CLINICAL STUDIES

Pulsus Alternans: Its Influence on Systolic and Diastolic Function in Aortic Valve Disease

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Left ventricular high fidelity pressure measurements and simultaneous biplane cineangiography were performed in 12 patients with severe aortic valve disease (aortic stenosis in 10, aortic insufficiency in 1 and combined valve lesion in 1). Left ventricular contractility was estimated from maximal rate of left ventricular pressure rise (max dP/dt), peak measured velocity of contractile element shortening (Vpm) and mean circumferential fiber shortening velocity. Left ventricular relaxation was assessed in 12 patients from the time constant (T) of the decline in left ventricular pressure; this constant was calculated from a nonlinear regression analysis of pressure and time (method 1) and a linear regression analysis of pressure and negative dP/dt (method 2). Left ventricular diastolic function was evaluated in nine patients from simultaneous diastolic pressure-volume relations during the strong and weak beats.

During pulsus alternans, heart rate and left ventricular end-diastolic pressure remained unchanged, whereas peak systolic pressure (220 versus 204 mm Hg, p < 0.01) and end-systolic pressure (101 versus 95 mm Hg, p < 0.01) were significantly higher during the strong beat than during the weak beat. Max dP/dt was alternating (2,162 versus 1,964 mm Hg, p < 0.05), whereas the peak velocity of contractile element shortening remained unchanged (1.21 versus 1.18 ML/s). Systolic shortening of the left ventricular minor axis was significantly (p < 0.02) greater during the strong (24%) than during the weak (19%) beat, but that of the left ventricular major axis remained essentially unchanged (8 versus 7%). The time constant (T) demonstrated only slight alternation during the strong beat (method 1: 54 ms, method 2: 58 ms) and during the weak beat (method 1: 57 ms, method 2: 67 ms, p = NS). Diastolic pressure-volume relations showed no changes during pulsus alternans. Left ventricular end-diastolic volume was 148 ml/m² during the strong and 146 ml/m² during the weak beat; systolic ejection fraction was significantly higher during the strong than during the weak beat (48 versus 43%, p < 0.02).

It is concluded that pulsus alternans is a systolic phenomenon with alternation in left ventricular contractility, but nonsignificant changes in left ventricular relaxation and diastolic function. Although contractility was enhanced, the time constant (T) of the decline in left ventricular pressure did not change significantly during the strong beat, because the increase in peak systolic pressure offset almost completely the decrease in T associated with the increase in contractile state. The alternation of systolic shortening is the result of changes in contractility and not of a Frank-Starling mechanism since preload remained unchanged.

Pulsus alternans, first described by Traube in 1872 (1), is characterized by an alternation of strong and weak ventricular contractions with a regular cardiac rhythm (2,3). Pulsus alternans has been considered a sign of severe ventricular dysfunction, usually found in the presence of hypertensive or coronary artery disease and aortic stenosis. Two fundamental mechanisms that may explain ventricular alternation in patients with ventricular dysfunction are: 1) the Frank-Starling mechanism with alternation in diastolic volume, and 2) alternating myocardial contractility in the absence of changes in diastolic volume (4-6). Numerous studies (2-6) on the genesis of pulsus alternans have been published, but the results have been contradictory. In this study, we examined the effects of pulsus alternans on systolic contraction, left ventricular relaxation and diastolic function in patients with severe aortic valve disease, employing simultaneous high fidelity pressure measurements and biplane cineangiography.

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Methods

Patients. Twelve patients (four women and eight men) with a mean age of 54.5 years (range 33 to 69) were studied. All patients underwent left and right heart catheterization for diagnostic purposes. Ten patients had severe aortic stenosis with a mean systolic pressure gradient of 74 mm Hg; nine of them had slight aortic regurgitation (regurgitant fraction as determined by thermodilution ≤ 0.20; mean regurgitant fraction 0.15). The average aortic valve area was 0.56 cm². One patient had severe aortic incompetence (regurgitant fraction 0.67) and another had severe combined aortic valve disease (systolic pressure gradient 66 mm Hg, regurgitant fraction 0.50).

