The Relationship Between the Strength of the Human Heart Beat and the Interval Between Beats


SUMMARY In 15 patients undergoing cardiac catheterization and pacing tests, the left ventricular (LV) pressure and its maximum rate of rise (LV dP/dt max) were measured with catheter-tip manometers. Atrial or ventricular pacing at a single steady frequency (the pacing frequency) was followed by a test pulse at a varying interval (test pulse interval). In 14 subjects in whom it was examined, the contractile response after the test pulse increased with test pulse interval to reach a maximum plateau value — the optimum contractile response (OCR). In five cases, further prolongation of the test pulse interval decreased the contractile response. The optimum test pulse interval occurred at 800–900 msec. An increase in the pacing frequency before the introduction of the test pulse caused a progressive increase in OCR, in contrast to the minor effects on LV dP/dt max of the control beats. Similar results were recorded in four other patients in whom contractile response was assessed from the rate of rise of right ventricular pressure. These results indicate that with tachycardia, the interval between beats is insufficient to allow maximum contractile performance (presumed to be activated by calcium ions) to develop. The true effect of increasing heart rate is only revealed by the relationship between OCR and the preceding frequency of contraction.

RECENT STUDIES in isolated muscle and in intact animal hearts have given insight into the mechanisms relating contractile behavior, electrical events in the cell membrane and the interval between beats.1-8 These studies have demonstrated dependence of contractile force of a beat upon the interval preceding it and the force, action-potential duration, and timing of the beats leading up to that interval. These findings have been interpreted in terms of calcium fluxes into and within the cell. The concept has arisen of an intracellular calcium store whose contents are discharged to activate the contractile proteins on each depolarization. This store takes a finite time to refill, and thereafter loses calcium by leakage if depolarization is delayed; thus, an optimum interval between beats exists. The store is filled from two sources: calcium released from the contractile proteins on the previous beat and calcium entering the cell during the depolarization phase of previous action potentials. Thus, there is also dependence upon the force and frequency of preceding beats.

Interval-strength relationships in animal preparations can be explained by such a model, and we wished to establish whether it was also applicable in man. We therefore examined the relationship between an index of contractile force and beat-to-beat interval in conscious human subjects with and without coronary artery disease.

Methods

Patients

Each patient gave informed consent before the study, which had been approved by the Ethical Committee of the Brompton Hospital. Subjects were studied during the course of diagnostic cardiac catheterization, without premedication. We did not make the decision to perform cardiac catheterization. Clinical and catheterization findings for the patients in whom we studied mechanical performance of the left ventricle are listed in table 1. Eight of these (group A) had no significant hemodynamic abnormality; seven
TABLE 1. Clinical and Catheterization Findings

