In-Vitro Studies of Myocardial Asynchrony and Regional Hypoxia

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ABSTRACT
Ten pairs of cat papillary muscles were arranged in tandem to study their individual and combined length-tension and force-velocity relationships. Physiologic asynchronous contraction (up to 60 msec) of the pair of muscles produced a change in the individual force-velocity relations of each muscle which was characteristic of a change in muscle length; i.e., there was an alteration of tension developed without a change in the maximum measured velocity of shortening. On the ascending limb of the length-active tension curve, asynchronous stimulation (average time interval 32 msec) increased the force developed (5.3 ± 1.4%) by the tandem pair, as compared to synchronous stimulation.

When one muscle was made hypoxic for 20 minutes, its force development was reduced by 64 ± 3%, and paradoxical motion occurred. After 2 minutes of reoxygenation, the time to peak tension was slightly prolonged, while the time for isometric tension to relax to one-half its peak value was increased to 234 ± 27% of control. During this period the contraction pattern of the tandem pair was out of phase (asynergic), even though they were stimulated synchronously. Thus transient asynergy associated with regional myocardial ischemia may be explained in part by these observed alterations in the time course of contraction and relaxation.

ADDITIONAL KEY WORDS
relaxation force-velocity relation cat papillary muscle isometric length-tension relation paradoxical motion asynergy

Localized abnormalities of contraction of the ventricular wall may importantly influence overall myocardial function although the remainder of the heart may not be primarily impaired (1, 2). Thus, in acute and chronic coronary heart disease, localized areas of the ventricular wall with inadequate coronary perfusion may contract poorly (hypokinesia), fail to contract (akinesia), or may even expand during the course of systole (dyskinesia) (1). Furthermore, different areas of the ventricular wall may contract out of phase with one another (asynergy).

However, the detailed function of these localized areas of abnormally contracting myocardium has not been defined. Aside from assuming that localized ischemic areas of the myocardium do not generate normal forces, there is no information to explain gross asynchrony of the ventricle. Some degree of delay of electrical activation has been noted in the normal heart (3-5), and abnormalities of conduction and electrical activation in the abnormal heart might augment this "physiologic asynchrony." However, abnormalities of conduction and delays in myocardial activation are not uniformly noted in coronary disease. These small differences in activation time thus cannot explain significant asynchrony of ventricular contraction as a whole.

To study the direct effect of asynchrony on cardiac muscle and, further, to assess the interactions of normal and hypoxic muscle, a preparation was devised for studying two cat
right ventricular muscles arranged in series. These studies have shown that asynchrony of contraction may result not only from depression of force development in one muscle relative to another but from variations in the duration of muscular contraction (active state) which occur consequent to both the development of, and the recovery from, hypoxia.

**Methods**

A pair of papillary muscles, removed from right ventricles of cats anesthetized with intraperitoneal sodium pentobarbital (40 mg/kg), were placed in separate muscle baths containing Krebs bicarbonate solution which was maintained at a constant temperature of 29°C and aerated with 95% O₂-5% CO₂. One end of each muscle was held firmly in a spring-loaded lucite clip which formed a rigid extension of a tension transducer (Statham G1-4-250). The other end of each muscle was attached to the tip of a separate isotonic lever system (equivalent mass 100 mg each). Each muscle was stimulated by direct-current electrical pulses of 5 msec duration and a voltage of 10% above threshold, at a frequency of 12/min, delivered through platinum mass electrodes placed parallel to the muscle. Tension, extent and velocity of shortening of the muscle, and a stimulus artifact were recorded together on a multichannel oscillograph (Hewlett-Packard 8858). The isotonic lever systems have been previously described (6). Instantaneous velocity of shortening was obtained by electrical differentiation (Electronic Gear UD 20) of each shortening trace. The maximum rate of tension development (dP/dt) was measured from the tension trace. Following a 1- to 2-hour period of equilibration, passive and active length-tension curves were obtained for each muscle by progressively increasing the length of the isometrically contracting muscle in 0.1-mm increments, beginning from zero resting tension and continuing until developed tension was maximal. At the muscle length at which developed tension was maximal (Lmax), paired stimuli were applied to both muscles together and that it recorded the relative motion of the point between the muscles. The preload of the two muscles in series was added to the other end of lever 2 above the top muscle. After placing a stop (2B), just above the tip of lever 2, any additional load added to this lever would be encountered only when muscle contraction ensued and would thus become afterload. Two stimulators were connected so that the muscles could be stimulated either synchronously or with any desired time interval between the stimuli. Force-velocity relations of the two muscles arranged in series were obtained under both synchronous and asynchronous conditions by measuring the peak velocity of isotonic shortening as afterload was progressively increased. Peak velocity of shortening of the sum of both muscles was obtained from lever 2, and the peak velocity of the upper muscle was obtained by subtracting that of the lower muscle. The passive and active length-tension relations of the combination were obtained as previously described for the individual muscles by sequential increases in the isometric length of the synchronously contracting combination. At the top of the length-active tension curve, paired stimuli were applied to both muscles together and
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each muscle alone. The effects of asynchronous stimulation, with the time interval between stimuli increased from 0 to 200 msec in 10- to 20-msec increments, were examined both at the top of the length-active tension curve and 25% to 50% below the apex of the curve.

