Postextrasystolic Potentiation and Its Contribution to the Beat-to-Beat Variation of the Pulse During Atrial Fibrillation

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Background. Beat-to-beat variations in the pulse during atrial fibrillation (AF) have conventionally been attributed to time-dependent changes in filling. We have explored the possibility that they are dependent on the intrinsic myocardial interval force relation.

Methods and Results. Left ventricular (LV) contractility (maximum rate of rise of pressure, LV dP/dt\text{max}) and ascending aortic blood velocity were measured during cardiac catheterization in 15 patients with AF. Beats preceded by an interval of less than 500 msec were excluded from analysis to reduce the confounding influence of incomplete mechanical restitution. The LV dP/dt\text{max} was then related to the prepreceding interval. An inverse relation consistent with postextrasystolic potentiation was obtained in all 15 patients (Spearman's rank correlations, \(-0.56\) to \(-0.86; p\leq0.0001\)). This relation was confirmed in three patients during pacing that overrode the AF and introduced single-interval variations into steady-state pacing. The ECG sequences from six of the AF patients were used to drive isometrically contracting guinea pig papillary muscle and human right ventricular tissue (n=7); the same inverse relation was demonstrated. On a beat-by-beat basis, the maximum rate of rise of force in the isolated muscle correlated well with LV dP/dt\text{max} in the patients \((r=0.50-0.86, p\leq0.0001)\). The relation of the integral of aortic velocity (AVI, proportional to stroke volume) to prepreceding interval was also inverse, whereas important correlations were demonstrated between LV dP/dt\text{max} and AVI (Spearman's rank correlations, \(0.27-0.95; p\leq0.0001)\).

Conclusions. This study demonstrates that postextrasystolic potentiation contributes to the characteristic beat-to-beat variation of the pulse in AF. (Circulation 1992;86:1223–1232)

KEY WORDS • interval force relation • mechanical restitution • contractility • Frank-Starling mechanism

Atrial fibrillation (AF) is characterized by the irregularity of the pulse, not only with respect to time but also with beat-to-beat variation in the mechanical response. This can be detected clinically in a varying blood pressure and intensity of the pulse. Such variations have traditionally been ascribed to time-dependent changes in ventricular filling\(^1\)-\(^3\) acting through the Frank-Starling mechanism.\(^4\)-\(^6\) There is, however, another mechanism that can influence cardiac performance and is time dependent but is independent of myocardial fiber length or ventricular volume. This is the interval–force mechanism,\(^7\) which is active in the intact human heart and can profoundly influence the force of contraction.\(^8\)

A single short interval modifies the force of contraction of a number of subsequent beats. The early beat is weak because of incomplete mechanical restitution,\(^9\) whereas the subsequent beats are strengthened or potentiated. This phenomenon has been known as postextrasystolic potentiation since it was first described by Langendorff.\(^10\) Subsequently recognized by many others, this inverse relation of a potentiated beat to its prepreceding interval has been rigorously explored in isolated muscle by Hoffman et al\(^11\) and in the isolated heart by Siebens et al.\(^12\) The decay of potentiation occurs over up to six subsequent beats. Postextrasystolic potentiation and its modification by disease has previously been evaluated in humans during pacing studies.\(^13\)-\(^15\) The purpose of the present study was to explore the possible contribution of this phenomenon to beat-to-beat variations in mechanical performance during AF. The spontaneous interval variation allows the role of postextrasystolic potentiation to be assessed in humans without having to impose a pacing protocol that necessarily alters the pattern of conduction and thereby the mechanical response of the heart. Although a number of studies have recognized a role of postextrasystolic potentiation during AF,\(^16\)-\(^18\) to our knowledge, no other investigation in man has addressed the confounding influence of mechanical restitution. The present study was designed to systematically explore and compare the impact of sequential interval changes under the circumstances of postextrasystolic potentiation on left ventricular contractility, left ventricular ejection indexes, and isolated muscle contracting at constant length.

