproducibility
There was no difference in P-wave amplitudes, QRS dura-
tion, and PQ duration between the two Fontan subgroups or
between the arrhythmic Fontan group and control group
(Table 2). The intra-observer standard deviation for maxi-
mum, minimum P-wave durations and P-wave dispersion
were 10.2, 6.6, and 10.9 ms, respectively, and the corre-
sponding interobserver variability was 0.05%, 0.22%, and
0.48%, respectively. The percentage difference in maximum,
minimum P-wave durations and P-wave dispersion were
2.5%, 3.2%, and 5% within observers and 2.7%, 4.6%, and
6% between observers.

Echocardiographic Characteristics
Right atrial dimension was greater in the arrhythmia group
than in the no-arrhythmia group (6.4 ± 1.4 versus 5.0 ± 1.0 cm,
P = 0.01). There was no significant difference in right atrial
dimension between patients who had atiopulmonary or
atrioventricular connection and those had total cavopulmo-
nary connection (5.9 ± 1.4 versus 5.2 ± 2.1 cm, P = 0.38).
There were no significant differences in left atrial dimension,
degree of systemic atiopulmonary valve regurgitation, and
systemic ventricular function between the two patient sub-
groups (Table 3). Right atrial dimension was not related to
age (r = 0.21, P = 0.36) or to time since Fontan operation
(r = 0.07, P = 0.78).

Relation Between ECHO and ECG Measurements
Both maximum P-wave duration and P-wave dispersion
correlated significantly with right atrial dimension (r = 0.55,
P = 0.002 and r = 0.56, P = 0.002, respectively, Figure 3). In
contrast, there was no correlation between left atrial dimen-
sion and maximum P-wave duration (r = 0.37, P = 0.09) or
P-wave dispersion (r = 0.34, P = 0.15).

Discussion
Our study shows that maximum P-wave duration and
P-wave dispersion are prolonged in adults who had previ-
ous Fontan procedures compared with healthy controls;
these prolongations are even greater in Fontan patients
with a history of sustained atrial tachyarrhythmias than in
those without. Right atrial size is also significantly larger
in the arrhythmia group compared with the no-arrhythmia
group. Furthermore, these electrical and structural abnor-
malities are interrelated.

Adult Fontan
Meticulous follow-up and early treatment of complications
have allowed more patients with Fontan modifications to
survive into adulthood. This ever-increasing population, how-
ever, remains particularly vulnerable to late atrial
tachyarrhythmias (AF and IART). The cumulative fre-
cuency of electrographically documented, late sustained atrial
tachyarrhythmia in our cohort was 61%, at a mean of
12.0 ± 5.5 years from the index Fontan procedure, despite the
exclusion—by study design—of patients with permanent
atrial arrhythmias or pacemakers. This high prevalence of
arrhythmias in this patient population mirrors the findings
from previous studies.

ECG Markers
We have found that as a group, patients who had the Fontan
procedure had a significantly longer maximum P-wave dura-
tion and P-wave dispersion than healthy controls. Among the
TABLE 2. Electrocardiographic Data

<table>
<thead>
<tr>
<th></th>
<th>Arrhythmia Group (n=19)</th>
<th>No-Arrhythmia Group (n=14)</th>
<th>Control Group (n=20)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, bpm</td>
<td>62.1±10.0</td>
<td>75.4±16.1</td>
<td>73.7±11.4</td>
<td>&lt;0.05* NS</td>
</tr>
<tr>
<td>P-wave duration, ms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum P-wave duration</td>
<td>159.0±27.9</td>
<td>122.6±28.3</td>
<td>99.6±7.1</td>
<td>&lt;0.001* &lt;0.05*</td>
</tr>
<tr>
<td>Minimum P-wave duration</td>
<td>72.3±18.1</td>
<td>68.3±8.1</td>
<td>65.7±8.1</td>
<td>NS NS</td>
</tr>
<tr>
<td>P-wave dispersion</td>
<td>90.7±30.0</td>
<td>50.3±18.5</td>
<td>33.9±8.9</td>
<td>&lt;0.001* &lt;0.05*</td>
</tr>
<tr>
<td>P-wave amplitude, ms</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum P-wave amplitude</td>
<td>3.0±1.8</td>
<td>2.5±0.9</td>
<td>1.6±0.3</td>
<td>NS NS</td>
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<tr>
<td>Minimum P-wave amplitude</td>
<td>0.8±0.4</td>
<td>0.9±0.3</td>
<td>0.8±0.1</td>
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<tr>
<td>P-wave amplitude dispersion</td>
<td>2.2±1.5</td>
<td>1.6±0.7</td>
<td>0.8±0.2</td>
<td>NS NS</td>
</tr>
<tr>
<td>PQ interval, ms</td>
<td></td>
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<tr>
<td>Maximum PQ interval</td>
<td>221.6±53.2</td>
<td>188±41.7</td>
<td>165.8±29.2</td>
<td>NS NS</td>
</tr>
<tr>
<td>Minimum PQ interval</td>
<td>154.8±36.7</td>
<td>134.1±34.5</td>
<td>124.6±18</td>
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<td>PQ interval dispersion</td>
<td>66.8±30.3</td>
<td>54.0±28.6</td>
<td>41.2±26.4</td>
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</tr>
<tr>
<td>QRS duration, ms</td>
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<tr>
<td>Maximum QRS duration</td>
<td>133.6±21.8</td>
<td>118.3±22.0</td>
<td>98.4±11.6</td>
<td>NS NS</td>
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<tr>
<td>Minimum QRS duration</td>
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<td>72.2±25.8</td>
<td>60.8±9.1</td>
<td>NS NS</td>
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<tr>
<td>QRS dispersion</td>
<td>53.3±21.2</td>
<td>46.1±14.0</td>
<td>37.6±14.8</td>
<td>NS NS</td>
</tr>
</tbody>
</table>

*P<0.05.