Coronary arteriography, performed in all patients, revealed coronary artery disease in four: one vessel disease with, respectively, a 50 and 90% stenosis of the left circumflex coronary artery in two patients and two vessel disease with, respectively, a 50 and 100% stenosis of the left anterior descending coronary artery and a 90 and 50% stenosis of the left circumflex coronary artery in two patients. There were no regional wall motion abnormalities in any of these four patients. Pulsus alternans occurred spontaneously in six patients and after an extrasystole in another six patients. Two patients also had right ventricular pulsus alternans. During cineangiography, nine patients showed alternation of left ventricular systolic pressure. No electrical alternans was observed in any of the 12 patients.

Catheterization and cineangiography. Informed consent was obtained from all patients. Premedication consisted of 10 mg of chlordiazepoxide (Librium) given orally 1 hour before the procedure. Left ventricular pressure was measured with a transseptally introduced 7F Millar micromanometer (7). The micromanometer was calibrated by superimposing the high fidelity pressure tracing on the conventional pressure tracing. Before insertion, the micromanometer was balanced and set at zero. The frequency response of the recording system, including the tip transducer and the direct current amplifier, was flat beyond 100 Hz. Aortic pressure was measured through a fluid-filled 8F pigtail catheter. A peripheral lead of the standard electrocardiogram and the phonocardiogram were also recorded.

Left ventricular cineangiography was performed at a speed of 50 frames/s in the right and left anterior oblique projections, with simultaneous recordings of left ventricular high fidelity pressure, first derivative of left ventricular pressure, the electrocardiogram and a numerical code that appeared on both the cinefilm and the pressure recordings. The pressure recordings were made on an Electronics for Medicine DR 16 VR 12 oscillograph at a paper speed of 200 or 250 mm/s (Fig. 1).

Pressure and volume data were determined on a frame by frame basis at 20 ms intervals for a strong and the following weak beat. End-diastole was defined as the last cineframe before the rapid upstroke of dP/dt after atrial con-
traction, and end-systole from the crossover point of aortic pressure at the incisura and left ventricular pressure. Left ventricular volumes were calculated according to the area-length method (8) and systolic ejection fraction was calculated as: end-diastolic volume = end-systolic volume + end-diastolic volume $\times 100$. Extrasystolic and postextrasystolic beats were excluded from the angiographic analysis. The range of normal values was established from 20 patients with atypical chest pain or a functional murmur (9); ejection fraction in this group ranged from 57 to 83% (mean 68).

**Measures of left ventricular contractility.** Left ventricular contractility was assessed from isovolumic contractile and angiographic ejection phase indexes. The maximal rate of rise (max dP/dt) of left ventricular pressure and the peak measured velocity of contractile element shortening ($V_{pm}$) were determined according to our standard technique (10). Endocardial circumferential fiber shortening velocity at the left ventricular minor axis ($V_{cf}$) was determined from the right anterior oblique angiographic silhouette. Mean normalized systolic ejection rate was determined from biplane cineangiography by dividing left ventricular ejection fraction by systolic ejection time (11).

**Indexes of left ventricular relaxation.** The time constant ($T$) of left ventricular pressure decay (in milliseconds) was calculated from peak negative dP/dt to mitral valve opening (12). Mitral valve opening was determined from the left ventricular pressure tracing, assuming that the opening occurred at a pressure 5 mm Hg higher than the end-diastolic pressure (13). In contrast to Weiss et al. (14), who calculated the time constant of pressure decay from a log pressure versus time plot that assumed that the pressure intercept is constant, we used an approach that takes into account changes in baseline pressure, which are especially important in patients with chronic pressure overload (9,13). Two methods were used to calculate the time constant of left ventricular pressure decay ($T$).

**Method 1.** In this method, assuming that the pressure decay is an exponential process, the time constant ($T$) was calculated from the general equation:

$$P = A + B \cdot e^{-\alpha t},$$

where $P$ = left ventricular pressure (mm Hg), $A$ = pressure intercept (mm Hg), $B$ = pressure at peak negative dP/dt ($P_0$) minus $A$ (mm Hg), $\alpha$ = slope of the left ventricular pressure-time curve and $t$ = time (ms). The time constant was defined as: $T = 1 / \alpha$ (ms). The three constants $A$, $B$ and $\alpha$ were calculated using a nonlinear curve-fitting program (STATS-eleven, Hammond-software, Göttingen, West Germany), where these constants were determined by an iteration procedure (Fig. 2). The difference between the calculated and the observed pressure was usually very small, and the average residual sum of squares was 0.25 ± 0.33.

