Effect of Tension on Induction of Automaticity by Epinephrine in Papillary Muscle

By I. R. Innes, M.D., and H. D. Sanders, Ph.D.

It has often been reported that increased arterial blood pressure leads to the production of cardiac arrhythmias. Similarly, increased pacemaker activity occurs when various cardiac tissues are stretched and recently Keatinge also showed that quiescent isolated rabbit atrium or ventricle will start to beat when the pressure inside is raised.

The present experiments were designed to determine the effects of increase in tension upon induction of pacemaker activity (automaticity) in cat papillary muscle. An isolated preparation of this muscle is especially suitable for such a study since it is normally quiescent but can be excited by epinephrine. The threshold dose of epinephrine required to induce repetitive contractions remains the same for several hours and changes in threshold due to increased tension on the muscle can readily be determined.

Methods

Papillary muscles of 1.0 to 1.5 mm in diameter were taken from the right ventricles of 34 cats (0.4 to 0.7 kg) killed by a blow on the head. These muscles were suspended vertically in a 10-ml bath containing Krebs-Henleit solution bubbled with 95% oxygen and 5% carbon dioxide and kept at 37°C. Tension was recorded isometrically with a Baldwin strain gauge and a Grass polygraph. The upper end of the muscle was attached by a thread to the strain gauge. The lower end was attached to a glass rod which could be raised or lowered in relation to the strain gauge by a Palmer rack-work "x" block.

Slow changes in tension on the muscle were made by altering the muscle length in this way. In experiments where tension was to be applied rapidly, a 4 or 9 g weight was suspended from the strain gauge. The tension on the muscle was then adjusted by moving the rack so that the total tension registered on the polygraph record was 5 or 10 g. The tension on the muscle was therefore 1 g. The tension could be changed rapidly to 5 or 10 g by removing the weight with a lever. The time course of the tension change when the weight was removed was followed in several experiments by running the polygraph paper at 50 mm/sec. The tension change was always completed within 0.2 sec. Tension changes due to removal and immediate replacement of the weight were completed within 0.8 sec.

A tension of one gram was kept on each muscle before tests were begun. Only initially quiescent muscles were used. The concentration of l-epinephrine required to cause repetitive contractions was found by adding the drug in increasing concentrations. Each dose remained in the bath for two minutes and the bath was washed out between doses. Five minutes were allowed to elapse after an ineffective dose before a larger dose was given. In most experiments the bath concentration of epinephrine was increased at each addition by a factor of 3 or 3.3, but in some early experiments the concentration was doubled. The criterion for the threshold dose of epinephrine to induce automaticity was arbitrarily taken as the smallest dose which caused at least five contractions within ten seconds. When this criterion was met by the same dose of epinephrine in two successive determinations this dose was termed the "epinephrine threshold." The concentrations tested ranged from $10^{-10}$ to $10^{-6}$ g/ml, calculated as the free base. After a dose of epinephrine caused automaticity no further drug additions were made for 15 minutes. All experiments began with a determination of the epinephrine threshold of the muscle at one gram tension. The tension was raised either rapidly, within 0.2 second, or slowly, over 4 seconds, and the epinephrine threshold redetermined. It was clear that short-lived changes of threshold could be shown only if the test dose
TABLE 1

