Mechanism of Sustained Mechanical Alternans

Effect of Variations in Ventricular Filling Volume

David Adler, Srdjan Nikolic, Edmund H. Sonnenblick, and Edward L. Yellin

This study investigates the phenomenon of sustained mechanical alternans (SMA) through the use of quantitative criteria. Discrete analysis is used to demonstrate that the hemodynamic variables during SMA are governed by a simple mathematical relation. The analysis shows that the value of the slope created by the two alternating beats on the stroke volume (SV)–end-diastolic volume (EDV) plane is \( \gamma = (\mu - 1)(1 + \beta)/(\mu - \beta) \), where \( \mu = SV_v/SV_w \), and \( SV_v \) and \( SV_w \) denote the strong and weak beats, respectively, in the presence of one contractile state, and the beats associated with the higher and lower contractile states, respectively, in the presence of two alternating contractile states; \( \beta = FV_v/FV_w \), where \( FV_v \) and \( FV_w \) are the filling volumes after \( SV_v \) and \( SV_w \), respectively. This equation is valid, whether SMA is exhibited in the presence of one or two contractile states and irrespective of the SV–EDV functional relation. Assuming constant afterload, a criterion based on this slope (\( \gamma \)) is described to determine if SMA is caused by variations in EDV and FV. The slope of the SV–EDV curve in the presence of one contractile state (denoted as \( \gamma \)) was determined directly (34 runs in eight dogs) by preventing FV in a beat, after a steady state, using a remote-controlled mitral valve. The slope \( \gamma = 0.892 \pm 0.078 \) was found to agree with data in the literature. In 10 other dogs, mitral flow and aortic flow were measured in 55 series of SMA. In 51 series, \( \gamma \) was greater than 1. Because the experimental slope in the presence of one contractile state, \( \gamma_i \), is smaller than or equal to 1, the possibility that one contractile state is involved in this series is rejected. On the other hand, when two contractile states are involved, the slope that the two successive beats create on the SV–EDV plane, \( \gamma_i \), is determined by connecting the two SV–EDV relations. This slope tends to be greater than 1. Thus, in these 51 series, SMA cannot be explained as a result of the Frank-Starling mechanism and variations in FV but as a result of two alternating contractile states. In the other four series, the value of \( \gamma \) can be compatible either with the presence of one contractile state or with two alternating contractile states. This quantitative analysis enables the classification of the various types of SMA into subcategories with well-defined features. The quantitative analysis presented here shows that the common genesis of SMA is an alternating contractile state. (Circulation Research 1991;69:26–38)

Pulsus alternans, or sustained mechanical alternans (SMA), exhibited in cardiac muscle is a striking phenomenon that has fascinated physicians and biologists for more than a century.\(^1\) It is characterized by an alternation between strong and weak contractions with a regular cardiac rhythm. It occurs in the presence of myocardial disease, or in either spontaneous or induced tachycardia, without apparent myocardial abnormality.

SMA can occur in the isolated cardiac muscle without changes in initial muscle length. In such a case, the predominant view is that it is the result of changes in the contractile state of the muscle.\(^2-4\) In a previous model,\(^5,6\) the changes in the contractile state were attributed to intracellular movements of calcium, where the basic mathematical relations underlying sustained or transient alternations were developed.

From the Department of Biomedical Engineering (D.A.), Hadassah University Hospital, Jerusalem, Israel; the Department of Medicine (E.H.S.), Division of Cardiology, Cardiovascular Research Center; and the Department of Cardiothoracic Surgery and Department of Physiology and Biophysics (S.N., E.L.Y.), Albert Einstein College of Medicine, Bronx, N.Y.


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Address for reprints: David Adler, PhD, Head, Department of Biomedical Engineering, Hadassah University Hospital, Ein Kerem P.O. Box 12000, Jerusalem, Israel 91120.

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SMA in the beating heart represents a more complex phenomenon, because hemodynamic variables also are involved. Various contradictory views regarding the genesis of the phenomenon have been suggested. The main views are 1) SMA is caused by the Frank-Starling mechanism secondary to alternations in end-diastolic volume (EDV),7,8 or 2) SMA is caused by alternating contractile states of the myocardium.9–13 In addition, several reports attributed SMA to alternating filling volume (FV)14–16 or to a decreased amount of FV.8,17 Other investigators detected variations in FV or its duration but considered them to be secondary rather than primary causes of SMA.18,19 No difference was discerned in diastolic filling durations13,20 or other diastolic parameters10,21 in other studies.

It is difficult to distinguish between primary causative factors capable of initiating and maintaining SMA and secondary factors on the basis of alternation in measurable variables observed in the studies reported. On the contrary, our basic approach is to apply mathematical thinking in the search for theoretical prerequisites that will enable us to attain and maintain this type of steady-state phenomenon and to determine by appropriate measurements if these prerequisites have been met.

Analysis was made in a previous article22 of the theoretical prerequisites for attainment and maintenance of SMA under conditions of constant and alternating contractile states in the beating heart. The previous study assumed, as a first approximation, that FV is constant. On the basis of this assumption and the scanty experimental data available from the literature regarding the stroke volume (SV)–EDV slope, the Frank-Starling mechanism was ruled out as the causative factor of SMA.

