Inhibition of Reflex Vasoconstriction after Experimental Coronary Embolization in the Dog

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ABSTRACT

The possibility that failure of vascular resistance to increase contributes to hypotension after myocardial infarction was examined in the hindlimbs of dogs following embolization of the coronary arteries. Vascular resistance did not change significantly during sustained severe hypotension after embolization in either the intact hindlimb or in simultaneously autoperfused innervated and denervated hindlimbs using constant flow. In nonembolized animals, an immediate large increase in hindlimb vascular resistance occurred when equivalent hypotension was produced by stimulation of the distal end of the sectioned vagus nerve. Lack of such response during hypotension after embolization suggested that inhibition of reflex vasoconstriction had occurred. Bilateral cervical vagotomy allowed normal reflex vasoconstriction to proceed during hypotension after infarction. These data indicate that (1) since vascular resistance is unchanged in both innervated and denervated hindlimbs, normal neurogenic vascular tone is sustained during hypotension after myocardial infarction and (2) the baroreceptor reflex, which normally promotes vasoconstriction during hypotension, is inhibited reflexly following myocardial infarction, probably by activation of cardiac vagal afferents.

ADDITIONAL KEY WORDS hypotension vasoconstriction acacia cardiogenic shock myocardial infarction coronary embolization hindlimb autoperfusion sympathetic stimulation cervical vagotomy reflex inhibition

More than 80% of patients with cardiogenic shock die (1-3). In many instances death is undoubtedly due to the massive loss of functioning myocardium. Since Gootnick and Knox (8) noted a lack of correlation between the amount of viable myocardium present during life and the occurrence of shock in patients dying after suffering multiple myocardial infarctions, shock might also be due in part to failure of total peripheral resistance to increase (4-7).

Compensatory adjustments in peripheral resistance after coronary occlusion have been examined in animal experiments with widely divergent results (9, 10). Increases in peripheral resistance (11-13) and lack of such increases (14-17) have been reported during experimental myocardial infarction. Differences in the experimental techniques or conditions used may account for these conflicting results. These include: (a) the necessity for thoracotomy to gain access to the coronary vessels (11, 13, 16), (b) study of coronary occlusion which failed to produce sustained or severe hypotension (11, 13, 16), (c) possible deterioration of the animals with time (12), and (d) lack of continuous blood flow measurement (11).

Experimental data pertaining to reflex changes in vascular resistance measured directly in an individual vascular bed during sustained, severe hypotension due to myocardial infarction have not been published. The experiments reported in this study were undertaken to observe reflex changes in...
hindlimb vascular resistance in order to examine directly the possibility that failure of vascular resistance to increase contributes to postinfarction hypotension. Possible mechanisms responsible for such failure were also investigated.

Methods

Fifty adult mongrel dogs of both sexes weighing 16 to 28 kg were anesthetized with pentobarbital sodium (30 mg/kg iv). All animals underwent tracheotomy, exposure of the left carotid artery and vagus nerve in the neck, right brachial artery cannulation for blood pressure determination, and brachial vein cannulation for administration of a 0.9% saline infusion and for administration of test drugs. In some animals the right carotid sinus nerve was exposed in the region of the carotid bifurcation. Blood pressures were measured with Statham arterial pressure transducers and recorded on a Beckman Type R Dynograph. No antiarrhythmic or paralytic agents were used. Artificial ventilation (Harvard respirator pump) was provided only for those animals undergoing bilateral vagotomy to avoid respiratory embarrassment associated with removal of pulmonary vagal afferents which inhibit inspiration.

Myocardial infarction was produced by injecting styrene divinyl benzene copolymer beads (Dow Chemical) suspended in heparinized arterial whole blood, through a double lumen stainless steel catheter with a balloon at the tip, as described by Agress et al. (17). The catheter was passed through the left carotid artery and the tip placed above the aortic valve. When the balloon was inflated with 25 ml of air, injected by syringe through the outer cannula, systemic arterial pressure recorded through the brachial artery cannula fell to near zero. Thus a closed compartment between the inflated balloon and the aortic valve was created; the only exits from this compartment were the coronary arteries. The inner cannula of the catheter was used to inject microspheres and to measure aortic pressure.