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**Table 1. Patient Details**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Drugs</th>
<th>ECG</th>
<th>Diagnosis</th>
<th>Cardiothoracic ratio</th>
</tr>
</thead>
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<td>M</td>
<td>47</td>
<td>W, D</td>
<td>+75</td>
<td>Alcoholic cardiomyopathy</td>
<td>13.5/30</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>66</td>
<td>D, B, As</td>
<td>+45</td>
<td>Alcoholic cardiomyopathy</td>
<td>15.5/32</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>51</td>
<td>D, W</td>
<td>+45</td>
<td>Alcoholic cardiomyopathy</td>
<td>18/37</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>69</td>
<td>D, Ca, D*</td>
<td>+45</td>
<td>Ischemic heart disease</td>
<td>16/33</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>58</td>
<td>D*, D</td>
<td>+105</td>
<td>Atrial septal defect</td>
<td>14.5/27.5</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>69</td>
<td>D*, D, A, N</td>
<td>+45</td>
<td>Restenosis mitral valve</td>
<td>15.2/27.9</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>64</td>
<td>D, Ca</td>
<td>0, LVH</td>
<td>Cardiomyopathy, postmyocarditis</td>
<td>16/32</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
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<td>17/26.5</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
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<td>D, D*, N, Ca</td>
<td>+15, RBBB1</td>
<td>Dilated cardiomyopathy</td>
<td>18/27.5</td>
</tr>
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<td>72</td>
<td>D, A</td>
<td>+60</td>
<td>Alcoholic cardiomyopathy</td>
<td>20/34</td>
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<td>M</td>
<td>60</td>
<td>D, D*, B</td>
<td>-30</td>
<td>Dilated cardiomyopathy</td>
<td>18/34</td>
</tr>
<tr>
<td>12</td>
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<td>53</td>
<td>D</td>
<td>+105</td>
<td>Mitral stenosis</td>
<td>15/28</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>46</td>
<td>D, D*</td>
<td>+60</td>
<td>Dilated cardiomyopathy</td>
<td>17.5/29.5</td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>68</td>
<td>Ca</td>
<td>-40</td>
<td>Alcohol-induced atrial fibrillation</td>
<td>15/5.32</td>
</tr>
<tr>
<td>15</td>
<td>M</td>
<td>74</td>
<td>D, O</td>
<td>-60</td>
<td>Ischemic heart disease</td>
<td>14/28</td>
</tr>
</tbody>
</table>

M, male; F, female; A, Angiotensin converting enzyme inhibitor; As, aspirin; B, bronchodilators (inhaled); Ca, calcium channel blockers; D, digoxin; D*, diuretics; N, nitrates; O, oral hypoglycemic; W, anticoagulation; LBBB1, left bundle branch block; RBBB1, right bundle branch block. ECG numbers denote axis.

**Methods**

**Patient Studies**

Fifteen patients in AF who were undergoing cardiac catheterization for diagnostic purposes were studied. Patients with AF from a variety of etiologies were investigated (see Table 1). The only exclusion criteria were 1) mitral regurgitation, because under these circumstances the maximum rate of rise of left ventricular pressure (see below) could not have been isovolumic and therefore not a valid measurement of contractility; and 2) patients with aortic stenosis, because the catheter used in the study (see below) was stiffer than conventional catheters and unsuitable for retrograde entry to the left ventricle via a diseased aortic valve. The study was approved by the relevant ethical committees and written informed consent was obtained before the study from each patient. All patients were studied on their normal medication and a benzodiazepine as premedication. They were studied in the supine position and measurements made during quiet respiration.

Measurements of left ventricular performance were made using a single catheter (8F) bearing a tip manometer (Gaeltec) positioned in the left ventricle to give high-fidelity recordings of left ventricular pressure and an electromagnetic velocity transducer19 sited in the ascending aorta to measure aortic blood velocity. The catheter-tip manometer was used in conjunction with a Hewlett-Packard or a Gaeltec carrier amplifier and the Mills velocity transducer in conjunction with the SE Medic electromagnetic flowmeter. Velocity signals were calibrated electronically, with zero flow being taken as the signal in late diastole. Aortic velocity was integrated using a Gould integrating circuit (Gould 13/4615/70 integrator amplifier) to give systolic aortic velocity integral (AVI, sometimes referred to as stroke distance), which is proportional to stroke volume (stroke volume is derived from AVI by multiplying by the aortic cross-sectional area). The maximum rate of rise of left ventricular pressure ($LV \text{d}P/\text{d}t_{\text{max}}$) was obtained by electronic differentiation of pressure20 using Hewlett-Packard or Gaeltec differentiating modules with cutoff frequency set at 50 Hz or above. The catheter-tip manometer was calibrated against a sphygmomanometer, with zero pressure being taken as the signal at the moment of withdrawal from the femoral artery. The differential signal was calibrated by passing a sawtooth electrical signal of known amplitude and frequency through the differentiator at the end of each experiment.

In all patients, an attempt was made to optimize both the aortic velocity and left ventricular pressure signals by adjusting the catheter position. In some patients, we could only obtain one or the other as a good quality signal, and we then usually elected to record left ventricular pressure.