The objectives of this study were 1) to develop a criterion for determining if SMA can be initiated and maintained by the Frank-Starling mechanism when it is accompanied by various degrees of FV variations (assuming unchanged contractile state); 2) to analyze the theoretical relations between SV, FV, and the slope created on the SV–EDV plane by the two alternating beats during SMA caused by alternating contractile states; 3) to measure the SV–EDV slope when the contractile state is invariant; and 4) to measure the mitral and aortic flows during SMA and to test whether the experimental data meet the theoretical conditions and what the implications are for the genesis of SMA.

Methods

Theory

Description of basic mathematical relations governing the hemodynamic variables during sustained mechanical alternans. Let us assume that the heart exhibits SMA. To simplify the analysis, we have excluded the effect of aortic pressure on the initiation and maintenance of SMA from this study. The following relations must exist, independently of the cause of this phenomenon:

\[
FV_w + FV_s = SV_w + SV_s \tag{1}
\]

\[
EDV_w = EDV_w - SV_w + FV_w \tag{2}
\]

where SV_w and SV_s denote the weak and strong beats, respectively, in the presence of one contractile state, and the beats associated with the lower and higher contractile states, respectively, in the presence of two alternating contractile states. As will be demonstrated later, the latter does not necessarily imply SV_w > SV_s. FV_w and FV_s are the filling volumes after SV_w and SV_s, respectively. EDV_w and EDV_s are the end-diastolic volumes preceding SV_w and SV_s, respectively.

Let \( \beta \) denote the slope that the two alternating beats create on the SV–EDV plane, in the general case of SMA, that is,

\[
\gamma = \frac{SV_s - SV_w}{EDV_s - EDV_w} \tag{5}
\]

Using Equations 1–5, we obtain

\[
\gamma = \frac{\mu - 1}{\mu - \beta (1 + \beta)} \tag{6}
\]

Equation 6 can be written in another useful way as

\[
\mu = \frac{1 + \beta - \gamma \beta}{1 + \beta - \gamma} \tag{7}
\]

The results of the quantitative analysis of Equation 6 are presented in Table 1. This analysis enables us to classify the various types of SMA conveniently into well-defined subcategories, to reveal their hidden hemodynamic features, and to investigate the causative factors of SMA. Note that Equation 6 is applicable to any SMA, independent of its cause and of the functional SV–EDV relation. However, the specific implications of this equation for hemodynamic behavior during SMA have to be analyzed when the specific cases, presented in the two following sections, are considered.

Sustained mechanical alternans initiated by imposed alternations in filling volume in the presence of one contractile state. To test the effect of the Frank-Starling mechanism on the initiation of SMA, let us assume that the heart is in a steady state with unchanged, contractile state, heart rate, and afterload. An alteration in the contractile state of the
cardiac muscle by inotropic interventions leads, for unchanged afterload and heart rate, to a change in SV for any given physiological value of EDV. Thus, a given contractile state will be defined in this study by a unique SV—EDV relation for any given afterload and heart rate. For simplicity of demonstration, we have analyzed only the linear SV—EDV relation, which seems to describe the behavior of both cardiac muscle and the beating heart. Let this relation have the general linear form

\[ SV = \gamma (EDV - EDV_0) \]  

where \( \gamma \) is the linear slope of the SV—EDV relation, and \( EDV_0 \) is the threshold value of EDV when there is no SV for a given contractile state, afterload, and heart rate; that is, the intraventricular pressure does not exceed the given systemic pressure, and the valve remains closed. A change in the contractile state that leads to a change in SV for any given EDV thus can be accomplished either with an altered EDV\(_0\) and an unchanged \( \gamma \), with a change in \( \gamma \) and unchanged EDV\(_0\), or with changes in both.

Note that the analysis carried out in the preceding section (Equations 1–7) is applicable to the conditions presented here, where \( \gamma \) is a specific case of \( \gamma \).

The limited data in the literature, supported by our experimental results and presented below, indicate that \( \gamma \) is close to 1. Moreover, accepting that there is a unique end-systolic pressure—volume relation (ESPVR), as a first approximation, when the contractile state, heart rate, and afterload are unchanged, implies that \( \gamma \) is equal to 1.

The ejection—filling curves provide a convenient graphic method of obtaining the SV response to volume perturbation. Two such curves of the linear case are plotted for the two realistic values \( \gamma = 0.8 \) (Figure 1A) and \( \gamma = 1 \) (Figure 1B). The bold line in each curve represents Equation 8. The ventricle initially is in a common steady state, where FV is equal to SV. Then, as a result of a perturbation of imposed alternation in FV, the SV response is obtained graphically. Note that the next EDV value is obtained graphically by subtracting SV (output) and adding FV (input). The subtraction is conveniently accomplished by plotting the end-systolic volume line (the thin line).