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Aortic pressure (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
<th>ECG</th>
<th>( \beta ) block used</th>
<th>( \text{LV} ) dP/dt max (mm Hg/sec)</th>
<th>EF (%)</th>
<th>CAD</th>
<th>LV angiogram</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>55</td>
<td>M</td>
<td>120/70</td>
<td>4.3</td>
<td>NAD</td>
<td>+</td>
<td>1725</td>
<td>73</td>
<td>None</td>
<td>Normal</td>
</tr>
<tr>
<td>2</td>
<td>59</td>
<td>M</td>
<td>140/80</td>
<td>–0.8</td>
<td>NAD</td>
<td>–</td>
<td>2390</td>
<td>79</td>
<td>None</td>
<td>Minor inferior dyskinesis</td>
</tr>
<tr>
<td>3</td>
<td>53</td>
<td>M</td>
<td>150/85</td>
<td>6.4</td>
<td>NAD</td>
<td>+ (1840)</td>
<td>1600</td>
<td>76</td>
<td>None</td>
<td>Normal</td>
</tr>
<tr>
<td>4</td>
<td>55</td>
<td>F</td>
<td>135/85</td>
<td>13.5</td>
<td>NAD</td>
<td>–</td>
<td>2800</td>
<td>90</td>
<td>None</td>
<td>Normal</td>
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<tr>
<td>5</td>
<td>40</td>
<td>F</td>
<td>145/90</td>
<td>13.0</td>
<td>NAD</td>
<td>–</td>
<td>2375</td>
<td>64</td>
<td>None</td>
<td>Abnormal anterolateral relaxation</td>
</tr>
<tr>
<td>6</td>
<td>55</td>
<td>M</td>
<td>110/55</td>
<td>8.6</td>
<td>NAD</td>
<td>–</td>
<td>1600</td>
<td></td>
<td>None</td>
<td>Normal</td>
</tr>
<tr>
<td>7*</td>
<td>38</td>
<td>M</td>
<td>125/70</td>
<td>10.4</td>
<td>1st-degree AV block</td>
<td>–</td>
<td>1250</td>
<td>80</td>
<td>–</td>
<td>Normal</td>
</tr>
<tr>
<td>8</td>
<td>46</td>
<td>F</td>
<td>150/80</td>
<td>3.7</td>
<td>NAD</td>
<td>–</td>
<td>2350</td>
<td>75</td>
<td>–</td>
<td>Normal</td>
</tr>
<tr>
<td>Mean (n = 8)</td>
<td>48</td>
<td>135/77</td>
<td>7.4</td>
<td>2041</td>
<td>77</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group B</th>
</tr>
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<tbody>
<tr>
<td>9</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>11</td>
</tr>
<tr>
<td>12</td>
</tr>
<tr>
<td>13</td>
</tr>
<tr>
<td>14</td>
</tr>
<tr>
<td>15</td>
</tr>
<tr>
<td>Mean (n = 7)</td>
</tr>
</tbody>
</table>

*Patient 7 was paced from the right ventricle; all other patients were paced from the right atrium.

Abbreviations: LVEDP = left ventricular end-diastolic pressure; AV = atrioventricular; NAD = nothing abnormal detected; RBBB = right bundle branch block; LVH = LV hypertrophy; EF = ejection fraction; CAD = coronary artery disease.

(group B) had coronary artery disease (more than 50% stenosis of one or more coronary arteries). We carried out four right ventricular (RV) studies, two in patients with no hemodynamic abnormality and two in patients with coronary artery disease. Seven other studies were abandoned, five because the catheter-tip manometer could not be positioned in the left ventricle and two because of transient rhythm disturbances during the pacing procedures. There were no other complications of the procedure.

Two of the subjects with normal findings and five with coronary artery disease were taking \( \beta \)-adrenergic blocking drugs at the time of the study.

Procedures

A catheter-tip manometer was passed into the left ventricle through either the right femoral or right brachial artery in 15 patients. In four patients, a catheter-tip manometer was advanced through a right antecubital vein to the right ventricle. A stable position was sought in which no ectopic activity was induced. Pacing was performed with a bipolar electrode, introduced through an antecubital vein or the right femoral vein, and was positioned with its tip on the lateral wall of the right atrium, or in one case, at the apex of the right ventricle. Pacing was performed with a 2-msec square-wave stimulus of 3 V.

Equipment and Measurements

Left ventricular (LV) or RV pressure was measured with Gaeltec catheter-tip manometers. We confirmed that their resonant frequency was greater than 500 Hz. After stabilization in water at constant temperature, gain and baseline drift were less than 0.5% for as long as 6 hours, and the output was linear with pressure up to 300 mm Hg. The manometer bridge was activated by either a Devices 2190 carrier amplifier or a Gaeltec S7A transducer control unit. Pressure signals were amplified and recorded at low gain for peak systolic pressure and high gain for right and left ventricular end-diastolic pressures (RVEDP or LVEDP).

The pressure signal was differentiated electronically to obtain the rate of change of right and left ventric-
ular pressure (RV or LV dP/dt) using a Gaeltec STA unit or a purpose-built differentiator. Both of these had output and phase-lag linearly related to frequency up to 200 Hz.

