Laboratory Investigation

Contractility

Alternating contractility in pulsus alternans studied in the isolated canine heart

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Abstract

We examined pulsus alternans in seven isolated, perfused canine left ventricles ejecting into a simulated arterial impedance. Left ventricular pressure-volume loops were measured during pulsus alternans while filling-source pressure was lowered. In all cases two distinct linear end-systolic pressure-volume relationships (ESPVRs) were noted for the strong and weak beats. The slopes of the ESPVRs of the strong beats were significantly greater than those of the weak beats (mean difference 0.9 ± 0.6 mm Hg/ml, p < .01), while the intercepts were not significantly different (mean difference 0.06 ± 0.5 ml). Diastolic pressure-volume relationships for the strong and weak beats were not significantly different, excluding incomplete relaxation as a cause of pulsus alternans. Although the weak beats had both a smaller preceding end-diastolic volume and a larger end-systolic volume, the presence of two distinct ESPVRs for the strong and weak beats shows there is alternating ventricular chamber contractility in pulsus alternans that is not solely due to the Starling mechanism. The magnitude of alternation in pump function parameters such as pressure and stroke volume during pulsus alternans reflects the complex interactions of alternating contractile state with alternations in preload and afterload.


Pulsus Alternans consists of alternating strong and weak beats with a constant beat-to-beat interval. Since its first description by Traube in 1872,1 the mechanism of this phenomenon has been debated and two main theories have been advanced. One theory attributes the alternating strength of ventricular contraction to alterations in end-diastolic volume.2-4 with incomplete diastolic relaxation proposed to account for the alternating changes in volume.5,6 The other theory proposes primary alteration in the intrinsic contractile state of the myocardium with secondary changes in end-diastolic volume.6-9

Earlier studies of pulsus alternans have been limited in their ability to accurately measure both ventricular volume and pressure. Measurements of end-diastolic volume or diameter have given conflicting results, with some investigators failing to find beat-to-beat changes in some patients.10-12 Afterload pressure, an important determinant of ventricular ejection, has often been difficult to control and quantify in the intact ventricle under physiologic conditions.

To investigate the hemodynamic mechanisms of pulsus alternans while controlling afterload and accurately measuring ventricular pressure and volume, we induced pulsus alternans by pacing in seven isolated, perfused canine left ventricles ejecting into a simulated arterial impedance. Filling-source pressure was reduced to generate a series of pressure-volume loops. This allowed us to derive the slope (Eso) of the end-systolic pressure-volume relationship (ESPVR) as an index of ventricular contractility for the strong and weak beats.

Methods

Surgical preparation. The preparation consisted of an isolated canine heart with its coronary arteries cross-perfused from a support dog. Seven pairs of mongrel dogs weighing 20 to 25 kg were used. Each pair was anesthetized with 25 mg/kg iv sodium pentobarbital. The chest of one dog was opened after artificial ventilation was begun. The subclavian artery and right atrium were cannulated and connected to the femoral arteries and veins of the support dog. After ligation of the azygous vein, superior and inferior vena cava, brachiocephalic artery, descending aorta, and pulmonary hila, each heart was removed from the chest and suspended over a funnel (figure 1).

The coronary arteries were then cross-perfused with arterial blood from the support dog by a peristaltic pump (Harvard Apparatus Company, Inc., model 1215) that pumped blood into the oversewn aortic root of the isolated heart. A disk oxygenator (Pemco, Inc., model 710) was placed parallel to the support dog so that oxygenated blood could be obtained from either the support dog or oxygenator. The coronary perfusion line passed through a water jacket that maintained the temperature at 37°C.

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Coronary arterial pressure was measured by a catheter placed in the oversewn aortic root via the brachiocephalic trunk. The perfusion pump servocontrolled mean coronary arterial pressure at 80 mm Hg.

The pericardium was removed and the right atrium opened to allow coronary sinus venous outflow to drain into a funnel for return to the support dog or oxygenator. The left and right ventricles were vented. The left atrium was opened, the chordae tendineae of the mitral valve were cut, and a thin balloon with an unstressed volume of 55 ml was mounted on a metal adaptor and fitted into the left ventricle. After the adaptor was sewn to the mitral valve anulus, it was connected to a servocontrolled piston pump that filled the balloon in the left ventricle with a defined filling-source pressure and resistance. A constant volume of tap water filled the piston pump and balloon, and a linear motor that drove the piston controlled the water volume in the balloon. Ventricular ejection of the water in the balloon was controlled as if the ventricle was ejecting into a computer-simulated arterial impedance. The vent through the left ventricular apex prevented any fluid build-up between the balloon and the endocardium. Echocardiographic examination of prior preparations has shown a tight fit between the balloon and the endocardium. Wires were attached directly to the left atrium for pacing.