When \( 1 > \gamma > 0 \) (Table 1, case 1), SMA can be obtained only when filling before the strong beat is augmented (\( \mu > 1 / \beta \)). In this case, the resulting degree of alternation in SV is smaller than the imposed degree of alternation in FV (\( \mu < 1 / \beta \)). The ejection filling curve for \( \gamma = 0.8 \) (Figure 1A) demon-

**Figure 1.** Ejection—filling curves for two linear functional dependencies between stroke volume (SV) and end-diastolic volume (EDV) (thick line). Thin lines represent end-systolic volume obtained by subtracting SV from EDV (solid arrow pointing to left). Initially, the ventricle is in a common steady state (SS), until an alternating filling with a ratio \( \beta = 0.5 \) is imposed. After ejection, the filling volume (FV) (dashed arrow pointing to the right) determines the next EDV (vertical dotted arrow) and therefore the SV value. The latter is designated as sustained mechanical alternans: SMA(s) for the strong beat and SMA(w) for the weak beat. To the right of each curve, FV values (\( \beta = FV/FV_s \)) and the graphically obtained SV values (\( \mu = SV/SV_s \)) are drawn to an arbitrary scale. Panel A: For \( \gamma = 0.8 \), the resulting degree of alternation in SV is smaller than the imposed degree of alternation in FV. A transient response (TR) is obtained before the SMA response. Panel B: For \( \gamma = 1 \), the degree of alternation in SV is the same as the imposed degree of alternation in FV.

**Table 1.** Classification of Sustained Mechanical Alternans According to Equation 6

<table>
<thead>
<tr>
<th>Case</th>
<th>( \beta )</th>
<th>( \mu )</th>
<th>( \gamma )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \beta &lt; 1 )</td>
<td>( \mu &gt; 1, \mu &lt; 1/\beta )</td>
<td>( 1 &gt; \gamma &gt; 0 )</td>
</tr>
<tr>
<td>2</td>
<td>( \beta &lt; 1 )</td>
<td>( \mu &gt; 1, \mu &lt; 1/\beta )</td>
<td>( \gamma = 0 )</td>
</tr>
<tr>
<td>3</td>
<td>( \beta &lt; 1 )</td>
<td>( \mu &gt; 1, \mu &lt; 1/\beta )</td>
<td>( 2 &gt; \gamma &gt; 1 )</td>
</tr>
<tr>
<td>4</td>
<td>( \beta = 1 )</td>
<td>( \mu = 1 )</td>
<td>( \gamma = 2 )</td>
</tr>
<tr>
<td>5</td>
<td>( \beta = 1 )</td>
<td>( \mu = 1 )</td>
<td>undefined</td>
</tr>
<tr>
<td>6</td>
<td>( \beta = 1 )</td>
<td>( \mu &gt; 1, \mu &gt; \beta )</td>
<td>( \gamma = 2 )</td>
</tr>
<tr>
<td>7</td>
<td>( \beta = 1 )</td>
<td>( \mu &gt; 1, \mu &lt; \beta )</td>
<td>( \gamma = 0 )</td>
</tr>
<tr>
<td>8</td>
<td>( \beta = 1 )</td>
<td>( \mu &gt; 1, \mu &lt; \beta )</td>
<td>( \gamma = 0 )</td>
</tr>
<tr>
<td>9</td>
<td>( \beta = 1 )</td>
<td>( \mu = 1 )</td>
<td>( \gamma = 0 )</td>
</tr>
<tr>
<td>10</td>
<td>( \beta &gt; 1 )</td>
<td>( \mu &gt; 1, \mu &lt; \beta )</td>
<td>( 2 &gt; \gamma &gt; 1 )</td>
</tr>
<tr>
<td>11</td>
<td>( \beta &gt; 1 )</td>
<td>( \mu &lt; 1, \mu &lt; 1/\beta )</td>
<td>( \gamma = 1 )</td>
</tr>
<tr>
<td>12</td>
<td>( \beta &gt; 1 )</td>
<td>( \mu &lt; 1, \mu &lt; 1/\beta )</td>
<td>( 1 &gt; \gamma &gt; 0 )</td>
</tr>
</tbody>
</table>

See text for explanations.
strates this type of response (after a short transient response).

When \( \gamma = 1 \) (Table 1, case 2), implying that \( \mu = 1/\beta \), the degrees of alternation are the same during SMA for both FV and SV. As can be noted in this case (Figure 1B), there is no transient after the perturbation.

When \( 2 > \gamma > 1 \) (Table 1, case 3), SMA can be obtained only when the filling before the strong beat is augmented (\( \mu > 1 \) and \( \beta < 1 \)). In this case, the resulting degree of alternation in SV is greater than the imposed degree of alternation in FV (\( \mu > 1/\beta \)).

It should be noted that in both cases (Table 1, cases 1 and 3), the closer the value of \( \gamma \) to 1, the lesser the discrepancy between the degrees of variation in FV and SV. Because realistic \( \gamma \) values are in the vicinity of 1, a small discrepancy between the degrees of variation in FV and SV has to be expected, when SMA is imposed by FV alternations in the presence of one contractile state.

An important conclusion can be derived from the case \( \beta = 1 \); that is, \( FV_o = FV \) (Table 1, case 4). This case shows that when there are no forced alternations in filling volume, the value of \( \gamma \) must attain the unrealistic value of 2 to initiate SMA. Thus, the possibility that SMA can be initiated as a result of the Frank-Starling mechanism under the most common condition of invariant FV is precluded. This conclusion is compatible with our different method of analysis, previously applied, assuming constant filling.

Case 5 represents the common steady state that can be obtained with any slope.

**Effect of alternating filling during sustained mechanical alternans initiated by alternating contractile state.**

In this category, we assume that SMA is initiated by two alternating contractile states. These contractile states are assumed to be represented by two distinct SV–EDV relations. As in the preceding section, the effect of systolic pressure is excluded. Note that the analysis carried out above (Equations 1–7 and Table 1) is applicable to the conditions presented here. In this category, \( \gamma \) represents the slope that the two successive beats create on the SV–EDV plane, and this slope connects the two SV–EDV functions (Figure 2).