As a model of regional ischemia, the lower muscle was made hypoxic by bubbling 95% N₂-5% CO₂ through its bath (Po₂ about 10 mm Hg). The isometric tension developed by the combination and the relative movement of lever 1 between the muscles were recorded. Intermittently, the tension developed by the lower muscle alone was determined by fixing the middle lever with stops 1A and 1B (Fig. 1). Thus the isometric tension developed by the hypoxic muscle only could also be recorded at specified intervals. After hypoxic periods of 20 to 30 minutes, the lower muscle was reoxygenated with 95% O₂-5% CO₂ and further measurements were obtained during the subsequent 1- to 2-hour period of recovery.

Data are given as means ± standard error.

Results

LENGTH-TENSION RELATIONS

Length-tension relations of the resting and activated muscle were obtained for each muscle separately and for each pair of muscles arranged in series. In Figure 2, the passive and active length-tension curves from a representative pair of muscles have been illustrated. Muscle I was thinner than muscle II and thus developed only about half as much tension at the apex of the length-active tension curve (L_max), at a resting tension only half as great as that of muscle II. Note also that the pair of muscles in series developed only slightly less tension than muscle II alone. When the pair of muscles was stimulated simultaneously, the relative movement of the lever between them (Fig. 1, lever 1) depended on the position of each on the length-tension curve. For example, at zero resting tension (Fig. 2), muscle I developed 3.5 g, and thus stretched muscle II, which could develop only 2.0 g. At a resting tension of 0.4 g, both muscles developed 4.5 g, so that there was no movement of the lever between them. However, the stronger muscle was only at the midportion of the ascending limb of the length-tension curve and the weaker muscle was at its apex. At resting tensions greater than 0.4 g, muscle II developed more tension than muscle I and thus stretched it during contraction. Thus at higher preloads the stronger muscle dominated the performance of the two together. Near the apex of the active length-tension curve the relative movement of the lever between the muscles was minimal, despite the greater tension development of the larger muscle. However, when the weaker muscle was not stimulated, it was stretched 5.4 ± 0.4% (n = 10) by the activated stronger muscle while tension fell 19.0 ± 3.4% (n = 10). Some pairs of muscles were more evenly matched in terms of cross-sectional area and developed tension, so that the tension developed by the two in series tended to be an average of the tension developed by the individual muscles. The average tension developed by the stronger muscles was 7.95 ± 1.16 g and by the weaker muscles, 5.05 ± 1.31 g; the combination of the two
muscles in series developed 6.87 ± 0.65 g (n = 10).

When the muscles are arranged in series, the resting tension across each muscle is identical. Thus when the combination of muscles was at \( L_{\text{max}} \) (Fig. 2), muscle II was at the apex of its own length-tension curve and muscle I was elongated beyond \( L_{\text{max}} \), the apex of its length-active tension curve. However, since muscle I was then on a very stiff portion of its passive length-tension relation, it was minimally stretched by muscle II when both were stimulated. The resting tension at \( L_{\text{max}} \) for the stronger muscles averaged 2.61 ± 0.50 g, the weaker muscles, 0.81 ± 0.14 g, and the combination, 2.35 ± 0.28 g (n = 10).

**ASYNCHRONOUS STIMULATION**

1. **Tension Development.**—Following placement of the pair of muscles at the apex of its combined length-tension curve, the two muscles were first stimulated simultaneously and then asynchronously with the time interval between stimuli being increased in increments of 10 to 20 msec to a total separation of 200 msec. The order of stimulation of muscles was then reversed. The resting length and tension of the pair of muscles were then decreased so that developed tension fell by 25% to 50%, and the sequence of asynchronous stimulation was repeated. A representative experiment is illustrated in Figure 3, using the same pair of muscles as in Figure 2. The time to peak tension, the developed tension, and rate of tension development (dP/dt) are plotted as a function of the time interval of asynchrony, both when muscle I was stimulated first (○) and when muscle II was stimulated first (●).

