Serial assessment of left ventricular diastolic function after Fontan procedure

Y F Cheung, D J Penny, A N Redington

Abstract

Objective—To assess longitudinal changes in systemic ventricular diastolic function late after the Fontan procedure.

Design and patients—Prospective study of 13 patients at 2.8 (2.0) years (early) and again at 11.4 (2.0) years (late) after the Fontan procedure by Doppler echocardiography with simultaneous ECG, phonocardiogram, and respirometer.

Setting—Tertiary paediatric cardiac centre.

Results—The isovolumic relaxation time (IVRT) was significantly longer, and E wave deceleration time, E and A wave velocities, and E:A velocity ratio were reduced compared to normal both early and late after the procedure. The mean (SD) z score of IVRT decreased significantly from +2.50 (1.00) to +1.24 (0.80) (p = 0.002), and the z score of the E wave deceleration time decreased from −1.69 (1.31) to −2.40 (1.47) (p = 0.03) during follow up. The A wave deceleration time also tended to decrease (early 80 (12) ms v late 73 (11) ms, p = 0.13) with increased follow up. There were no changes of the E and A wave velocities and E:A velocity ratio. The E wave velocity was inversely related to IVRT both early (r = −0.82, p = 0.001) and late (r = −0.59, p = 0.034) after the operation. The prevalence of diastolic flow during isovolumic relaxation decreased from 85% (11/13) to 38% (5/13) (p = 0.04), while that of mid diastolic flow increased from 23% (3/13) to 77% (10/13) (p = 0.02) between the two assessments.

Conclusions—Left ventricular diastolic function remains highly abnormal late after the Fontan procedure. The longitudinal changes demonstrated on follow up are compatible with reduction of left ventricular compliance in addition to persisting abnormalities of relaxation.

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Keywords: diastolic function; Fontan procedure

A progressive deterioration in functional status occurs during long term follow up of patients after the Fontan procedure.1–3 The absence of other predicting risk factors suggests that the Fontan state itself or the transition to it is the risk factor for such decline.4 However, the precise mechanism to account for such deterioration is unknown. While ventricular systolic function is relatively well preserved after the Fontan procedure,4,5 diastolic dysfunction has been reported in several studies of early and medium term survivors.6–8 The acute preload reduction which occurs as a result of transition to the Fontan state leads to an increase in mass:volume ratio and inappropriate “hypertrophy” of the left ventricle.9 Coincident with this, there is evidence of impaired ventricular relaxation manifested by prolonged isovolumic relaxation time (IVRT),6,7 a reduction in the early rapid filling,6–8 abnormal wall motion,9 and intracavitary flow during isovolumic relaxation.8 Regression of this hypertrophy has been shown in follow up studies demonstrating a ventricular mass:volume ratio similar to that preoperatively at one to three years postoperation,4,11 although abnormal ventricular relaxation remains.7 Besides its deleterious effect on early diastolic filling, impaired relaxation may result in a state of reduced ventricular compliance. Thus, in hypertrophic cardiomyopathy, delayed relaxation with continued interaction of the contractile elements results in an increase in intraventricular pressure in all phases of diastolic filling.10 Furthermore, there is evidence that chronic reduction of preload to the left ventricle can cause reduction in compliance.11 This could have important adverse consequences were it to occur in patients after the Fontan procedure, in whom a chronic reduction of pulmonary blood flow results in long term preload reduction of the ventricle.11

This study examines prospectively Doppler indexes of left ventricular diastolic function in a cohort of patients studied in detail early and late postoperatively in order to assess any longitudinal changes associated with the Fontan circulation.

