Myocardial Contractility Is Not Constant During Spontaneous Atrial Fibrillation in Patients

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Background—The variation in stroke volume and pulse pressure characteristic of atrial fibrillation is usually ascribed to time-dependent ventricular filling, implying a single positive relationship between end-systolic pressure and volume, which defines a single state of myocardial contractility. We tested the hypothesis that contractility also varies.

Methods and Results—We measured the left ventricular pressure and volume continuously with a conductance catheter and its preceding interval and is always seen in mammalian cardiac preparations, such as isolated myocytes and isolated trabeculae; there is an increase in the force of contraction as the stimulus interval lengthens until restitution is complete (in humans and most mammals, at ≈800 to 1000 ms). In such preparations, initial muscle length can be kept constant, but in the intact human, with increasing interval, end-diastolic volume also increases progressively and increases force of contraction by means of the Frank-Starling mechanism.

There are 2 other interval-strength effects: (1) postextrasystolic potentiation, which is the phenomenon responsible for the strong contractions after the interval that follows a short interval (it has previously been demonstrated that such postextrasystolic potentiation contributes to pulse variation during atrial fibrillation), and (2) the decay of postextrasystolic potentiation, which has a time course of several beats.

The present study explores the hypothesis that the beat-by-beat hemodynamic changes of atrial fibrillation are associated with beat-by-beat changes in contractility. We recorded beat-by-beat changes in left ventricular pressure-volume loops in atrial fibrillation patients during cardiac catheterization and then constructed end-systolic pressure-volume relationships.

Key Words: arrhythmia • cardiac volume • hemodynamics • intervals • ventricles • mechanics
Methods

Atrial Fibrillation Studies

Six unselected patients with chronic atrial fibrillation without aortic or mitral valve disease were studied at cardiac catheterization after diagnostic angiography (Table 1). In accordance with the Helsinki agreement, the study was subject to local ethical committee approval, and all patients had given signed informed consent. The only patients specifically excluded from the study were patients with valve prostheses; those with aortic valve disease, in whom passage of the study catheter across a diseased valve could have been hazardous; and those with mitral regurgitation, because this would have prejudiced the isovolumic contraction period. Apart from these exclusions, we studied unselected patients entering the catheter laboratory who had atrial fibrillation with clinical features summarized in Table 1.

Protocol

Patients fasted on the day of the procedure, omitting regular medication. There was therefore a minimum period of 12 hours since the last dose of any drug and >24 hours for once-daily drugs. This allowed half-decay of concentration of those drugs affecting myocardial contractility, the slowest decay being of once-daily digoxin. Patients received 10 mg temazepam 1 hour before the study or no premedication. A 7F conductance catheter was used, with a 2.5F micromanometer inserted through the central lumen. The catheter was introduced into the left ventricle from the right femoral artery under fluoroscopy and was positioned so that the distal electrode was in the apex of the left ventricle and the proximal electrode at the aortic valve orifice; this gave simultaneous recordings of left ventricular pressure and volume. These signals, together with the ECG, were recorded during quiet respiration onto a personal computer and displayed continuously as functions of each other to give pressure-volume cycles. After the correct phase relations of all segmental volumes were ensured, data were collected and total volume was derived from the sum of segmental volumes. The micromanometer was zeroed to atmospheric pressure at midchest level and calibrated against a standard signal from an amplifier.

Conductance-derived ventricular volume was related to true left ventricular volume measured in 2 different ways: (1) in the atrial fibrillation patients by cineangiography (with measured magnification factors permitting calculation of left ventricular volume by the method of Dodge et al\textsuperscript{20}) and (2) in the control patients by comparing conductance stroke volumes with thermodilution-derived stroke volumes. Although the use of 2 different methods for estimating absolute ventricular volume may create a systematic error between the 2 patient groups, this study is concerned primarily with beat-to-beat variations in volume within individual patients, thus making this potential error irrelevant.