![Figure 2](image-url)
mm Hg for the strong and 0.37 ± 0.49 mm Hg for the weak beat (mean values ± 1 standard deviation).

**Method 2.** In this method, after differentiation of left ventricular pressure versus time, the time constant T* was calculated from the general equation:

\[ P = A^* + B \cdot e^{-\alpha*t}, \]

where

\[ \frac{dP}{dt} = -\alpha^*(P - A^*), \]

or:

\[ T^* = \frac{1}{\alpha^*} = -\frac{P - A^*}{dP/dt}, \]

where \( P \) = left ventricular pressure (mm Hg), \( t \) = time (ms), \( \alpha^* \) = slope of the \( dP/dt \) versus \( P \) curve and \( A^* \) = pressure intercept at \( dP/dt = 0 \) (mm Hg). The two constants \( \alpha^* \) and \( A^* \) were calculated from a linear regression equation where negative \( dP/dt \) was plotted versus left ventricular pressure (Fig. 2). The correlation coefficients were good in all patients (mean ± standard deviation 0.97 ± 0.02 for the strong beat and 0.96 ± 0.02 for the weak beat).

**Left ventricular diastolic function.** This was assessed from simultaneous diastolic pressure-volume plots during the strong beat and the following weak beat (Fig. 3).

**Left ventricular geometry.** This was assessed from the left ventricular long- to short-axis ratio at end-diastole and end-systole, as well as from systolic shortening of the long and short axis.

**Statistical analysis.** Statistical comparisons between the strong and weak beats were performed by the paired Student’s \( t \) test. Mean values ± 1 standard deviation are given in all tables and figures.

**Results**

**Standard hemodynamic variables (Table 1).** Heart rate and left ventricular end-diastolic pressure remained unchanged from the strong to the following weak beat, whereas
Table 1. Hemodynamic Data

<table>
<thead>
<tr>
<th>Beat</th>
<th>HR</th>
<th>LVEDP</th>
<th>LVSP</th>
<th>ESP</th>
<th>EDVI</th>
<th>EF</th>
<th>ET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong</td>
<td>97 ± 11</td>
<td>25 ± 7</td>
<td>220 ± 38</td>
<td>101 ± 9</td>
<td>148 ± 52</td>
<td>48 ± 10</td>
<td>289 ± 27</td>
</tr>
<tr>
<td>Weak</td>
<td>97 ± 11</td>
<td>25 ± 7</td>
<td>204 ± 37</td>
<td>95 ± 10</td>
<td>146 ± 49</td>
<td>43 ± 10</td>
<td>272 ± 32</td>
</tr>
</tbody>
</table>

* *p < 0.02, *p < 0.005, *p < 0.001. EDVI = end-diastolic volume index (ml/m²); EF = ejection fraction (%); ESP = end-systolic pressure (mm Hg); ET = ejection time (ms); HR = heart rate (min⁻¹); LVEDP = left ventricular end-diastolic pressure (mm Hg); LVSP = left ventricular peak systolic pressure (mm Hg).

left ventricular peak systolic and end-systolic pressures were significantly higher during the strong beat. The angiographic end-diastolic volume remained unchanged during pulsus alternans, but systolic ejection fraction was significantly higher during the strong beat than during the weak beat (48 versus 43%, *p < 0.02).

**Measures of left ventricular contractility (Table 2).**

**Isovolumic contractile indexes.** Maximal dP/dt was significantly increased during the strong beat compared with the weak beat, whereas peak measured velocity of contractile element shortening did not change significantly during pulsus alternans.

**Anisovolumic ejection phase indexes.** Mean circumferential fiber shortening velocity was significantly greater during the strong beat than during the weak beat, whereas mean normalized systolic ejection rate was slightly but not significantly higher during the strong beat than during the weak beat. This was due to the decreased left ventricular ejection time during the weak beat.

**Indexes of left ventricular relaxation (Table 3).**

Isovolumic relaxation time was slightly but not significantly shorter during the strong beat than during the weak beat. Peak negative dP/dt remained unchanged during pulsus alternans. The time constants of left ventricular pressure decay (T and T*) and the pressure intercepts (A and A*) remained unchanged during the strong and weak beats, although T and T* were slightly smaller during the strong beat. There was a good agreement between T and T* (*r = 0.987) and between A and A* (*r = 0.976)."