Patients and method

Thirteen subjects (seven male and six female), who underwent the Fontan operation at mean (SD) 5.5 (3.2) (range 1.5 to 12.5) years old, were studied at 2.8 (2.0) (early) and again 11.4 (2.0) years (late) after the operation. These subjects belonged to the cohort of 25 patients described in our previous study on incoordinate ventricular relaxation after the Fontan procedure.6 Twelve patients were not available for follow up owing to death (n = 5), migration (n = 2), refusal (n = 2), and loss of contact (n = 3). Of the 13 patients restudied, nine had tricuspid atresia (with the ventriculo-arterial connection concordant in seven, discordant in one, and double outlet left ventricle in one), three had double inlet ventricle, and one had pulmonary atresia with intact ventricular septum. Before the Fontan procedure, nine
patients had undergone insertion of a systemic pulmonary arterial shunt and two had undergone pulmonary arterial banding. The remaining two had undergone the Fontan operation as a primary procedure. Atrophicpulmonary anastomosis was performed in 10 patients, total cavopulmonary connection in one, and in two the rudimentary ventricle was incorporated into the anastomosis.

DOPPLER ECHOCARDIOGRAPHIC ASSESSMENT

Doppler echocardiographic assessment was performed as described in our previous study. Simultaneous respirometer, ECG, and phonocardiograms were recorded. All recordings were made at a paper speed of 100 mm/s. The previous recordings, obtained in identical fashion, from all 13 subjects were retrieved for reanalysis.

The R-R interval, the duration of total electromechanical systole (TEMS), IVRT, and deceleration time of the atrioventricular flow occurring between the early diastolic flow and atrial systolic flow. IVRT and E wave velocity was assessed by linear regression analysis. A value of \( p < 0.05 \) was considered significant.

Results

TIME INTERVALS

The R-R interval was significantly longer at follow up than at the first assessment (885 (111) ms vs 723 (109) ms, \( p < 0.001 \)). In contrast, the z score of IVRT decreased from +2.50 (1.00) to +1.24 (0.80) (\( p = 0.002 \)) (fig 1), while the z score of E wave deceleration time decreased from −1.69 (1.31) to −2.40 (1.47) (\( p = 0.03 \)). Despite the shortening of the age standardised IVRT on late follow up, it remained significantly longer than normal (table 1). In contrast, the age standardised E wave deceleration time remained persistently shorter than normal. The A wave deceleration time tended to decrease with time (early 80 (12) ms vs late 73 (11) ms, \( p = 0.13 \)).

<table>
<thead>
<tr>
<th>Time intervals, and atrioventricular flow velocity and ratios, early and late after the Fontan operation</th>
<th>Early</th>
<th>Late</th>
<th>Normal reference</th>
<th>Early versus late (p value)</th>
<th>Normal versus early (p value)</th>
<th>Normal versus late (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-R interval (ms)</td>
<td>885 (111)</td>
<td>723 (109)</td>
<td>–</td>
<td>&lt; 0.001</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>IVRT (ms)</td>
<td>88 (13)</td>
<td>86 (7)</td>
<td>–</td>
<td>NS</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>z score of IVRT</td>
<td>+2.5 (1.00)</td>
<td>+1.24 (0.8)</td>
<td>0.0 (1.0)</td>
<td>0.002</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>E wave deceleration time (ms)</td>
<td>119 (25)</td>
<td>115 (27)</td>
<td>–</td>
<td>NS</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>z score of E wave deceleration time</td>
<td>−1.69 (1.31)</td>
<td>−2.4 (1.47)</td>
<td>0.0 (1.0)</td>
<td>0.03</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>A wave deceleration time (ms)</td>
<td>80 (12)</td>
<td>73 (11)</td>
<td>–</td>
<td>0.13</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>E wave velocity (cm/s)</td>
<td>47 (20)</td>
<td>50 (11)</td>
<td>92 (14) (3–8 years) 88 (14) (13–17 years)</td>
<td>NS</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>A wave velocity (cm/s)</td>
<td>32 (12)</td>
<td>33 (12)</td>
<td>42 (11) (3–8 years) 39 (8) (13–17 years)</td>
<td>NS</td>
<td>0.003</td>
<td>0.02</td>
</tr>
<tr>
<td>E:A velocity ratio</td>
<td>1.6 (0.6)</td>
<td>1.7 (0.6)</td>
<td>2.4 (0.7) (3–8 years) 2.3 (0.6) (13–17 years)</td>
<td>NS</td>
<td>&lt; 0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>E:(E + A) velocity ratio</td>
<td>0.6 (0.07)</td>
<td>0.6 (0.07)</td>
<td>–</td>
<td>NS</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>
and those with persistent IVR flow profiles between patients with disappearance of diastolic isovolumic relaxation (IVR) flow.