An ECG was monitored throughout the study with recordings made for periods of 1–2 minutes, and from these recordings, sequences of 100–200 beats free of beats showing any aberration of conduction were selected for analysis. (Aberrent conduction may of itself modify the mechanical response.) We should stress the term postextrasystolic potentiation is used throughout this article to describe the relation between prepreceding interval and the contractile response of a beat that is potentiated when the preceeding interval is shorter than that allowing complete mechanical restitution. It is not used to imply an abnormal focus of excitation of the early beat or extrasystole. Recordings were made onto electromagnetic tape using a Racal tape recorder (Store 4). They were subsequently played out at high gain using an inkjet chart recorder (Mingograph 800) with a paper speed of 50 mm/sec. Measurements were made using a digitizing table and a desktop computer.

Three of the patients were overpaced from the right ventricle using conventional catheter-mounted bipolar pacing electrodes. Steady-state pacing was established for several minutes using a voltage just above threshold. The steady-state interval was the slowest feasible for the underlying heart rate in order to allow complete or near-complete mechanical restitution. A single interval
variation orextrasystole (from the same pacing site) was then introduced with an immediate return to the steady state such that the postextrasystolic interval was the same as that of the steady state. After 10 beats, the extrasystolic interval was repeated. A range of interval variations was introduced with individual intervals repeated once or twice. The range of interval variations was from the shortest to the longest possible in any given patient and was usually in the range of 300–1,200 msec. As in the recordings of spontaneous AF, a continuous record of left ventricular pressure, aortic velocity, and ECG was made.

**Isolated Cardiac Muscle Studies**

Isolated cardiac muscles were stimulated to contract isometrically using ECG sequences borrowed from some of the AF patients. The responses were then compared with the isovolumic contractions measured in the patients from whom the AF sequences had been borrowed, i.e., when both were driven by the identical sequence of intervals. The rationale behind using isolated cardiac muscle was to eliminate the effect of muscle length and to see whether under these circumstances the interval force behavior that had been identified in the patients during AF persisted.

Guinea pigs weighing 200 g or less were killed by cervical dislocation and subsequent division of a carotid. Papillary muscles were resected from the tricuspid valve apparatus and right ventricle in Tyrode's solution that had been buffered with sodium bicarbonate and aerated with a mixture of 95% oxygen and 5% carbon dioxide at room temperature to give a pH of 7.4. The muscle was mounted in a horizontal apparatus between a stationary hook and a tension transducer, where change in tension was detected by a silicon beam strain gauge (AE 801, AME Horten, Norway). The muscle was perfused with Tyrode’s solution and aerated as above. The Tyrode’s was not recirculated and was maintained at a temperature of 37°C. The temperature was monitored using a thermocouple attached to the tension transducer. The pH of the Tyrode’s was measured throughout the experiment.

The human right ventricular tissue was resected during repair of a Fallot’s defect. The heart had been exposed to standard cardioplegic solution, and the tissue was transported in Tyrode’s solution. A single trabecula was dissected from the resected specimen. All other experimental details are as described for the guinea pig tissue.

The preparations were stimulated with square pulses 2 msec wide and 1.5 times the threshold voltage. The stimulus pattern was generated by a programmable pulse generator (Digitimer D4030, Devices Ltd., Welwyn Gdn City, UK) coupled to a stimulator (Devices, DS2). The muscle was paced continuously at 1 Hz for an hour, during which time a steady state was obtained. Six of the AF sequences selected for analysis from the patients were then used to drive the isolated muscles. An electromagnetic tape recording of the selected ECG sequences was used to drive the digitimer, and in each case, both the timing of the output from the digitimer and the timing of the contractions were checked against the original ECG sequence. After each AF sequence, there was a return to the steady state for 2 minutes. Each individual sequence was itself repeated on three or four occasions and between one and four different AF sequences used in each muscle. To ensure that each muscle preparation demonstrated the expected patterns of restitution and postextrasystolic potentiation, the muscle was paced using a similar protocol to that described for humans but with a steady-state interval of 1,000 msec and a return to this interval after each extrasystole for 30 seconds.

The experiments were performed with the muscle length held at 95% of the length that gave maximum force. Force was measured using the strain gauge but was also differentiated to give the rate of change of force (dF/dt) using a differential amplifier (Gould 13-461571). The calibration of dF/dt was as described for LV dP/dt. The maximum rate of change of force (dF/dt\textsubscript{max}) was compared with LV dP/dt\textsubscript{max} because we were not able to measure force directly in humans but used the maximum rate of change of left ventricular pressure as the best available measure of contractility; it seemed logical to compare this with the maximum rate of change of force in isolated tissue, and 2) dF/dt\textsubscript{max} has been shown to correlate well with calcium release within the cell.\textsuperscript{22,23} Data were recorded both onto electromagnetic tape (as for the human data) and using an inkjet recorder (Mingograph 800). Data were measured from the ink record using the same digitizing system.

