Idiopathic restrictive cardiomyopathy in childhood

A diastolic disorder characterized by delayed relaxation

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Six children with idiopathic restrictive cardiomyopathy were evaluated. Electrocardiographic evaluation disclosed left atrial dilatation and repolarization abnormalities. Echocardiographic examination showed gross left atrial enlargement (182 ± 29% of predicted values, P < 0.001) in the presence of normal left ventricular cavity dimensions (99 ± 6%, P: ns). Left ventricular wall thickness varied from normal to mild concentric hypertrophy (septum: 116 ± 16%, P < 0.05). Global left ventricular systolic function was normal or slightly subnormal; however, the relaxation was significantly delayed throughout diastole. E/A ratio was 4-1 ± 1.4 and deceleration time 94 ± 7 ms. Marked ventricular filling occurred in mid-diastole as could be deduced from a prominent mid-diastolic mitral L wave on the Doppler flow tracing. Early filling contributed 56 ± 6%, mid-diastolic filling 28 ± 4% and atrial contraction 16 ± 3% to total ventricular filling as estimated by determining E-area, L-area and A-area, respectively. The left ventricular pressure curve showed a steady decline during mid-diastolic filling. This implies that the driving force for mid-diastolic filling is not the increased left atrial pressure but suction by the ventricle. The restrictive haemodynamics are therefore not caused by increased intrinsic stiffness of the ventricular wall, but most likely result from serious dysfunction and delay of the active relaxation of the ventricle. Progression of the disease was observed in three out of six patients, resulting in death or extreme low cardiac output. The three other patients remained clinically stable during the follow-up period of 6–10 years.

Key Words: Restrictive cardiomyopathy, childhood, haemodynamics.
Table 1 Patient characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Additional diagnosis</th>
<th>Age at first symptom or presentation</th>
<th>Presenting symptom</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>m</td>
<td>none</td>
<td>8-9</td>
<td>Asthma</td>
<td>Death, 9-3 years</td>
</tr>
<tr>
<td>2</td>
<td>f</td>
<td>VSD, LSCV</td>
<td>4-8</td>
<td>Stroke syncpe</td>
<td>No evolution</td>
</tr>
<tr>
<td>3</td>
<td>f</td>
<td>none</td>
<td>3-4</td>
<td></td>
<td>Transplant, 11-5 years</td>
</tr>
<tr>
<td>4</td>
<td>m</td>
<td>none</td>
<td>13-6</td>
<td></td>
<td>No evolution</td>
</tr>
<tr>
<td>5</td>
<td>m</td>
<td>none</td>
<td>3-1</td>
<td>Pulmonary infection</td>
<td>No evolution</td>
</tr>
<tr>
<td>6</td>
<td>f</td>
<td>lentigines</td>
<td>9-7</td>
<td>Asthma</td>
<td>Transplant, 13 years</td>
</tr>
</tbody>
</table>

VSD: ventricular septal defect; LSCV: left superior caval vein.

None of the patients had a family history of cardiomyopathy. There was no evidence for eosinophilia or myopathy. All the parents were screened by echocardiography for cardiomyopathy; no abnormality could be detected.

**Results**

Mean age at the time of presentation was 6.2 ± 3.5 years (range 1.4–9.7 years). Four patients were symptomatic and presented with different complaints. Two patients had been followed for several months in the respiratory clinic for atypical asthma. One patient suffered from a syncope during exercise. Six years prior to this incident she had been investigated at another institution for a transient hemiparesis. In retrospect this was probably due to an embolus from the left atrium which was at that time already dilated on a chest roentgenogram. Computerized tomographic examination of the brain performed upon re-evaluation 6 years after the hemiparesis revealed an old cerebral infarction. In one patient dyspnoea and recurrent pulmonary infections were the presenting symptoms. In these four symptomatic patients the mean interval between the first symptom and the diagnosis of restrictive cardiomyopathy was 2.5 ± 2.6 years (range 0–6.5 years). The remaining two patients were asymptomatic at the time of diagnosis and the echocardiographic finding of restrictive haemodynamics was fortuitous: one patient had been followed for a small ventricular septal defect and the other patient was referred after mild cardiac enlargement was discovered on a chest X-ray taken after a blunt chest trauma.