Microspheres 290 to 350μ in diameter were obtained by passing a mixture of the beads through nos. 45 and 50 U. S. Standard sieves. Microscopic examination of a random sample of the microspheres indicated that the mean diameter was 330μ. Because coronary injection of acacia recommended for microsphere suspension by Agress et al. (14, 17) and Jacobey et al. (18) produced hypotension in control animals, heparinized arterial whole blood was utilized for the suspending medium in subsequent experiments. Ten mg/kg microspheres were suspended in 20 ml of heparinized dog blood. This was placed in a 125 ml aspirator bottle. Even dispersion of the spheres in the medium was maintained by a magnetic stirrer (Fisher Scientific). The outflow tube of the aspirator bottle was connected by a rubber tube to one arm of the three-way stopcock attached to the inner lumen adapter of the balloon catheter. Through a glass Luer Lok syringe attached to the other arm of the three-way stopcock, the desired volume of the blood-microsphere dispersion could be drawn up from the aspirator bottle for embolization. After near-zero systemic blood pressure was produced by inflating the occluding balloon, embolization was accomplished by injecting the contents of the syringe. Approximately six ventricular contractions occurred from the time of embolization to the release of the occluding balloon to insure complete delivery of the spheres into the coronary arteries. An initial dose of 2.0 mg/kg microspheres was followed as necessary by doses of 2.0 mg/kg or less until a 40% or greater reduction in mean arterial pressure was obtained. Examination of kidneys from six dogs showed no embolization in these organs, indicating that the balloon had effectively limited the microspheres to the coronary arteries.

Serial electrocardiograms were recorded during control and postinfarction periods. Standard limb and exploratory precordial leads were recorded on a Sanborn Viso-Cardiette.

Flow Measurement in the Intact Hindlimb.—The right femoral artery was exposed in the thigh below the femoral ring and a small muscular branch of the artery cannulated with polyethylene tubing. Flow was measured continuously by a square-wave electromagnetic flowmeter (Carolina Medical Electronics) using a previously calibrated Invivometric flow transducer. Results were recorded on the Beckman Dynograph. The zero flow level was determined periodically during the experiment by producing transient total occlusion of the artery with an arterial clamp below the flow transducer.

Measurements of changes in vascular resistance in the hindlimb due to vasoconstrictor and vasodilator stimuli were made during the control period and after the animal had been in the hypotensive state for one-half hour without evidence of significant recovery. Vasocostriction

Precaution was taken in these experiments to use approximately 10 more ml of air than was required to occlude the aorta. This precaution was successful in preventing any microspheres from reaching the kidney and, presumably, other vital organs and muscle and skin. As also noted by Jacobey et al. (18), microspheres can be, for all practical purposes, restricted to the heart. Thus, with appropriate precautions, the leakage of microspheres noted by Agress et al. (17) need not occur.
was produced by injection of norepinephrine into a cannulated muscular branch of the femoral artery and by electrical stimulation of the lumbar sympathetic trunk. Reflex vasodilatation was produced by electrical stimulation of the right carotid sinus nerve with a bipolar stainless steel electrode. The sympathetic chain and carotid sinus nerve were stimulated for 30 seconds using a Grass stimulator, the former at 15 v, 5, 10 and 20 cps and 2-msec pulse duration and the latter at 6 v, 50 cps and 2-msec pulse duration. Vascular resistance (R) of the limb was calculated by the formula R = arterial pressure (mm Hg)/limb blood flow (ml/min).

Unilateral Hindlimb Perfusion.—Cervical dissection and laparotomy were performed as in the variable flow experiments. After anticoagulation with heparin sodium (5 mg/kg iv) and ligation of collateral vessels to the innervated hindlimb to be perfused, the right and left external iliac arteries were divided and a shunt was created between the distal end of the external iliac artery of the limb to be perfused and the proximal end of the contralateral external iliac artery. Blood was directed to the perfused limb through Silastic tubing (Dow Corning) (50-ml capacity) by means of a constant flow Sigmamotor pump (Model T6S). Perfusion pressure, which was set initially by adjustment of the pump to equal systemic mean arterial pressure was monitored by a Statham arterial pressure transducer connected to a side arm of the distal cannula. Flow remained constant throughout each experiment so that changes in perfusion pressure varied directly with changes in vascular resistance. A delay in transit time through the shunt of 30 to 60 seconds, depending on flow rate, permitted reflex changes in hindlimb vascular resistance resulting from systemic drug effects to occur before the direct effect on limb vasculature of the intravenously administered drug (either norepinephrine or sodium cyanide) occurred.

In addition to the test stimuli used in the variable flow experiments, reflex vasodilatation produced by norepinephrine (1 μg/kg iv) and reflex vasoconstriction resulting from 60 seconds of asphyxia (produced by occlusion of the tracheal cannula), bilateral common carotid artery occlusion and sodium cyanide (0.2 mg/kg iv) were measured before and after infarction. The order of administration of the stimuli was randomized. As in the variable flow preparation, the responses after infarction to the above stimuli were not tested until the animal was in the hypotensive state for 30 minutes without signs of recovery.