**Analyses**

Cardiac contractions that follow a very short interval are weak because of incomplete mechanical restitution.\textsuperscript{9,24,25} As the interval lengthens, the force of contraction increases until a plateau is reached where mechanical restitution is complete: about 800 msec in humans.\textsuperscript{26} Beats after the weak beat are potentiated; the degree of potentiation is inversely proportional to the extrasystolic or prepreceding interval and is only fully expressed if the potentiated beat is itself potentiated.\textsuperscript{11} Thus, in AF, incomplete mechanical restitution may complicate examination of the potentiating effect of the prepreceding interval. Those beats preceded by an interval of less than 500 msec were therefore excluded from analysis. (A 500-msec gat- ing interval was chosen by trial and error as a compromise between full restitution and the loss of excessive data points through more rigorous gating. In the absence of mitral stenosis, a 500-msec preceding interval should also allow completion of ventricular filling; see "Discussion.") We also excluded from analysis beats after intervals of more than 1,300 msec to ensure LV dP/dt\textsubscript{max} was reached during isovolumic contraction (see "Discussion"). The remaining beats were then correlated with their prepreceding interval. These principles were applied to both the patient and the isometrically contracting muscle data. These relations were then analyzed using Spearman’s rank correlation because this analysis makes no assumptions about the nature of a relation between two variables.\textsuperscript{27}

**Results**

Good-quality left ventricular pressure and LV dP/dt\textsubscript{max} signals were obtained in all patients studied (Figure 1), but reliable integration of aortic velocity was feasible in only 11 of the 15 (see Table 2).

**LV dP/dt\textsubscript{max} During Spontaneous AF in Humans**

An inverse relation between prepreceding interval and contractility, blurred by some scatter but character-
A characteristic of postextrasystolic potentiation was demonstrated in all 15 patients. A typical result is shown in Figure 2A. A significant negative correlation between contractility and prepreceding interval was obtained in every patient when tested by Spearman's rank correlation analysis (see Table 3).

**Pacing Studies in Humans and Isolated Cardiac Muscles**

Three of the 15 patients studied were paced (patients 6, 10, and 12), with the introduction of single-interval variations or extrasystoles during steady-state pacing. All three patients demonstrated typical patterns of postextrasystolic potentiation (Figure 3A). Here, where the only deviation from the steady state is the introduction of a single-interval variation, the apparent scatter noted within these relations during the spontaneous AF is largely absent. Using a protocol similar to that used in the paced patients, an inverse relation typical of postextrasystolic potentiation was similarly demonstrated in the isolated cardiac muscles during isometric contraction (Figure 3B).

When the muscles were stimulated to contract in response to the AF sequences, the beat-to-beat variation in $dF/dt_{max}$ closely resembled the pattern of variation in LV $dP/dt_{max}$ in the patients from whom the sequences had been borrowed. This finding was confirmed by the demonstration of inverse relations between $dF/dt_{max}$ and prepreceding interval typical of postextrasystolic potentiation (Figure 2B) in all the isolated muscles in response to the AF sequences, with patterns of scatter reminiscent of that obtained in the patients (Figure 2A). Table 4 shows Spearman's rank correlations for preceeding intervals and $dF/dt_{max}$ from this data, which are close to the values obtained from the patients for the identical sequences (also shown in Table 4). When the isometric responses to a particular AF sequence were compared with the isovolumic responses obtained in the patient from whom the sequence had been borrowed, there was a clear linear correlation between the two variables. A typical

**Table 2. Patient Details**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>RR intervals (seconds)</th>
<th>LV</th>
<th>CAD</th>
<th>LVEDP (mm Hg)</th>
<th>Peak LVSP (mm Hg)</th>
<th>AVI (cm)</th>
<th>LV $dP/dt_{max}$ (mm Hg/sec)</th>
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</thead>
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<td>1</td>
<td>0.36–0.98</td>
<td>G3</td>
<td>N</td>
<td>2.5–22</td>
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<td>0–10.5</td>
<td>150–1,750</td>
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<td>G1</td>
<td>2</td>
<td>–2.5–30</td>
<td>55–140</td>
<td>0–9</td>
<td>450–2,350</td>
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<td>4.5–21</td>
<td>1,460–2,150</td>
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<td>M</td>
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<td>0–9</td>
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<td>N</td>
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<td>625–1,250</td>
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<td>3</td>
<td>–4–10</td>
<td>75–130</td>
<td>No data</td>
<td>450–1,450</td>
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</tbody>
</table>

