Severe Pulsus Alternans Associated with Primary Myocardial Disease in Children

Observations on Clinical Features, Hemodynamic Findings, Mechanism, and Prognosis

By Leonard C. Harris, M.D., M.R.C.P., Quang X. Nghiem, M.D., Melvyn H. Schreiber, M.D., and John M. Wallace, M.D.

PULSUS ALTERNANS, first described by Traube in 1872, is a phenomenon of alternately higher and lower peak systolic pressure in the presence of regular rhythm and independent of respiratory variation. It has been described most commonly in hypertensive and coronary artery disease, syphilitic heart disease, and acquired aortic stenosis, seldom in congenital aortic stenosis, and only occasionally in myocardial disease. It more commonly affects the left ventricle but may affect the right ventricle alone or both ventricles either concordantly or discordantly.

The present report describes the occurrence of pulsus alternans in five children under 6 years of age with primary myocardial disease. One child died and the pathological features were those of cardiomyopathy. Attention in this paper has been directed toward the clinical features, hemodynamic findings, response to drugs, mechanism, and the prognosis of pulsus alternans.

Clinical Material

Case 1

This Negro male was well until the age of 4 years and 9 months when he suddenly developed right-sided weakness while playing. On admission to this hospital on September 8, 1962, the patient had right hemiparesis, a grade I apical systolic murmur, and marked cardiac enlargement with congestive heart failure. An electrocardiogram showed left ventricular hypertrophy with inverted T waves in leads V5 and V6. The ASO titer was 166, CRP was negative, and sedimentation rate 4 mm in 1 hour. Transaminase, SGOT and SGPT, initially 54 and 32 units, rose to 120 and 80 units, respectively, over a period of 2½ weeks. The patient improved after digitalization and was discharged, but he was again hospitalized on May 28, 1963, with congestive failure following discontinuation of digitalis. A grade II holosystolic murmur and a third sound were heard at the apex. A mumps skin test was negative. Pulsus alternans was first noted on femoral arterial tracings with concordant right ventricular alternans during cardiac catheterization (table 1), and at times alternate pulse beats were not palpable. A left ventriculogram showed a moderate degree of mitral regurgitation and heart volume data are shown in table 2. The patient's course was more rapidly downhill during the last year of illness, and death occurred in cardiac failure 3 years after the initial symptoms.

Autopsy was performed. The weight of the heart was 200 g (normal average for age, 110 g). The ventricles, atria, and the mitral ring were dilated. There was mild endocardial thickening with yellowish-gray discoloration in the left ventricular outflow tract. Microscopy revealed areas of endocardial fibrosis. In the left ventricular outflow tract myocardial fiber degeneration was present in areas adjacent to the endocardium. Fibrosis was present in the central core of posterior papillary muscles in the left ventricle and an organizing mural thrombus was present. There was no evidence of elastic proliferation. In the right ventricle, there were also areas of subendocardial muscle fiber degeneration. An area of pulmonary infarction, cystic encephalomalacia in the right external capsule of the brain, and also a recent splenic infarct were present. The clinical and pathological picture appeared to be similar to that described by Becker in a personal communication and by