<table>
<thead>
<tr>
<th>Number of muscles</th>
<th>Threshold concentration of epinephrine, g/ml</th>
<th>Ratio of threshold concentration, g/10 g</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At constant tension of 1 g</td>
<td>After sudden increase to 10 g tension</td>
</tr>
<tr>
<td>16</td>
<td>&gt; 1 x 10^-6</td>
<td>1 x 10^-6 to 1 x 10^-6 &gt; 1 to &gt;1000</td>
</tr>
<tr>
<td>2</td>
<td>1 x 10^-6</td>
<td>2 x 10^-6 to 4 x 10^-7 5 to 25</td>
</tr>
<tr>
<td>1</td>
<td>3 x 10^-6</td>
<td>1 x 10^-7 30</td>
</tr>
<tr>
<td>10</td>
<td>1 x 10^-4</td>
<td>3 x 10^-7 to 1 x 10^-8 3.3 to 100</td>
</tr>
<tr>
<td>1</td>
<td>1 x 10^-7</td>
<td>5 x 10^-8 2</td>
</tr>
<tr>
<td>1</td>
<td>3 x 10^-6</td>
<td>1 x 10^-8 3</td>
</tr>
<tr>
<td>1</td>
<td>1 x 10^-8</td>
<td>3 x 10^-9 3</td>
</tr>
<tr>
<td>1</td>
<td>1 x 10^-9</td>
<td>1 x 10^-9 1</td>
</tr>
</tbody>
</table>

of epinephrine was already in the bath when the tension change occurred. Accordingly test doses of epinephrine for redetermination of the threshold were added to the bath before the tension was increased. Responses to epinephrine in the control threshold determinations usually began within a few seconds of addition of the drug and invariably within 30 seconds. In re-determinations of the threshold the tension increase was made two minutes after epinephrine was added to the bath, when it had become certain that the dose of epinephrine was ineffective at one gram tension. Determinations were made also when tension was restored slowly or rapidly to the original level. In some experiments tension was raised and very quickly reduced, the whole operation taking 0.8 second. In other experiments the higher tension was maintained for 25 minutes. The muscles consistently adapted to the increased tension for the first 15 minutes and constant tension was maintained only by continuous adjustment of the muscle length. Tension usually did not fall during the remaining 10 minutes. In many cases threshold determinations were made under different conditions of tension in a single muscle preparation, e.g., with rapidly and slowly applied tension, with the increased tension sustained or with the tension restored to the control value.

**Results**

**EFFECT OF INCREASED TENSION WITHOUT EPINEPHRINE**

The tension on 41 papillary muscles was increased rapidly or slowly (0.2 or 4 sec) from 1 to 5 or 10 g. The tension increase did not cause any quiescent muscle to contract when no epinephrine was in the bath.

**EFFECT OF INCREASED TENSION ON INDUCTION OF AUTOMATICITY BY EPINEPHRINE**

Tension was rapidly increased (0.2 sec) from 1 to 5 or 10 g and rapidly restored to the initial value (total time 0.8 sec) in 34 experiments. Increased sensitivity to epinephrine appeared in all but one preparation. Table 1 shows the change in epinephrine threshold in 34 preparations when the tension was rapidly raised to 10 g. Sixteen muscles which failed to contract under 1 g tension in response to epinephrine in a dose of 10^-8 g/ml contracted in the presence of an equal or much lower concentration of epinephrine when the tension was increased. In one case the preparation responded to a concentration one-thousandth of the previously ineffective concentration. The sensitivity was most commonly increased by a factor of 30 or 100; the increase in sensitivity was greatest in preparations whose sensitivity to epinephrine was low at 1 g tension. Seven muscles were tested with tension increases to both 5 and 10 g, rapidly applied and removed. The epinephrine threshold was lowered at 5 g tension and further lowered at 10 g tension in all seven (fig. 1).

Threshold determinations were repeated in all preparations after the initial tension was restored. The sensitivity to epinephrine reverted to its original level in every case.

Six experiments were done to determine the effect of gradually increasing the tension to 5 or 10 g. The tension was raised over 4 seconds in the presence of graded concentrations of epinephrine. No change in threshold occurred, even when the increased tension was maintained for 15 to 25 minutes.

None of the preceding experiments indi-
FIGURE 1
Effect of application of tension on minimal epinephrine concentration needed to induce automaticity in cat papillary muscle. Columns represent "epinephrine threshold" under different tension conditions in a single experiment.