Data Acquisition and Analysis

The conductance-derived volume signal was generated and processed by a Sigma 5DF signal conditioning and processing unit (Leycom) using a value of blood resistivity determined immediately before each data acquisition. It was transferred directly into custom software in a dedicated microcomputer through a 12-bit, 16-channel analog-to-digital (A/D) converter (DT 282 Data Translation). Segmental volumes were checked for phase relation to simultaneous pressure and intracavity ECG signals and centered in the A/D ranges.

TABLE 1. Patient Details

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age, y</th>
<th>Diagnosis</th>
<th>Drugs Used</th>
<th>LVEDD, cm</th>
<th>CAD, n</th>
<th>LVEDP, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>M</td>
<td>66</td>
<td>IHD</td>
<td>As, Ca, β</td>
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<td>9.4</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>61</td>
<td>IHD</td>
<td>As, β, ISMN</td>
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<td>14.5</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>60</td>
<td>IHD</td>
<td>As, Ca</td>
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<td></td>
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<tr>
<td>4</td>
<td>M</td>
<td>50</td>
<td>IHD</td>
<td>As, ISMN</td>
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<td>14.2</td>
<td></td>
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<tr>
<td>AF patients</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>M</td>
<td>60</td>
<td>DC</td>
<td>W</td>
<td>5.4</td>
<td>N</td>
<td>4.6</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>57</td>
<td>PC</td>
<td>W, D, As</td>
<td>5.7</td>
<td>N</td>
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</tr>
<tr>
<td>3</td>
<td>M</td>
<td>67</td>
<td>IHD</td>
<td>β</td>
<td>4.4</td>
<td>1</td>
<td>5.1</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>65</td>
<td>DC</td>
<td>W, D, A, β</td>
<td>6.1</td>
<td>N</td>
<td>20.9</td>
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<tr>
<td>5</td>
<td>M</td>
<td>63</td>
<td>DC</td>
<td>W, D, A, D*</td>
<td>7.3</td>
<td>N</td>
<td>12.3</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>71</td>
<td>IHD</td>
<td>A, ISMN, D*</td>
<td>ND</td>
<td>3</td>
<td>12.5</td>
</tr>
</tbody>
</table>

LVEDD indicates left ventricular end-diastolic dimensions as measured by routine transthoracic echocardiography (not performed in the surgical patients); CAD, number of coronary arteries with critical stenoses (>50%, N—all coronary arteries normal); LVEDP, left ventricular end-diastolic pressure; HD, ischemic heart disease; DC, dilated cardiomyopathy; PC, previous thoracotomy for lung disease; As, aspirin; Ca, calcium antagonist; β, β-adrenergic receptor antagonist; ISMN, isosorbide mononitrate; W, warfarin; D, digoxin; A, ACE inhibitor; D*, diuretics; ND, not measured.
Conductance-derived volumes were displayed and recorded and were later corrected to true volumes by off-line computer, in accordance with the procedures described in the previous section. The pressure signal was imported directly into the same software as the volume signal and displayed and recorded in real time.

End systole was defined as the time at which the ratio of pressure to volume was maximal; pressure and volume at this time were added, for each beat, into a Microsoft Excel file as end-systolic pressure and volume. Other variables determined and entered into the Excel file were heart rate, end-diastolic volume, stroke volume, and maximum rate of rise of left ventricular pressure (LV dP/dt max).

The relationships between end-systolic pressure and volume were determined by linear regression and by Spearman rank correlation by use of InStat (Graph Pad Inc). The latter was done in anticipation that some data sets might be nonlinear. Linear regression and Spearman rank correlation were also carried out between (dependent variable first) (1) end-systolic volume and preceding R-R interval, (2) end-systolic volume and prepreceding R-R interval, (3) LV dP/dt max and preceding R-R interval, and (4) LV dP/dt max and prepreceding R-R interval.