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# Table 1

## Findings on Cardiac Catheterization

<table>
<thead>
<tr>
<th>Case</th>
<th>Date</th>
<th>Body surface area (m²)</th>
<th>Drug</th>
<th>Maximal difference of peak systolic pressure of large and small beats (mm Hg)</th>
<th>Heart rate per min</th>
<th>&quot;Average&quot; stroke index (ml/beat/m²)</th>
<th>% change with isoproterenol</th>
<th>Cardiac index (L/min/m²)</th>
<th>% change with isoproterenol</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6/28/63</td>
<td>—</td>
<td>On digitoxin</td>
<td>F.A. 22 R.V. 10</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>5/8/64</td>
<td>0.77</td>
<td>On digitoxin</td>
<td>0 0 75 41.7</td>
<td>—</td>
<td>—</td>
<td>3.13</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>4/27/65</td>
<td>0.80</td>
<td>None</td>
<td>60 10 35.1</td>
<td>—</td>
<td>—</td>
<td>3.08</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>With isoproterenol I. V.</td>
<td>62 11 50.9</td>
<td>+45</td>
<td>5.43</td>
<td>+76</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>6/16/64</td>
<td>0.59</td>
<td>On digitoxin</td>
<td>11 6 30.2</td>
<td>—</td>
<td>—</td>
<td>2.17</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>4/30/65</td>
<td>0.63</td>
<td>On digitoxin</td>
<td>63 15 65.4</td>
<td>—</td>
<td>—</td>
<td>5.68</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>With isoproterenol I. V.</td>
<td>63 15 66.3</td>
<td>+1</td>
<td>7.22</td>
<td>+27</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>1/26/65</td>
<td>0.65</td>
<td>On digitoxin</td>
<td>33 19 33.2</td>
<td>—</td>
<td>—</td>
<td>3.37</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>7/1/65</td>
<td>0.68</td>
<td>On digitoxin</td>
<td>0 0 41.1</td>
<td>—</td>
<td>—</td>
<td>4.17</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>With isoproterenol I. V.</td>
<td>0 0 35.5</td>
<td>-14</td>
<td>5.12</td>
<td>+23</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>3/12/64</td>
<td>0.54</td>
<td>On digitoxin</td>
<td>18 7 37.4</td>
<td>—</td>
<td>—</td>
<td>4.31</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>8/2/65</td>
<td>0.71</td>
<td>None</td>
<td>23 8 32.1</td>
<td>—</td>
<td>—</td>
<td>4.31</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Deslanoside I. V.</td>
<td>25 6 45.6</td>
<td>—</td>
<td>—</td>
<td>4.80</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>8/9/65</td>
<td>0.73</td>
<td>On digitoxin</td>
<td>10 0 41.9</td>
<td>—</td>
<td>—</td>
<td>4.67</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>9/23/65</td>
<td>0.73</td>
<td>On digitoxin</td>
<td>0 0 44.6</td>
<td>—</td>
<td>—</td>
<td>4.01</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>With isoproterenol I. V.</td>
<td>26 0 63.9</td>
<td>+43</td>
<td>6.39</td>
<td>+59</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

### Mean change with isoproterenol

<table>
<thead>
<tr>
<th></th>
<th>F.A.</th>
<th>R.V.</th>
<th></th>
<th>R.V.</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change with isoproterenol</td>
<td>+18</td>
<td>+45</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Abbreviations:
- F.A. = femoral artery
- R.V. = right ventricle
becker and associates in south africa as “cardiovascular collagenosis,” which is of undetermined etiology.

**case 2**

this patient, a sibling of patient 1, developed fever and cardiac failure at 4½ years of age, 2 years after the onset of his brother’s initial symptoms. pulsus alternans was detected at the radial pulse by palpation and was confirmed by external carotid arterial pulse tracings. a grade i systolic ejection murmur was heard medial to the apex and recorded phonocardiographically, only with the alternate large pulse beats. an electrocardiogram showed evidence of left ventricular hypertrophy. a chest roentgenogram showed marked generalized cardiac enlargement with normal vascular markings. digitalization was followed by rapid improvement. a mumps skin test was negative. relevant cardiac catheterization data are shown in table 1. concordant pulsus alternans was present in the femoral artery and the right ventricle (fig. 1).

a biplane left ventriculogram showed no evidence of mitral insufficiency. end-systolic and end-diastolic left ventricular volumes are shown in table 2. nineteen months after the onset of the illness, the patient is moderately active, with some diminution of heart size. pulsus alternans is now present only after exercise.

**case 3**

this 4-year, 3-month-old negro female was hospitalized with a history of fever and cough and signs of cardiac failure for 3 weeks. no murmurs were present, but a third heart sound was present. pulsus alternans, suspected clinically, was confirmed by an external carotid arterial tracing. an electrocardiogram showed an qrs of +20°, left ventricular hypertrophy, and right atrial enlargement. a chest roentgenogram showed moderate cardiac enlargement and normal vascular markings. following improvement with digitalization, femoral arterial and right ventricular alternans were independently recorded at cardiac catheterization (table 1). pulsus alternans disappeared at the time of a left ventriculogram, and no mitral regurgitation was present. four months later pulsus alternans, present in femoral arterial tracings, had disappeared from the right ventricle. when last seen 5 months after the first symptoms, she was enjoying moderate physical activity.