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**FIGURE 3**

The effect of asynchronous stimulation on the isometric contraction of a representative pair of cat papillary muscles in series at the apex of the length-active tension curve (left) and on the ascending limb of the curve (right). Time to peak tension (TPT), developed tension, and rate of tension development (dP/dt) are plotted as a function of the time interval of asynchrony, both when muscle I was stimulated first (○), and when muscle II was stimulated first (●).
tension, and the rate of tension development (dP/dt) are plotted relative to the interval between stimuli. On the left in Figure 3, the muscles are at the apex of the length-tension curve, while on the right they are at the midportion of the ascending limb of the curve. At the top of the length-tension curve (left), the time to peak tension gradually increased as the degree of asynchrony increased. Developed tension was unchanged until the time interval between stimuli reached 40 msec, following which it slowly declined. The rate of isometric tension development (dP/dt) followed a similar pattern. However, at a resting tension of 0.8 g (right), there was an initial increase in the tension developed by the combination when muscle I, the weaker muscle, was stimulated first, reaching a peak increase in 30 to 60 msec. As before, time to peak tension was prolonged. These changes in tension development may be explained by the fact that muscle I, the weaker of the two, was very close to the apex of its length-tension curve (Fig. 2). When stimulated first, it stretched the stronger muscle (II) to a longer initial fiber length prior to its contraction, and thus produced an increase in the tension development of the combination. However, when muscle II was stimulated first, it stretched muscle I, which was already near Lmax so that the tension developed by muscle I could not be increased. With early activa-
tion, muscle II shortened down its own length-tension curve, and the tension developed by the pair declined (Fig. 3). The dP/dt changes in Figure 3 generally followed the changes in developed tension. At the top of the length-tension curve, potentiation of developed tension was not observed with asynchrony in any of the 10 pairs of muscle. However, along the ascending limb of the length-tension curve, asynchrony produced an increase in developed tension (5.3 ± 1.4%) similar to that in Figure 3, in 9 of 10 pairs, including pairs of muscles that were nearly evenly matched for force development. Such an increase in tension, however, was seen only when the weaker muscle was stimulated first and not in the reverse situation.

2. Force-Velocity Relations.—Force-velocity relations were obtained by measuring the peak velocity of shortening (electronically differentiated) for a series of isotonic contractions while afterload was sequentially increased from zero to isometric force development. The velocity of the lower muscle was measured directly by differentiation of the output of the length transducer associated with lever 1 (Fig. 1). The peak velocity of the combined muscles was similarly measured from the length transducer associated with lever 2 (Fig. 1). The peak velocity of the upper muscle was calculated as the difference between the peak velocities obtained from lever 2 and lever 1.

At each afterload, three isotonic contractions were obtained: one synchronous contraction and two asynchronous contractions with each muscle stimulated 40 to 60 msec before the other. With this minor degree of asynchrony, the plateau of peak velocity of levers 1 and 2 always overlapped so that the difference between them could be used as a measure of the peak velocity of the upper muscle.

A representative experiment is illustrated in Figure 4. Since three isotonic contractions were obtained at each afterload there are three separate force-velocity relations for muscle I, muscle II, and the pair of muscles. The peak velocities of shortening are shown for synchronous contraction when muscle I was stimulated first and when muscle II was stimulated first. When muscle I was stimulated first, at each afterload the peak velocity of muscle I was reduced and the peak velocity of muscle II was greater than that with synchronous stimulation. When muscle II was stimulated first, opposite effects occurred. The reason for these alterations in force-velocity relations is understandable in terms of the known effects of changes in preload and initial muscle length on force-velocity relations. With increasing preload there is little or no change in the maximum measured velocity of shortening despite an increase in the isometric tension developed (Po) (8). At any given afterload, however, the velocity of shortening is greater with the larger preload. Thus, in Figure 4, when muscle I was stimulated first, it stretched muscle II (increased the preload) and produced a greater peak velocity of shortening in muscle II. When muscle II was stimulated first, it stretched muscle I and effectively reduced its own preload by shortening during the isometric phase so that the peak velocity of shortening of muscle II during the isotonic phase was reduced. These predictable alterations in force-velocity relations produced by asynchrony were seen in all 10 pairs of muscles, regardless of their relative size or the amount of tension they developed.