The physical findings at presentation were normal in three patients. Two patients had an increased jugular venous pressure and hepatomegaly. None of these patients had oedema nor evidence of ascites. Two patients had a cyanotic flush due to low cardiac output. Two patients had murmurs of tricuspid (2) or mitral (1) regurgitation. One patient had small lentigines which was diagnosed as lentiginosis.

Electrocardiogram

All six patients were in sinus rhythm and all had electrocardiographic evidence of gross left atrial enlargement (Fig. 1). Biventricular hypertrophy was observed in three patients. The total P wave amplitude in lead V1 was 0.52 ± 0.23 mV (range 0.2–0.8 mV). Four patients met the criteria for left ventricular hypertrophy and one patient met those criteria for right ventricular hypertrophy[11]. None of the patients had an abnormal Q wave or pseudoinfarct pattern. The QTc was 420 ± 40 ms; mild prolongation up to 460 ms was noted in only one patient. Repolarization abnormalities were present as the T wave was notched or biphasic in five patients.

Chest X-ray

At presentation, all patients had pulmonary venous congestion and some degree of cardiomegaly, predominantly due to left atrial dilatation (cardiothoracic ratio at presentation 0.58 ± 0.08, range 0.49–0.69). During follow-up a significant increase of the cardiac silhouette was observed in the patients with progression of the disorder. In those patients pulmonary vascular markings became more prominent. Kerley B lines developed and small intrascissural effusions could be detected.

Doppler echocardiography

All patients had a normal orientation of cardiac chambers and large vessels. None had an apical obliteration or abnormal bright echoes on the endocardial surface. Patient data are summarized in Table 2. The left ventricular cavity had a normal end-diastolic dimension (99 ± 6% of body surface area predicted values, normal 95% confidence interval, range 90–110%; P: ns) with a
Figure 1 12-lead electrocardiogram of a patient with restrictive cardiomyopathy at the age of 13 years. The P wave is diagnostic for left atrial dilatation. The T wave is biphasic.

Table 2 Echocardiographic data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>Standard deviation</th>
<th>Normal values (97% CI)</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>LVEDD (%)</td>
<td>99</td>
<td>6</td>
<td>90-110</td>
<td>ns</td>
</tr>
<tr>
<td>IVS (%)</td>
<td>116</td>
<td>16</td>
<td>81-119</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>PWT (%)</td>
<td>117</td>
<td>14</td>
<td>84-116</td>
<td>ns</td>
</tr>
<tr>
<td>Aorta (%)</td>
<td>89</td>
<td>3</td>
<td>84-116</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Left atrium (%)</td>
<td>182</td>
<td>29</td>
<td>83-117</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>FS (%)</td>
<td>30</td>
<td>3</td>
<td>27-41</td>
<td>ns</td>
</tr>
<tr>
<td>LA/Ao</td>
<td>2-6</td>
<td>0-5</td>
<td>0-8-1-3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Relax^ (%)</td>
<td>56</td>
<td>7</td>
<td>77-92</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>E-area (%)</td>
<td>56</td>
<td>6</td>
<td>57-73</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>L-area (%)</td>
<td>28</td>
<td>4</td>
<td>0-5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>A-area (%)</td>
<td>16</td>
<td>3</td>
<td>4-34</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>E/A-ratio</td>
<td>4-2</td>
<td>1-4</td>
<td>1-7-2.5</td>
<td>&lt;0.001</td>
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<tr>
<td>A/E-ratio</td>
<td>0-37</td>
<td>0-08</td>
<td>0.44-0.66</td>
<td>&lt;0.001</td>
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<tr>
<td>Dec.time (ms)</td>
<td>95</td>
<td>7-7</td>
<td>97-197</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