**case 4**

this 3-year, 10-month-old caucasian male developed bronchopneumonia at age 4 months and attacks of cardiac failure at age 10 months and 17 months. when first seen at 2½ years of age by the authors, he was in congestive heart failure and responded well to digitalization. a grade i systolic ejection murmur and a third sound were heard at the apex. pulsus alternans, not detectable clinically, was recorded by an external carotid arterial tracing. an electrocardiogram showed evidence of left ventricular hypertrophy with inverted t waves in lead v6. a chest roentgenogram showed a markedly enlarged, globular heart with evidence of pulmonary venous congestion. a right ventricular cineangiogram showed moderate left atrial and left ventricular enlargement with diminished left ventricular pulsations. relevant catheterization data after control of cardiac failure are shown in table 1. pulsus alternans was recorded in the femoral artery and right ventricle. no follow-up has been possible.

**case 5**

this 5-year, 10-month-old negro male was well until the age of 5 years 7 months when cardiac

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**table 2**

left ventricular end-diastolic and end-systolic volumes in pulsus alternans

<table>
<thead>
<tr>
<th>Case</th>
<th>Volume (ml)</th>
<th>Large heart beat</th>
<th>Small heart beat</th>
<th>Volumetric alternation</th>
<th>“Average” heart beat</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>End-diastolic (EDV)</td>
<td>268</td>
<td>252</td>
<td>16</td>
<td>6.3</td>
</tr>
<tr>
<td></td>
<td>End-systolic (ESV)</td>
<td>166</td>
<td>204</td>
<td>38</td>
<td>18.6</td>
</tr>
<tr>
<td></td>
<td>Stroke (SV)</td>
<td>102</td>
<td>48</td>
<td>54</td>
<td>112.0</td>
</tr>
<tr>
<td></td>
<td>Ejection fraction (SV/EDV)</td>
<td>38%</td>
<td>19%</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>End-diastolic</td>
<td>282</td>
<td>270</td>
<td>12</td>
<td>4.4</td>
</tr>
<tr>
<td></td>
<td>End-systolic</td>
<td>221</td>
<td>253</td>
<td>32</td>
<td>12.6</td>
</tr>
<tr>
<td></td>
<td>Stroke</td>
<td>61</td>
<td>17</td>
<td>44</td>
<td>259.0</td>
</tr>
<tr>
<td></td>
<td>Ejection fraction</td>
<td>22%</td>
<td>6%</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>
failure which responded well to digitalization developed insidiously. He developed congestive cardiac failure 3 months after treatment with digitalis had been discontinued at which time he was first seen by the authors. Pulsus alternans was palpated and was confirmed by external carotid arterial tracings. A grade II systolic ejection murmur was maximal at the left lower sternal border and a third sound heard at the apex. An electrocardiogram showed evidence of left ventricular hypertrophy. A chest roentgenogram showed moderate cardiac enlargement with normal vascular markings. A mumps skin test was positive without a previous history of mumps. Cardiac catheterization was performed when clinical manifestations of heart failure had subsided following digitalization (table 1). Concordant pulsus alternans was shown in the right ventricle and femoral artery. This patient is living and moderately active 5 months after the known onset of his illness.

Methods of Hemodynamic Study

Pulses were recorded through a no. 20 Courmand needle in the brachial or femoral artery or, for contour only, by a pick-up cup placed over the carotid or brachial artery, transmitting the impulse through a piezo-electric microphone to an Electronics for Medicine recorder. Other pressures were measured through a no. 6 Lehman catheter. Cardiac output was measured by the dye-dilution method of Hamilton using Cardio-Green dye. Left ventricular catheterizations in cases 1 and 2 were performed via the femoral artery using the Seldinger technique. Left ventricular ejection time (LVET), duration of total systole (DTS), and isovolumetric contraction time (ICT) were recorded and measured as previously

Figure 1

Pressure tracings recorded simultaneously in the femoral artery and right ventricle in case 2. Time lines are 0.1 second apart. Note the concordant alternans. In alternate femoral arterial pulses, complexes are almost invisible (see arrows). The R-R interval shows alternation, with longer intervals encompassing small beats, but no significant abnormality is seen on the electrocardiogram.
described. Respirations were recorded by a nasal thermistor. Left ventricular relaxation time was measured from the dicrotic notch of the carotid arterial tracing to the O point of an apex cardiogram. This interval was found to be more reproducible than measuring from the second heart sound to the O point, which introduces a small but constant error. Diastole was measured from the dicrotic notch to the onset of the following R wave.

