Effect of Epinephrine and Norepinephrine on Coronary Circulation

By ROBERT M. BERNE, M.D.

Studies on the intracoronary administration of epinephrine and norepinephrine in the beating, fibrillating or potassium-arrested dog heart indicate that the primary action of these compounds on the coronary vessels is vasoconstriction. The vasodilation observed with epinephrine and norepinephrine is probably secondary to the increased rate of myocardial metabolism induced by these drugs.

SINCE the early part of the present century numerous reports have appeared concerning the effect of epinephrine on the coronary vessels. Although there is almost general agreement that epinephrine produces coronary vasodilation there is considerable disagreement as to whether this vasodilator response represents a direct effect on the coronary vessels or is secondary to the stimulating action of epinephrine on myocardial metabolism. The conflicting results which have given rise to this difference of opinion may be due to several factors. Among these factors are (a) use of crude and unstable hormone preparations, (b) use of isolated hearts perfused with salt solutions that are poor in oxygen, (c) species differences, (d) extrapolation of results obtained on isolated vessel strips to the intact coronary circulatory system, (e) failure to maintain a constant perfusion pressure, (f) use of coronary sinus outflow as a measure of coronary blood flow (CBF), (g) failure to assess correctly the effects of extravascular compression on CBF, and (h) lack of data permitting correlation of myocardial oxygen consumption, coronary sinus blood oxygen tension, and CBF.

The present study was designed to eliminate or control many of the variables which have made determination of the direct effect of epinephrine and norepinephrine (levarterenol) on coronary vessels difficult. Beating, fibrillating, and arrested heart preparations with continuous recording of CBF and coronary sinus blood oxygen tension have been employed in an attempt to achieve this objective.

METHODS

Thirty-nine technically satisfactory experiments were performed on open-chest dogs. A fibrillating dog heart preparation was used in 35 experiments and an intact beating heart in four. Dogs used in this study weighed between 16 and 24 Kg. and were anesthetized with intravenously administered sodium pentobarbital (30 mg./Kg.).

Fibrillating Heart Preparations. The left coronary artery was approached through the fourth left intercostal space and artificial respiration was instituted. Following the administration of heparin the coronary artery was cannulated with an Eckstein cannula and was initially perfused via a carotid artery. When all surgical procedures were completed ventricular fibrillation was induced and the heart was supplied with blood from the femoral arteries of a donor dog. By means of cannulas placed in the coronary sinus and right ventricle of the fibrillating heart, cardiac venous blood was collected and periodically returned to the donor dog. Precise regulation of perfusion pressure was accomplished by means of a pump perfusion system interposed between the donor dog and the cannulated left coronary artery of the experimental animal. Mean CBF was measured by an optically recording rotameter and perfusion pressure by a Gregg manometer. A polyethylene covered platinum electrode for polarographic recording of blood oxygen tension was placed in the coronary sinus outflow tubing as close to the cannula as possible. The polarograph was wired to an optically recording galvanometer and records of coronary sinus blood oxygen tension were inscribed.

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on the same photographic paper as were perfusion pressure and CBF. In most of the experiments only directional changes in coronary sinus blood oxygen tension were obtained. However, in several experiments the instrument was calibrated against flowing blood of different oxygen tension at a temperature of 37 C., and the results expressed as partial pressure of oxygen in mm. Hg. Blood oxygen tension was measured by modification of the method described by Riley.7

In 6 experiments, intramyocardial pressure was recorded by a very sensitive optically recording Gregg manometer, in a manner similar to that employed by Gregg and Eckstein8 in the beating heart. A one- to two-centimeter segment of femoral vein was threaded through the left ventricular wall so as to lie completely within the myocardium. One end of the vein was ligated and the other connected to the manometer. This closed system was filled with saline to a pressure which gave maximal sensitivity upon deformation of the vein segment. The system was calibrated at the conclusion of the experiment by recording manometer deflections over a wide range of increments in hydrostatic pressure applied externally to the vein segment after its removal from the heart.