The left ventricular pressure in the balloon was measured with a catheter-tipped micromanometer (Millar model PC 380). Ventricular pressure and volume, coronary arterial pressure, and arterial pressure in the support dog were recorded on an eight-channel chart recorder. Left ventricular pressure and volume were digitized on-line by a computer (LSI-11) and stored on magnetic tape. Ventricular pressure-volume loops were also monitored on-line with an x-y storage oscilloscope and photographed by a Polaroid camera.

Experimental protocol. Prolonged, stable pulsus alternans was usually seen near the end of an experiment when the pacing rate was increased to 160 beats/min in a weakened heart. When pulsus alternans was observed, the filling-source pressure was initially held constant to ensure that stable, reproducible strong and weak beats were occurring. Heart rate, coronary perfusion pressure, and afterload system parameters were held constant throughout the experiment. After stable, reproducible strong and weak beats were observed at a constant filling-source pressure, the pressure was continuously lowered over 20 sec to generate a series of pressure-volume loops.

Measurements of strong and weak beats were compared with a two tailed paired t test. A p value of <.05 was considered to indicate significance. Values are expressed as mean ± SD.

Results

Pressure and volume recordings from one of the hearts with pulsus alternans are shown in figure 2, A. Similar results were seen in the six other preparations. In all cases, end-systolic and end-diastolic volume alternated, with the strong beat starting at a larger end-diastolic volume and ending with a smaller end-systolic volume compared with the weak beat.

Figure 2, B, shows the pressure-volume loops corresponding to the pressure and volume recordings of A. The signal moved in a counterclockwise direction.

**FIGURE 1.** The isolated, cross-perfused heart preparation. See text for description.
around the pressure-volume loops. Diastolic filling, isovolumetric contraction, ventricular ejection, and isovolumetric relaxation are seen for both the strong and weak beats. Simulated vascular parameters (afterload impedance) and filling-source pressure (simulated left atrial pressure) were held constant. The pressure-volume loops of all the strong beats were virtually identical, as were the pressure-volume loops of the weak beats. This reproducibility was required before we proceeded to alter filling-source pressure.

The alternations in end-diastolic volume suggested the Starling mechanism was playing some role in the pressure differences seen in pulsus alternans in this preparation. We therefore matched the weak beat labeled No. 1 with a strong beat labeled No. 6 that had a nearly identical end-diastolic volume (figure 3). This strong beat occurred 5 beats later in the experiment, after filling pressure had been progressively lowered and while afterload impedance was held constant. Despite nearly identical end-diastolic volumes (approximately 38 ml), the strong beat had an end-systolic pressure of 124 mm Hg and a volume of 31 ml compared with an end-systolic pressure of 119 mm Hg and volume of 35 ml for the weak beat. End-systole was defined as the point at which pressure divided by volume was at a maximum.

A photograph of the x-y oscilloscopic tracing of the pressure-volume loops in pulsus alternans in one isolated heart is shown in figure 4. These pressure-volume loops were generated by lowering filling-source pressure while afterload system parameters were held constant. By lowering filling-source pressure, a composite of pressure-volume loops were generated with alternating strong and weak beats. The strong and weak beats define two different linear ESPVRs.

To assess the possibility of incomplete relaxation as a mechanism, we examined a diastolic pressure-volume relationship that consisted of the points of lowest diastolic pressure with the companion volume from each of the pressure-volume loops. To examine changes in ventricular contractility, we defined an ESPVR consisting of the points in each of the pressure-volume loops when pressure divided by volume was at a maximum. The diastolic and end-systolic relationships from the pressure-volume loops of figure 4 are illustrated in figure 5. The diastolic pressure-volume points from alternating strong and weak beats all seem to lie on the same line. In contrast, the strong and weak beats defined two clearly separated linear ESPVRs with nearly identical intercepts; however, the end-systolic pressure-volume points of the strong beats had a significantly greater $E_{iso}$ compared with that of the weak beats.