Arterial Po₂, Pco₂ and pH were measured by a pH/Gas Analyzer (Instrument Laboratory) in five of these animals during the control period and after 60 minutes of hypotension.

Bilateral Hindlimb Perfusion.—The possible effects of humoral factors on hindlimb vascular resistance were studied in the autoperfused denervated hindlimb and compared to the changes occurring in the contralateral autoperfused, innervated hindlimb. These studies utilized a left retroperitoneal flank approach to facilitate access to both sympathetic chains. After anticoagulation with heparin sodium (5 mg/kg iv) a shunt was established between the lower abdominal aorta and both external iliac arteries by Y-shaped Silastic perfusion tubing. Both hindlimbs were perfused at a constant flow (the two tubes were passed through a single Sigmamotor pump) throughout the experiment with perfusion pressure initially set to equal systemic mean arterial pressure.

Reflex vasodilatation in response to systemic hypertension induced by norepinephrine (1 μg/kg iv) and reflex vasoconstriction in response to 60 seconds of asphyxia were elicited to confirm the presence of these reflexes in both limbs. Following this, one of the lumbar sympathetic chains at the L4 level was transected. The previously mentioned stimuli were again administered to verify that these reflexes were abolished in the sympathectomized limb. During postembolic hypotension, the changes in perfusion pressure in both limbs were recorded. At the conclusion of the experiments, the intact limb was also sympathectomized and the change in perfusion pressure recorded.

To measure reflex changes in response to hypotension produced by a cause other than coronary embolization, a sham-operated preparation identical to the above bilateral perfusion preparation with unilateral sympathectomy was prepared. The aortic balloon catheter was inserted as in the other studies but no microspheres were injected. The distal end of the cut right vagus nerve was stimulated through a bipolar electrode for 5 minutes by a Grass stimulator (6 v, 5 to 20 cps at 2 msec) to produce bradycardia and hypotension.

Statistical analysis of these data employed analysis of variance using randomized complete block designs with orthogonal comparisons and grouped or paired comparison Student’s t-tests (19). A probability level of 0.05 or less was used as the criterion for significance.

Results

Flow Measurements in the Intact Hindlimb.—Blood pressure reductions averaged 45% following embolization in the seven animals studied. As the example on the right in Figure
Effect of coronary artery embolization on vascular resistance in the hindlimb. The experiment on left is from a preparation in which the limb was perfused at constant flow, and that on the right is from a preparation in which blood flow was measured in the intact limb. MBP = mean brachial blood pressure; BP aortic = aortic blood pressure; PP = perfusion pressure; all are in mm Hg. Spheres refer to intracoronary injection of microspheres at the listed dose. ECG’s for each experiment are shown 5 and 60 minutes after injection of microspheres. II = Standard lead II; V = precordial lead. In neither type of experiment does resistance change significantly, despite marked hypotension. During embolization, limb perfusion pressure falls because inflation of the balloon reduces the amount of blood available to the pump.

1 illustrates, flow decreased proportionately; consequently, calculated hindlimb vascular resistance did not change in the immediate postinjection period. A summary of the effects of embolization on blood pressure and hindlimb vascular resistance of seven animals at 5, 30 and 60 minutes after embolization is found in Table 1.

During hypotension there was a tendency for responses to vasoconstrictor stimuli to be reduced. Vasoconstriction in response to 2 μg of intra-arterial norepinephrine and to sympathetic chain stimulation at 20 cps was reduced significantly. The degree of reflex vasodilatation produced by carotid sinus nerve stimulation was not changed during hypotension. Table 2 summarizes these experiments.

Resistance Changes in the Perfused Hindlimb.—The example shown on the left in Figure 1 demonstrates that pressure in the hindlimb perfused at constant flow did not increase despite a 50% reduction in mean arterial pressure. Results from eight such experiments are summarized in Table 1. Mean arterial pressure in these experiments was reduced significantly, while hindlimb perfusion pressure was not changed at any time after embolization.

The effects of embolization on vasoconstrictor responses are summarized in Table 2. Vasoconstriction resulting from electrical stimulation of the sympathetic chain at 10 and 20 cps and vasoconstriction in response to 1 μg of intra-arterial norepinephrine was reduced significantly. The overall average reduction in response to sympathetic stimulation was 66%, and the average reduction in vasoconstriction in response to intra-arterial norepinephrine was 25%. Reflex vasoconstriction in response to...
common carotid artery occlusion was reduced significantly, as was expected because of the already lowered blood pressure. Reflex vasoconstriction in response to chemoreceptor stimulation (asphyxia and sodium cyanide) was not altered significantly during hypotension. Vasodilator reflexes resulting from electrical stimulation of the right carotid sinus nerve and from hypertension induced by intravenous norepinephrine remained intact.