These signals and the surface ECG (standard lead II) were recorded with a Micromovements M10-120A light-beam oscillograph recorder, and on magnetic tape (Racal Store 4 instrumentation recorder). The light-beam recorder had a frequency response flat ± 5% to 200 Hz. For pacing, a Devices 2533 isolated stimulator was used in conjunction with a Digitimer 4030 pulse generator.

The catheter-tip manometers were calibrated hydraulically (after several minutes of immersion in water) at room temperature at the end of each experiment. To correct for temperature drift of the manometer, atmospheric pressure was also recorded when the catheter was removed from the body (at body temperature). 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. Time intervals between beats were measured from the commencement of the inscription of the R wave of the ECG tracing.

Coronary arteriograms and LV angiograms were analyzed by two experienced observers. Ejection fraction was measured by the method of Chatterjee et al. 6

All experimental recordings were made at relaxed end-expiration.

Protocols

Mechanical Response to Varying Test Pulse Intervals (fig. 1)

Stimuli were applied at a regular, predetermined rate (1.4 or 2 Hz), chosen to exceed the sinus rate of the patient, until a steady state of pressure and LV dP/dt max was achieved (the priming period). A test stimulus was then applied at another predetermined interval after the last stimulus of the priming period. Each test pulse interval (TP) was examined twice to yield results in duplicate. The procedure was then repeated with the same priming frequency but a different TP. Thus, a series of intervals was examined, the shortest determined by the refractory period of the atrioventricular node and the longest by the spontaneous heart rate of the subject. The mechanical response (i.e., LVEDP and LV dP/dt max) during the priming period and of the contraction resulting from the test pulse were recorded and measured. In two patients with normal hemodynamics, the whole protocol was repeated with a different priming frequency. In one of these subjects, the protocol at a single priming frequency was done a third time with the catheter-tip manometer in the ascending aorta.

Mechanical Response to Changes in Priming Frequency (fig. 1B)

From the above experimental procedure, an interval could be selected that produced the greatest LV dP/dt max — the optimum TP (OTPI). The effect of a number of different frequencies upon the contraction occurring after the OTPI was examined. Again, at each priming frequency, a steady state was achieved (six to 10 contractions) and then a test stimulus was applied at OTPI, the mechanical response of which was examined. The lowest priming frequency used was dictated by the spontaneous heart rate, and the highest frequency was 2.5 or 3 Hz.

Leg Raising Maneuver

To examine the influence of LVEDP on LV dP/dt max, the LVEDP was varied transiently by passive elevation of the subject’s legs to about 80°. This maneuver was performed with pacing to keep heart rate constant, and recordings were made of LVEDP and LV dp/dt max before and immediately after elevation of the legs.

Results

The results were similar in the subjects with normal hearts and in the patients with coronary artery disease. The results from the two groups have therefore

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**Figure 1.** Pacing protocols. (A) Protocol for examining the mechanical response to varying test pulse intervals. The a is the interval of the priming period. The b is the test pulse interval. TP is the test stimulus. (B) Protocol for examining the influence of priming frequency upon optimum contractile response. The a, a', a'' are the beat-to-beat intervals of the priming frequencies. The b is the optimum test pulse interval.
been pooled. A typical series of experimental records is shown in figure 2.

Mechanical Response to Varying Test Pulse Intervals

The test contractile response was normalized by taking the ratio of LV dP/dt max of the test pulse to LV dP/dt max during the priming period. This ratio was plotted against the TPI. A typical result is shown in figure 3. All TPI curves demonstrated an ascending limb, i.e., the contractile response rose with increasing TPI to a maximum. In five cases, further prolongation of TPI produced a fall in contractile response (descending limb of the curve), so that an interval at which the contractile response was maximal could be identified (OTPI). In 10 subjects, the longest TPI that could be studied was 1000 msec, so information concerning the descending limb was scanty. From the curves that did not demonstrate a descending limb, OTPI was taken as the shortest interval at which the maximum value of LV dP/dt max was reached. The mean value for OTPI determined in 14 subjects in whom a complete study was performed was 810 msec. In neither of the two subjects in whom TPI curves were measured at two priming frequencies was there any change in OTPI with priming frequency. Furthermore, OTPI did not differ significantly between subjects in whom this protocol was performed at 1.4 Hz (825 ± 10 msec) (+ SEM) and at 2.0 Hz (807 ± 13 msec).