PAIRED STIMULATION

Paired electrical stimulation (sustained postextrasystolic potentiation) was initiated with the muscles at the apex of the length-tension curve in each muscle alone and in the combination of muscles. The results are summarized in Table 1. The tension developed by the combination was intermediate between the stronger and weaker muscles for both single and paired stimulation. However, the time to peak tension of the combination was not decreased as much, nor the dP/dt increased as much, as for the individual muscles. This may reflect the slight mismatch between pairs of muscles in terms of the time to peak tension during single stimulation.

EFFECTS OF HYPOXIA

After control measurements of tension...
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TABLE 1

<table>
<thead>
<tr>
<th></th>
<th>Single stimulation</th>
<th>Paired stimulation</th>
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<tr>
<td></td>
<td>T (g)</td>
<td>TPT (msec)</td>
</tr>
<tr>
<td>Stronger muscles</td>
<td>8.9 ± 1.1</td>
<td>370 ± 19</td>
</tr>
<tr>
<td>Weaker muscles</td>
<td>6.1 ± 0.6</td>
<td>401 ± 17</td>
</tr>
<tr>
<td>Combination</td>
<td>7.9 ± 0.5</td>
<td>374 ± 18</td>
</tr>
</tbody>
</table>

|                         | T (g)              | TPT (msec)         | dP/dt (g/sec) |
| Stronger muscles        | 15.6 ± 1.3         | 296 ± 9            | 99.0 ± 13.0   |
| Weaker muscles          | 10.6 ± 0.8         | 291 ± 8            | 69.4 ± 5.5    |
| Combination             | 12.5 ± 0.6         | 327 ± 10           | 63.7 ± 7.0    |

T = tension; TPT = time to peak tension.

Effect of 30 minutes of hypoxia and subsequent reoxygenation on the isometric contractions of a representative cat papillary muscle (●), the combination of the hypoxic muscle (II) and a normally oxygenated muscle (I) in tandem (●), and the tandem pair when only the oxygenated muscle (I) was stimulated (○). Tension, rate of tension development (dP/dt), time to peak tension (TPT), and the time for isometric tension to decline to half its peak value (RT/2) are plotted as a function of time during both the hypoxic and recovery periods. The relative movement of lever I between the muscles is plotted in millimeters as an upward bar when muscle I shortened and as a downward bar when muscle II shortened. Biphasic or triphasic movement of lever I is appropriately plotted by two or three bars.

Development at the apex of the length-tension curve, muscle II was made hypoxic by aerating its bath with 95% N₂-5% CO₂. The duration of hypoxia was 20 minutes in three
muscles, 25 minutes in three, and 30 minutes in three. Since the results were essentially the same, independent of the hypoxic interval, data were grouped together for analysis.

The results from a representative experiment with 30 minutes of hypoxia are shown in Figure 5. Tension, dP/dt, time to peak tension, the relative motion of the lever between the muscles, and the time required for isometric tension to fall to one-half its peak value (7) during relaxation have been plotted. The results for both muscles in tandem, the nonhypoxic muscle contracting against the unstimulated hypoxic muscle, and the hypoxic muscle alone are shown.

During the 30-minutes of hypoxia there was a reduction in the isometric tension developed by the hypoxic muscle (II) alone from 9.4 to 3.5 g, although the tension developed by the pair of muscles fell only from 7.2 to 4.8 g. The maximum dP/dt as well as the time to peak tension decreased during the period of hypoxia. Note that when the hypoxic muscle was unstimulated and thus functioned as an added passive series elastic element for muscle I, the tension developed remained constant during hypoxia. If contracture had developed in the hypoxic muscle, its passive length-tension relations would have become stiffer, and the tension developed during the hypoxic interval when only muscle I was stimulated would have increased. Since this tension remained constant, the passive length-tension relations of the hypoxic muscle were not grossly altered.

The relative motion of the lever between the muscles changed from biphasic during the control period, when the primary motion was a shortening of the stronger muscle II, to triphasic during hypoxia, with shortening of muscle I against the weakened muscle II. Thus paradoxical motion developed in muscle II during hypoxia.