Figure 1 indicates whether the increased sensitivity to epinephrine was caused by the rapid increase of tension or its rapid decrease. Accordingly additional tests were made on 5 of the 33 muscles where rapid tension changes had altered the threshold. The tension was rapidly increased to 10 g and kept at this level for several minutes. The epinephrine threshold was changed to the same extent by rapid application alone as by rapid application and removal of tension. Maintenance of the increased tension for a longer period did not prolong the duration of automaticity. Gradual withdrawal (4 seconds) of tension from these muscles failed to lower the epinephrine threshold.

Additional tests were made on the muscles in which slow addition of tension had failed to alter the epinephrine threshold. The tension was increased slowly and maintained for several minutes. The threshold was then determined while the tension was removed rapidly (0.2 second) or slowly (4 seconds). Neither procedure altered the epinephrine threshold.

EFFECT OF TENSION ON EPINEPHRINE-INDUCED CONTRACTIONS

Contractions in response to the threshold dose of epinephrine with the muscle at one gram tension usually began as soon as the drug was added and continued with regular rhythm and strength until the drug was washed out. If a second dose of epinephrine was applied shortly after the first dose was washed out the response again lasted throughout the whole period of exposure to the drug. In contrast, the contractions due to epinephrine in muscles sensitized by increased tension often continued for only 20 to 30 seconds although epinephrine remained in the bath. If the tension was increased a second time before the muscle had rested 15 minutes the duration of automaticity decreased to 3 to 5 seconds. Contractions induced by epinephrine were usually irregular in rhythm and strength when tension was rapidly applied. Contractions were always irregular in rhythm and strength when the tension was kept at 10 grams, although induced by the same concentration of epinephrine as had caused regular contractions at one gram (fig. 2).

Discussion

The results show that a sudden rise in tension on cat papillary muscle increases its sensitivity to induction of automaticity by epinephrine. The rate of rise of tension is an important factor, since an increase in tension applied over 0.2 second lowered the threshold to epinephrine while an equal increase applied over 4 seconds had no such effect. Moreover, the papillary muscles did not remain sensitized to epinephrine when the higher tension was sustained. The epinephrine threshold reverted to the control

FIGURE 2
Effect of tension on rhythm of epinephrine-induced automaticity in cat papillary muscle. a: Contractions induced by epinephrine (10^-7 g/ml), tension 1 g constant. b: Contractions induced by epinephrine (10^-7 g/ml), tension 10 g constant.
level in muscles to which tension had been applied rapidly, and was not raised when tension was applied slowly and then maintained. The observation that the sensitizing factor is the rapidity with which tension is applied rather than the presence of a high tension indicates that the increased sensitivity is not due to greater length of the muscle fibers. This is borne out by the experiments where high tension was sustained. Here the tension could be maintained only by repeated adjustments which increased the muscle length. This increase in length did not sensitize the muscle to epinephrine. Also, the muscle lengths at the end of slow and rapid stretch differ since the myocardium resists rapid change in length because of internal viscosity. Sudden application of tension will therefore result in a shorter muscle length than will slow application of an equal tension. This supports the conclusion that the sensitizing factor is not the greater length of the muscle fibers. It is possible, however, that the sensitizing factor is the rapidity with which the length is increased rather than the increase in tension. The rate of change of length in rapid application is certainly greater than that in the slower application, although the final length is considerably greater with slow application.

The short duration of automaticity after rapid increase in tension indicates that sensitization lasts only for a short time. The limitations of our method of threshold determination after the increased tension did not allow us to study the rate of decay in sensitivity during or after this short period. The briefness of the sensitization cannot be due to decay of the tension after its rapid application since maintaining the tension failed to prolong the reduction in threshold. It is possible that the short duration of sensitization may be due to accommodation of some factor resisting stretch, such as viscosity. Accommodation of such factors would have to occur within 4 seconds, for tension increases taking this time did not sensitize. On the other hand, muscle sensitized by rapidly applied tension showed automaticity for 30 seconds or more, pointing to a slower accommodation process. However, the continued presence of the factor precipitating automaticity may not be needed for continued pacemaker activity. Rapidly applied tension might sensitize only long enough for a single contraction to take place. The increased tension during this contraction might in turn sensitize the muscle enough to allow a second contraction. Thus each contraction would depend on increased sensitivity caused by the previous contraction.