Table 1 shows the data for all seven hearts. There was no significant difference between the diastolic pressure-volume relationships of the strong beats and those of the weak beats. The diastolic pressure-volume relations of the strong beats and weak beats in the seven preparations showed a mean difference in slope of $0.002 \pm 0.09$ mm Hg/ml and a mean difference in offset of the lines of $0.1 \pm 0.1$ mm Hg, neither difference being significant. This excludes incomplete relaxation as a cause of the differences seen in pulsus alternans in this preparation. However, as shown in figures 4 and 5, the strong and weak beats in the seven experiments define two linear ESPVRs with different slopes and nearly identical intercepts. In the seven preparations, the mean slope of the ESPVR lines was $5.6 \pm 2.4$ mm Hg/ml for the strong beats and $4.7 \pm 2.0$ mm Hg/ml for the weak beats, resulting in a mean difference of $0.9 \pm 0.6$ mm Hg/ml ($p = .007$). The mean difference in intercepts of the ESPVR lines be-

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**FIGURE 3.** Pressure-volume plot of 2 beats with nearly identical end-diastolic volumes. Beat 6 occurs 5 beats after beat 1.

**FIGURE 4.** Series of pressure-volume loops generated as filling pressure is lowered. Each strong beat alternates with a weak beat, and two distinct ESPVRs are evident.

**FIGURE 5.** Series of pressure-volume loops generated as filling pressure is lowered. Each strong beat alternates with a weak beat, and two distinct ESPVRs are evident.
cause of changes in end-diastolic volume led to a smaller end-diastolic volume from an incomplete relaxation and afterload in pulsed alternans has been controversial. Alternating end-diastolic volume (Frank-Starling mechanism) and incomplete relaxation have been used to explain the phenomenon. Wenckebach suggested that changes in preceding end-diastolic volume led to the observed changes in stroke volume, with the weak beat arising from a smaller end-diastolic volume and pressure because of decreased filling. Straub believed that the weak beat arose from a smaller end-diastolic volume accompanying by a higher end-diastolic pressure resulting from incomplete metabolic recovery. Mitchell et al. observed that the weak beat arose from a shorter initial fiber length with constant tension in an isotonically contracting papillary muscle preparation. In isometrically contracting preparations with constant external muscle length, there was still an alternation of weak and strong peak systolic tension with a corresponding high and low initial tension, respectively. The authors suggested that this resulted from incomplete relaxation. Additional support for the role of alternating end-diastolic volume was provided by Gleason and Braunwald's study of cineangiograms from patients with pulsed alternans: they found that the stronger beats were preceded by a larger end-diastolic volume. Echocardiograms have also documented alternating end-diastolic dimensions in patients with pulsed alternans.

In contrast, the myocardial theory advanced by Wiggers proposes that changes in ventricular contractility explain pulsed alternans and that changes in left ventricular end-diastolic pressure and volume are secondary to changes in contractility. Several observers have been unable to document a consistent correlation between end-diastolic diameter or volume and stroke volume in patients with pulsed alternans, and have suggested that changes in contractility, perhaps with a partial contribution from the Starling mechanism, account for the phenomenon. Guntheroth et al. have suggested that alternating potentiation and deletion of contractile elements occurs in those with pulsed alternans. Regional pulsed alternans has been documented in regional ischemia by ultrasonic crystal length measurement by Crozatier et al., who found no changes in end-diastolic lengths in either control or hypoxic areas of myocardium. Although no changes in systolic shortening were observed in nonhypoxic control regions, significant changes in systolic shortening occurred in the hypoxic region. However, possible regional differences in end-diastolic tension were not examined. Parmley et al. documented regional pulsed alternans with data suggesting that alternating potentiation and attenuation or deletion of contraction accounted for pulsed alternans.

**Discussion**

The role of changes in end-diastolic volume, contractility, diastolic relaxation, and afterload in pulsed alternans has been controversial. Alternating end-diastolic volume (Frank-Starling mechanism) and incomplete relaxation have been used to explain the phenomenon. Wenckebach suggested that changes in preceding end-diastolic volume led to the observed changes in stroke volume, with the weak beat arising from a smaller end-diastolic volume and pressure because of decreased filling. Straub believed that the weak beat arose from a smaller end-diastolic volume accompanying by a higher end-diastolic pressure resulting from incomplete metabolic recovery. Mitchell et al. observed that the weak beat arose from a shorter initial fiber length with constant tension in an isotonically contracting papillary muscle preparation. In isometrically contracting preparations with constant external muscle length, there was still an alternation of weak and strong peak systolic tension with a corresponding high and low initial tension, respectively. The authors suggested that this resulted from incomplete relaxation. Additional support for the role of alternating end-diastolic volume was provided by Gleason and Braunwald's study of cineangiograms from patients with pulsed alternans: they found that the stronger beats were preceded by a larger end-diastolic volume. Echocardiograms have also documented alternating end-diastolic dimensions in patients with pulsed alternans.