Drugs were administered with a Harvard pump. Biplane left ventriculograms were performed at a film rate of 4 per second (Schonander serial film changer) with simultaneous recording of electrocardiograms, femoral arterial pressure for pulse contour, and radiographic event marks. Biplane pairs of films were obtained in end diastole preceding both large and small beats and in end systole for large and small beats. The phases of the cycle were determined electrocardiographically. Left ventricular volume was measured by the method of Arvidsson. Cardiac output was measured by the dye-dilution method, 30 to 60 minutes before ventriculograms in cases 1 and 2. Normal values in children are those of Sproule and Simpson. Normal figures for ejection fractions in children are given by Miller and associates. Pacing was performed in cases 1 and 2 through a bipolar catheter introduced into the right atrium or right ventricle. Paired pacing was not used.

Results

No electrical alternans was observed at any time.

The magnitude of pulsus alternans is reflected by the difference between the systolic pressure of small and large beats (table 1). Systemic pulsus alternans in cases 1 and 2 was at times of such severe degree that alternate beats were not palpable and barely visible on pulse tracings (fig. 1). Pulsus alternans sometimes varied in degree or disappeared over intervals of only a few seconds (fig. 2). In case 3, pulsus alternans was recorded in the catheterization laboratory prior to the performance of a left ventriculogram, but shortly before the injection of contrast medium it disappeared and was

![Figure 2](http://circ.ahajournals.org/)

Case 1: A short interval of pulsus alternans in the femoral arterial tracing. Time lines are 1 second apart. The period of alternans is preceded by a Treppe effect. The higher systolic pressure of large beats reflects their greater stroke volume as compared with small beats. For the duration of the pulsus alternans, and for a few beats preceding the onset, P waves on the electrocardiogram are tall and peaked.
### Table 3

**Effects of Atrial Pacing on Duration (in Seconds) of Various Phases of the Cardiac Cycle in Case 1**

<table>
<thead>
<tr>
<th>Phase</th>
<th>Small beats</th>
<th>Large beats</th>
<th>Difference</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Including (n/2)</td>
<td>Preceding (n/2)</td>
<td>Following (n/2)</td>
</tr>
<tr>
<td>A. During resting state</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R-R interval</td>
<td>10</td>
<td>0.508</td>
<td>0.482</td>
<td>0.026</td>
</tr>
<tr>
<td>Q-S&lt;sub&gt;1&lt;/sub&gt;</td>
<td>10</td>
<td>0.080</td>
<td>0.075</td>
<td>0.005</td>
</tr>
<tr>
<td>Isometric relaxation</td>
<td>8</td>
<td>0.113</td>
<td>0.112</td>
<td>0.001</td>
</tr>
<tr>
<td>(S&lt;sub&gt;2&lt;/sub&gt; to O point)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carotid dicrotic notch to R</td>
<td>10</td>
<td>0.214</td>
<td>0.178</td>
<td>0.036</td>
</tr>
<tr>
<td>Carotid dicrotic notch to S&lt;sub&gt;1&lt;/sub&gt;</td>
<td>10</td>
<td>0.290</td>
<td>0.264</td>
<td>0.026</td>
</tr>
<tr>
<td>B. During atrial pacing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R-R interval</td>
<td>10</td>
<td>0.430</td>
<td>0.430</td>
<td>0</td>
</tr>
<tr>
<td>Carotid dicrotic notch to R</td>
<td>10</td>
<td>0.147</td>
<td>0.133</td>
<td>0.014</td>
</tr>
<tr>
<td>Carotid dicrotic notch to S&lt;sub&gt;1&lt;/sub&gt;</td>
<td>10</td>
<td>0.230</td>
<td>0.217</td>
<td>0.013</td>
</tr>
</tbody>
</table>

For each set of observations n is the number of measurements on both small and large consecutive beats.