Hoffman and Cranefield showed that stretch decreased the resting potential and increased multifocal pacemaker activity of the sino-atrial node. This suggests that a similar decrease in resting potential might be responsible for the increased ease with which epinephrine induced automaticity in the papillary muscle preparation after increased tension. However, Penefsky and Hoffman found that "mild" stretch of cat papillary muscle had no effect on the resting potential. In contrast, when the muscle was stretched beyond the length which allowed contractions of maximal tension, the resting potential decreased considerably. The resting tension in these experiments was not reported and muscles were allowed to equilibrate for 5 to 10 minutes after stretching before recordings were made. Therefore we cannot correlate these observations with our experiments. On the other hand Dudel and Trautwein reported that the resting potential of cat papillary muscle fibers was unchanged under a tension of 1000 g/cm². Our observations showed that tension changes leading to a total tension of 85 to 370 g/cm² altered the sensitivity to epinephrine. However, the rate of application of tension in the experiments of Dudel and Trautwein is not indicated and it is possible that rapid tension changes may transiently alter the muscle resting potential. Since rapid application of tension failed to induce contractions in the absence of epinephrine, it is apparent that tension alone did not cause sufficient depolarization to initiate an action potential.

Sensitization of cardiac muscle to epineph-
rine by rapidly increased tension may well account for ventricular arrhythmias which are induced by epinephrine in the presence of anesthetics. Nickerson and Nomaguchi showed that these arrhythmias were precipitated when the arterial blood pressure was rising due to injected epinephrine rather than during the period when the arterial blood pressure was at its peak. During the rise in arterial blood pressure due to a dose of epinephrine, the rise in ventricular muscle tension developed from the resting muscle tension at diastole will be greater with each succeeding heart beat until the highest intraventricular pressure is reached. According to the present results the increasing tension developed within the muscle should cause progressively increasing sensitivity to induction of automaticity by epinephrine. When this sensitivity reaches a high enough level we might expect beats of ventricular origin. The time taken for the increase of intraventricular pressure and therefore also of the tension developed by ventricular muscle during a cardiac cycle is roughly the same as the time taken in our experiments for the rapid application of tension. Isometric contraction and the maximum ejection phase normally take less than 0.2 second. Tension increases of 70 to 340 g/cm² caused a great increase in sensitivity to epinephrine in our experiments. We have calculated from formulae outlined by Burton that ventricular muscle tension during systole will be approximately the same as the tensions used in our experiments. The rapidity and degree of tension development in the cardiac cycle appear to be enough to sensitize the muscle to epinephrine. Irregularity of contractions induced by epinephrine after a sudden tension increase or with high, sustained tension is consistent with the concept that tension is at least part of the cause of the pressure sensitive cardiac arrhythmias.

Summary

Sudden increase in tension on the quiescent isolated cat papillary muscle from 1 to 5 or 10 g lowered the threshold concentration of epinephrine needed to induce automaticity. The threshold was lowered for no longer than 30 seconds. Slow changes in tension did not lower the threshold. Sustained tension of 5 or 10 g did not change the threshold, nor prolong the lowering of threshold resulting from sudden increase in tension. Contractions of muscles after a sudden rise to 10 g tension or sustained at this level were irregular in rhythm and strength, in contrast to the contractions of muscles under 1 g tension. Sensitization of cardiac muscle to epinephrine by tension changes progressively increasing with each successive beat may account for the effects of elevation of arterial blood pressure in cyclopropane-epinephrine and other arrhythmias.

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