LVEDD: left ventricular end-diastolic dimension; IVS: interventricular septum dimension; PWT: posterior wall thickness; FS: fractional shortening; LA/Ao: ratio of left atrium size to aortic diameter; relax^: increase in left ventricular dimension 200 ms after minimal end-systolic value; Dec.time: deceleration time of the E wave.

normal or mildly impaired systolic function (fractional shortening 30 ± 3%, range 27-35%). The left ventricular outflow tract remained wide open throughout systole. There was no systolic anterior motion of the mitral valve in any patient. The left ventricular wall thickness on M-mode was within normal range or just beyond the upper limit. The septum measured 116 ± 16% of body surface area predicted values (normal 95% confidence limits, range 81-119%, P<0.05), and the posterior wall measured 117 ± 14% of body surface area predicted values (normal 95% confidence limits, range 84-116%, P: ns). At initial presentation no significant localized hypertrophy was detected. However, during follow-up mild eccentric mid-ventricular to apical hypertrophy was observed in four patients. The aortic root diameter was at the lower end of the normal range (89 ± 3% of body surface area predicted values, normal 95% confidence limits, range 84-116%, P<0.01). By contrast, the left atrium was grossly dilated in all patients (182 ± 29% of body surface area predicted values, normal 95% confidence limits, range 83-117%, P<0.001) (Fig. 2) and the ratio left atrium/aorta was significantly increased (2.8 ± 0.6; normal 0.8-1.3[12], P<0.001).

The left ventricular cavity slowly expanded throughout diastole (Fig. 3). At 200 ms after the minimal end-systolic value, the left ventricular dimension had increased by only 56 ± 7% (range 49-66%) of the total systolic-diastolic expansion (age-matched controls: 84 ± 4%, range 77-92%, P<0.001). In all patients an L
Figure 3  M-mode of left ventricle. There is no significant ventricular hypertrophy. The left ventricular cavity expands very slowly throughout diastole.

motion on the mitral valve echocardiogram was observed. This corresponded in time with a prominent mid-diastolic mitral flow velocity wave (L wave). Three diastolic waves could be identified in these patients. The first wave was positively identified as the E wave and not isovolumic relaxation flow\(^1\). The mitral E wave had a very short deceleration time (94 ± 7 ms, range 63–120 ms), suggesting a very rapid equalization of the diastolic atrial and ventricular pressure gradient. Only one patient had a very short reversal of flow between the E and L waves. One patient had a mild degree of mitral valve regurgitation on Doppler examination. In those patients with significant right atrial dilatation, both an L motion and prominent L wave could be observed on the right ventricular side.

The area under the E wave, L wave and A wave was calculated. Early filling contributed 56 ± 6% (normal values: 55 ± 4%, P<0.01), mid-diastolic filling 28 ± 4% (normal values: <5%; P<0.001)\(^4\) and atrial contraction 16 ± 3% (normal values: 20 ± 7%; P<0.01) to total ventricular filling.

At the time of severe cardiac failure in the preterminal phase, a small pericardial effusion was observed in two patients. Spontaneous contrast in both atria was present in the three patients with the largest atrial dilatation.

Cardiac catheterization

The mean left atrial pressure or mean pulmonary capillary wedge pressure was elevated in all patients (21 ± 3 mmHg, range 16–24 mmHg), causing mild retrograde pulmonary hypertension (mean pulmonary artery pressure 29 ± 10 mmHg, range 18–37 mmHg). Right atrial pressures were within normal limits (5 ± 2 mmHg, range 3–9 mmHg). The right atrial oxygen saturation was subnormal (66 ± 7%) suggesting a diminished cardiac output. The left ventricular pressure curve did not show a typical square root or dip-plateau pattern. All pressures remained well above the zero line. After the rapid filling wave, the pressure decreased during mid-diastole (Fig. 4(a)). All patients had a very prominent A wave (28 ± 6 mmHg). The levophase of a pulmonary injection demonstrated an extremely dilated left atrium. The contrast whirled for several cardiac cycles in the left atrium with very slow progression to the left ventricle. Left ventricular angiography demonstrated a significantly delayed expansion of the cavity throughout diastole.