**Left ventricular geometry (Table 4).** The long/short axis ratio was similar at end-diastole for the strong and the weak beat, but was slightly although not significantly larger at end-systole during the strong beat than during the weak beat. Systolic shortening of the short axis showed significant alternations during pulsus alternans, whereas shortening of the long axis showed only minor alternations during the strong and weak beats.

**Discussion**

Frank-Starling effect or alternating contractility?

Pulsus alternans is often a manifestation of advanced myocardial dysfunction in valvular and coronary heart disease or dilated cardiomyopathy. Alternating contractions occurring simultaneously in the left and right ventricle (concordant alternans) or beats with strong left but weak right ventricular contractions alternating with weak left and strong right ventricular contractions (discordant alternans) were reported (5,6). We observed concordant alternans of the left and right ventricle in 2 of our 12 patients; discordant alternans was seen in none. Spontaneous pulsus alternans was observed in six patients; in the other six patients, pulsus alternans occurred after an extrasystole. All 12 patients in our series had severe aortic valve disease with moderately depressed myocardial function (left ventricular ejection fraction was 48 and 43%, respectively, for the strong and the weak beat; in the 20 control patients it averaged 68%). Severe ventricular dysfunction was considered necessary for the occurrence of pulsus alternans, although the exact mechanism is still not known.

There are two principal theories for the genesis of pulsus alternans: 1) Frank-Starling mechanism with alternation of

Table 2. Measures of Left Ventricular Contractility

<table>
<thead>
<tr>
<th>Beat</th>
<th>Max dP/dt</th>
<th>Vpm</th>
<th>Vcf</th>
<th>MNSER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong</td>
<td>2162 ± 532</td>
<td>1.21 ± 0.35</td>
<td>0.82 ± 0.46</td>
<td>1.67 ± 0.35</td>
</tr>
<tr>
<td>Weak</td>
<td>1964 ± 475</td>
<td>1.18 ± 0.37</td>
<td>0.68 ± 0.34</td>
<td>1.60 ± 0.33</td>
</tr>
</tbody>
</table>

*p < 0.05. Max dP/dt = maximal rate of rise in left ventricular pressure (mm Hg/s); MNSER = mean normalized systolic ejection rate (end-diastolic volumes/s); Vcf = mean circumferential fiber shortening velocity of the left ventricular minor axis (circumferences/s); Vpm = peak measured velocity of contractile element shortening (ML/s).
Table 3. Indexes of Left Ventricular Relaxation

<table>
<thead>
<tr>
<th>Beat</th>
<th>IVRT (ms)</th>
<th>Max - dP/dt (mm Hg/s)</th>
<th>T (ms)</th>
<th>A (ms)</th>
<th>T* (ms)</th>
<th>A* (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong</td>
<td>65 ± 23</td>
<td>1787 ± 346</td>
<td>54 ± 28</td>
<td>-19 ± 25</td>
<td>58 ± 26</td>
<td>-23 ± 23</td>
</tr>
<tr>
<td>Weak</td>
<td>57 ± 15</td>
<td>1783 ± 350</td>
<td>57 ± 38</td>
<td>-23 ± 35</td>
<td>67 ± 35</td>
<td>-31 ± 27</td>
</tr>
</tbody>
</table>

A = pressure intercept (mm Hg); A* = pressure intercept at dP/dt = 0 (mm Hg); IVRT = isovolumic relaxation time (ms); Max - dP/dt = maximal rate of left ventricular pressure decline (mm Hg/s); T and T* = time constant of left ventricular pressure decay (ms).

the end-diastolic volume, and 2) alternating myocardial contractility of the ventricle in the absence of changes in diastolic volume. Several studies (2–6) focused on the systolic phenomenon of pulsus alternans, but only a few examined the effect on left ventricular relaxation and diastolic function. Thus, the purpose of the present study was to evaluate the effects of pulsus alternans on systolic function, left ventricular relaxation and diastolic function in patients with severe aortic valve disease.