Control Studies
To ensure that the previously described unique positive pressure-volume relationship was obtained in our hands with the above methods, we subjected to similar analysis pressure-volume data from patients in sinus rhythm undergoing cardiothoracic operations for coronary artery bypass graft surgery. Pressure-volume curves were performed in these surgical patients as part of a separate study to examine the effects of l-arginine on postoperative left ventricular performance. The data given are baseline data from patients before any intervention or l-arginine administration. We present these data only to demonstrate that, in our hands, the end-systolic pressure-volume curve is the same as published by others. Left ventricular volume changes were achieved by variation in the venous return by means of vena caval slings. These patients are described in Table 1.

Results
Satisfactory pressure-volume loops were recorded in 6 atrial fibrillation patients and 4 control patients. A typical sequence of beats, showing the great variability of volume and pressure with R-R interval change from beat to beat, is shown in Figure 1B and compared with sinus rhythm in Figure 1A.

Typical data sets for a control patient and an atrial fibrillation patient are shown in Figure 2A and 2B. All results...
for end-systolic pressure-volume relationships are summarized in Table 2. In the control patients, these 2 variables were extremely tightly and positively correlated in accordance with previous reports; this indicates that our standard pressure-volume methodology yields the same result in sinus rhythm that was previously established.21–23 The correlations between end-systolic volume and pressure in atrial fibrillation were either statistically nonsignificant or significantly negative. This means that during atrial fibrillation, the end-systolic pressure-volume points are jumping from beat to beat from one positive pressure-volume relation to another, ie, each beat has a different contractility. The results in all patients are consistent with this behavior.

We reasoned that arterial pressure with its baroreceptor control was achieving a measure of end-systolic pressure clamp and that the contractility changes were manifest primarily as end-systolic volume variation. We therefore used end-systolic volume as a negative index of contractility for beat-to-beat analysis.

The variation in end-systolic volume showed statistically significant negative relations with the preceding interval (Figure 3, Table 3), ie, the longer the preceding interval, the more the left ventricle emptied. As expected, there was some scatter that precluded distinction in most cases between linear and nonlinear relationships (Table 3); the scatter is due to the other force-interval effects (see introduction) but did not obscure the presence of an end-systolic volume/preceding interval relationship. The data in Figure 3 are fitted by a 2-phase exponential decay curve fit (Prism, Graph Pad Inc), in line with mechanical restitution in isolated cardiac muscle preparations.12,14,24,25

The variation in end-systolic volume also showed statistically significant positive relations with prepreceding interval (Figure 4, Table 3); ie, the shorter the interval before the preceding interval, the more the left ventricle emptied. The effect of scatter due to other force-interval effects was similar to that for mechanical restitution (Table 3). The data in Figure 4 are fitted by a single exponential association curve fit (Prism, Graph Pad Inc) in accordance with previous data on interval dependence of postextrasystolic potentiation.13,26

The presence of positive relationships between LV dP/dt max and preceding R-R interval were shown by significant positive correlations (Figure 5, Table 4); this confirms previous findings, but our data showed more scatter due to the absence of “gating.”27 a process by which data with short prepreceding intervals are excluded. The increase in LV dP/dt max with preceding interval was associated with increasing end-dia-

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**Figure 3.** Relationship, during atrial fibrillation, between end-systolic volume and preceding R-R interval. As preceding interval gets longer, left ventricle empties more.
stolic volume; the result therefore does not confirm the presence of mechanical restitution. The presence of negative relationships between LV dP/dt max and prepreceding interval (Figure 6, Table 4) confirms previous findings.6 In this case, LV dP/dt max is not associated with end-diastolic volume, so that the result does indicate the presence of postextrasystolic potentiation.

Discussion

The results of this study disprove the hypothesis that the beat-to-beat changes in hemodynamics during atrial fibrillation are entirely due to changes in left ventricular filling, because this hypothesis would require myocardial contractility to be constant, ie, end-systolic pressure and volume would lie along a single positive relationship. This is clearly not the case (Figures 1 and 2; Table 2).