Fontan patients, those with arrhythmia had even longer maximum P-wave duration and greater P-wave dispersion than those without arrhythmia. Maximum P-wave duration ≥134 ms and P-wave dispersion ≥66 ms had a good sensitivity and specificity in identifying the patients with a history of atrial tachyarrhythmias who had the Fontan procedure.

Our data are in concordance with studies in patients without congenital heart disease who have lone paroxysmal AF, and studies in patients with persistent AF after coronary bypass graft surgery. However, studies in patients with Fontan circulation appeared to have shown conflicting results. Weber et al found no difference between P-wave duration measured (by convention) from lead II of surface ECG and propensity of atrial tachyarrhythmias. More recently Tuzcu et al showed a difference when P-wave duration was assessed by signal-averaged ECG.

The apparent conflict probably is due to the method by which P-wave duration was assessed. We suspect that the abnormal right atrial structure and disposition in patients who had the Fontan procedure may render the convention of measuring P-wave duration from a single predetermined ECG lead suboptimal. Atrial tissue heterogeneity and grossly abnormal atrial anatomy result in highly variable atrial activation among patients who had the Fontan procedure. Therefore, P-wave duration measured from a single constant lead may not provide a consistent platform for comparison. Two strategies to circumvent this inconsistency are (1) to measure the P-wave in 3 dimensions and then apply signal averaging, as used by Tuzcu et al, or (2) the simpler approach of selecting the longest P-wave duration in the 12-lead surface ECG, as applied in this study.

This hypothesis is further substantiated by the consistent finding of greater P-wave dispersion in patients with Fontan circulation and its relation to right atrial size. A more heterogeneous and tortuous pathway of atrial activation in addition to a prolonged activation time in the enlarged Fontan atria may be responsible for the widening of P-wave dispersion.

TABLE 3. Echocardiographic Data

<table>
<thead>
<tr>
<th></th>
<th>Arrhythmia Group (n=19)</th>
<th>No-Arrhythmia Group (n=14)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>LA dimensions, cm</td>
<td>5.3±1.1</td>
<td>4.9±0.9</td>
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<td>RA dimensions, cm</td>
<td>6.3±1.4</td>
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<td>Atrioventricular valve regurgitation</td>
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<td>9</td>
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</tr>
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<td>Grade IV</td>
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<td>Systemic ventricular function</td>
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<tr>
<td>Grade I</td>
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<td>Grade II</td>
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<td>Grade III</td>
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<tr>
<td>Grade IV</td>
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</tbody>
</table>

LA indicates left atrium; RA, right atrium.
Atrioventricular valve regurgitation: I, absent; II, mild; III, moderate; IV, severe.
Systemic ventricular function: I, normal (EF >60%); II, mild dysfunction (EF, 40% to 59%); III, moderate (EF, 20% to 39%); IV, severe (EF<20%).

*P<0.05.
Study Limitations
The fact that patients with arrhythmia who had the Fontan procedure were all receiving class III antiarrhythmic agents, whereas none of the patients without arrhythmia were receiving similar therapy, is an important potential confounding factor. Antiarrhythmic agents are known to affect conduction and could, therefore, in principle, affect P-wave duration. However, objective studies have shown that there is no significant effect of sotalol on P-wave duration. More importantly, it is not plausible that antiarrhythmic therapy could cause the right atrium to dilate so significantly. Clearly, there is a relation between right atrial size and P-wave duration (and dispersion) in our patients who had the Fontan procedure. It is therefore biologically far more plausible that the mechanism runs from disease to atrial dimension and thence to P-wave properties than in any other direction.

Conclusions
Maximum P-wave duration and P-wave dispersion on sinus 12-lead surface ECG are longer in patients late after Fontan procedures compared with healthy controls. Both of these P-wave measurements are even longer in Fontan patients with history of sustained atrial tachyarrhythmias and correlated well with atrial dimension. This observation represents an atrial mechano-electrical remodeling phenomenon parallel to an increase in arrhythmia propensity in this vulnerable population and warrants further investigation.

Acknowledgments
Dr Wong is funded by the Wellcome Trust. Dr Davlouros received support from the Royal Brompton Clinical Research Committee and the Hellenic Society of Cardiology and Dr Gatzoulis from the British Heart Foundation. The authors are indebted to the late Anne Munro for her undivided secretarial support.

References

Mechano-Electrical Pathogenesis of Atrial Arrhythmia in Fontan Circulation
Because of chronic pressure overload and the absence of a subpulmonary ventricle, the right atrium is invariably distended in adults who had previous Fontan procedures. Our finding that distention is greater in the arrhythmia group than in any other direction. Thence to P-wave properties than in any other direction. Because of chronic pressure overload and the absence of a subpulmonary ventricle, the right atrium remodels and dilates. The structural remodeling and dilatation occur in parallel to the change in electrophysiological properties, as manifested by the atrial conduction delay and the imbalance of the conduction homogeneity. Consequently, the alteration of atrial structural characteristics and electrical behavior either in isolation, or—more likely—in combination, provide the substrate to promote and sustain reentry arrhythmias (AF and IART).22

Figure 3. Correlation between right atrial dimension and A, maximum P-wave duration, and B, P-wave dispersion in patients with previous Fontan procedures.


Mechano-Electrical Interaction Late After Fontan Operation: Relation Between P-Wave Duration and Dispersion, Right Atrial Size, and Atrial Arrhythmias

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_Circulation_. 2004;109:2319-2325; originally published online May 10, 2004; doi: 10.1161/01.CIR.0000129766.18065.DC

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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