**Intact Beating Heart.** The left coronary artery and coronary sinus were cannulated as for the fibrillating heart preparation but arterial blood was obtained from a carotid artery and coronary sinus blood was routed to the right jugular vein. A special T cannula was placed in the tubing just proximal to the coronary artery cannula for the purpose of housing the bristle of the flowmeter used to measure phasic coronary inflow. Phasic CBF was optically recorded, as were coronary sinus blood oxygen tension, aortic pressure, and perfusion pressure. In certain instances in which aortic pressure served as perfusion pressure, rigid tubing conducted the blood from the carotid artery to the left coronary artery.

In fibrillating and beating heart preparations, all rapid injections and infusions were made into the tubing leading to the left coronary artery. Epinephrine and norepinephrine were dissolved, just prior to use in 0.9 per cent sodium chloride solution containing ascorbic acid in a concentration of 0.001 per cent. Single rapid injections of epinephrine and norepinephrine were made in a volume of 0.05 to 0.1 ml. of 0.001 per cent ascorbic acid in isotonic saline; constant infusions of the drugs were made in the same solvent at a rate of 0.93 ml./min. At these injection and infusion rates administration of the solvent alone was without effect on CBF. Arterial and cardiac venous blood samples for determination of myocardial oxygen consumption were obtained simultaneously from the tubing conducting blood to and from the coronary vascular bed, respectively. The oxygen content of these blood samples was determined in duplicate by the method of Roughton and Scholander.11 At the conclusion of each experiment the perfused portion of the heart was stained with india ink, excised and weighed.

**RESULTS**

**Fibrillating Heart.** Single rapid intracoronary injections of epinephrine and norepinephrine in the fibrillating dog heart produced an initial decrease in CBF followed by an increase of flow of longer duration. CBF started to decline within 2 to 7 sec. after the injection of the drug, reached a minimal level in 4 to 8 sec. and then began to increase. Time of onset and duration of effects were in part related to the initial flow rate and the dose of the drug. Oxygen tension in the coronary sinus blood showed a decrease which occurred at approximately the time that CBF started to increase. Figure 1 depicts the effect of 0.5 µg. of norepinephrine on CBF and coronary sinus blood oxygen tension. With perfusion pressure constant, CBF decreased from a control flow of 149 to 134 ml./min. and then rose to a peak of 162. Coronary sinus blood oxygen tension fell from 25 to 20 mm. Hg. When corrections are made for the transit time of the blood from the heart to the polarograph electrode (about 4 sec. in this experiment) and the delay in response of the polarograph galvanometer (about 2 sec.), the reduction in blood oxygen tension brought
Table 1.—Effect of Intracoronary Epinephrine and Norepinephrine on Coronary Blood Flow and Coronary Sinus Blood Oxygen Tension in the Fibrillating Heart

<table>
<thead>
<tr>
<th>Dose (mg.)</th>
<th>No. of exps.</th>
<th>Average minimum flow per cent of control</th>
<th>Average maximum flow per cent of control</th>
<th>Average maximum deflection of galv.†</th>
<th>No. of exps.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.05</td>
<td>1</td>
<td>100 (95-100)</td>
<td>100 (105-118)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.13</td>
<td>2</td>
<td>100 (90-96)</td>
<td>110 (105-110)</td>
<td>2</td>
<td>7</td>
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<td>0.25</td>
<td>6</td>
<td>95 (90-90)</td>
<td>123 (106-130)</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>0.50</td>
<td>3</td>
<td>95 (92-98)</td>
<td>117 (103-130)</td>
<td>17</td>
<td>30</td>
</tr>
<tr>
<td>1.00</td>
<td>4</td>
<td>94 (88-98)</td>
<td>121 (103-138)</td>
<td>33</td>
<td>41</td>
</tr>
<tr>
<td>2.00</td>
<td>5</td>
<td>94 (82-95)</td>
<td>128 (111-128)</td>
<td>41</td>
<td>41</td>
</tr>
<tr>
<td>4.0-6.0</td>
<td>5</td>
<td>91 (81-94)</td>
<td>129 (79-100)</td>
<td>31</td>
<td>35</td>
</tr>
<tr>
<td>10.0</td>
<td>1</td>
<td>80</td>
<td>113 (76-100)</td>
<td>56</td>
<td></td>
</tr>
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</table>

Table 1.—Effect of Intracoronary Epinephrine and Norepinephrine on Coronary Blood Flow and Coronary Sinus Blood Oxygen Tension in the Fibrillating Heart