**Table 2** Comparison of the follow up duration, time intervals, and atrioventricular flow profiles between patients with disappearance of diastolic isovolumic relaxation (IVR) flow and those with persistent IVR flow.

<table>
<thead>
<tr>
<th></th>
<th>Patients with disappearance of IVR (n=6)</th>
<th>Patients with persistent IVR flow (n=5)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>17.4 (3.7)</td>
<td>16.6 (2.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Duration since operation (years)</td>
<td>12.4 (2.1)</td>
<td>9.8 (0.8)</td>
<td>0.024</td>
</tr>
<tr>
<td>R-R interval (ms)</td>
<td>890 (109)</td>
<td>841 (40)</td>
<td>NS</td>
</tr>
<tr>
<td>IVRT (ms)</td>
<td>88 (8)</td>
<td>86 (8)</td>
<td>NS</td>
</tr>
<tr>
<td>z score of IVRT</td>
<td>+1.34 (1.00)</td>
<td>+1.01 (0.54)</td>
<td>NS</td>
</tr>
<tr>
<td>E wave deceleration time (ms)</td>
<td>106 (21)</td>
<td>124 (52)</td>
<td>NS</td>
</tr>
<tr>
<td>z score of E wave deceleration time</td>
<td>–2.77 (1.21)</td>
<td>–1.97 (1.80)</td>
<td>NS</td>
</tr>
<tr>
<td>A wave deceleration time (ms)</td>
<td>75 (13)</td>
<td>75 (8)</td>
<td>NS</td>
</tr>
<tr>
<td>E wave velocity (cm/s)</td>
<td>46 (9)</td>
<td>54 (13)</td>
<td>NS</td>
</tr>
<tr>
<td>A wave velocity (cm/s)</td>
<td>30 (10)</td>
<td>35 (16)</td>
<td>NS</td>
</tr>
<tr>
<td>E:A velocity ratio</td>
<td>1.7 (0.8)</td>
<td>1.7 (0.4)</td>
<td>NS</td>
</tr>
</tbody>
</table>

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**Discussion**

This study demonstrates changes in diastolic Doppler indices consistent with reduced compliance of the systemic ventricle and persisting abnormalities of relaxation late after the Fontan procedure. The z scores of IVRT and E wave deceleration time decreased significantly, and the A wave deceleration time tended to decrease at the late follow up assessment. Compared with normal, the z score of E wave deceleration time, E and A wave velocities, and E:A ratio were persistently lower, while the z score of IVRT was persistently higher both early and late after the operation. The prevalence of isovolumic intraventricular flow decreased while that of mid diastolic flow increased significantly on follow up.

Previous studies have shown impaired systemic ventricular relaxation early after the Fontan procedure, coincident with the increase in mass:volume ratio and acquired “hypertrophy” of the ventricle after acute preload reduction on transition to the Fontan state. Compared with our findings early after the operation, the age standardised IVRT and prevalence of abnormal isovolumic relaxation flow decreased significantly on follow up. It is likely that regression of the ventricular mass after volume unloading results in more coordinate relaxation and
improvement of the impaired ventricular relaxation. 11 Nonetheless, the fact that the age standardised IVRT remained significantly longer and E wave velocity lower than normal, after the Fontan procedure suggests persistent impairment. This is substantiated by the significant inverse relation between IVRT and E wave velocity. In the light of our other findings, all of which suggest a trend towards reduced ventricular compliance, an additional mechanism may be invoked to explain the longitudinal changes.