The patient with the small ventricular septal defect (Qp/Qs 1:3) was investigated invasively twice at

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the age of 6 and 17 years. The mean pulmonary capillary wedge pressure had increased from 16 to 24 mmHg.

Incremental atrial pacing was performed in the patient who had suffered syncope during exercise. The left ventricular end-diastolic pressure increased from 22 mmHg at a paced rate of 70 bpm to 32 mmHg at a rate of 150 bpm; the systolic pressure had decreased from 108 to 88 mmHg. Atrial pacing was interrupted because of chest discomfort and dizziness.

Pathology

Myocardial tissue of four patients was available for pathological examination (endocardial biopsy, one; epicardial biopsy, three; full thickness, three). The endocardial and epicardial biopsies revealed myocyte hypertrophy and only mild endocardial and interstitial fibrosis. This interstitial fibrosis was unevenly distributed and pericellular. Inflammatory cells (eosinophils, lymphocytes) were not observed. The nuclei of the myocytes were often enlarged, irregular, and hyperchromatic. The sarcoplasm appeared normal. These histopathological changes were considered as mild and non-specific. Electron microscopic examination was performed in two cases, confirming the light microscopic findings. The mitochondria appeared normal; no specific ultrastructural lesions were seen.

In the three cases with full thickness examination obtained at abdution or heart transplantation, there was extensive myofibre disarray in the core of the myocardial wall. In addition, an increased amount of loose and mesenchymal interstitial connective tissue was observed. At times, the myocytes were arranged in whorls around central foci of this connective tissue. The nuclei of the myocytes were often box-shaped and surrounded by a clear perinuclear halo. The endocardium and pericardium had a normal appearance. There was no evidence of hypertrophy of the wall of the small intramural coronary arteries.

Follow-up

During follow-up, one patient died and two required heart transplantation. One patient who was 9 years old and who was considered for transplantation, suffered a cardiac arrest during an intravenous pyruvate load performed at another institution to exclude a defect in pyruvate metabolism; he could not be resuscitated. Two patients underwent a successful transplantation at the age of 12 and 13 years for intractable, terminal heart failure with very low cardiac output. The three remaining patients are currently nearly asymptomatic. There is nearly no further clinical deterioration of their clinical condition. Calcium channel blockers have been tried in two patients for several months without significant echocardiographic changes.

Discussion

We described six children with a clinical syndrome characterized by restriction to left ventricular filling, resulting in massive left atrial dilatation, diminished cardiac output, and mild retrograde pulmonary hypertension. Restrictive haemodynamics, in the absence of pericardial pathology or in the absence of endocardial or valvar disease is characteristic for the clinical diagnosis of 'idiopathic restrictive cardiomyopathy'.

Pathophysiology

Restrictive physiology is classically characterized by an abrupt premature cessation of ventricular filling in early diastole, causing a dip-plateau pattern on the ventricular pressure tracing (for a recent review see(16). Ventricular filling therefore occurs early in diastole with nearly no significant mid- and late-diastolic flow. The physiology of most adult restrictive cardiomyopathies is characterized by consecutive changes in ventricular filling(17). Due to alterations in the mechanical properties of the myocardium caused by the underlying pathological process, the myocardium becomes stiffer with a left upward displacement of the pressure-volume curve and only a minor influence on the compliance. This results in delayed and diminished early filling and increased late filling during atrial contraction. At this stage the major driving force for left ventricular filling is the atrial push-out during contraction. Later in the restrictive process, compliance decreases leading to an increase of left atrial pressure throughout the cardiac cycle. This results in increased early filling and decreased late filling during diastole. The driving force for ventricular filling then becomes the push-in caused by the high atrial pressure. Typically, the ventricular mid-diastolic pressure increases during filling of the left ventricle. The 'classical' restrictive entities are haemodynamically characterized by: (1) a normal systolic function; (2) an equalization of end-diastolic pressures; (3) an increase in mean atrial and ventricular end-diastolic pressures; and (4) a typical dip-plateau pattern of ventricular filling.