Even though the analysis presented in Equations 1–7 is independent of the functional SV–EDV relation, let us assume for simplicity that the two contractile states are represented by two linear equations. As mentioned before, a change in contractility, which leads to a change in SV for any given EDV, can be accomplished either with an altered EDV or an unchanged \( \gamma \), with a change in \( \gamma \) and unchanged EDV, or with changes in both. Thus, the two contractile states are represented by the following two linear equations:

\[
SV_w = \gamma_1(EDV_w - EDV_{0,1})
\]

\[
SV_s = \gamma_2(EDV_s - EDV_{0,2})
\]

where \( SV_w \) and \( SV_s \) are the beats associated with the higher and lower contractile states, respectively. This implies that \( \gamma_2 \geq \gamma_1 \); \( EDV_{0,2} \leq EDV_{0,1} \). As will be demonstrated later, the latter does not necessarily imply \( SV \geq SV_w \) in all cases.

Figure 2 presents the ejection–filling curves associated with two distinct contractile states, with constant (panel A) and alternating (panels B–D) FV. Here, for simplicity, only the final SMA is presented without the transient that may lead to it from a regular steady state. Whereas Figure 2 represents four cases in which the ejection–filling curves demonstrate notable features, the other cases are represented in Figure 3 only by their FV and resultant SV patterns. The various subcategories of SMA represented in Table 1 have the following implications when the condition of two alternating contractile states is analyzed:

In cases 1–3, the FV before the beat with lower contractile state (\( \gamma_1 \)) is smaller than that with higher contractile state (\( \gamma_2 \)). It is evident in these cases that \( \mu \) will attain values greater than 1; that is, the augmented beat will be associated with the higher contractile state. Note that case 3 (Figure 2B) represents the condition in which the degree of alternation in FV is smaller than the degree of alternation in SV. Case 1 (Figure 3B) represents the opposite condition, and case 2 (Figure 3A) represents equality of the two.

Case 4, which refers to constant FV, implies that \( \gamma = 2 \), independent of the value of \( \mu \). Figure 2A presents the ejection–filling curve of a linear SV–EDV relation; however, \( \gamma = 2 \) is obtained also for a nonlinear SV–EDV relation, as we have shown previously.

In cases 6–12, the FV before the beat with lower contractile state (\( \gamma_1 \)) is greater than that with higher contractile state (\( \gamma_2 \)). Note that in cases 6–8, the augmented filling before the low contractile state (\( \gamma_1 \)) beat was not sufficient to reverse the inequality \( SV(\gamma_2) > SV(\gamma_1) \). However, when the degree of alternation in FV increases, the two beats become the same (case 9, Figure 3D), or their magnitude is even reversed (cases 10–12, Figures 3E and 3F); that is, the SV associated with the beat with higher contractile state is smaller than the other one.

It can be seen in Figure 2C that a negative \( \gamma \) (case 8) means that EDV associated with the greater SV is smaller than EDV associated with the smaller SV. It easily can be deduced from Figure 2C that \( \gamma = -\infty \) (case 7) implies equality of the two EDVs, and \( 2 < \gamma < -\infty \) (e.g., case 6, Figure 3C) implies that greater SVs are associated with greater EDVs. When two contractile states are involved, negative values of \( \gamma \), though not common, are possible, particularly in the presence of an imposed alternating inflow.

As mentioned before, the magnitude of the alternating beats can be reversed, and theoretically, three subcategories of this situation may exist, depending on the degree of alternation in FV relative to SV (cases 10–12). Figure 2D demonstrates that case 10, in which the degree of alternation in FV is smaller than the degree of alternation in SV, is unrealistic, because it implies that the slope of each SV–EDV relation, asso-
associated with each contractile state, must significantly exceed the value of 1. To some extent, this applies to case 11 (Figure 3E) as well. Thus, out of these three cases, only case 12 (Figure 3F) seems to be realistic.

**Protocols**

Two distinct protocols have been used, one for the study of SMA and the other for the evaluation of the slope of the SV–EDV curve during nonalternating conditions.

**Sustained mechanical alternans study.** Eleven adult mongrel dogs (25.6 ± 1.2 kg) were anesthetized with thiopental sodium (15 mg/kg i.v.), followed by intubation and artificial ventilation at 100% O₂ with a pressure-controlled respirator. Fentanyl (5–10 μg/kg) was administered every 30 minutes and supplemented with vecuronium (0.1 mg/kg). After a midline sternotomy and left thoracotomy at the fourth intercostal space, the heart was supported in a pericardial cradle. Pacing leads were either sutured to the right atrium (for atrial pacing) or to the left ventricle (for ventricular pacing), and the sinoatrial node was crushed to enable efficient pacing, when necessary.

During standard cardiopulmonary bypass, the left atrium was opened and a mitral flow probe was sutured to the mitral annulus. The atrium then was repaired and the dog weaned from the bypass. A noncannulating electromagnetic flow probe was placed around the cleaned ascending aorta. Micromanometers (Millar Instruments, Houston) were
placed in the left ventricle and the left atrium via the apex and pulmonary vein.

