Mechanisms of Pulsus Alternans

By Keith E. Cohn, M.D., Harold Sandler, M.D., and E. W. Hancock, M.D.

SUMMARY

The mechanisms of pulsus alternans were studied in three patients by cineangiographic determinations of left ventricular volume. In two patients with left ventricular disease, pulsus alternans occurred without detectable variation in left ventricular end-diastolic pressure (LVEDP) or end-diastolic volume (EDV), although in the second case these values did alternate in the initial postextrasystolic beats. Another patient with normal left ventricular function had brief postextrasystolic pulsus alternans associated with LVEDV alternations. Twenty-nine patients with valvular aortic stenosis who showed pulsus alternans during left heart catheterization were also studied. Persistent alternation in LVEDP occurred in eight, with transient LVEDP alternation appearing after extrasystoles in 22 cases. Cardiac cycle length and diastolic interval alternation occurred inconsistently.

Additional Indexing Words:

Starling's principle  Contractility  Aortic stenosis
Diastolic compliance  Volume angiography  Ventricular alternans

Pulsus alternans was described by Traube in the nineteenth century and has remained a subject of investigation and conjecture since that time. Two fundamental mechanisms have been proposed to explain ventricular alternation: (1) Wenckebach's and Straub's concept, based on Starling's principle, held that alternation in diastolic volume accounted for the alternating contractile force—an increased fiber length preceding the more powerful beats. (2) The "myocardial theory," originated by Gaskell, Hering, and Wiggers, suggests, on the other hand, that alternations in contractility occur in the absence of fluctuating ventricular diastolic volume. Either variations in the basic inotropic state of the myocardium or alternation in the number of cardiac fibers contributing to each systole could thereby induce this phenomenon. Several extensions of these theories have been proposed and will be discussed subsequently.

Although numerous studies have attempted to define the mechanism of mechanical alternans, the results have been conflicting and the subject remains incompletely understood. In the present paper this phenomenon has been studied in man, employing left heart catheterization and cineangiographic determinations of left ventricular volume. The results of this study indicate that several mechanisms are involved in ventricular alternation, and, therefore, that previous observations and apparently divergent theories concerning this subject may be consolidated into a unified concept.

Methods

Volume Angiography

Three patients with pulsus alternans were studied by left heart catheterization and angiographic determinations of left ventricular volume. Case 1, PS, was a 53-year-old man with hypertension, severe valvular aortic stenosis, and slight aortic insufficiency. Persistent pulsus alternans was detectable at the bedside and was associated with alternation in the intensity of the aortic systolic murmur. Case 2, LC, was a 54-year-old man with idiopathic cardiomyopathy and secondary mitral regurgitation. He had marked, intractable heart failure and a very large heart on roentgenogram. Patient 3, GC, was a 41-year-old woman from the Department of Medicine, Cardiology Division, Stanford University School of Medicine and the Palo Alto-Stanford Hospital, and the Division of Biotechnology, Ames Research Center, Moffett Field, Palo Alto, California.

From the Department of Medicine, Cardiology Division, Stanford University School of Medicine and the Palo Alto-Stanford Hospital, and the Division of Biotechnology, Ames Research Center, Moffett Field, Palo Alto, California.
with only mild aortic insufficiency. In patients 2 and 3, the alternation was transient, following ventricular extrasystoles, and in case 3, it was observed during cardiac catheterization only.

Left ventricular and left atrial pressures were obtained through a Brockenbrough transseptal catheter and recorded by means of Statham P23Gb pressure transducers on an Electronics for Medicine multichannel recorder. Cardiac output measurements were made by the Fick method.

Left ventricular volumes were calculated from single A-P plane cineangiograms taken at 48 frames per second after injection of 76% methylglucamine diatrizoate (Renografin) into the left atrium or left ventricle. The technique of Sandler and associates was employed in determining the volumes. In brief, the left ventricular chamber is considered to be an ellipsoid of revolution, and the volume

\[ V = \frac{8}{3\pi} \cdot \frac{A^2}{L} \cdot CF \]

where \( A \) is the planimetered area of the traced image of the LV chamber and \( L \) its maximal length. CF, the correction factor for geometric and spherical distortion, is obtained by photographing a 1-cm cross-hatched grid placed at the estimated center of LV mass, and by comparing the true and photographed areas encompassed by the left ventricular image. The calculated volume \( V \) was adjusted to actual volume \( V' \) by

\[ V' = 0.951V - 3.0 \]

this equation being previously determined by comparison of single plane and biplane volumes. All ventricular volumes were determined by tracing and planimetry on two separate occasions.