In the resting state the R-R interval including the small beat is longer than the R-R interval including the large beat. Isometric relaxation time is the same following both large and small beats. Carotid dicrotic notch to S<sub>1</sub> time or to R wave is longer preceding large beats.

During pacing the R-R interval is equalized, but pulsus alternans persists and alternation of the duration of dicrotic notch to R or to S<sub>1</sub> interval remains significant.
not present during the injection. Tilting the patients 45° in cases 1 and 2 with the head up or down had no discernible effect on the severity or pattern of pulsus alternans.

Right ventricular alternans was concordant with systemic pulsus alternans in cases 1, 2 (fig. 1), and 5. Right ventricular alternans was noted in addition to femoral arterial pulsus alternans in cases 3 and 4, but since the tracings were not recorded simultaneously, it is not known whether they were concordant.

Alternation of the beat-to-beat interval (R-R) was recorded in all cases in the resting state in the absence of electrocardiographic evidence of premature contractions. Although usually varying by about 0.02 second (table 3), maximal R-R variations of 0.08, 0.09, and 0.08 second, respectively, were occasionally noted in cases 1 (fig. 3), 2, and 3.

Pacing was performed independently from the right atrium and right ventricle in cases 1 and 2 (see table 3 for statistical significance). The following were noted: (1) Equalization of R-R intervals, with persistence of pulsus alternans to a lesser degree than before pacing was present (figs. 4a and b, and 5a). (2) Diminution of the degree of alternation of the diastolic intervals was present, but large pulse beats were still preceded by longer diastolic intervals than small beats, as in the resting state. (3) On discontinuing pacing, pulsus alternans immediately recurred to the same or a greater extent than in the resting state (figs. 4b, and 5a). (4) During one period in case 1 (fig. 5b), due to movement of the bipolar catheter tip in the right ventricle, pacing was intermittent. In this instance, there was a curious reversal of the previous pattern, pulsus alternans being more severe during pacing than during periods of interruption of pacing. In each instance, the change in degree was abrupt.

Volume

In cases 1 and 2, left ventricular volume was measured in late diastole preceding a large and a small beat and in end-systole for a large and a small beat; four determinations were made in each case. In all but one instance, the readings were made on successive cycles (table 2).

The end-diastolic volumes preceding large beats were, respectively, 4.4 and 6.3% greater than those preceding small beats, in cases 1 and 2. The end-systolic volume accompanying a large beat was 18.6% less than that for a small beat in case 1 and 12.6% less in case 2 (table 2).

Stroke volume was calculated by subtracting the end-systolic volume from the end-diastolic volume for large and small beats in each case. In the patient in case 2, who did not

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**Figure 3**

*Case 1: Pulsus alternans recorded in femoral artery, with alternation of R-R intervals and longer intervals following larger pulses. This pattern was seen frequently in cases 1, 2, and 3 and was less marked in cases 4 and 5.*
have mitral insufficiency, the average stroke volume* determined from the ventriculogram was 39 ml; it was 40 ml by the dye-dilution technique. In case 1 with mitral insufficiency, the average radiographically determined stroke volume was 75 ml while the average forward stroke volume determined by the dye-dilution technique was 30 ml. Therefore, the estimated average regurgitant volume per beat was 45 ml, representing the difference between the two figures.

Average ejection fractions of 28% and 14%, respectively, in cases 1 and 2 (table 2) were much below normal values.

Effects of Drugs on Pulsus Alternans

No effect on pulsus alternans was noted with the following drugs: (1) a mixture of Demerol, 25 mg, chlorpromazine, 6 mg, and promethazine hydrochloride, 6 mg/ml given intramuscularly: 1 ml/20 lbs, with a maximum of 2 ml (standard sedation used for procedures); (2) norepinephrine in the amount of 0.1 \( \mu g/\text{kg}/\text{min} \) with a maximum total infusion of 13.8 \( \mu g \); and (3) isoproterenol in the amount of 0.03 \( \mu g \) to 0.16 \( \mu g/\text{kg}/\text{min} \) in a concentration of 0.08 \( \mu g/\text{ml} \) in 5% dextrose in water to increase the pulse rate by 20 to 30 beats per minute.