Flows were measured with a two-channel flowmeter (Carolina Medical Electronics, King, N.C.). Pressures were calibrated for equal gain and common zero. Pressures, flows, electrocardiogram, and dP/dt were recorded at high speed, either with a photographic recorder (100 mm/sec; model DR-12, Electronics for Medicine, White Plains, N.Y.) or with a pen recorder (200 mm/sec; model 260, Gould Instruments, Cleveland, Ohio), to obtain accurate measurements of FV and SV. SV was measured in only 10 dogs; in one dog with constant controlled afterload, the aortic flow signal was not appropriate for analysis. The flow records were digitized with a sonic digitizer (GP-7, Science Accessories Corp., Stratford, Conn.) coupled to an IBM-PC. SV and FV were calculated from the integral of aortic and mitral flows.

Arterial pH and Pco_2 were measured periodically and maintained at normal levels by adjusting ventilatory volume or frequency or by administering intravenous sodium bicarbonate. When necessary, phenylephrine was infused to maintain arterial blood pressure, and lidocaine was given as either a bolus or infusion to control arrhythmias. Contractile function was controlled with infusions of dobutamine. The anesthetic level was monitored constantly by the absence of a corneal reflex and of a pain response, indicated by a sudden increase in heart rate or pressure. Data were recorded only when the dogs were in a stable steady state and with the respirator turned off. All data were recorded with the chest and pericardium open, so that the measured pressures were identical to the transmural pressures.

**Evaluation of γ by study of volume perturbations.**

The same procedure as described above was used to study another group of eight adult mongrel dogs (26.8±1.1 kg). In addition, a remote-controlled mitral valve, described in detail elsewhere, was implanted in series with an electromagnetic flow probe in the mitral annulus during the cardiopulmonary bypass. After a steady state was established, the remote-controlled mitral valve was closed during one complete diastole to prevent filling before the perturbed beat (Figure 4).

The slope of the SV-EDV curve caused by an abrupt change in EDV, as described above, can be calculated according to Equation 5, where w is replaced by steady state and s by p, where the ss and p subscripts relate to the steady-state and the perturbed hearts, respectively. It easily can be seen that the denominator equals SV_w. Because of the complete closure of the mitral valve before the perturbed beat, EDV_p-EDV_ss-SV_w. Thus

\[
\gamma = 1 - \frac{SV_p}{SV_{ss}}
\]

(11)

It should be noted that the opening aortic pressure is the same for the steady-state and the perturbed beats.

**Results**

**Determination of Stroke and Filling Volumes and γ During Sustained Mechanical Alternans**

SMA occurred spontaneously in four dogs (heart rate, 120–156 beats/min). In five dogs, high-rate atrial
pacing (138–282 beats/min) was used to initiate SMA with variable degrees of alternation. In three dogs, high-rate ventricular pacing (203–250 beats/min) was used to initiate SMA with a variety of FV conditions. Table 2 summarizes the results obtained in these three modes. Three typical recordings, which represent β=1, β<1, and β<1, are shown in Figure 5. The value of γ, the slope that the two alternating beats create on the SV–EDV curve, is computed with these measurements according to Equation 6. In Figure 6, the degree of alternation in SV, as defined by μ, is plotted versus the degree of alternation in FV, as defined by 1/β, for these 55 series. The lines for several critical values of γ, as defined by Equation 7, also are plotted. In seven series (in five dogs), either the weak contraction has no SV (five series, Figure 5C), or there was no filling after the strong contraction (one series), or both (one series). Because these null values yield values of infinity for μ and 1/β, these points were plotted off the scale.

Effect of Transient Changes in Filling Volume on Sustained Mechanical Alternans

Periodic appearances and disappearances of mechanical alternans occur, as can be detected from both low- and high-speed tracings in Figure 7A. These appearances solely are due to alternation in FV, caused by an effective atrial contribution every other beat. The timing of the atrial activation, compared with the ventricular activation, can be detected in the electrocardiogram trace, and the effective atrial contributions can be detected in the lower, more amplified, left ventricular pressure (LVP) trace. When no atrial contribution is detected, a regular steady-state response is obtained.

In three dogs, reported above, induced high-rate ventricular pacing leads to underlying SMA. As can be seen in Figure 7B, this underlying SMA is modulated by supraventricular enforced transient variations in FV due to atrioventricular disassociation. These variations in FV transiently modify the degree of alternation of SV and LVP. When FV is remarkably augmented by a well-synchronized atrial contraction (arrow), the magnitude of the beats of the underlying SMA are temporarily reversed; that is, the beat with bigger values of LVP and SV is now associated with the smaller beat of the underlying SMA.

Evaluation of the Value of γ in the Presence of One Contractile State

The value of γ was computed according to Equation 11, which was developed in “Methods.” For 34 runs in eight dogs, in which the mitral valve was totally occluded (see Figure 4), the value of γ obtained is 0.892±0.078, where SV₃ is 23.69±7.44 and SV₇ is 2.71±2.3.