Blood gases and pH were measured in five of these experiments (Table 3). After 60 minutes of hypotension, arterial P02 and pH were not significantly different from control values. Pco2 decreased but remained within the normal range.

The possibility that the reduction in vascular responsiveness to intra-arterial norepinephrine and sympathetic nerve stimulation during postembolic hypotension was due to deterioration of the animal with time was examined in four animals. Hindlimb perfusion and intra-coronary injection were performed by the same techniques described for those animals whose coronary arteries were embolized, except that microspheres were not injected. Sympathetic nerve stimulation and injection of intra-arterial norepinephrine were performed during the control period and repeated 60 minutes following sham embolization; systemic blood pressure did not change following sham embolization. As summarized in Table 2, after the 60 minute time interval, these vasoconstrictor responses were not significantly different from control values.

Resistance Changes in Independently Perfused Hindlimbs.—The possibility that a circulating vasodilator substance released during hypotension might be antagonizing, and thus masking, reflex vasoconstriction was investigated. Figure 2 demonstrates failure of vasoconstriction to occur in either the innervated or denervated hindlimbs immediately after the onset of hypotension resulting from coronary embolization. A small rise in perfusion pressure occurred in both limbs at 30 minutes. The reflex vasodilator response to norepinephrine-induced hypertension was preserved. Sympathectomy reduced perfusion pressure to innervated hindlimbs due to norepinephrine-induced hypertension. The reflex vasodilator response to norepinephrine-induced hypertension was not significantly different from control values. These results are consistent with the hypothesis that reflex vasodilator mechanisms were not significantly altered by coronary embolization.
### Table 2

**Influence of Coronary Embolization on Vascular Responses in Intact Limbs and in Limbs Perfused at Constant Flow**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Change in resistance (mm Hg/ml/min)</th>
<th>Constant flow</th>
<th>Change in perfusion pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After*</td>
<td>MD ± SE or CV</td>
</tr>
<tr>
<td>Norepinephrine (intra-arterial)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 μg</td>
<td>8.1</td>
<td>2.8</td>
<td>NS</td>
</tr>
<tr>
<td>2 μg</td>
<td>11.9</td>
<td>2.0</td>
<td>99%</td>
</tr>
<tr>
<td>Sympathetic nerve stimulation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 cps</td>
<td>2.9</td>
<td>1.5</td>
<td>NS</td>
</tr>
<tr>
<td>10 cps</td>
<td>3.3</td>
<td>2.1</td>
<td>79%</td>
</tr>
<tr>
<td>20 cps</td>
<td>6.9</td>
<td>2.9</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Carotid sinus nerve stimulation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.64</td>
<td>0.62</td>
<td>0.02 ± 0.5</td>
</tr>
<tr>
<td>Norepinephrine (1μg/kg iv)</td>
<td>−54</td>
<td>−50</td>
<td>4 ± 9</td>
</tr>
<tr>
<td>Asphyxia</td>
<td>15</td>
<td>10</td>
<td>5 ± 5</td>
</tr>
<tr>
<td>Common carotid artery occlusion</td>
<td>9</td>
<td>2</td>
<td>7 ± 2</td>
</tr>
<tr>
<td>Sodium cyanide (0.2 mg/kg iv)</td>
<td>16</td>
<td>17</td>
<td>1 ± 2</td>
</tr>
</tbody>
</table>

MD ± SE or CV refers to the mean difference ± SE when analyzed by paired t-tests and the coefficient of variability by analysis of variance. Number of animals in each experiment is in parentheses. NS = not significant.

*Hypotensive period — at least 30 minutes after embolization.
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### TABLE 3

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Hypotension</th>
<th>MD ± SE</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PO₂</td>
<td>78</td>
<td>76</td>
<td>2 ± 3.7</td>
<td>NS</td>
</tr>
<tr>
<td>pH</td>
<td>7.33</td>
<td>7.31</td>
<td>0.2 ± 0.01</td>
<td>NS</td>
</tr>
<tr>
<td>PCO₂</td>
<td>44.8</td>
<td>38.4</td>
<td>6.4 ± 1.1</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Mean values of blood gases in mm Hg and pH of 5 animals from the unilateral perfusion experiments determined during the control period and 60 minutes after emboli. MD = mean difference. P values obtained by paired t-test. NS = not significant.