Influence of Frequency on Steady-state
LV dP/dt max and OCR

The mechanical response (LV dP/dt max) at the OTPI or at the plateau of the TPI curve is termed the optimum contractile response (OCR). The OCR at each of three priming frequencies was determined in five normal subjects and four patients with coronary artery disease. The results were the same in both groups (figs. 4 and 5). The steady-state LV dP/dt max showed a slight rise with increasing priming frequen-

Figure 2. (A) Original record of a single pacing sequence from the protocol shown in figure 1A. Priming frequency is 2 Hz; test pulse interval is 900 msec. (B) The dP/dt signals during three pacing sequences from protocol shown in figure 1B. Note progressive increase in contractile response at optimum interval (last contraction in each sequence) with increasing priming frequency. LVEDP = left ventricular end-diastolic pressure; LVP = LV pressure.

Figure 3. Mechanical response to varying test pulse intervals from a patient with normal cardiac function paced at a priming frequency of 2 Hz. The mechanical response to the test stimulus is expressed as the ratio left ventricular (LV) dP/dt max of the test contraction (TP) to that of the preceding priming beats (SS).
dP/dt max increased in eight and decreased in five. The mean change was a rise of 0.24% (NS) per mm Hg increase in LVEDP (fig. 6).

In the four right-heart studies, RVEDP increased significantly in two patients. In one of them, RV dP/dt max did not change and in the other it fell 4%.

Discussion

This study shows that in man, as in intact dogs, the conventional relationship between steady-state contractile performance and heart rate is flat with only slight upward (positive staircase) or downward (negative staircase) trends. However, if a test beat after an interval of 800–900 msec is used to assess contractile performance, the results demonstrate a progressive increase with increasing heart rate (figs. 4 and 5). Thus, at least for contractions at this optimum interval, tachycardia actually augments contractile potential.

The choice of dP/dt max as an index of contractility was difficult because all such indexes have limitations. These were analyzed in detail by Van den Bos et al., LV dP/dt max is theoretically preferred and the simplest, provided catheter-tip manometers are used to measure the primary LV signal. Nevertheless, LV dP/dt max can depend on heart size, and this may vary when beat interval is changing. We therefore examined the dependence of dP/dt max on heart size in each experiment by passive leg raising. The leg-raising maneuver, performed at constant frequency of stimulation, significantly increased LVEDP in almost all patients, and has been shown to produce an increase in LV end-diastolic diameter. LV dP/dt max changed little (table 2). Furthermore, the pattern of force-frequency behavior we describe appeared...

**Beta-adrenergic Antagonist Therapy**

Patients receiving β-adrenergic blocking drugs responded to these studies in the same manner as untreated patients.

**Right-heart Studies**

Right-heart catheterizations were undertaken in four patients, two with coronary artery disease and two normal. With the catheter in the right ventricle, the RV dP/dt max was measured. Otherwise, the protocol was the same as that for the left-heart studies. The values of RV dP/dt max under steady-state conditions demonstrated considerably more scatter than those for LV dP/dt max under analogous conditions. The results for both the test pulse mechanical response and the frequency dependence of the steady-state contractile response and OCR were qualitatively similar to results in left-heart studies, but the scatter of the experimental data precludes definitive interpretation.