Discussion

The mechanism for the attainment and maintenance of a steady state constitutes a fundamental problem in physiology. In the beating heart, two possible steady states may exist: 1) the more common steady state, characterized by a constant rhythm and SV, which has been widely explained; and 2) the striking phenomenon of SMA, in which alternations occur between big and small SV with a constant

| Table 2. Hemodynamic Measurements During Sustained Mechanical Alternans |
|---------------------------|-------------|----------------|----------------|----------------|----------------|
| Type | No. of dogs | No. of SMA series (beats) | HR (beats/min) | β | μ | γ |
| SP | 4 | 16 (95) | 120–156 (136±11) | 1.02±0.2 | 2.2±1.7 | 2.52±0.78 |
| AP | 5 | 31 (210) | 138–282 (196±45) | 0.85±0.28 | 1.83±0.55 | 1.79±0.48 |
| VP | 3 | 13 (269) | 203–250 (222±17) | 0.43±0.4 | 3.05±1.6 | 3.21±3.86 |
| Total | 11† | 60 (574) | 120–282 (186±46) | 0.91±0.3 | 2.23±1.28 | 2.27±2.03 |

SMA, sustained mechanical alternans; HR, heart rate; β, ratio of ventricular filling (filling volume, FV) after the strong beat (FV₁) and after the weak beat (FV₅); FV₁/FV₅; μ, ratio of stroke volume (SV) of the strong beat and the weak beat (SVₛ/SV₅); γ, slope created by the two alternating beats on the SV–end-diastolic volume plane, computed according to Equation 6 (see text); SP, spontaneous pacing; AP, atrial pacing; VP, ventricular pacing.

*SVC could be measured only in 10 dogs (total of 55 series including 542 beats).
†Spontaneous and atrial-paced SMA in one dog.
rhythm. As a result of the intermittent operation of the heart, discrete analysis, as applied here, seems to be a useful tool for understanding the beat-to-beat behavior of the heart, in general, and of the SMA phenomenon, in particular.

Can Sustained Mechanical Alternans Be Initiated by Hemodynamic Factors?

In a previous study, it was theoretically shown that when FV is assumed constant, the Frank-Starling mechanism could not be the genesis of SMA because of a perturbation unless the SV~EDV curve had a slope of 2. According to the experimental data reported here (in the transient response to abrupt change in EDV) and evidence reported in the literature (in the steady state, discussed below), the slope of this curve is in the approximate range of 0.75–1. One of the main aims of this study was to investigate whether SMA can be initiated and maintained by the Frank-Starling mechanism (in the presence of one contractile state) under various conditions of FV.

As can be seen in Figure 6, the slopes are smaller than or equal to 1 only in four series of SMA out of 55. Thus, in 51 series, the possibility that SMA is initiated in the presence of a single contractile state is rejected, calling for alternating contractile states. In the remaining four cases, a single contractile state is theoretically possible, but not necessary, because slopes that are equal to or smaller than 1 also can be obtained in the presence of two contractile states. For example, in one case, was the result of SV = 0 and FV = 0; that is, there was no filling before the weak contraction, which had no resulting SV. Figure 8A shows how this case can be obtained theoretically by two alternating contractile states with realistic values for their SV~EDV slopes.

Effect of Filling Volume on Sustained Mechanical Alternans

The value of β can be modified, either by enforced supraventricular factors, such as asynchronous atrial contractions and modifications in valve opening,
by ventricular factors, via the secondary effects of the alternating contractile forces on FV,\textsuperscript{13,18,19} or by a combination of the two. Theoretically, enforced supraventricular alternating FV may be the causative factor of SMA (providing that the augmented inflow precedes the strong beat). Several such sporadic examples also are reported in the literature. It has been concluded\textsuperscript{15} in two patients that alternating atrial electromechanical dissociation that causes alternating strong and weak FVs either was the underlying mechanism of pulsus alternans or contributed to its occurrence. We have found (Figure 7A) that an augmented atrial filling at every other beat is the sole cause of aperiodic mechanical alternans. Another study in patients\textsuperscript{16} showed alternating failure of prosthetic valve opening, with alternating filling of the left ventricle. The presence of an unchanged contractile state and imposed alternating FV, because \( \gamma \) is approximately 1, implies that \( \mu = 1/\beta \); that is, the degree of alternation in SV will follow the degree of alternation in FV, with increased inflow preceding the strong beat (Figure 1B).

In the presence of SMA caused by myocardial factors, FV enforced by supraventricular factors will increase or decrease the degree of alternation of SV (i.e., \( \mu \)). This effect was shown experimentally (Figure 7B), when modulation of FV as a result of asynchronous atrial contractions caused by ventricu-

**Figure 6.** Plot of \( \mu \), the ratio between the stroke volumes of the strong beat \( (SV_s) \) and the weak beat \( (SV_w) \) as a function of \( 1/\beta \), the ratio between the filling volumes before the strong beat \( (FV_s) \), which denotes the filling after the weak beat) and before the weak beat \( (FV_w) \). Points represent values obtained during 55 runs of sustained mechanical alternans. Seven points represent runs that have either infinite value of \( \mu \), \( 1/\beta \), or both. Lines represent several selected values of \( \gamma \). Shaded area covers approximate values of \( \gamma \) that also can be obtained experimentally when only one contractile state is involved.