A dose of 0.06 mg. of either drug was without effect on CBF or coronary sinus blood oxygen tension. In none of the experiments was an increase in coronary sinus blood oxygen tension observed upon intracoronary administration of epinephrine or norepinephrine. Since epinephrine and norepinephrine enhance the vigor of the incoordinate contractions in ventricular fibrillation and may produce an initial reduction in CBF by means of increasing extravascular compression, measurements of myocardial pressure and left ventricular pressure were made during infusion of these drugs. Recording of intramyocardial pressure in six fibrillating heart preparations revealed a maximal change of ± 1 cm. of water upon intracoronary administration of epinephrine or norepinephrine. No change was observed in left ventricular pressure. A record taken from one of these experiments can be seen in figure 2 (top). To demonstrate that increases in intramyocardial pressure which might occur during the drug administration would be recorded, rapid injections of saline were made with a syringe through a no. 15 needle into the left ventricular cavity while perfusion pressure, CBF, left ventricular pressure, and intramyocardial pressure were recorded. Figure 2 (bottom) depicts such an experiment. It is apparent that with elevation of left ventricular pressure capable of producing a moderate reduction in CBF, a striking increase in intramyocardial pressure occurred.

In 7 fibrillating heart preparations, stimulation (30 to 300 v. at frequency of 50/sec.) of the left cardiac accelerator nerve produced a 10 to 100 per cent increase in CBF. An initial reduction in CBF was not observed, but coronary sinus blood oxygen tension was consistently reduced. The average time of

†Galvanometer deflections were always downward, indicating a decrease in coronary sinus blood oxygen tension.
EPINEPHRINE, NOREPINEPHRINE AND CORONARY CIRCULATION

Fig. 2 Top. Effect of intracoronary injection (arrow) of 5.0 μg of norepinephrine on intramyocardial pressure in the fibrillating dog heart; Pol., polarographic tracing of coronary sinus blood oxygen tension; P.P., perfusion pressure in mm. Hg; CBF, mean coronary blood flow in ml/min.; M.P., intramyocardial pressure in cm. of water; V.P., left ventricular pressure in mm. Hg. Bottom. Effect of a rapid injection of saline into the left ventricular cavity on intramyocardial pressure and coronary blood flow in the fibrillating dog heart.

onset of the increase in CBF following the initiation of cardiac sympathetic nerve stimulation was 6 sec. compared to 11 sec. following the injection of epinephrine or norepinephrine.

Intact Beating Heart. Estimation of the coronary vasoreactive properties of epinephrine and norepinephrine is difficult in the beating heart because of the effect these drugs have on extravascular compression. In late diastole, however, the myocardium is relaxed and changes in CBF observed at that phase of the cardiac cycle at constant perfusion pressures should indicate true changes in coronary resistance. The effect of an intracoronary injection of 1.0 μg of norepinephrine on phasic CBF, aortic pressure, and coronary sinus blood oxygen tension is seen in figure 3 (top).

Perfusion pressure was held constant at 100 mm. Hg. The peaks of the phasic flow curve represent maximal flow in diastole and the lowest points reached indicate the reduced flow or, more precisely, the reversed flow in early systole. There is no question that peak diastolic flow increased and systolic flow be-