CAD, coronary artery disease; N, normal vessels; M, minor disease. 1, 2, 3 refer to number of vessels with significant stenoses (>50%); LV, left ventricular function; N, normal; G, global impairment. G1, G2, G3 imply mild, moderate, and severe impairment, respectively (none of the patients had focal left ventricular dysfunction); LVEDP, left ventricular end-diastolic pressure; Peak LVSP, peak left ventricular systolic pressure; AVI, aortic velocity integral; LV $dP/dt_{max}$, peak rate of rise of left ventricular pressure. Ranges are shown in each case.
example is shown in Figure 4, and the linear correlation coefficients are listed in Table 5.

The AF sequences from six patients were used to stimulate papillary muscles from five guinea pigs and trabeculae from two patients undergoing surgical repair of a Fallot’s defect, giving a total of 66 sequences in seven muscles. In each muscle, the repeated responses to any one AF sequence were highly reproducible, with correlation coefficients of the order of 0.98. Therefore, the mean dF/dt max of each beat is calculated for the identical sequences and either compared with LV dP/dt max or related to prepreceding interval.

Ejection Indexes Measured as Aortic Velocity Integral or Stroke Distance

Good-quality aortic velocity signals were obtained in 11 of the 15 patients, and in 10 of these (1, 2, 3, 4, 5, 7, 8, 11, 13, and 14), an inverse relation between prepreceding interval and AVI was demonstrated (Figure 5 and Table 3). It is of note that the scatter previously observed in terms of LV dP/dt max not only persists into the relation between prepreceding interval and AVI but is actually more pronounced within this relation (see Figures 2A and 5). In these same 10 patients, there was a direct relation between contractility and AVI (Figure 6) that was always linear once the aortic valve was open. Table 3 shows Spearman’s rank correlations between LV dP/dt max and AVI for these patients.

The inverse relation between prepreceding interval and contractility observed in patient 6 was not carried through to the ejection indexes measured during the spontaneous arrhythmia. However, when a full range of extrasystoles was introduced into trains of steady pacing intervals of 800 msec, the inverse relation between prepreceding interval and AVI typical of postextrasystolic potentiation was also confirmed in this patient (see Figure 7).

Discussion

This study demonstrates a major influence of interval, under the circumstances of postextrasystolic potentiation, on beat-to-beat changes in the mechanical response of the left ventricle, both of isovolumic LV dP/dt max and of integrated aortic velocity, during spontaneous AF. The interval force behavior identified in the patients with AF was reproduced in the isolated muscles in response to the same timing of excitation when the effects of length were formally eliminated.

Fundamental to this study is the relation between LV dP/dt max during isovolumic contraction and left ventricular filling in humans. On theoretical grounds, an independence of LV dP/dt max from volume is not absolute; the theoretical argument that the overall effect of a change in volume on LV dP/dt max is likely to be small (and insignificant) does not exclude the possibility that in some situations, this influence may become significant. Thus, empirical validation is necessary. Perhaps predictably, there is a discordancy with respect to the influence of volume on LV dP/dt max within this litera-
ture, reflecting a range of experimental conditions and animals.29-31

Most relevant to the use of LV dP/dt\textsubscript{max} in the present study are catheter-based studies of LV dP/dt\textsubscript{max} in humans.26,32,33 Although these have consistently shown LV dP/dt\textsubscript{max} to be volume independent, some of these studies are subject to the criticism that reflex effects could not be excluded. This is true for the study of Sanghvi et al.32 who used a fluid-filled catheter and infusion to increase volume. The same limitation must apply to at least some of the patients studied by Pidgeon et al.26 in whom volume changes were produced by straight leg raising while pressure was recorded using a micromanometer. However, some of the patients in the study were taking \( \beta \)-adrenergic receptor blockers for clinical reasons, and they showed the same lack of volume dependence as the others, which makes a reflex effect unlikely. The study of Drake-Holland et al.33 was designed to address the limitations evident in these earlier studies. Volume changes were produced by tilting patients under validated \( \beta \)-blockade and continuous pacing. Again, LV dP/dt\textsubscript{max} failed to demonstrate any significant variation with changing volume.

In our own study, the presence of AF and impaired left ventricular function made such validation impracticable because it would have required \( \beta \)-blockade and over pacing combined with either tilt or fluid infusion. It was this very inability to explore and exclude a volume dependence of LV dP/dt\textsubscript{max} in the patients, however, that prompted the parallel studies in isometrically contracting isolated muscles. The resulting close correlations between LV dP/dt\textsubscript{max}, measured in the patients, and dP/dt\textsubscript{max}, measured in the muscles when length was held constant in response to the same sequential timing of excitation argues further in support of the view that LV dP/dt\textsubscript{max} was independent of preload (and afterload, but see also below) in these experiments.