The standardised E wave deceleration time was shorter than normal early after the operation and shortened further during follow up. Similarly, mid diastolic flow was also more prevalent. Shortening of the E wave deceleration time implies more rapid equalisation of the pressure between the pulmonary venous atrium and systemic ventricle, and has been demonstrated in many disease states associated with decreased ventricular compliance. 10–22 Mid diastolic flow arises from the re-establishment of a positive atrioventricular pressure gradient after its reversal with filling of the ventricle, the magnitude of which was increased with increased ventricular stiffness in a mathematical model, 17 and has been demonstrated in adults with hypertrophic cardiomyopathy and a raised left ventricular end diastolic pressure. 22

The small decrease in A wave deceleration further supports the possibility of decreased left ventricular compliance; a recent study in adults showed it to be associated with raised systemic ventricular filling pressure. 23 The exact mechanism for the proposed reduction of the ventricular compliance remains speculative. The substrate for its development may exist before the Fontan procedure. An increase in cross linking of types I and III collagen occurs in experimentally induced volume loaded left ventricular hypertrophy secondary to aortic valve fistula, 26 and clinical studies have shown an increased left ventricular myocardial fibrous tissue and an age related increase in subepicardial fibrosis in hearts with tricuspid atresia. 25 Reduction of left ventricular compliance has also been demonstrated in mitral stenosis where the left ventricle is chronically underfilled. 27 Reduced filling of the systemic ventricle that occurs after the Fontan procedure because of a persistently low cardiac output may similarly reduce the ventricular compliance. Finally, abnormalities of ventriculo-arterial coupling may have an adverse effect. Slowing of the ventricular relaxation velocity with increasing left ventricular afterload has been shown in animal studies, and postulated to be caused by the longer time required for disengagement of the greater number of cross bridges formed. 28 Increased systemic vascular resistance is characteristic in patients after the Fontan procedure, 29 although it is worth noting that angiotensin converting enzyme inhibition to reduce systemic vascular resistance failed to influence Doppler filling characteristics and led to reduced cardiac response to exercise in one study. 27

A potential limitation of this study is that Doppler indexes of left ventricular filling are influenced by age, 15 heart rate, 15 valvar regurgitation, 3 and loading conditions. 29 The age dependent indexes were standardised and expressed as a ratio to allow for meaningful comparison. The mean R-R interval increases by 20 ms per year of age from 3–18 years. 15 The strong association between age and heart rate makes it difficult to separate their individual contribution. There may also be alterations in loading conditions. Preload reduction occurs on transition to the Fontan state, but whether progressive reduction in preload has occurred on follow up is unknown. Nonetheless, the consequence would be lengthening of the E wave deceleration time, rather than shortening as observed. 22 Similarly, the increased systemic vascular resistance that occurs after the Fontan operation should prolong the deceleration time. 8 29

This study provides evidence of a progressive change in systemic ventricular diastolic function after the Fontan procedure. If confirmed by formal studies of ventricular compliance, increased ventricular stiffness may contribute to a progressive increase in pulmonary venous pressure, with significant implications for pulmonary blood flow and cardiac output. This may be one of the mechanisms underlying the functional deterioration late after the Fontan procedure.

VENTRICULAR FIBRILLATION PROVOKED BY CARDIOVERSION AND ASYNCHRONOUS PACING

A 57 year old women with sick sinus syndrome had been implanted with a Biotronik Pikos LP VVI pacemaker. Sinus rhythm was successfully restored by antiarrhythmic drugs three times during the past year. Because of recurrence of atrial fibrillation she was on permanent anticoagulant treatment. A recent attack of atrial fibrillation did not respond to antiarrhythmic treatment, therefore we planned a direct current cardioversion. The pacemaker was programmed to VOO mode with 50 beats/min frequency. The figure shows atrial fibrillation with high ventricular rate, as well as asynchronous pacing. No ventricular capture could be seen, because the pacemaker spikes were falling on the refractory period. The third pacemaker spike—which coincided with the beginning of the T wave—triggered the synchronisation of the cardioverter, resulting in ventricular fibrillation; she underwent immediate defibrillation.

The VOO mode or use of a magnet are recommended for protective purposes during certain interventions, like lithotripsy or electrocautery. Be cautious, however, as the VOO mode should be avoided during direct current cardioversion—as with our patient, the false synchronisation of the cardioverter may result in ventricular fibrillation.

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