<table>
<thead>
<tr>
<th>Exp. no.</th>
<th>Drug and dose</th>
<th>Peak diastolic CBF (ml/min.)</th>
</tr>
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<tr>
<td></td>
<td></td>
<td>Cont.</td>
</tr>
<tr>
<td>13</td>
<td>Nor. 1.0</td>
<td>90</td>
</tr>
<tr>
<td>14</td>
<td>Nor. 1.0</td>
<td>102</td>
</tr>
<tr>
<td>16</td>
<td>Nor. 10.0</td>
<td>282</td>
</tr>
<tr>
<td>15</td>
<td>Nor. 0.25</td>
<td>138</td>
</tr>
<tr>
<td>21</td>
<td>Nor. 5.0</td>
<td>135</td>
</tr>
<tr>
<td>17</td>
<td>Epi. 0.016</td>
<td>210</td>
</tr>
<tr>
<td>20</td>
<td>Epi. 0.031</td>
<td>210</td>
</tr>
<tr>
<td>22</td>
<td>Epi. 0.003</td>
<td>210</td>
</tr>
<tr>
<td>18</td>
<td>Epi. 0.003</td>
<td>204</td>
</tr>
<tr>
<td>19</td>
<td>Nor. 0.003</td>
<td>207</td>
</tr>
<tr>
<td>23</td>
<td>Epi. 0.125</td>
<td>216</td>
</tr>
<tr>
<td>24</td>
<td>Epi. 0.25</td>
<td>216</td>
</tr>
<tr>
<td>25</td>
<td>Epi. 0.50</td>
<td>222</td>
</tr>
<tr>
<td>26</td>
<td>Nor. 0.50</td>
<td>222</td>
</tr>
<tr>
<td>27</td>
<td>Epi. 1.0</td>
<td>222</td>
</tr>
<tr>
<td>28</td>
<td>Nor. 1.0</td>
<td>222</td>
</tr>
<tr>
<td>29</td>
<td>Epi. 5.0</td>
<td>264</td>
</tr>
<tr>
<td>30</td>
<td>Nor. 5.0</td>
<td>270</td>
</tr>
</tbody>
</table>

*Galvanometer deflections were always downward, indicating a decrease in coronary sinus blood oxygen tension.
came more negative following norepinephrine, but prior to the increase in peak diastolic flow an initial decrease occurred. To illustrate the initial decrease in peak diastolic CBF and the increase in backflow in early systole, lines connecting the points of maximum flow (peaks) and those of minimum flow, during the control period, have been extended into the period of early flow change induced by the norepinephrine. Coronary sinus blood oxygen tension decreased in this experiment and the decrease started at approximately the time that CBF began to rise. These results should be compared to those obtained with acetylcholine (fig. 3, bottom).

A total of 4 phasic flow experiments were performed and the data for these experiments are presented in table 2. With increasing doses of epinephrine and norepinephrine the initial decrease in peak diastolic flow changed very little, whereas the late increase became greater and the polarograph indicated a greater reduction in coronary sinus blood oxygen tension.

Potassium-Arrested Heart. Visible myocardial contractions in the perfused fibrillating heart were stopped by intracoronary injection of potassium chloride and the heart maintained in the arrested state by a continuous intracoronary infusion of this salt administered at a constant rate. The actual amount of potassium chloride infused was not recorded, but was an amount just necessary to prevent myocardial contractions. During the potassium arrest, epinephrine or norepinephrine were injected as single rapid injections in seven experiments, or as continuous infusions over a period of 2 to 3 min. in 2 experiments. There were a total of 15 trials in the 9 experiments, and in all but one instance the
Intracoronary injection (arrow) of 5.0 μg of epinephrine in the potassium-arrested heart. P.P., perfusion pressure in mm. Hg; CBF, mean coronary blood flow in ml./min.

drugs produced only a decrease in CBF. In the experiment in which CBF rose to above control levels, after an initial decrease, the heart began to beat rhythmically within a few seconds of the norepinephrine injection. Figure 4 illustrates the effect of a rapid intracoronary injection of 5 μg of epinephrine in the potassium-arrested heart. The effects of infusion of epinephrine and norepinephrine on CBF in the quiescent heart are seen as experiments nos. 30 and 31 in table 3.

**Myocardial Oxygen Consumption.** Epinephrine and norepinephrine increase CBF and reduce coronary sinus blood oxygen content, and consequently induce large increases in myocardial oxygen consumption in the fibrillating heart (table 3). Thirty-three trials with epinephrine and norepinephrine were made in 17 fibrillating heart preparations, and the results are presented graphically in figure 5. In figure 5 CBF in per cent above control is plotted against myocardial oxygen consumption in per cent above control. With one exception epinephrine and norepinephrine produced much greater increases in cardiac oxygen consumption than in CBF. The average increase in CBF was 38 per cent, whereas the average increase in myocardial oxygen consumption was 126 per cent.

Since it is possible that part of the vasodilator action of epinephrine and norepinephrine may be secondary to an hypoxic effect of these drugs on the myocardium, experiments were conducted in which the heart muscle was supplied with large quantities of oxygenated blood in the presence of epinephrine and norepinephrine. An example of such an experiment is given by figure 6. At a perfusion pressure of 50 mm. Hg, CBF was 44 ml./min., coronary sinus blood oxygen content was 6.2 vol. per cent, and myocardial oxygen consumption was 2.7 ml./min. At the same perfusion pressure an infusion of 20 μg. of epinephrine per minute resulted in an increase in CBF, associated with a reduction in coronary sinus blood oxygen content to 3.6 vol. per cent.