**Leg-raising Maneuver**

Every patient performed a leg-raising maneuver. The results are given in table 2. During left-heart studies, LVEDP increased significantly (Wilcoxon rank-sum analysis) in all but two patients, while LV
qualitatively similar whether LV dP/dt max showed a minor increase or decrease with an increase in LVEDP. The changes in LVEDP occurring during the pacing protocols were in a similar range to those studied in the leg-raising maneuver, and LV dP/dt max is undoubtedly sensitive to inotropic intervention while being relatively insensitive to LV volume changes. When the relationship between OCR and priming frequency was explored (fig. 1B), LVEDP preceding the test beats was constant because the OTPI was constant. For the same reason, we would not anticipate changes in aortic end-diastolic pressure during this protocol. Aortic end-diastolic pressure would be expected to change during the protocols shown in figure 1A. However, dP/dt max would not be influenced by this as long as it remained an isovolumic event,7 which was the case when this protocol was used in dogs.4 We could not measure LV and aortic pressure simultaneously. In one normal subject, we repeated the protocol shown in figure 1A with the catheter-tip manometer in the ascending aorta. By measuring the time from initial QRS deflection to LV dP/dt max, and to the initial upstroke of the aortic pressure at end-diastole, we confirmed that at every TPI, dP/dt max preceded aortic valve opening. This patient had an atroventricular conduction defect, and we obtained TPIs up to 1300 msec. This was longer than any other interval examined during this study. We therefore believe that under the circumstances of our study, LV dP/dt max was an isovolumic event, and that the changes we have documented in LV dP/dt max do represent changes in contractility.

We do not believe that our results were influenced by changes in autonomic tone. There was no difference in response between patients taking and those not taking β-adrenergic antagonists. Changes in priming frequency were not always made in the same order, but our results were consistent. Also, the rise in OCR always occurred within a few beats after the priming frequency was increased.

We performed studies with the pressure catheter in the right ventricle in the hope that we might not need to catheterize the left ventricle. However, the RV dP/dt signals were distorted by irregular high-frequency spikes, which we think were due to mechanical instability of the catheter tip. The scatter introduced into the results rendered the right-heart studies impractical.

Our results accord with observations during the same sequences of pacing in isolated rabbit cardiac muscle in which isometric peak tension was measured at constant presystolic length.14 We have already extended these studies to anesthetized dogs,4 where we found behavior similar to that in isolated muscle.

The behavior we describe in this report has been demonstrated in part in humans. Anderson et al.10 reported an increase in contractility as TPI was increased from the shortest interval possible; but it is not clear that they explored intervals longer than the priming interval (450 or 600 msec), and they did not describe a descending limb in the normal heart. The slight rise in LV dP/dt max under steady-state conditions with increasing frequency has been noted in isolated hearts, in intact anesthetized and conscious animals and in man.15–18 This slight increase contrasts with the progressive increase in OCR with increasing frequency found in this study (figs. 4 and 5), in isolated cardiac muscle and in the anesthetized dog.

One can interpret these results, in terms of the possible underlying mechanisms at a cellular level, by postulating a two-compartment calcium model.2 Calcium taken up from the contractile proteins during relaxation enters the first (uptake) compartment. The OTPI is then the interval required for the maximal transfer of calcium ions from the first compart-
ment to the second (release) compartment. The force of the next contraction is dependent upon the content of calcium in the second compartment, which is released by the next action potential to activate the contractile apparatus. The decline in contractility with TPIs longer than the optimum can be attributed to a slow loss of calcium from the release compartment.

When increased frequency shortens the interval between beats to less than the OTPI, transfer of calcium to the releasable store is curtailed, and contractile response reflects this in the steady state. However, OCR increases, indicating an overall increase in intracellular calcium available to the contractile apparatus. We propose that this builds up after an increase in frequency due to a transient excess of calcium entry over efflux from the system.

We have described force-frequency behavior in normal hearts and shown that in subjects with coronary artery disease but normal or only mildly abnormal LV function, qualitatively similar behavior is maintained. In that the relationships described in this paper may indirectly reflect some features of excitation-contraction coupling and calcium handling by the cell (i.e., explore intrinsic cellular contractile function), these analyses may be useful in evaluating subjects with more severe heart muscle disease.

References
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