**Left Heart Catheterization in Aortic Stenosis**

Hemodynamic data from 29 patients with valvular aortic stenosis and ventricular alternans who were studied with left heart catheterization were analyzed. In most instances left ventricular pressures were recorded through a PE-50 catheter introduced into that chamber through a Ross needle, and arterial pressures were obtained through a Courmand needle in the brachial artery or catheter in the central aorta. Cardiac cycle length (R-R interval) and an estimate of diastolic filling period—measured as the interval from dicrotic notch to onset of left ventricular systole—were determined during the cycles demonstrating pulsed alternans. An indistinct dicrotic notch prevented accurate measurement in several of the cases. It is also noted that when brachial artery pressures are employed the dicrotic notch follows the onset of diastole, so that the true diastolic interval is somewhat greater than the obtained value.

**Results**

**Volume Angiography**

*Persistent Pulsus Alternans*

In case 1, persistent ventricular alternans was observed in the absence of alternation of left ventricular end-diastolic pressure (LVEDP) and LV end-diastolic volume (EDV) (table 1, figs. 1 and 2). Alternations were present in the left ventricular systolic pressure, arterial pressure, stroke volume, left ventricular rate of pressure rise (2,600 mm Hg per second in the stronger versus 1,600 in the weaker beats), and left ventricular rate of emptying (360 versus 280 ml per second). The larger beats were associated with a normal end-systolic volume (ESV) and stroke volume, and near normal ejection fraction (EF), whereas in the smaller beats the EF was diminished and the ESV elevated. The “a” wave alternated slightly, 17 mm Hg before the larger and 12 mm Hg before the smaller contractions, but did not affect left ventricular end-diastolic pressure since the PR interval was prolonged (fig. 2). The cycle length

**Figure 1**

Sequential changes in left ventricular chamber volumes are plotted from case 1, a patient with aortic stenosis and pulsed alternans. Alternation in end-systolic volume and stroke volume occurs, although the left ventricular end-diastolic volume does not vary significantly.
and diastolic filling period alternated intermittently, changing by 0.01 to 0.025 second, but the pulsus alternans frequently was recorded in the absence of measurable variation in these parameters. The cardiac index was 2.9 L/min/m² at rest, rising to 4.9 with exercise, and the “exercise factor” was almost normal at 515 ml cardiac output rise per 100 ml increase in oxygen consumption.

**Postextrasystolic Pulsus Alternans**

In case 2, ventricular extrasystoles induced prolonged runs of pulsus alternans, continuing for 10 to 30 beats. The first postextrasystolic contraction produced a larger systolic pressure and stroke volume and was initiated by an increased EDV (table 1). Although the ventricular systolic pressure alternation continued, the following two beats were initiated by equal LVEDP’s and EDV’s, these values, however, being lower than in the first postextrasystolic contractions. The left ventricular peak rate of pressure rise was 2,200 mm Hg per second in the stronger and 1,680 mm Hg per second in the weaker contractions, and the more powerful systoles emptied more rapidly (220 versus 170 ml per second). Severe left ventricular failure was evidenced by the elevated left ventricular end-diastolic pressure, failure of the cardiac output to rise with exercise, extremely high end-diastolic volume and end-systolic volume, and abnormally low ejection fractions. Slight variations

### Table 1

**Pressure and Volume Measurements in Three Patients with Pulsus Alternans**

<table>
<thead>
<tr>
<th></th>
<th>EDV (ml)</th>
<th>ESV (ml)</th>
<th>SV (ml)</th>
<th>EF</th>
<th>LVEDP (mm Hg)</th>
<th>LV systolic pressure (mm Hg)</th>
<th>Brachial artery pressure (mm Hg)</th>
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<td></td>
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<tr>
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<td>78</td>
<td>.51</td>
<td>12</td>
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<td>188/127</td>
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<tr>
<td></td>
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<td>69</td>
<td>87</td>
<td>.56</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Weak contractions</td>
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<td>90</td>
<td>60</td>
<td>.40</td>
<td>12</td>
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<tr>
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<td>31</td>
<td>137</td>
<td>.81</td>
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<td>115</td>
<td>.75</td>
<td>—</td>
<td>—</td>
<td>136/65</td>
</tr>
</tbody>
</table>

Abbreviations: EDV = end-diastolic volume; ESV = end-systolic volume; SV = stroke volume; EF = ejection fraction (SV/EDV); LVEDP = left ventricular end-diastolic pressure.

The averages of multiple pressure measurements are recorded in case 1 to eliminate respiratory variations.