![Graph](image-url)
TABLE 3.—Effect of Infusion of Epinephrine and Norepinephrine on Coronary Blood Flow and Myocardial Oxygen Consumption at Different Perfusion Pressures

<table>
<thead>
<tr>
<th>Exp. no.</th>
<th>Perfusion Pressure (mm Hg)</th>
<th>CBF (ml/min/100 g heart)</th>
<th>O2 Abs./O2 Con. (vol. %)</th>
<th>Cor. Sin. O2 Con. (vol. %)</th>
<th>Qo./min/100 g (Gm. Heart)</th>
<th>Drug and dose (mg/ml)</th>
</tr>
</thead>
</table>

Fibrillating hearts
11 60 34 15.5 11.6 1.3 Epi. 4
60 65 14.7 6.5 3.4 Epi. 4
110 149 14.4 12.5 2.5 Epi. 4
108 149 14.9 11.5 5.1 Epi. 4
19 50 44 12.4 6.2 2.7 Epi. 40
50 81 12.3 3.6 6.8 Epi. 40
104 143 11.3 2.7 2.3 Epi. 40
102 143 11.6 6.1 7.0 Epi. 40
98 190 11.6 6.1 7.0 Epi. 40
20 50 40 18.8 12.1 2.6 Epi. 50 stat
50 53 19.0 7.4 6.2 Epi. 50 stat
94 100 17.7 16.2 1.5 Epi. 50 stat
94 106 17.3 9.1 8.7 Epi. 50 stat
90 152 17.3 9.1 8.7 Epi. 50 stat
20 40 37 17.2 12.8 1.6 Nor. 40
40 51 17.5 4.7 6.6 Nor. 40
82 108 17.4 14.7 2.9 Nor. 40
81 100 16.9 6.2 10.7 Nor. 40
80 133 16.9 6.2 10.7 Nor. 40
22 44 26 15.6 10.6 1.3 Epi. 50 stat
42 35 15.1 4.4 3.8 Epi. 50 stat
76 89 17.1 15.0 1.9 Epi. 50 stat
76 88 17.0 9.5 6.6 Epi. 50 stat
72 116 17.0 9.5 6.6 Epi. 50 stat
23 29 40 16.3 8.9 2.6 Epi. 40
31 74 15.1 3.8 7.4 Epi. 40
62 95 15.6 11.7 3.3 Epi. 40
63 86 15.2 7.2 6.1 Epi. 40
25 28 28 12.3 8.1 1.2 Epi. 40
24 36 13.4 2.5 3.9 Nor. 40
70 132 14.3 13.4 2.6 Epi. 50
70 123 14.2 10.0 5.2 Nor. 40
28 50 31 13.7 7.8 1.8 Epi. 50
50 65 13.7 4.3 6.2 Epi. 50
102 91 15.8 13.8 1.8 Epi. 50
103 86 15.9 8.4 6.5 Epi. 50

Potassium-arrested hearts
30 58 54 12.4 11.5 0.5 Nor. 33
62 24 11.5 7.7 0.9 Nor. 33
31 50 70 9.4 9.4 0 Epi. 33
49 66 9.5 6.5 2.0 Epi. 33

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and an increase in cardiac oxygen consumption to 6.8 ml./min. At a perfusion pressure of 102 mm Hg control coronary sinus blood oxygen content was 9.7 vol. per cent. Infusion of 40 μg. of epinephrine per minute at this perfusion pressure produced a decrease of coronary sinus oxygen content to 6.1 vol. per cent, and an increase in cardiac oxygen consumption to 7.8 ml./min. However, the drug was without effect on CBF. To indicate that the coronary vessels were capable of further dilation, 50 μg. of acetylcholine were injected into the left coronary artery toward the end of the second epinephrine infusion and produced a 33 per cent increase in CBF.