Although our patients share significant restriction to ventricular filling, the haemodynamics in the present patient group differs markedly from this classical pattern as there was no abrupt cessation of early ventricular filling, no dip-plateau pattern, no increase in mid-diastolic pressure, and no equalization of end-diastolic pressures. The observation that left atrial pressures were markedly elevated without a concomitant increase in right atrial pressures, suggests that the left ventricle is predominantly involved in the restrictive process. In the classical restrictive entities the elevated atrial pressure is the main driving force for ventricular filling with a further increase in mid-diastolic pressure associated with ventricular filling. This makes atrial 'push-in' the basic mechanism for filling a poorly compliant ventricle. In our observations, a remarkable
decline in left ventricular pressure was observed during mid-diastolic inflow. Filling associated with pressure decrease can only be explained by a further relaxation of the ventricle which causes blood to be 'pulled-in' from the atria. The pressure decline during filling is proof of ventricular suction during mid-diastole.

This pull-in effect could be caused by two different mechanisms. One theoretical possibility is that passive elastic recoil is delayed by a very important viscose element which only interferes in diastole (as systole is nearly normal). This mechanism appears extremely unphysiological and is therefore very unlikely to cause this degree of diastolic dysfunction. It is more likely that the late suction of the ventricle is caused by a delayed relaxation of the ventricle.

Idiopathic restrictive cardiomyopathy of childhood as a disorder of active relaxation

Relaxation is an active mechanism requiring energy to lower intracellular calcium which results in the disconnection of actin–myosin bridges. Different hypotheses can be formulated concerning the underlying cause of the restrictive process. Myocardial relaxation abnormalities may be linked to abnormal calcium sequestration during diastole, abnormal binding of calcium to the contractile proteins, or abnormal mechanical characteristics of the contractile apparatus or the myocardial interstitium. Morgan et al. showed that in cardiomyopathies the decline in free calcium following activation is slow and prolonged, and correlates with a slow decline in muscle tension measured simultaneously. Interestingly, the repolarization abnormalities such as biphasic or notched T waves observed in our patients suggest abnormal ion movements during diastole, which could involve abnormal calcium handling. Abnormal calcium sequestration could have different causes. In this respect, it is interesting to mention that decreased expression of the SR Ca$^{2+}$ ATPase (SERCA) was described in hypertrophic and failing myocardium (for a recent review see Arai et al.). Except for problems with the enzymes responsible for Ca$^{2+}$ removal, problems with energy supply could also explain the prolonged relaxation. This could be the reason for the catastrophic effect of a pyruvate infusion in one of our patients. The cardiac arrest which occurred proves that pyruvate loading was not tolerated and may have resulted in severe adenosine triphosphate depletion.

Some of the characteristics of the restrictive disorder are reminiscent of hypertrophic cardiomyopathy. Recent studies at the clinical, cellular and molecular level have already demonstrated that what is commonly called 'hypertrophic cardiomyopathy' is a very heterogeneous group of diseases. This is confirmed on the molecular levels as different mutations in different genes are involved. Common to all familial hypertrophic cardiomyopathies is that one of the contractile proteins is abnormal (β-myosin heavy chain, α-tropomyosin or troponin T). The basic problem thus seems to be a sarcomeric disorder with a secondary hypertrophic response. The clinical entity observed in our patients fulfils some of the criteria of the definition of hypertrophic cardiomyopathy. However, left ventricular wall thickness was either within normal limits or showed only a mild degree of concentric hypertrophy. Myocardial cell disarray and the increased transverse diameter of the myocytes are characteristic and constant morphological features of hypertrophic cardiomyopathy. However, the presence of abnormally arranged cardiac muscle cells is not pathognomonic for hypertrophic cardiomyopathy. It has been pointed out that areas with disarray are widely dispersed and may occur in hearts with congenital and acquired diseases, as well as in normal hearts, both fetal and adult. The pathological features of 'idiopathic' restrictive cardiomyopathy have not been well defined and only sporadic cases have been described. The exact relationship between restrictive and hypertrophic cardiomyopathy needs to be determined further. Maybe the recent advances in the molecular basis of cardiomyopathies will give more insight in this question.