It was not our intention to use the data from the control patients for comparison but rather simply to show that the same research team performing the atrial fibrillation study, with the same apparatus, could reproduce the type of results frequently confirmed in the literature (Figure 1A). Indeed, these patients could not be compared with the atrial fibrillation patients, because the former had normal contractile function and were studied below the physiological range of volume, resulting in good tracings (Figure 1A). By contrast, the atrial fibrillation patients had variably poor left ventricular function and were studied over a much larger range of volumes, leading to less stable loops and evidence of incoordinate contraction during the isovolumic contraction and relaxation periods (Figure 1B).

The conclusion that contractility is not constant from beat to beat might be expected, in view of earlier findings that postextrasystolic potentiation occurs during atrial fibrillation.6 However, we have also shown that as the preceding interval gets longer, the left ventricle empties more (Figure 3, Table 3). The main determinant of end-systolic volume is the end-systolic pressure, ie, a decrease in end-systolic pressure causes a decrease in end-systolic volume. In the case of the relationships explored in our atrial fibrillation patients, however, as the preceding interval gets longer, the end-systolic

![Figure 4](image-url)  Relationship, during atrial fibrillation, between end-systolic volume and interval before preceding interval. As prepreceding interval gets shorter, left ventricle empties more.

![Figure 5](image-url)  Relationship, during atrial fibrillation, between maximum rate of rise of left ventricular pressure (LV dP/dt max) and preceding R-R interval.

TABLE 3. Statistical Results

<table>
<thead>
<tr>
<th>Patient</th>
<th>1 (n=32)</th>
<th>2 (n=16)</th>
<th>3 (n=39)</th>
<th>4 (n=44)</th>
<th>5 (n=27)</th>
<th>6 (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESV vs previous R-R, ie, is mechanical restitution present?</td>
<td>Slope $\leq 0.05$ or $P_{(r)} &lt; 0.05$ = yes.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slope</td>
<td>$-4.6513$</td>
<td>$-33.045$</td>
<td>$-12.823$</td>
<td>$-5.6295$</td>
<td>$-46.895$</td>
<td>$-35.606$</td>
</tr>
<tr>
<td>$P_{(slope)}$</td>
<td>$0.1243$</td>
<td>$0.0153$</td>
<td>$0.0030$</td>
<td>$0.0570$</td>
<td>$0.0003$</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>$r$</td>
<td>$-0.2352$</td>
<td>$0.4536$</td>
<td>$-0.4801$</td>
<td>$-0.3034$</td>
<td>$-0.6627$</td>
<td>$-0.8190$</td>
</tr>
<tr>
<td>$r^2$</td>
<td>$0.0553$</td>
<td>$0.2057$</td>
<td>$0.2305$</td>
<td>$0.0920$</td>
<td>$0.4392$</td>
<td>$0.6708$</td>
</tr>
<tr>
<td>$r_s$</td>
<td>$-0.3179$</td>
<td>$-0.6348$</td>
<td>$-0.4787$</td>
<td>$-0.3005$</td>
<td>$-0.5780$</td>
<td>$-0.6763$</td>
</tr>
<tr>
<td>$P_{(r_s)}$</td>
<td>$0.0355$</td>
<td>$0.0004$</td>
<td>$0.0031$</td>
<td>$0.0595$</td>
<td>$0.0025$</td>
<td>$0.0021$</td>
</tr>
</tbody>
</table>

ESV vs preceeding R-R, ie, is postextrasystolic potential present? Slope $+ ve$, $P_{(slope)} < 0.05$ or $r_s + ve$, $P_{(r_s)} < 0.05 =$ yes.