Eight such experiments were conducted in the fibrillating heart (table 3) and in each experiment epinephrine or norepinephrine produced a severalfold increase in myocardial oxygen consumption, but only induced an elevation of CBF at low perfusion pressures when coronary sinus blood was relatively poor in oxygen. Acetylcholine injections indicated that the coronary vessels were not maximally dilated at the higher perfusion pressures during drug administration.

In 2 experiments (table 3, nos. 30 and 31) epinephrine and norepinephrine were administered at a constant rate to the potassium-arrested heart. Although control cardiac oxygen consumption was negligible, epinephrine and norepinephrine increased the oxygen uptake of the quiescent heart.

DISCUSSION

In the fibrillating dog heart perfused with blood at a constant pressure, epinephrine and norepinephrine, over a wide dose range, produced an initial transient decrease in CBF followed by a prolonged increase associated with a reduction of coronary sinus blood oxygen tension. The reduction in CBF could not be attributed to augmentation of the rate and force of the incoordinate ventricular contractions, since measurement of intramyocardial pressure failed to detect a significant change in pressure within the walls of the left ventricle. These observations suggest
that the primary effect of epinephrine and norepinephrine on the coronary vessels is one of vasoconstriction.

In 1938 Katz et al.\textsuperscript{12} studied the effect of commercial epinephrine in the isolated fibrillating dog and cat heart perfused with oxygenated blood. In the dog heart vasodilation occurred in all but one experiment and was occasionally preceded by transient vasoconstriction. These observations are in agreement with the present study except for the lack of consistency in the initial vasoconstriction in the studies of Katz et al.\textsuperscript{12} This difference could possibly be due to the method of CBF measurement they used, a method which did not permit continuous recording of CBF. Since the initial reduction in CBF is small and of short duration, it could have been masked in their studies. Similar observations of an early, transient decrease in CBF in the fibrillating dog heart following epinephrine administration were made by Garcia-Ramos et al.\textsuperscript{13} The fact that these investigators did not consistently observe the initial reduction in CBF may also be attributed to the method of measuring CBF, a procedure involving the recording of coronary sinus and right atrial outflow on smoked paper by means of a float and stylus.

The observation that coronary sinus blood oxygen tension invariably fell following the injection of effective doses of epinephrine and norepinephrine is significant. If these drugs were primarily vasodilators, then it would be expected that coronary sinus blood oxygen tension would increase, as was observed with acetylcholine in the beating heart (fig. 3, \textit{bottom}). Furthermore, the onset of the decline in coronary sinus blood oxygen tension (and presumably myocardial oxygen tension) occurred approximately 11 seconds after injection of epinephrine or norepinephrine, and coincided with the increase in CBF, whereas the increase in coronary sinus blood oxygen tension following injection of acetylcholine occurred in about 2 seconds, a time which approximates the onset of the reduction in flow observed with epinephrine and norepinephrine. The delayed onset of coronary vasodilation with epinephrine and norepinephrine compared with acetylcholine (a delay which cannot be attributed to changes in extravascular pressure) and the good correlation in time of the onset of dilation produced by epinephrine and norepinephrine with their metabolic effect on the myocardium, lend support to the contention that the vasodilator effect of these compounds is secondary to their effect on myocardial metabolism.

It is interesting that, following left cardiac accelerator nerve stimulation in the fibrillating heart, an initial decrease in CBF was not observed and the onset of the increase in CBF and the reduction in coronary sinus blood oxygen tension occurred earlier than it did following the injection of epinephrine and norepinephrine. The reason for this difference in response may be that the sympathetic fibers reach the myocardium directly, whereas infused drugs must pass through the capillaries and interstitial spaces and into the muscle cells. If cardiac sympathetic stimulation produced coronary dilation, then a transient increase in coronary sinus blood oxygen tension would be expected. Such an increase in coronary sinus blood oxygen tension with accelerator nerve stimulation was not observed.

In most of the experiments, the polarograph indicated no change in coronary sinus blood oxygen tension during the early reduction in CBF following epinephrine and norepinephrine. In a few instances a slight early decrease was observed. Actually, a decrease would be expected, since there is no reason to expect that cardiac oxygen consumption is reduced, and it has been repeatedly observed in the present study that mechanical reduction in coronary inflow is associated with a prompt fall in coronary sinus blood oxygen tension. The absence of a consistent reduction in coronary sinus blood oxygen tension during the period of reduced CBF following epinephrine and norepinephrine is probably due to the small magnitude and duration of the flow reduction.