Changes in interval as seen in AF will affect the end-diastolic pressure in the aorta, and so the question of whether LV dP/dt\textsubscript{max} is dependent on aortic pressure is also relevant. There is a consensus from animal studies that as long as LV dP/dt\textsubscript{max} is reached during the isovolumic phase before aortic valve opening, it is

**Figure 3.** Plots show data recorded from patient 6 (panel A) during right ventricular pacing (with the pacing protocol shown in the inset) and during isometric contraction of guinea pig muscle A (panel B) in response to pacing with a similar protocol. SS, steady state during pacing at a basic interval; ESI, variable extrasystolic interval. The basic interval is chosen to allow full mechanical restitution and is 800 msec in panel A (where all beats shown have a preceding interval of 800 msec) and 1,000 msec in panel B (so all beats shown have a preceding interval of 1,000 msec). Both sets of data again show an inverse relation between contractility and prepreceding interval typical of postextrasystolic potentiation. Scatter seen in Figures 2A and 2B is no longer evident here, where the only interval variation is the introduction of a single extrasystole into a train of steady-state beats.

**Table 4.** Spearman Rank Correlations Between Prepreceding Intervals and Contractility Measured as Left Ventricular dP/dt\textsubscript{max} in Patients and as dF/dt\textsubscript{max} in Isolated Muscles

<table>
<thead>
<tr>
<th>AF sequence</th>
<th>1</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>10</th>
<th>15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>-0.73</td>
<td>-0.86</td>
<td>-0.72</td>
<td>-0.81</td>
<td>-0.79</td>
<td>-0.81</td>
</tr>
<tr>
<td>Guinea pig A</td>
<td>-0.71</td>
<td>-0.71</td>
<td>-0.71</td>
<td>-0.87</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Guinea pig B</td>
<td>-0.62</td>
<td>-0.62</td>
<td>-0.62</td>
<td>-0.79</td>
<td>-0.79</td>
<td>-</td>
</tr>
<tr>
<td>Guinea pig C</td>
<td>-0.71</td>
<td>-0.71</td>
<td>-0.71</td>
<td>-0.79</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Guinea pig D</td>
<td>-0.79</td>
<td>-0.63</td>
<td>-0.63</td>
<td>-0.76</td>
<td>-0.76</td>
<td>-</td>
</tr>
<tr>
<td>Guinea pig E</td>
<td>-0.46</td>
<td>-0.46</td>
<td>-0.46</td>
<td>-0.64</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>RV 1</td>
<td>-0.86</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>RV 2</td>
<td>-</td>
<td>-0.58</td>
<td>-0.58</td>
<td>-</td>
<td>-</td>
<td>-0.78</td>
</tr>
</tbody>
</table>

Atrial fibrillation (AF) sequences 1–15 identify the patients from whom they are borrowed.

**Figure 4.** Plot shows a typical linear relation between the contractile response of the left ventricle in patient 1, measured as left ventricular (LV) dP/dt\textsubscript{max} during isovolumic contraction, and the response of the isolated papillary muscle from guinea pig A, measured as dF/dt\textsubscript{max} during isometric contraction in response to the same ECG sequence. (All beats have a preceding interval of 500 msec or more.)
largely unaffected by changes in aortic diastolic pressure. This condition is likely to be met if the aortic diastolic pressure remains above 50 mm Hg at least up to intervals of 1 second, and this applies in humans at intervals up to 1,300 msec. At very long intervals or low aortic pressures, LV dP/dt max will be limited by aortic valve opening, with an underestimation of contractile force. In the present study, data measured after intervals of more than 1,300 msec were excluded, so that LV dP/dt max should reflect contractility alone.

All the patients studied consistently demonstrated a powerful influence of prepreceding interval on contractility. This effect of prepreceding interval on contractility was confirmed in the studies of isolated muscle contracting at constant length where the inverse relations seen in the patients were found both when borrowed AF sequences were used to drive the muscles and when conventional pacing protocols were used.