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**Figure 2**

Case 1. The left ventricular pressure recordings of typical “strong” and “weak” beats have been superimposed and traced. Left ventricular systolic pressures and “a” wave heights alternate, but the end-diastolic pressures (ED) remain constant. Note that the pressure in late diastole rises more slowly preceding the less powerful contractions, suggesting that dynamic diastolic compliance also alternates.
in cycle length and duration of diastole were recorded, the weaker beats beginning 0.01 second earlier than the more forceful ones.

Alternation of the left atrial "V" wave (37 versus 35 mm Hg) and "a" wave heights alternate, the larger "a" precedes and the smaller "V" present during the weaker systoles (fig. 3). This "a" wave oscillation failed to produce variation in LVEDP during much of the ventricular alternation, since first-degree A-V block was present and the atrial contraction wave was dissipated before left ventricular contraction began.

Case 3 manifested only brief periods of pulsus alternans, lasting four to five beats after a premature ventricular contraction. During the angiogram a premature beat produced a long compensatory pause, and the subsequent three contractions demonstrated pulsus alternans with concomitant alternation of end-diastolic volume (table 1). The more powerful first and third postextrasystolic beats began with higher EDV's than the second, smaller contraction. Left ventricular emptying rates also alternated, 510 and 560 ml per second during the augmented beats and 325 ml per second with the smaller one. Only brachial arterial pressures were recorded during filming, so that there were no simultaneous left ventricular pressure measurements. The cardiac performance was essentially normal with normal resting and exercise cardiac indices (3.8 and 6.0 L/min/m^2) and normal LVEDP (5 mm Hg).

**Ventricular Alternation in Valvular Aortic Stenosis**

Twenty-nine instances of ventricular alternans were culled by surveying left ventricular catheterization records from 96 patients with valvular aortic stenosis, an incidence of 30%. The alternation was persistent in two cases and was "prolonged"—lasting 10 or more beats—in 11 cases. The alternation developed during tachycardia in nine patients, two with atrial arrhythmias and five after inhalation of amyl nitrite. In all 29 of the cases, induction or accentuation of the alternans followed a premature contraction.

An elevated left ventricular end-diastolic pressure greater than 12 mm Hg was present in 18 of the cases. Alternation in LVEDP accompanied ventricular alternans consistently in only eight patients. The higher diastolic
pressure preceded the stronger contraction in these instances. In many of the other instances of ventricular alternans, alternation in LVEDP was evident during the first 2 or 3 beats following an extrasystole. In 22 cases the LVEDP preceding the first postextrasystolic beat was greater than that of the second, weaker contraction, and in 16 instances there was diastolic pressure alternation in the first three cycles following the premature beat. The usual sequence, therefore, was for postextrasystolic ventricular alternans to be associated with a Starling phenomenon initially, but in many cases for systolic pressure alternation to continue after the diastolic pressure alternation had disappeared (fig. 4). In two additional patients left ventricular diastolic pressure alternation occurred with a higher LVEDP preceding the less forceful contraction (fig. 5).

When evident at all, the magnitude alternation in left ventricular end-diastolic pressure was generally small, amounting to 1 to 3 mm Hg. The ventricular diastolic pressure preceding the first postextrasystolic contraction, however, often was 10 to 15 mm Hg greater than the next, and the degree of alternation diminished thereafter. The degree of left ventricular systolic pressure alternation averaged 29 mm Hg, ranging from 5 to 65 mm Hg. In postextrasystolic ventricular alternans the magnitude of systolic pressure alternation usually declined gradually until the phenomenon was finally extinguished. At the onset the ventricular alternation averaged 40 mm Hg (range 10 to 80 mm Hg), falling to approximately 5 mm Hg before termination. In a majority of instances the magnitude of variation in arterial systolic pressure was considerably smaller, amounting to only 15 to 30% of the left ventricular systolic pressure alternation. Thus, the systolic gradient also showed alternation.

Consistent alternation of the R-R interval or of the diastolic filling period was detected in only two cases. In eight additional patients these intervals did alternate during the first 2 to 4 postextrasystolic cycles (fig. 4). The shorter interval preceded the smaller beats. Variation in diastolic duration was generally small, being approximately 0.02 to 0.04 second.