**Figure 7.** Panel A: Periodic appearance and disappearance of mechanical alternans resulting from atrial contribution. In the low-speed tracing, a previous periodic appearance of mechanical alternans can be detected, mainly in the traces of aortic flow (AF) and left ventricular pressure (LVP). In the high-speed portion, initiation of another periodic mechanical alternans can be seen. This periodic mechanical alternans results from effective atrial contraction every other beat, as can be detected in both the electrocardiogram (ECG) trace and the lower, more amplified, LVP trace. AP, aortic pressure. Panel B: A series of beats demonstrating underlying sustained mechanical alternans, further modulated by variations in ventricular filling due to ventricular pacing. Note that when mitral flow (MiF) is remarkably augmented by well-synchronized atrial contraction (arrow), the magnitude of the alternating LVP and stroke volume are temporarily reversed. AoF, aortic flow; LAP, left atrial pressure.
lar pacing changed the degree of alternation of the underlying SMA. The underlying SMA was found to be caused by alternating contractile states according to the value of $\gamma$ associated with it. When the augmented filling precedes the beat with higher contractile state, the degree of alternans increases and vice versa.

In our study, SMA was obtained either spontaneously (16 series in four dogs), by rapid ventricular pacing (13 series in three dogs), or by atrial pacing at a high rate (31 series in five dogs). A variety of means by which $\text{FV}$ could be modified was obtained by use of this method. As shown in Table 2, when $\text{SMA}$ was obtained spontaneously, $\text{FV}$ was approximately constant in most of the runs ($\beta=1.01\pm 0.2$), with $\gamma$ exceeding 1 in all series ($\gamma=2.52\pm 0.78$; minimal $\gamma=1.46$). However, when $\text{SMA}$ was obtained either by ventricular or by atrial rapid pacing, the divergence in $\beta$ from the value of 1 increased in both directions. Furthermore, pacing the same heart in the same condition with different heart rates usually led to different values of $\beta$ and $\mu$. Incomplete relaxation, which usually happens at very high rates, seems to lead to $\beta<1$ (Figure 5C). The estimated ejection-filling curve of a subgroup of five experimental runs, with $\mu=\varphi$, $\beta<1$, and $1<\gamma<2$, which can be easily identified in Figure 6, is presented in Figure 8B. Note that the experimental case presented in Figure 5C belongs to the same subgroup.

Behavior of End-Diastolic Volume During Sustained Mechanical Alternans

Many studies report that $\text{EDV}$ is greater for the strong beat, whereas other studies show no statistically significant changes between the alternating beats. It also has been demonstrated that when $\text{EDV}$ is greater before the strong beat, significant variations in end-diastolic pressure (EDP) do not necessarily appear. This can be explained by incomplete relaxation, which usually, but not necessarily, accompanies SMA, especially in very high heart rates. Although we did not measure EDV directly, Equation 5 and Figure 2C show that greater EDV for the weak beat would imply a negative value of $\gamma$. We did not obtain any negative value of $\gamma$ during our steady-state studies. In two cases, the values of $\gamma$ were very high (7.55 and 15.34). Such high values indicate that the two EDVs are almost equal. A negative value of $\gamma$ is possible when two contractile states are accompanied by alternating filling in which the filling before the low contractile state beat is sufficiently augmented (Figure 2C). Sufficient augmentation has been defined (Table 1, case 8) as $\beta>\mu$, which means that the degree of alternation is greater for inflow than for outflow.

Greater EDV before the strong beat can be the result of two factors: 1) greater end-systolic volume (ESV) after the weak beat, or 2) augmented filling after the weak beat. ESV is reported to be smaller after the strong beat. Because $\gamma$ is in the vicinity of 1 when one contractile state is involved, ESV would have to be approximately constant. Thus, smaller ESV after the strong beat supports the existence of alternating contractile states during SMA in the above studies.

As mentioned above, greater EDV before the strong beat also can be the result of an augmented filling before this beat. No direct measurements of $\text{FV}$ during SMA could be found in the literature. However, several investigators have found that the diastolic filling period preceding the strong beat is significantly longer than that preceding the weak beat in patients and in open-chest dogs. Other investigators have found no significant difference in the diastolic filling period in open-chest dogs, or in patients. In view of the experimental data presented in this article, the contradictory results indicated in the studies mentioned above may depend on whether the filling before the strong beat...
beat is augmented, equal, or reduced. As our experimental results indicate, all of these three possibilities may occur.

It should be emphasized that no hypothetical assumption has been made to obtain Equations 6 and 7, which remain valid as long as the ventricle is in an SMA, that is, in a real steady condition (assuming that the negligible unbalance of Equation 1, caused by coronary flow, is ignored). The causative factor of SMA, or the curvature of the SV–EDV curve (or curves) involved, has no bearing on the validity of this equation. Equation 6, unlike Equation 5, has the advantage that it can be calculated solely by flow values. Furthermore, because relative values are used, no calibration is needed for either inflow or outflow. It may be noted that Equation 6 can be used as a tool for checking the validity of EDV measurements by comparing values of $\gamma$ obtained from Equations 5 and 6 during SMA.