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**TABLE 1**

**Pressure-volume relationships (n = 7)**

<table>
<thead>
<tr>
<th></th>
<th>Strong beats</th>
<th>Weak beats</th>
<th>Difference</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>End-systole</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean $E_0$ (mm Hg/ml)</td>
<td>5.6 ± 2.4</td>
<td>4.7 ± 2.0</td>
<td>0.9 ± 0.6</td>
<td>.007</td>
</tr>
<tr>
<td>Mean intercept (ml)</td>
<td>9.2 ± 3.5</td>
<td>9.2 ± 3.3</td>
<td>0.06 ± 0.5</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Diastole</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean slope (mm Hg/ml)</td>
<td>0.5 ± 0.1</td>
<td>0.5 ± 0.1</td>
<td>0.002 ± 0.09</td>
<td>NS</td>
</tr>
<tr>
<td>Mean offset (mm Hg of the 2 lines)</td>
<td>—</td>
<td>—</td>
<td>0.1 ± 0.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

ESPVRs and pressure-volume relationships for the lowest diastolic pressure are compared for the strong and weak beats.
The role of incomplete relaxation has also been questioned. Noble and Nutter\textsuperscript{6} examined pulsus alternans in open-chest dogs and found the end-diastolic circumference preceding the strong beat greater than that of the weak beat without changes in end-diastolic tension. Guntheroth et al.\textsuperscript{8} found a positive correlation between the lowest left ventricular early diastolic pressure and the following stroke volume, the opposite of what would be expected if failure of relaxation caused pulsus alternans. Nayler and Robertson\textsuperscript{7} showed alternating contractility in an isometric papillary muscle preparation without significant changes in end-diastolic tension, contrary to the results of Mitchell et al.\textsuperscript{3}.

Finally, Guntheroth et al.\textsuperscript{8} have commented on the negative correlation between preceding aortic diastolic pressure and left ventricular stroke volume. The lower aortic diastolic pressure following the weak beat provides a lower afterload for the subsequent strong beat. Although they concluded that changes in afterload and ventricular diastolic volume alone could not sustain pulsus alternans, these factors would exaggerate the effect of alternating contractility on stroke volume.

Part of the controversy relates to the difficulty in accurately measuring contractile state independent of changes in load. Accurate, simultaneous measurements of pressure and volume have been difficult in the intact ventricle. In addition, possible changes in afterload as the experiment proceeded would be difficult to control in an intact preparation. We were able to accurately measure both pressure and volume while controlling preload and afterload system parameters.

Although the isolated heart preparation offers several advantages for the examination of pulsus alternans, it also has some limitations. Under these conditions the heart is not exposed to reflex changes that may play a role in pulsus alternans. The arterial impedance and ventricular filling systems are computer simulated. The experiment examines the global pump function of the intact ventricle and does not measure regional differences in muscle properties. Finally, since data were gathered at pacing rates of 140 to 160 beats/min, the results may apply only to pulsus alternans induced by rapid pacing.

In our preparation, the alternating contractile state and loading system interact to produce the systolic and diastolic pressure and volume differences seen in pulsus alternans. The weaker beats were always preceded by smaller end-diastolic volumes as compared with the stronger beats. This suggests changes in end-diastolic volume play a role in pulsus alternans. However, as shown in figure 3, beats with identical end-diastolic volume still show significant changes in end-systolic volume and pressure, demonstrating that the Starling mechanism alone is insufficient to explain pulsus alternans. Although the matched beats have nearly identical end-diastolic volumes, the preceding diastolic relaxation could well be different. To examine the possible role of incomplete relaxation we compared the pressure-volume relations with use of the lowest diastolic pressures following strong and weak beats (figure 4). There was no significant difference in this relationship for the strong compared with the weak beats, suggesting incomplete relaxation was not present.

Although the afterload impedance parameters were constant, the actual beat-by-beat afterload pressure did vary, with the lower aortic pressure following the weak beat providing a lower afterload pressure for the subsequent strong beat. Although we did not vary afterload system parameters, this alternation of aortic end-diastolic pressure undoubtedly plays a role in determining the degree of subsequent systolic emptying.

Finally, examination of $E_s$ for the strong and weak beats showed significant changes in slope in all seven preparations, indicating significantly greater ventricular chamber contractility for the strong beats. In this isolated preparation the alternating pressure changes reflect both the alternating contractile state and the interaction of these changes in contractility with the simulated vascular system.

Thus, pulsus alternans is the result of alternating contractile state. It is important to recognize, though, that the magnitude of the alternation in pump function parameters such as pressure and stroke volume during pulsus alternans reflects the complex interactions of alternating contractile state with the alternations in preload and afterload.

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References

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