**Discussion**

The results indicate that a variety of physiological conditions may be associated with pulus alternans. In patients 1 and 2, both with definite left ventricular disease, alternation in systolic pressure and stroke volume occurred without detectable alternation in left ventricular end-diastolic pressure or end-diastolic volume, although in the second case alternation in these values did appear in the immediate postextrasystolic beats. In patient 3, who had normal left ventricular function, the mechanical alternation was brief and restricted to the postextrasystolic period; there was a concomitant alternation in left ventricular end-diastolic volume. Normal left ventricular dynamics were further evidenced in this patient by the normal ejection fractions, end-systolic volumes, and end-diastolic volumes in both the stronger and the weaker contractions. Contrariwise, in the presence of severe heart failure (case 2), all of the beats had

*Figure 5*

Left ventricular (LV) and brachial arterial (BA) pressure record from a patient with aortic stenosis and pulsus alternans. In this instance a higher left ventricular end-diastolic pressure preceded the more powerful cycles.
PULSUS ALTERNANS

decreased ejection fraction and marked enlargement in end-diastolic volume and end-systolic volume. Case 1 had more occult left ventricular dysfunction, and only the less powerful of the contractions produced a diminished ejection fraction and increased end-systolic volume.

The absence of alternation of left ventricular end-diastolic pressure and volume in several of the cases indicates that ventricular alternans may occur without involving the Starling mechanism. These observations, Supporting the "myocardial theory" of pulsus alternans, are confirmed by other recent studies.8-11 Mechanical alternans has been recorded from isolated isometric papillary muscle strips where end-diastolic tension and length remained constant.8 Lendrum and associates9 also noted mechanical alternation in the isovolumic-beating left ventricle of the dog, and Cooper and associates10 found ventricular alternation in patients with aortic stenosis to be unassociated with left ventricular end-diastolic pressure variation.

It therefore appears that alternation in the contractile state of the myocardium underlies at least some instances of pulsus alternans. The precise mechanism governing this is undefined but probably involves some fundamental aspect of myocardial function, such as alternation in electrophysiological properties, excitation-contraction coupling, or perhaps the positive and negative inotropic effects of activation (PIEA and NIEA of Blinks and Koch-Weser).12

It is also unknown whether these mechanical alternations are due to variations merely in the number of fibers contributing to each systole,1-6 or whether alternation in contractile force of some or all of the myocardial cells occurs.11 There has been scant experimental work directed at answering these questions. Green13 produced pulsus alternans by constricting the left anterior descending coronary artery in dogs and noted that in the weaker beats the ischemic area of myocardium either contracted insufficiently or, at times, actually lengthened during systole. With the stronger beats a more effective shortening in the ischemic area occurred. It has also been shown by other investigators that mechanical alternans may coexist with alternations in the configuration of the transmembrane action potential, the fibers exhibiting "electrical alternans" being scattered throughout the myocardium.14 These lines of evidence indicate that individual cells, localized or diffusely spread through the heart, may alternate their electrical and mechanical properties. Whether every cardiac fiber is involved in ventricular alternans, and whether portions of the myocardium are hyposystolic or totally asystolic cannot be stated at this time. In the angigrams of our three patients, however, there was no indication that any form of asynchronous contraction occurred.

The conclusions concerning the "myocardial theory" in no way negate the possibility that the Starling principle underlies some instances of pulsus alternans, nor are they necessarily contradictory to previous studies supporting this view.15,16 In fact, our findings in cases 2 and 3 and in many of the patients with aortic stenosis support this mechanism, especially in the postextrasystolic variety of pulsus alternans. Other studies are also in accord. Cleason and Braunwald17 reported biplane angiographic left ventricular volume measurements in a child with valvular aortic stenosis and postextrasystolic pulsus alternans and found the end-diastolic volume to alternate slightly (EDV's = 78, 70, 76, and 72 ml). Harris and associates18 also noted small alternations in left ventricular end-diastolic volume in two children with cardiomyopathy and ventricular alternans. In both studies, however, only 4 to 6 photographic frames per second were recorded, and it remains possible that either the variations are insignificant or that true end-diastole was not invariably determined. Mitchell and associates,19 in studies employing both the isometric papillary muscle strip and the intact dog heart, observed that during tachycardia-induced pulsus alternans the weaker beat was invariably preceded by shorter myocardial fiber lengths.
It therefore seems that, although not essential for pulsus alternans, the Starling mechanism does in many instances contribute to or precipitate this phenomenon. Alternations in ventricular end-diastolic pressure and volume may begin after an extrasystole; yet, the mechanical alternans can continue even after these cease to vary.

It is also apparent that alternation in end-diastolic volume may be the consequence rather than cause of pulsus alternans.20 The stronger beat produces a small end-systolic volume which, for a given duration of diastole, leads to a decrease in the subsequent end-diastolic volume. The next weakened contraction terminates with a large residual volume, and the following end-diastolic volume is thereby augmented.21 Hence, ventricular alternans, whatever its genesis, may, by inducing the Starling mechanism, become a self-sustaining event.