Immediately after reoxygenation, the most striking changes in the first 3 minutes were a prolongation of time to peak tension and the time for isometric tension to decline 50% in muscle II. This was reflected in the relative movement of lever 1 by a late systolic shortening of muscle II. Because of the prolongation of contraction in the reoxygenated muscle (Table 2), major degrees of asynchronous contraction were induced, and the normal muscle stretched the weaker (recovering) muscle initially, and the weaker stretched the normal late in contraction. This principle is well illustrated in Figure 6. After 60 minutes of reoxygenation, most values had returned to their control levels, including the relative movement of lever 1. A summary of the average changes observed in all the pairs of muscles during and following hypoxia of one of them are shown in Table 3.

### Table 2

<table>
<thead>
<tr>
<th>Min</th>
<th>n</th>
<th>P₀</th>
<th>dP/dt</th>
<th>TPT</th>
<th>RT₀/sec</th>
</tr>
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<tr>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>9</td>
<td>66.3 ± 7.3</td>
<td>89.0 ± 11.3</td>
<td>76.5 ± 2.3</td>
<td>76.4 ± 4.5</td>
</tr>
<tr>
<td>20</td>
<td>9</td>
<td>36.3 ± 2.6</td>
<td>53.2 ± 6.0</td>
<td>70.7 ± 2.3</td>
<td>73.4 ± 6.2</td>
</tr>
<tr>
<td>30</td>
<td>3</td>
<td>32.7 ± 1.7</td>
<td>46.5 ± 1.7</td>
<td>74.0 ± 6.0</td>
<td>83.5 ± 6.5</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>35.2 ± 3.8</td>
<td>31.2 ± 1.9</td>
<td>117.0 ± 16.7</td>
<td>234 ± 27.3</td>
</tr>
<tr>
<td>10</td>
<td>8</td>
<td>58.2 ± 5.7</td>
<td>47.5 ± 4.3</td>
<td>116.7 ± 2.3</td>
<td>128 ± 6.4</td>
</tr>
<tr>
<td>20</td>
<td>8</td>
<td>79.4 ± 5.8</td>
<td>65.9 ± 5.5</td>
<td>116.2 ± 2.8</td>
<td>122.2 ± 6.1</td>
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<tr>
<td>60</td>
<td>6</td>
<td>87.0 ± 1.6</td>
<td>90.5 ± 2.8</td>
<td>95.8 ± 3.4</td>
<td>89.8 ± 3.4</td>
</tr>
<tr>
<td>80</td>
<td>8</td>
<td>90.7 ± 3.8</td>
<td>92.3 ± 2.9</td>
<td>96.7 ± 3.3</td>
<td>91.0 ± 4.7</td>
</tr>
</tbody>
</table>

Data are percent of control. P₀ = isometric tension developed; TPT = time to peak tension; RT₀/sec = time required for isometric tension to fall to one-half its peak value.
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FIGURE 6
Representative interaction of a normal cat papillary muscle in series with another muscle (II), which was made hypoxic for 20 minutes and then reoxygenated. The top panels of each set indicate the relative motion of lever 1 between the two muscles (Figure 1). The middle panels illustrate the isometric contraction of the two muscles in series combination, while the lower panels show the isometric contractions of the hypoxic muscle (II) alone. Tracings were obtained under control conditions, following 20 minutes of hypoxia of muscle II only, 2 minutes after reoxygenation of muscle II, and one hour later.

Discussion
In the present study, the effects of one papillary muscle on another when contracting in series has been studied in relation to normal contraction, asynchronous stimulation, and hypoxia. The force of contraction of the pair tended to reflect the force development of the stronger muscle, although it also depended on the initial length of each muscle and its relative position along the length-active tension curve. At smaller resting tensions, the thinner muscle was at more nearly optimal lengths and thus tended to be dominant, while at higher resting tensions the larger muscle moved up the curve and became predominant.

Physiologic degrees of asynchronous stimulation did not lead to significant depressions of force development or speed of contraction. To a large extent, the preservation of muscle performance despite asynchronous activation...
TABLE 3
Alterations in the Mechanics of Contraction of the Tandem Pair of Muscles