With the intravenous use of 2.5 to 4.3 \( \mu g/\text{kg}/\text{min} \) of atropine with a maximum infusion of 0.21 mg in case 1, no effect on pulsus alternans was noted. In case 2, with an induced pulse rate of 165 per minute, pulsus alternans disappeared for 30 minutes.

In case 1, no effect on the pulsus alternans was observed by discontinuing and restarting oral administration of digitoxin. In case 5, deslanoside, 0.022 mg/kg, was administered intravenously over a 10-minute period with continuous monitoring of femoral arterial pressure. Pulsus alternans was not altered during observation for 1 hour. The following day the patient was digitalized with digitoxin.

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*The term “average stroke volume” is used because of the alternation of stroke volume with large and small beats. It represents the mean stroke volume for small and large beats.
Seven days later the degree of alternans had diminished in the femoral artery to 10 mm Hg, with short intervals of normal pulsations. The resting cardiac output was unchanged (table 1).

Pertinent catheterization data with administration of digitalis or isoproterenol are recorded in table 1.

**Left Ventricular End-Diastolic Pressure**

In 90 left ventricular complexes in case 1 and 43 in case 2, end-diastolic pressures were measured in two or three groups where consecutive complexes had a characteristic contour. Though the end-diastolic pressure preceding individual large beats was not higher in every pair of consecutive beats, presumably due to respiration, statistical analysis in case 1 showed the mean end-diastolic pressure preceding large beats to be higher than that preceding small beats by 3.7 mm Hg (P < 0.001). The mean end-diastolic pressure for large beats was 27.9 (SD 2.67) and for small beats 24.2 mm Hg (SD 2.55). In case 2 there was a marked respiratory effect and the end-diastolic pressure difference between large and small beats was not significant (P < 0.1).

**Cardiac Output**

Cardiac output at rest varied from slightly low to normal in four patients tested (table 1). The administration of isoproterenol five times to a total of four patients resulted in a mean increase in “average” stroke index of 18% and a mean increase in cardiac index of 45%. The greatest increases in both stroke...
and cardiac index occurred in case 1, 6 months before his death (table 1).

**Phases of Systole and Diastole**

Beat-to-beat changes in the duration of systolic phases and of duration of diastole for case 2 are shown in figure 6. There was no significant variation in isometric relaxation time for large and small beats (table 3).

**Discussion**

The presence of pulsus alternans may be diagnosed clinically, using a sphygmomanometer, or more directly by recording the external carotid arterial pulse. Palpation of the pulse alone may be misleading. If the pulsus alternans is severe, the small beats may be imperceptible, giving the impression of bradycardia unless the heart is simultaneously

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*Figure 6*

Case 2: The duration in seconds, of diastole ($S_2S_1$), left ventricular ejection time (LVET), duration of total systole (DTS or $S_1S_2$), and isovolumetric contraction time (ICT), measured from an external carotid tracing with a phonocardiogram. ICT represents the time difference between the corresponding $S_2S_1$ and LVET measurements. The diastolic intervals measured precede the corresponding $S_2S_1$, LVET, and ICT. Thus shorter diastolic intervals precede $S_1S_2$, LVET, and ICT for small beats. The ICT for small beats is markedly prolonged but is normal for large beats.
auscultated or an electrocardiogram is monitored. On the other hand, when it is mild (less than 20 mm Hg), it may be difficult to detect by palpation. In this series auscultation provided a clue to its presence in only one case in which an alternating systolic ejection murmur was heard only with large beats.

Pulsus alternans was unusually severe in the patients reported here. In one series of cases of various etiologies in adults the maximal pressure difference between large and small beats was 30 mm Hg and in another series of cases of acquired aortic stenosis it was 43 mm Hg compared with maximal differences of 60 and 63 mm Hg in the femoral arterial pressures of small and large beats in cases 1 and 2. Right ventricular alternans was also prominent (table 1 and fig. 1).