The human AF data consistently showed considerable variation in contractility for any given preceeding interval (Figure 2A). The most likely explanation of this scatter is that contractility of a given beat is influenced by a number of earlier intervals. In favor of this was the observation that when all intervals except a single interval were held constant, as in those patients who were overpaced, the variation virtually disappeared (Figure 3A). In addition, a similar pattern of scatter was seen when the isometrically contracting muscles were paced with the AF sequences (Figure 2B) that could be similarly eliminated by holding constant all intervals except a single-interval variation (Figure 3B). This again suggests that the scatter is a function of a continuous variation in the interval such that on any beat, the influences of a number of earlier intervals are having an effect. Responses during isometric contraction and during isovolumic contraction to the identical timing of stimuli behave in a similar fashion. This is further evidence that the variations in LV dP/dt max reflect interval change per se and are independent of accompanying volume changes, i.e., LV dP/dt max is a valid measurement of contractility in humans.

The patients also demonstrated an inverse relation between preceeding interval and AVI, confirming

**TABLE 5. Linear Correlation Coefficients Between Left Ventricular dP/dt max Recorded in a Given Patient During Isovolumic Contraction and dF/dt max Recorded in Isolated Muscle Contracting Isometrically in Response to ECG Sequence Borrowed From the Same Patient**

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>10</th>
<th>15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guinea pig A</td>
<td>0.84</td>
<td>0.81</td>
<td>0.82</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guinea pig B</td>
<td>0.71</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guinea pig C</td>
<td>0.71</td>
<td>0.76</td>
<td>0.72</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guinea pig D</td>
<td>0.80</td>
<td>0.79</td>
<td>0.79</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guinea pig E</td>
<td>0.50</td>
<td>0.60</td>
<td>0.56</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV A</td>
<td>0.77</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV B</td>
<td>0.77</td>
<td>0.86</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Numbers (1–15) identify the patients from whom the atrial fibrillation sequences have been borrowed (numbers as per other tables).

**FIGURE 5.** Plot shows inverse relation between preceeding RR interval and aortic velocity integral typical of postextrasystolic potentiation. Data recorded during spontaneous atrial fibrillation from patient 1. Data points have preceding intervals ranging from 500 to 980 msec.

**FIGURE 6.** Plot shows data from patient 7 recorded during spontaneous atrial fibrillation showing a typical relation between contractility, measured as left ventricular (LV) dP/dt max, and ejection indexes, measured as aortic velocity integral.

**FIGURE 7.** Plot shows data from patient 6 during right ventricular pacing, showing the inverse relation typical of postextrasystolic potentiation between extrasystolic interval (which is equivalent to the preceeding interval) and aortic velocity integral of the potentiated beat. The only deviation from the 800-msec steady-state interval is the introduction of single extrasystoles, so all data points shown have a preceding interval of 800 msec. SS, steady state; ESI, extrasystolic interval.
that the potentiating effect of a short interval is carried through to the pulse in AF. The only exception to this observation was found in patient 6, which is not surprising, given the combination of mitral stenosis and intervals that fall predominantly within the range that allows full mechanical restitution (greater than 800 msec in humans) and so outside the range that induces postextrasystolic potentiation. The shortest intervals in this patient of 680 msec will therefore only have a weak potentiating effect, but even this effect can be detected in terms of LV dP/dt$_{\text{max}}$, which is simply a measure of contractility. However, the presence of significant mitral stenosis in this patient (peak mitral valve gradient of 37 mm) means that ventricular filling will be delayed, and so there may be quite marked changes in ventricular filling as preceding intervals vary from 680 to 1,250 msec. Such fluctuations in volume could obscure the weak potentiating effect of the shortest intervals. Indeed, when patient 6 was overpaced and a full range of extrasystoles introduced, an inverse relation between prepreceding interval and AVI, typical of postextrasystolic potentiation, was confirmed. These beats all had a preceding interval of 800 msec.

Within the inverse relation between prepreceding interval and AVI, there is scatter more marked than the scatter noted in LV dP/dt$_{\text{max}}$. The probable explanation is that an additional variable, aortic diastolic pressure or “afterload,” will now contribute to the variations in ejection indexes as aortic end-diastolic pressure varies with preceding intervals over the range of 500–1,300 msec. Although such variations may add to the scatter, the inverse relation of postextrasystolic potentiation is clearly dominant.

The early literature on the mechanism of beat-to-beat mechanical changes in AF is dominated by the influence of preceding interval; this was either considered to effect the pulse changes by varying diastolic filling or through the effect on aortic diastolic pressure such that after a long interval, this pressure would be low and so a stronger pulse would follow. Interest in the prepreceding interval followed animal work on simulated or induced AF that demonstrated an inverse relation between prepreceding interval and the isotropic state of the cardiac muscle.