**Slope of the SV–EDV Relation in the Presence of One Contractile State**

We previously have demonstrated that the value of $\gamma$, that is, the slope of the SV–EDV curve, determines the type of response as a result of a volume perturbation for invariant FV$^{22}$ and for variant FV in this study. In the steady state, this slope defines the ability of the ventricle to maintain its ESV (and end-systolic pressure) during sustained volume loading. Thus, it has clinical importance. However, only scanty data are reported in the literature relating to the SV–EDV curve in the steady state, in general, and to its slope as a response to abrupt change in EDV (transient response), in particular. From data for isolated hearts with constant controlled afterload$^{30}$ and in patients with uncontrolled afterload,$^{7}$ the slope of the SV–EDV curve in the steady state is estimated to be approximately 1. This is in general agreement with our transient response slope (0.892±0.078). In isolated muscle, the slope between muscle shortening and muscle length, and between sarcomere shortening and sarcomere length, was found to be approximately 0.8.$^{23}$ The value of $\gamma$ also can be estimated indirectly. In isolated papillary muscles contracting isotonically, the length to which the muscle shortens has been shown to be virtually independent of the initial length for a given contractile state and afterload.$^{31}$ Moreover, by definition, a unique ESPVR implies that ESV is constant and unaffected by variations in EDV, when contractile state and afterload are kept constant.$^{32}$ Constant ESV, even in the presence of changing EDV, implies that the dependence of SV on EDV is linear, with a slope of 1. The almost unique ESV, when afterload was kept unchanged despite changes in EDV, found in isolated supported dog hearts, implies a slope in the vicinity of 1. In summary, the slope of the SV–EDV curve for either transient or steady-state responses appears to be in the vicinity of 1. This implies that the SV–EDV relations representing two distinct contractile states, associated with two distinct ESPVR, are approximately parallel, with a slope of approximately 1. Thus, for the theoretical cases in Figure 2, we chose slopes of 0.8 and 0.9 to represent the real cases. Obviously, the same conclusions would be obtained if parallel slopes with the exact value of 1, or any other value, were plotted. Graphically, we present only the linear relation, which seems to reflect the real relation.$^{23,24}$ However, as has been stressed in “Theory,” the fundamental relations developed here (such as Equation 6) are independent of the SV–EDV relation. As previously demonstrated,$^{22}$ the application can be extended easily to nonlinear cases.

**Effect of Afterload**

This study concentrated on the effect of variations in EDV and FV on SMA. Thus, variations in aortic pressure were not included in the basic schemes proposed here, despite their importance in determining the beat-to-beat variations of SV. The latter was demonstrated by a discrete analysis of SV variations induced by continually varying changes in loading conditions.$^{33,34}$ However, in a systems-oriented model like the one presented here, isolation of the effect of specific factors seems to be both a legitimate and effective approach. The development of quantitative criteria that will determine when the combination of changes in preload and afterload will lead either to a decayed transient or to a transient mechanical alternans, or even initiate SMA, is the subject of a separate study. It should be noted that the ESPVR is a suitable tool for describing the effect of aortic pressure on SV in the steady state but not when a transient response is involved. The approach presented in this study is different from the one that underlines ESPVR and is independent of it. However, approximate reference can be made to the ESPVR in the steady state by the equation $EDV_0 = V_d + (P/Emax)$, where $V_d$ represents the intercept of the ESPVR line with the volume axis, $Emax$ represents its slope, and $P$ represents the approximate end-systolic pressure associated with the unique SV–EDV curve, with $EDV_0$ as its intercept.

**Genesis of Myocardial Sustained Mechanical Alternans**

The suggested causative factors of SMA can be classified into two major categories: hemodynamic and myocardial. Our study shows that the genesis of SMA is usually myocardial. Several myocardial factors have been suggested, such as partial asystole,$^{35}$ incomplete relaxation,$^{19}$ and changes in the contractile state of the muscle.$^{2–4,9–13}$ The latter can in turn have several phenomenological interpretations.$^{2–4,9}$ We have developed a model that explained this in terms of calcium movements within the framework of excitation–contraction coupling$^{5,6}$ for the following reasons. In corroboration of other reports,$^{10,13,21,26}$ we have noticed that SMA can be achieved with a complete relaxation (Figures 5A and 5B), especially when the heart rate is not excessively high. Recently, several studies$^{36–38}$ confirmed the assumptions and predictions of our previous
model.\textsuperscript{5,6} It has been shown that SMA can be achieved in a single cardiac cell with a constant calcium inward current.\textsuperscript{36} It also was demonstrated that during SMA, the strong beats were associated with a taller peak of acquirorin light, which seems to reflect intracellular calcium,\textsuperscript{37–38} supporting the hypothesis\textsuperscript{36} that alternans is caused by intracellular calcium cycling involving the sarcoplasmic reticulum. Based on the existing evidence, partial asystole and incomplete relaxation cannot be ruled out as the causative factors of SMA, at least in several instances. Nevertheless, they clearly cannot be the causative factors in other instances. Thus, it seems more reasonable to attribute the genesis of SMA to a more common factor, such as the excitation–contraction coupling machinery. Furthermore, the fact that several types of transient mechanical alternans with variable times of persistence (including SMA, which may be considered as having very long persistence)\textsuperscript{39} can be induced by interval-dependent disturbances supports the idea that SMA is an integral part of the interval–strength relation, which can be explained in terms of intracellular movements of calcium.\textsuperscript{5,6}

Conclusion

Based on versatile experimental data, this discrete model, which uses explicit quantitative criteria, has proved to be an effective tool for the resolution of the controversy concerning the primary causes of SMA. It shows that the common genesis of SMA is myocardial. However, in rare circumstances, supraventricular-enforced sustained alternation in FV may lead to SMA in the presence of one contractile state. A criterion for identification of the latter also is provided.

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D Adler, S Nikolic, E H Sonnenblick and E L Yellin

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