Variation of the degree of pulsum alternans was seen at times even when patients appeared to be in a steady state, and it may appear and disappear over short intervals of time without evidence of an electrocardiographic arrhythmia (fig. 2). During one study in case 1, episodes of pulsum alternans were accompanied by peaked P waves, not seen in other cases (fig. 2), suggesting temporary right atrial strain for all beats during these periods.

Etiology of Pulsus Alternans

Theories of the etiology of pulsum alternans may be summarized as follows: (1) alternate deletion of myocardial contractile elements,19,20 and (2) alternation of left ventricular end-diastolic volume, larger end-diastolic volumes preceding large beats in accordance with Starling's law, without necessarily invoking alternate deletion of contractile elements. Gleason and Braunwald21 based support for this theory22-25 on demonstration of higher end-diastolic volumes preceding large, as compared with small, beats in a case of aortic stenosis.

Factors which may influence the left ventricular end-diastolic volume are as follows:

1. The duration of diastole: The observations in cases 1 and 2 in this study showed shorter diastolic intervals preceding small beats than large beats (fig. 6 and table 3). Gleason and Braunwald21 found this usually to be the case but noted an exception to it. In case 1 in this series diastole preceding a small beat remained shorter than before a large beat even when R-R intervals had been equalized by pacing (table 3).

2. Left ventricular residual volume: In cases 1 and 2 a larger left ventricular residual volume after small beats was demonstrated (table 3), as in the case of Gleason and Braunwald.21 This would contribute to a larger left ventricular end-diastolic volume preceding the following large beat.

3. Failure of the left ventricle to recover metabolically after large beats, leading to impaired ventricular relaxation and filling before the following small beat: In case 1 the absence of beat-to-beat alternation of the isometric relaxation time (table 3) does not lend support to this theory.

It has been stated that a weak beat can result from a higher, equal, or lower left ventricular end-diastolic pressure compared with the end-diastolic pressure preceding a large beat.22 Though this was true in some cases for individual beats, analysis of left ventricular end-diastolic pressure for a large number of beats showed a slightly but significantly higher pressure preceding large beats. Since a difference of 1 to 2 cm H2O may substantially affect the end-diastolic fiber length and stroke work of the subsequent beat,22 a left ventricular end-diastolic pressure difference of 3.7 mm Hg is of importance.

The end-diastolic volume differences preceding small and large beats are relatively small (4.4 and 6.3%) and may fall within the range of normal variation. However, in the three cases thus far studied by Gleason and Braunwald21 and the authors, a similar qualitative alternation has been observed, a higher end-diastolic volume in each case preceding a large beat. This evidence, coupled with similar variation of end-diastolic pressure suggests that the conclusions to be drawn are probably valid. However, further determinations of left ventricular volume are indicated in cases of pulsum alternans.
On the basis of the present studies and those of others, it is suggested that the mechanism of pulsus alternans includes greater left ventricular volumes and pressures preceding large beats as compared with small beats. However, even when preceding small beats, left ventricular end-diastolic volume was large and was followed by a longer isometric contraction time (often greatly prolonged) than is found with large beats. In the authors' patients the difference between left ventricular end-systolic volumes was larger for large and small beats, than that reported by Gleason and Braunwald. The difference may be attributable, at least in part, to the presence of aortic stenosis in their patient, whereas in the patients reported on herein, no obstruction to the left ventricular outflow tract or aortic valve was present. In the present report the difference in left ventricular end-systolic volume between large and small beats was not predictable from the small difference between end-diastolic volumes. The long isovolumetric contraction times preceding small beats, in spite of large preceding left ventricular end-diastolic volumes, suggests that, in addition to Starling's law, reduced myocardial contractility is a factor in production of small beats. Alternate deletion of contractile elements may be this factor, but no direct evidence can be offered.

Some points may be mentioned which appear not to be causes of the mechanism disorder in this study. These include alternation of the R-R interval, wide variations of heart rate, respiration, and posture. Though pulsus alternans may be precipitated by premature ventricular contractions, alteration of the electrical sequence of depolarization did not appear to be a significant factor in this investigation.