Standard hemodynamic measurements showed alternating systolic contractions with significant changes in peak systolic and end-systolic pressure, whereas heart rate remained unchanged during pulsus alternans. Significant changes in left ventricular preload could not be detected in our study because left ventricular end-diastolic pressure and volume remained the same during the strong and weak beats (Table 1). Thus, the Frank-Starling mechanism can be ruled out as a cause for the alternation of systolic contractions in the present study. Evaluation of left ventricular contractility showed alternation of maximal dP/dt and circumferential fiber shortening velocity during the strong and weak beats, confirming the concept of alternating contractility as the major cause for alternations in systolic contractions during pulsus alternans (Table 2). Qualitatively, the same results were obtained when the four patients with coronary artery disease were evaluated separately. There was no significant difference between the patients with and without coronary artery disease. Alternating contractions were mainly seen in the short axis of the left ventricle, whereas shortening of the long axis remained practically unchanged during pulsus alternans.

The genesis of alternating contractility in patients with severe aortic valve disease remains unclear, but may be related to changes in calcium transport of the heart muscle cells. Beat to beat variations in calcium concentration in the heart muscle cell could explain the occurrence of pulsus alternans. Hashimoto et al. (16) recently showed that calcium channel blockers may abolish electrical alternans in dogs with acute ischemia, but there was no consistent effect on mechanical alternans, suggesting a different mechanism for electrical and mechanical alternans. In our 12 patients, we did not find mechanical alternans accompanied by electrical alternans.

Left ventricular relaxation in pulsus alternans. There was no significant change in the rate of relaxation as assessed with either method 1 or 2 (Table 3). Both time constants T and T* were slightly shorter during the strong beat than during the weak beat. The slightly increased speed of relaxation during the strong beat could be explained by the higher contractile state (14,15); however, the difference in the time constant between the strong and the weak beat was not significant. An increase in afterload is known to be associated with a decrease in the rate of relaxation (17); that is, a higher systolic pressure in itself leads to a decrease in the speed of relaxation or an increase in the time constant of decline in left ventricular pressure. Thus, these two mechanisms—increased contractility, which is associated with an increased speed of relaxation, and increased afterload, which is associated with a decreased speed of relaxation—counterbalance the effect of pulsus alternans on left ventricular relaxation.

Another explanation for the discrepancy between increased contractility and no change in left ventricular relaxation may reside in a mechanism similar to that of postextrasystolic potentiation. In patients with postextrasystolic potentiation, left ventricular contractility is enhanced, but the rate of relaxation is decreased during the potentiated beat (18). This effect is known to occur with the administration of calcium, and might explain why contractility is augmented during the strong beat but relaxation remains unchanged in the presence of increased calcium concentration. Thus, the dissociation between systolic contraction and

Table 4. Left Ventricular Geometry

<table>
<thead>
<tr>
<th>Beat</th>
<th>SbSA (cm²)</th>
<th>SbLA (cm²)</th>
<th>L/Med</th>
<th>L/Mes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong</td>
<td>24.7</td>
<td>8.0</td>
<td>1.8</td>
<td>2.3</td>
</tr>
<tr>
<td>Weak</td>
<td>19.1</td>
<td>7.0</td>
<td>1.8</td>
<td>2.1</td>
</tr>
</tbody>
</table>

*p < 0.02. L/Med = long/short axis ratio at end-diastole; L/Mes = long/short axis ratio at end-systole; SbSA = systolic shortening of the left ventricular long axis (%); SbLA = systolic shortening of the left ventricular short axis (%).
relaxation could be explained by a change in calcium concentration in the heart muscle cell. Nevertheless, the overall effect of pulsus alternans on left ventricular relaxation is small and relaxation is regulated to be constant during alternation of systolic contractions.

**Passive diastolic function in pulsus alternans.** Diastolic pressure-volume relations showed no major changes in diastolic chamber properties during alternation of systolic contractions (Fig. 3). In all nine patients with simultaneous pressure-volume plots, the diastolic pressure-volume relations had the same curve characteristics during the strong and weak beats. Thus, diastolic function is unchanged during pulsus alternans, which occurs in parallel to the small changes in left ventricular relaxation during alternation of systolic contractions.

**Implications.** Our study supports the concept that pulsus alternans is a systolic phenomenon with alternations in left ventricular contractility but no changes in left ventricular relaxation and diastolic function. The alternation of systolic shortening is the result of changes in left ventricular contractility and not a Frank-Starling mechanism because preload remains unchanged. The genesis of alternating contractility in patients with severe aortic valve disease remains unclear, but seems to be related to functional problems at the cellular level.

**References**