In humans, Karliner et al. examined factors influencing ejection indexes derived from angiographic measurements of volume in patients with AF and concluded that postextrasystolic potentiation was a contributing factor because volume changes could not account for the inverse relation between prepreceding interval and ejection indexes. However, 60% of the patients had mitral regurgitation, which confuses the issue because in the presence of mitral regurgitation, ejection indexes may increase as ventricular function declines.

Gibson et al. investigated patients in AF with a Starr-Edwards valve in the aortic position using the time between onset of the QRS and opening of the valve (QA1 interval) as an indicator of the contractile state of the ventricle. In only 15 of the 19 patients they studied was there a correlation between QA1 interval and preceeding interval; this they attributed to postextrasystolic potentiation.

In the present study, the striking linearity of LV dP/dt$_{\text{max}}$ with AVI confirms the importance of the interval–force relation on the pulse. The complex question of the relative contributions of mechanical restitution, postextrasystolic potentiation, and the Frank-Starling mechanism to the beat-to-beat variations of the pulse in AF is beyond the scope of this study. However, some insight into the relative contributions of contractility and volume, under the circumstances of postextrasystolic potentiation, can be gained.

Volume was not specifically measured in this study, but in the absence of mitral stenosis, the restriction of analysis to those beats with a preceding interval of 500 msec or more should ensure completion, or near completion, of ventricular filling on all beats being examined for potentiation. This view is consistent with the demonstrations of Wiggers and Katz and later Noble et al. and Horwitz and Bishop that a rapid phase of ventricular filling, early in diastole, is followed by a period of diastasis. Where atrial systole is preserved, this is followed in late diastole by a second rapid phase of filling. In AF, this late component is lost and so the time course of ventricular filling, in the absence of mitral stenosis, will be limited to the early diastolic phase described for sinus rhythm. We have confirmed in our own laboratory that filling in AF is effectively complete within 500 msec. This suggests that any potentiating effects of short preceeding intervals on contractile or ejection indexes, as demonstrated in this study, are not mediated by volume changes. This is consistent with the findings of a number of studies in both animals and humans that have shown that the influence of volume on potentiation is either minimal or absent.

Studies in isolated muscles also confirm that both mechanical restitution and postextrasystolic potentiation occur in the absence of changes in sarcomere length. What, then, is the mechanism of this interval-mediated potentiation? From studies in isolated muscles, there is overwhelming evidence that the changes in stimulus interval that determine these relations are associated with changes in the concentration of calcium ions released in the vicinity of the contractile proteins upon activation. These changes in calcium in turn parallel the changes in tension.

To explain the complex sequence of events that follows excitation, a number of authors have proposed a model with, in its simplest form, functional uptake and release compartments for calcium. Calcium entering the cell during the action potential passes into the uptake compartment. It is subsequently passed to the release compartment: this is the time-dependent step that determines mechanical restitution. This calcium is then available for release on the subsequent depolarization. If the interval preceding depolarization is short, relatively little calcium will have been transferred. The resulting contraction is weak or poorly restituted. At the end of such a beat, several mechanisms will have contributed to increased calcium in the uptake compartment: 1) reduced calcium transfer to the release compartment during the preceding diastole; 2) the reduced intracellular calcium transient associated with a poorly restituted beat will offer less opposition to calcium inflow through the second inward current resulting in increased calcium entry during that action potential; 3) again, as a function of the low concentration of intracellular calcium ions released on activation, the driving force to calcium extrusion...
through the Na⁺/Ca²⁺ exchange will be reduced during the extrasystole.

If the ensuing depolarization now follows an interval sufficiently long to allow mechanical restitution, that depolarization will result in the release of these enhanced levels of calcium to the contractile proteins. If subsequent beats follow intervals that allow full restitution, a proportion of this calcium is recirculated, the remainder being extruded. As a result, the potentiation decays over a number of beats until a steady state is regained when net calcium influx is equal to net efflux from the cell. It must be stressed that the compartments are strictly functional and, at the time of writing, have no anatomic counterpart and indeed may be part of a single anatomic structure. The most commonly accepted site of such calcium storage is the sarcoplasmic reticulum.  

It is postulated that the network of tubules, which wrap around the myofibrils, are involved in the uptake of calcium ions from the contractile proteins, upon relaxation, whereas the functional sarcoplasmic reticulum is thought to release calcium on activation.

The results of the present study are consistent with these mechanisms and confirm the importance of the interval-force relation on the varying strength of the pulse in AF by demonstrating that the potentiation influence of a short prepreceding interval on the pulse is a function of the interval per se. This observation was true for patients with mild, moderate, and severe left ventricular disease as well as those with normal (or near normal) left ventricular function.

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Postextrasystolic potentiation and its contribution to the beat-to-beat variation of the pulse during atrial fibrillation.

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