In connection with the sequence of depolarization the pacing studies were of interest. Breath-holding in an attempt to equalize R-R intervals, was not possible in such small children. Pacing established that wide alternation of duration of R-R may occur with true pulsus alternans. The sudden increase in its magnitude on discontinuing pacing may be due to myocardial fatigue since the pacing rate was always faster than the resting rate. In support of this, greater augmentation of pulsus alternans was recorded on discontinuing the most rapid pacing rates. In addition, in one of the siblings subjected to pacing, pulsus alternans, absent at rest at a later date, could be precipitated by exercise. Regarding the reversal of the pattern of pulsus alternans during intermittent pacing from the right ventricle (fig. 5b), no adequate explanation has been established. The possibility of a lag of response during frequent induction and cessation of pacing was considered, but the abrupt change in pulsus alternans at the beginning and end-points throws doubt on this explanation. Pacing from the right atrium and right ventricle also shows that alternans is not dependent on any given sequence of electrical conduction.

Right ventricular alternans was present in five cases and was known to be concordant with alternans in the left ventricle in three of them. Histological changes in the right ventricle were present in case 1 and may have been related to the right ventricular alternans. Significant pulmonary hypertension was not demonstrated in any case at cardiac catheterization and is thus excluded as a cause.

It is tempting to examine nervous or humoral factors in pulsus alternans because of its tendency to appear, disappear, or change its magnitude spontaneously. However, most of the evidence from the present study is negative in this connection. Stimulation of β-sympathetic receptors (isoproterenol and norepinephrine), α-sympathetic receptors (norepinephrine) and blockade of cholinergic receptors (atropine) did not augment it. Sedation with Demerol, chlorpromazine, and promethazine hydrochloride appeared to have no effect.

Because of the severity of the pulsus alternans and its generally assumed grave prognostic importance, an increase in the “average” stroke volume following administration of isoproterenol was not anticipated. Generally, little or no increase occurred, but in case 1 an increase in “average stroke volume” of
45% during administration of isoproterenol was recorded 6 months before the patient's death in cardiac failure. The finding of a fairly recent left ventricular thrombus at autopsy suggests that the thrombus may have played a role in the deterioration of function and subsequent demise.

The relatively long survival time in these cases of severe pulsus alternans supports the contention of Ryan and associates28 that the prognosis for patients with pulsus alternans is more dependent on the underlying pathology than on the presence of pulsus alternans per se. Certainly, severe pulsus alternans need not necessarily indicate impending death within a few months.

Myocardial disease has been demonstrated in one case only, but it can reasonably be assumed to be similar in his sibling. The clinical picture has been similar in the other cases with the exception of an earlier onset in case 4. However, no proof can be presented that the remaining three patients have morphological abnormalities similar to the siblings in cases 1 and 2. The condition appears to be "cardiovascular collagenosis" according to B.J.P. Becker (personal communication) and his associates9 or "cryptogenic heart disease."29 The slides of myocardial sections in case 1 have been reviewed by Becker who is of the opinion that the disease in this child is similar to that seen in South Africa, most commonly in the Bantu.9, 30

Summary

Five children, including two siblings, with clinically similar primary myocardial disease, were studied. One of the siblings expired 3 years after the onset of symptoms, and autopsy showed features of "cardiovascular collagenosis (endocardiomypathy)." Moderate-to-severe pulsus alternans was present in all cases and persisted even after control of cardiac failure and return to moderate physical activity. No electrical alternans or bigeminy was observed.

Cardiac catheterizations were performed on all patients. Left ventricular volume was radiographically determined in the siblings. Left ventricular end-diastolic volume was calculated as greater, and end-systolic volume smaller, for large beats as compared with small beats. Though alternating, end-diastolic volume was abnormally large, preceding both small and large beats. End-diastolic pressure alternated in the same way. Beat to beat (R-R) interval, alternating by as much as 0.09 second, was equalized by pacing in the right atrium and right ventricle, with persistence of pulsus alternans to a lesser degree. Isovolumetric contraction time was prolonged preceding small beats in spite of the large preceding end-diastolic volumes.

The data appear to be consistent with Starling's law but suggest that impaired contractility, possibly due to alternate deletion of contractile elements, is an additional etiological factor.

References

SEVERE PULSUS ALTERNANS


Severe Pulsus Alternans Associated with Primary Myocardial Disease in Children: Observations on Clinical Features, Hemodynamic Findings, Mechanism, and Prognosis

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