Although the variable of extravascular compression is difficult to evaluate in the intact
beating heart, the preparation is more physiological than is the perfused fibrillating heart. Since extravascular compression is at a minimum and is undergoing minimum changes at the end of diastole, Green and his colleagues have used CBF measurements made in late diastole as an index of caliber changes in the coronary vessels. Their studies with epinephrine and other pressor amines revealed only an increase in phasic CBF in late diastole. This has been interpreted to mean that these compounds are coronary vasodilators. In the present study the beating heart perfused at a constant pressure showed an initial decrease in late diastolic CBF with intracoronary injection of epinephrine and norepinephrine, followed by an increase, associated with a fall in coronary sinus blood oxygen tension (fig. 3 and table 2). These observations closely parallel those made in the fibrillating heart. Although the observations and conclusions reported by Denison et al. are not in agreement with those of the present study, the continuous phasic flow records they present show an initial decrease in peak diastolic CBF which resembles the flow change seen in figure 3. The increase in backflow during early systole (fig. 3), a manifestation of the increase in extravascular compression, is similar to that reported by Denison et al.

On the basis of coronary sinus phasic flow measurements, Wiggers has concluded that epinephrine is a coronary vasoconstrictor. This is in agreement with our conclusions, but it is difficult to compare results obtained by means of phasic inflow measurements with those of phasic outflow. Coronary sinus outflow occurs chiefly during ventricular systole when inflow is low and is presumably a result of the emptying of cardiac veins, venules and capillaries by ventricular compression. During diastole at a time when coronary inflow is large, coronary sinus outflow is low since blood is filling the empty vessels which are no longer compressed. Epinephrine significantly increases the force of ventricular contraction and could lead to more complete emptying of the cardiac veins, venules and capillaries in systole, and consequently a greater uptake of blood by these vessels in the subsequent diastolic period. This could account for Wiggers' findings of an increase in coronary sinus outflow during the time occupied by systole plus isometric relaxation and a slight reduction in outflow during diastole. Furthermore, the measurement of coronary sinus outflow was made at a time when aortic pressure had already increased and the metabolic effect of epinephrine on the heart would have been manifest. Mean inflow in the fibrillating heart and peak diastolic inflow in the beating heart show an increase at this time.

In the potassium-arrested heart in which extravascular compression is certainly not a factor influencing CBF, intracoronary injection of epinephrine and norepinephrine produced a reduction in CBF without a subsequent increase. In the arrested heart myocardial metabolism is greatly reduced and epinephrine and norepinephrine do not induce a very large increment in myocardial oxygen consumption (table 3). These observations are consistent with the idea that the increase in CBF observed with epinephrine and norepinephrine is secondary to the stimulatory action of these compounds on myocardial metabolism. In the absence of a large increase in cardiac oxygen consumption, the primary constrictor action of epinephrine and norepinephrine is unmasked and persists for a longer period of time than in the beating or fibrillating heart. The time of onset of the constriction following injection of epinephrine and norepinephrine is equal to that observed in the beating and fibrillating heart preparations, adding further support to the contention that the primary effect of these compounds on the coronary vascular bed is vasoconstrictor. These data are not in accord with those of Auykut in the isolated guinea pig heart perfused with Ringer’s solution. However, the differences in the preparations and the method of flow measurements make comparisons difficult. An important point in regard to the interpretation of results obtained with vasoactive compounds in the potassium-arrested heart is the effect of
potassium per se on CBF. In low concentrations, potassium produces coronary dilation,\(^{18, 19}\) whereas in high concentrations vasoconstriction is produced.\(^{18}\) Attempts were made to avoid variation in CBF attributable to potassium by infusing potassium chloride at a constant rate for long control periods before injection or infusion of epinephrine. These results alone would not be sufficient to attribute a primary vasoconstrictor action to epinephrine and norepinephrine, but when considered in the light of the other observations in this report they take on greater significance.