<table>
<thead>
<tr>
<th>Min</th>
<th>n</th>
<th>P₀</th>
<th>( \frac{dP}{dt} )</th>
<th>TPT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Hypoxia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>9</td>
<td>77.9 ± 5.0</td>
<td>89.7 ± 6.6</td>
<td>91.1 ± 8.1</td>
</tr>
<tr>
<td>20</td>
<td>9</td>
<td>66.6 ± 5.6</td>
<td>67.8 ± 4.8</td>
<td>103.8 ± 6.9</td>
</tr>
<tr>
<td>30</td>
<td>3</td>
<td>77.0 ± 5.1</td>
<td>71.3 ± 3.7</td>
<td>114.3 ± 8.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recovery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>70.3 ± 7.0</td>
<td>65.2 ± 6.3</td>
<td>105.5 ± 4.9</td>
</tr>
<tr>
<td>10</td>
<td>9</td>
<td>81.6 ± 4.0</td>
<td>66.4 ± 6.6</td>
<td>111.2 ± 5.0</td>
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<tr>
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<td>89.2 ± 2.7</td>
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<tr>
<td>80</td>
<td>3</td>
<td>99.0 ± 2.1</td>
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<td>99.0 ± 4.0</td>
</tr>
</tbody>
</table>

See footnote, Table 2.

could be explained by the relative position of the muscle along the length-active tension curve. Thus, if a muscle placed at a shorter than optimal length, the early contraction of its series mate would tend to elongate its fibers, thus leading to its subsequent generation of greater force. From this it would appear that asynchronous activation produces less functional impairment than one might anticipate, and early in contraction may serve to stretch some of the fibers to more advantageous lengths. Such phenomena may occur during the so-called "entrant" phase of ventricular contraction, which Wiggers (9) has described in the intact heart. This 10- to 20-msec period precedes the very rapid rise in ventricular pressure and may well contain these local readjustments in fiber length.

It has been shown that under normal conditions there is an orderly delay in the depolarization of different parts of the intact ventricle (3). Furthermore, Hotta (5) has shown that the temporal spread of mechanical activation parallels the described pattern of electrical depolarization. From the geometry of the ventricle, one might expect that contraction in one region of the wall would result in increased stress in other segments of the wall, since any increase in the pressure of a fluid will be transmitted equally in all directions. Thus, it is of considerable interest that the tension development of the tandem pair of isolated papillary muscles is augmented when the resting tension is moderate and the interval between stimuli is of the same order as that observed in the intact ventricle. This phenomenon may be similar to the observations in the intact heart that show an expansion of the circumferential diameter of the ventricle early in contraction (10). The mechanical advantage from this early stretch of fibers higher onto the length-active tension curve is apparent.

The present study also suggests a possible explanation for asynchronous contraction and paradoxical motion during hypoxia. With the development of hypoxia, the time to peak tension was substantially shortened, and force development declined. However, with reoxygenation, a marked prolongation of the time to peak tension and delay in relaxation ensued, so that peak force development was restored before restoration of the speed of contraction. The net result of such changes in the course of the active state was that early in contraction the nonhypoxic muscle was contracting against the weaker hypoxic muscle and tended to elongate it. Later in the course of contraction, the muscle which was recovering from hypoxia predominated because of its slow relaxation rate, and thus it tended to stretch the normal muscle (Fig. 6). The relative motion between the two muscles thus reflected this dissociation of the time course of the tension development of the individual
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contractions, as altered by either the occurrence of, or the recovery from, hypoxia.

Segmental ischemia of the heart has long been known to result in varying degrees of asynchrony of ventricular contraction (2), although the underlying mechanisms have not been elucidated. When surgical or pathological observations have revealed compromised or frankly scarred myocardium, the cause of such abnormal wall motion is intuitively apparent. However, in a significant number of cases, pathological study has shown little gross structural abnormalities in hearts in which asynergic contraction has clearly been demonstrated (11). Although delays or alterations in electrical activation in excitation have been suggested as a cause of such asynchrony of contraction, such delays are not uncommon (11).

The present in-vitro studies offer an alternative explanation for these functional aberrations and may help to explain both persistent and transient asynchrony of ventricular contraction. This hypothesis is based on variations in the time course of force development, and its relation to hypoxia and recovery. Although electrical activation may also be abnormal, its occurrence would not be necessary. Furthermore, peak force development in different areas of the ventricular wall need not be severely depressed but only delayed in time.

Thus, a mechanism for transient asynergy during anginal episodes has been suggested by the present study. The period of recovery from periods of hypoxia is marked by severe alterations in the time course of contraction; both the time required for peak tension to be developed and the time tension is maintained are prolonged for several minutes after hypoxia. Other experiments have shown that this effect on the time course of contraction is also manifest after only a very few minutes of hypoxia (unpublished observations). Thus short intervals of hypoxia may be a cause of the asynergy observed with anginal attacks (12).

Acknowledgments

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References