Variations in cycle length or diastolic duration have also been implicated in mechanical alternans.18, 22, 23 The stronger beat may have a prolonged ejection period with consequent shortening of the succeeding diastole. The next systole may therefore be weakened, secondary to (1) its onset before ventricular relaxation is completed, (2) inadequate ventricular filling with decreased fiber stretch, and (3) decrease in the time available for “rest potentiation.”19, 21, 23–26 The less powerful contraction by virtue of its slight premature and shorter ejection period would, conversely, induce a stronger subsequent beat. This can be attributed to postextrasystolic potentiation, augmented diastolic filling, and increased time available for rest potentiation to develop.

Our studies indicate that variation in cycle length and diastolic duration was not invariably involved in cardiac alternation, but that they, too, participate at times, especially during the first several postextrasystolic beats. Tachycardia, another common inductor of pulsus alternans,27, 28 may act partly by diminishing the time available for diastole. Mitchell and associates19 confirmed this view in isometrically beating papillary muscle strips by demonstrating that in tachycardia-induced mechanical alternans the weaker systoles were preceded by higher diastolic tension, presumably due to incomplete ventricular relaxation. During normal heart rates, however, the slight changes in diastolic duration described herein and elsewhere would be less likely to infringe significantly on ventricular recovery or filling. Elimination of cycle-length alternation by cardiac pacemaker has been shown to diminish but not abolish pulsus alternans, indicating that, while not essential, the alternating R-R interval does contribute to the pulsus alternans.18 It furthermore seems reasonable that, as is true of the Starling mechanism, much of the cycle length and diastolic filling-period variation may be secondary to mechanical alternans rather than primary.22

We conclude, therefore, that several mechanisms may contribute to pulsus alternans. Alternation in ventricular end-diastolic volume (the Starling mechanism) and alternation in contractile force without end-diastolic volume or pressure change (the “myocardial” theory) may act separately or synergistically. Alternation in cardiac cycle length and time available for ventricular filling or relaxation may further influence these basic determining factors. Persistent alternans is associated with relatively severe left ventricular disease and appears to be mainly on the basis of the myocardial mechanism. Postextrasystolic alternation may occur with slight or no ventricular dysfunction and appears mainly due to the Starling mechanism.

Several subsidiary points are brought out by this study. In valvular aortic stenosis, alternation of the arterial pulse is significantly smaller than the ventricular alternation, due to the attenuating effect of the obstruction. Often the arterial pressure alternation was scarcely evident. Cooper and associates10 and Hancock and Fleming29 have noted similar findings. In four cases of muscular subaortic stenosis and postextrasystolic ventricular alternans—not otherwise included in this study—an even more complex relationship between arterial and left ventricular systolic pressure
change was noted. In the first beat after the premature contraction, the ventricular systolic pressure was greatest due to postextrasystolic potentiation, and the arterial pressure was diminished because of the increased obstruction. The next ventricular contraction was smaller but the arterial systolic pressure was increased, since this diminished ventricular contraction was associated with less marked stenosis. In the following beats showing ventricular alternans, the arterial pressure oscillation was especially “damped,” failing to alternate at all in three cases. Hence, alternation in the obstructing orifice size served initially to induce a discordant arterial and ventricular alternation, and later virtually to obliterate the arterial pressure alternations. These findings emphasize the difficulty in detecting ventricular alternation at the bedside or from arterial pressure records alone in patients with aortic stenosis. Since the systolic gradient alternates, alternation in the intensity of the systolic murmur may be of diagnostic value (case 1). Pulmonary alternans, detectable clinically in the pulse would therefore suggest that a substantial aortic pressure gradient is not present, and that left ventricular failure is due to some other cause than aortic stenosis.

The alternations of left atrial pressure waves as demonstrated in cases 1 and 2 are noteworthy and have been seen rarely by others. The varying “V” wave in case 2 is merely induced by alternation in the regurgitant flow. Alternation of the “a” wave is more provocative and suggests that alternation in atrial contractile force was present or that alternation in ventricular distensibility occurred. In case 1 the diastolic pressure rose more rapidly in the presystolic phase of the stronger beats, whereas the less powerful contractions were preceded by a more gradually sloping late diastolic pressure rise (fig. 2). Thus, although both cycles attained identical end-diastolic volumes and pressures, the possibility remains that diastolic dynamic compliance was alternating. This idea is indirectly supported by the recent reports

that augmentation of systolic force will increase diastolic compliance.

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References

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