| Slope | $7.8931$ | $40.329$ | $12.352$ | $6.7404$ | $36.277$ | $34.791$ |
| $P_{(slope)}$ | $0.0041$ | $0.0049$ | $0.0092$ | $0.0345$ | $<0.0145$ | $0.0012$ |
| $r$ | $0.4390$ | $0.5657$ | $0.4467$ | $0.3533$ | $0.5026$ | $0.7345$ |
| $r^2$ | $0.1927$ | $0.3200$ | $0.1996$ | $0.1248$ | $0.2526$ | $0.5396$ |
| $r_s$ | $0.5844$ | $0.4635$ | $0.4971$ | $0.4101$ | $0.4943$ | $0.7270$ |
| $P_{(r_s)}$ | $<0.0001$ | $0.0259$ | $0.0001$ | $0.0130$ | $0.0165$ | $0.0014$ |

Slope, $P$, $r$, $r^2$ pertain to linear regression; $r_s$, Spearman correlation coefficient (nonparametric) and $n$, number of ESV/R-R data pairs entered into regression.
pressure remains more or less constant. We suggest that this is because it is determined by systolic arterial pressure and that this is determined, in turn, by baroreceptor and other reflexes that buffer arterial pressure and keep it more or less constant. We therefore suggest that the only way in which end-systolic volume could have got smaller as preceding interval increased is by leftward shifts of the end-systolic pressure-volume curve, ie, increasing myocardial contractility.21–23

If this argument is accepted, we can confirm that the result (Figure 3) indicated the presence of mechanical restitution during beat-to-beat changes in atrial fibrillation. This could not be definitively shown previously by use of LV dP/dt max (Figure 5),27 if one assumes that that index is sensitive to the accompanying changes in end-diastolic volume.

An even greater difficulty encountered in a previous study27 involved the attempt to claim that stroke volume was an important determinant of varying contractility. In view of the positive relationship between stroke volume and end-diastolic volume in our patients with atrial fibrillation, we would rather conclude that both mechanisms contribute to the beat-to-beat variations in stroke volume.

The findings of this study are entirely consistent with earlier animal models of atrial fibrillation in which the effects of interval and volume could be more easily separated, and preceding as well as prepreceding interval was shown to be an important determinant of varying contractile function.29–31 Edmands and colleagues32 induced experimental atrial fibrillation in dogs and related the rate of change of tension (from strain gauges stitched into the left ventricular free wall) to pulse pressure. They found that the inotropic variation correlated better with pulse pressure than did either end-diastolic pressure or filling time. More recently, using a computerized nuclear probe to assess relative change in ventricular volume during atrial fibrillation, Gosselink et al7 concluded that “the interval force relation explains the varying left ventricular performance during atrial fibrillation over the entire range of R-R intervals,” and that “the contribution of the Frank Starling mechanism to varying left ventricular performance during atrial fibrillation remains a matter of doubt and debate.” In view of the positive relationship between stroke volume and end-diastolic volume in our patients with atrial fibrillation, we would rather conclude that both mechanisms contribute to the beat-to-beat variations in stroke volume.

### TABLE 4. Statistical Results

<table>
<thead>
<tr>
<th>Patient</th>
<th>Slope (LV dP/dt max vs previous R-R)</th>
<th>Slope (LV dP/dt max vs prepreceding R-R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (n=44)</td>
<td>234.70</td>
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<tr>
<td>2 (n=29)</td>
<td>526.18</td>
<td>-470.79</td>
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<tr>
<td>3 (n=21)</td>
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<td>-574.91</td>
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<tr>
<td>4 (n=18)</td>
<td>836.91</td>
<td>-817.99</td>
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<tr>
<td>5 (n=27)</td>
<td>131.02</td>
<td>-287.88</td>
</tr>
<tr>
<td>6 (n=20)</td>
<td>224.83</td>
<td>-460.83</td>
</tr>
</tbody>
</table>

- Slope, $P$, and $r^2$ pertain to linear regression; $r_s$, Spearman correlation coefficient (nonparametric) and n, number of LV dP/dt max/R-R data pairs entered into regression.
Beat-to-Beat Contractility in Atrial Fibrillation

References

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