Clinical profile

The clinical picture in our patient group was varied. Rapid deterioration with low cardiac output and death was observed in three patients. This was characterized by increasing left atrial dilatation as seen on the serial electrocardiograms, chest roentgenograms and echocardiograms. Repeat catheterization in one of our patients showed a significant increase of the left ventricular filling pressure and pulmonary artery pressure. The remaining three patients show no sign of further clinical deterioration: after 6–10 years of follow-up they are still doing well and report few or no symptoms except for mild to moderate exercise intolerance. Moreover, there are no reasons to suspect any further deterioration of their cardiac function.

The clinically different groups may represent a spectrum of disorders belonging to the same pathophysiological category. At one end of the spectrum, the restrictive disorder is characterized by rapidly evolving diastolic dysfunction with extreme slow relaxation. At presentation the patients are symptomatic and they develop signs of cardiac failure and/or low cardiac output before adolescence. Echocardiographically they are characterized by large L waves on mitral inflow patterns. As further clinical deterioration occurs very quickly, cardiac transplantation is the only treatment. At the other end of the spectrum the restrictive disorder is characterized by a diastolic dysfunction which is nearly asymptomatic and does not deteriorate further during a follow-up period of 6–10 years throughout adolescence. In these patients the restrictive disorder was fortuitously diagnosed. Due to the small number of patients, statistical comparisons in our series are not feasible and larger patient groups need to be compared.
This could perhaps delineate better the similarities and differences between both clinical entities.

Some aspects of these rare clinical entities in children have previously been described. Mehta et al. reported on the M-mode echocardiographic findings of restrictive cardiomyopathy in five children. The left ventricular ejection variables were normal. In contrast, the isovolumic relaxation time was prolonged and the relaxation of the ventricular wall was significantly delayed. The M-mode echocardiogram in their report shows a prominent L motion of the mitral valve. All the observations made in this patient population are nearly identical to those made in our patient group. In this study, however, no clinical follow-up is reported. Maki et al. reported an atypical form of cardiomyopathy in a 7-year-old boy. Left ventricular filling was critically impaired, and consequently pulmonary venous congestion predominated in the clinical presentation. There was no obvious hypertrophy of the interventricular septum and left ventricular free wall. The clinical diagnosis in this child was, therefore, restrictive cardiomyopathy. Also, all clinical data and tracings in this patient are similar to those obtained in our patients, including a mild decline of left ventricular mid-diastolic pressure.

**Limitations of the study**

Due to the rare nature of the disorder only a small number of patients could be included in this study. To obtain more insight into the diversity of idiopathic restrictive cardiomyopathy larger groups need to be studied. Another shortcoming of the present study is that left ventricular pressure tracings were not obtained with high-fidelity micro-tip catheters. However, interpretation of mid-diastolic pressure tracings beyond the rapid filling wave is possible with fluid-filled catheters as changes in pressure are then slow, with relatively small changes in volume.

**Conclusion**

Idiopathic restrictive cardiomyopathy is a rare disorder, also in childhood. In this age group delayed relaxation appears to be the basic pathophysiological problem. The clinical profile varies from death prior to puberty to a nearly asymptomatic presentation throughout adolescence.

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**References**