Myocardial oxygen consumption has been shown to correlate well with CBF under different experimental conditions.\(^{1}\) In the present study, epinephrine and norepinephrine produced a proportionately greater increment in myocardial oxygen consumption than in CBF (fig. 5), indicating an increase in the extraction of oxygen from blood perfusing the myocardium. These data do not support the idea that epinephrine and norepinephrine are primary vasodilators of the coronary vessels. Coronary vasodilators like nitroglycerin\(^{20}\) produce increases in coronary sinus blood oxygen content without changes in myocardial oxygen consumption. If epinephrine and norepinephrine were predominantly coronary vasodilators, then an increase in coronary sinus blood oxygen content would be expected.

To what extent vasodilation occurring with epinephrine and norepinephrine is secondary to the hypoxic effect of these compounds on the myocardium is indicated by the experiments presented in table 3. At high perfusion pressures which provided the heart with an adequate amount of oxygen (as evidenced by the high coronary sinus blood oxygen levels), epinephrine and norepinephrine produced large increases in cardiac oxygen consumption, but minimal changes in myocardial oxygen consumption. If epinephrine and norepinephrine were predominantly coronary vasodilators, then an increase in coronary sinus blood oxygen content would be expected.

In the potassium-arrested heart epinephrine and norepinephrine produced an increase in cardiac oxygen consumption despite a reduction in CBF. These findings do not support the conclusions of Century\(^{24}\) and Hermann et al.,\(^{25}\) based on heart muscle slice studies, that epinephrine increases myocardial oxygen consumption only in contracting muscle. Oxygen consumption of the contracting myocardium is greatly enhanced by epinephrine as a result of the inotropic and chronotropic action of this hormone, but it also appears to exert a calorogenic effect on relaxed myocardium.

**SUMMARY**

The effects of intracoronary epinephrine and norepinephrine have been studied in the beating, fibrillating and arrested dog heart. In the fibrillating heart these compounds produced an initial decrease in coronary blood flow (CBF) of short duration followed by an increase of longer duration which was associated with a reduction in coronary sinus blood oxygen tension. The early reduction in CBF was not due to an increase in extravascular compression. In the beating heart, peak diastolic CBF, at constant perfusion pressure,
showed the same changes as did mean CBF in the fibrillating heart, and the decrease in coronary sinus blood oxygen tension occurred at the time that peak diastolic CBF began to rise. In the potassium-arrested heart epinephrine and norepinephrine produced only a reduction in CBF.

Myocardial oxygen consumption was increased to a greater extent than was CBF by an intracoronary infusion of epinephrine or norepinephrine.

These results are interpreted to mean that these drugs are primarily coronary vasoconstrictors and their vasodilator action is secondary to their stimulating effect on myocardial metabolism. Evidence has been presented indicating that the vasodilator effect of epinephrine and norepinephrine is due in large part to hypoxia of the heart muscle induced by these drugs.

**REFERENCE**

**SUMMARIO IN INTERLINGUA**

Le effectos del administration intracoronari de epinephrina e norepinephrina esseva studiate in cordes canin (1) normal, (2) fibrillante, e (3) arrestate. In cordes in fibrillation, le compositos mentionate produceva un breve reduction initial del fluxo de sanguine coronari (FSC), sequite per un augmento plus prolongede que esseva associate con un reducite oxygen tension del sanguine in le sinus coronari. Le reduction initial de FSC non resultava de un reduction in le compression extravascular. In cordes pulsante, diastolic FSC maximal, a constante pressiones perfusional, monstrovava le mesme alterationes como FSC medie in cordes fibrillante, e le reduction del valor de oxygen tension del sanguine in le sinus coronari occurrueva al mesme, tempore quando le diastolic FSC maximal comenciava augmentar se. In cordes arrestate per medio de chloruro de kalium, epinephrina e norepinephrina produceva solmente un reduction del valor de FSC.

Le consumption myocardial de oxygeno esseva augmentate plus marcatemente que le valor de FSC per le infusion intracoronari de epinephrina o de norepinephrina.

Iste resultatos es interpretate como indiciam-te que le drogas in question es primarimente vasoconstrictores coronari e que lor action vasodilatatori es secundari a lor effecto stimulatori super le metabolismo myocardial. Es presentate observationes que indica que le effecto vasodilatatori de epinephrina e norepnephrina resulta in grande parte ab le hypoxia myocardial que illos induce.
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Effect of Epinephrine and Norepinephrine on Coronary Circulation

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