Acute reduction in perfusion pressure by sympathetic denervation of the hindlimb in the hypotensive state was not significantly different from that produced by sympathectomy of the opposite hindlimb before embolization. The degree to which resistance recovered following acute sympathectomy was also not significantly different.

**Hypotension Produced by Vagus Nerve Stimulation.**—An example of vasoconstriction resulting from hypotension produced by stim-

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**FIGURE 2**

Effect of coronary artery embolization on perfusion pressure in simultaneously perfused innervated (intact) and denervated hindlimbs. Norepi = intravenous injection of norepinephrine. Spheres = intracoronary injection of microspheres. Because of the high pressure measured through the aortic cannula during balloon inflation, the needle recording aortic pressure was deflected onto the brachial pressure tracing. Post Lumbar Symp-X = response obtained after intact lumbar sympathetic chain had been sectioned. Times after embolization are shown above the tracings. Abbreviations as in Figure 1.

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ulation of the distal end of the right vagus nerve is shown in Figure 3. A summary of the changes in arterial and bilateral hindlimb perfusion pressures in seven animals made hypotensive by vagus nerve stimulation is shown in Table 4. Hypotension produced by stimulation of the right vagus nerve could be maintained for 5 minutes without producing cardiac arrest. The reduction in mean arterial pressure produced by this method was essentially the same as that occurring during the first 5 minutes of hypotension following embolization. While perfusion pressure did not increase significantly during the first 5 minutes in the innervated limbs of 13 dogs sustaining hypotension due to coronary embolization, a large, almost immediate, significant increase in perfusion pressure occurred following hypotension induced by stimulation of the vagus nerve.

Perfusion Pressure Changes Following Postembolic Hypotension in Vagotomized Dogs.—Changes in perfusion pressure in the innervated autoperfused hindlimb during hypotension in 5 animals vagotomized prior to embolization were compared to the changes that occurred in perfusion experiments in which the vagi were intact. As summarized in Table 5, animals vagotomized prior to embolization of the coronary arteries responded to a comparable reduction in blood pressure by an immediate increase in hindlimb perfusion pressure. The magnitude of this increase was significantly greater at all time intervals than the small increases in perfusion pressure that occurred in animals in the postembolic hypotensive state with intact vagi. This large increase was similar to the increase in perfusion pressure occurring in the experiments in which hypotension was induced by vagal stimulation. The dose of microspheres required to lower blood pressure by 40% was $4.8 \pm 1.1$ mg/kg in nonvagotomized and $9.1 \pm 1.6$ mg/kg in vagotomized animals.

In two animals, bilateral vagotomy was performed after 20 minutes of hypotension. Average changes in blood pressure and limb perfusion pressure were as follows. Blood pressure was reduced by embolization from 120 to 65 mm Hg; vagotomy increased blood
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**TABLE 4**

<table>
<thead>
<tr>
<th></th>
<th>Min after embolization</th>
<th>During vagal stimulation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 (13)</td>
<td>30 (11)</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>100</td>
<td>103</td>
</tr>
<tr>
<td>After emboli</td>
<td>52</td>
<td>54</td>
</tr>
<tr>
<td>MD = SE</td>
<td>48 ± 5</td>
<td>49 ± 4</td>
</tr>
<tr>
<td>P*</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Perfusion pressure (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intact limb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>124</td>
<td>131</td>
</tr>
<tr>
<td>After emboli</td>
<td>13 ± 5</td>
<td>148</td>
</tr>
<tr>
<td>MD = SE</td>
<td>8 ± 5</td>
<td>17 ± 4</td>
</tr>
<tr>
<td>P*</td>
<td>NS</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Denervated limb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>95</td>
<td>95</td>
</tr>
<tr>
<td>After emboli</td>
<td>101</td>
<td>112</td>
</tr>
<tr>
<td>MD = SE</td>
<td>6 ± 4</td>
<td>17 ± 5</td>
</tr>
<tr>
<td>P*</td>
<td>NS</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Number in parentheses is number of animals; decrease with time is due to death of animals.
MD = mean difference; NS = not significant.
*Mean changes in blood and perfusion pressures during 5 minutes of vagal stimulation are compared to changes in these variables 5 minutes after onset of hypotension; obtained by grouped t-tests.
†Perfusion pressure increases in the innervated limb resulting from stimulation of the vagus nerve were significantly greater than those 5 minutes after coronary embolization.
‡Obtained by paired t-tests.
§Control is value at zero time averaged for the number of dogs that survived at 5, 30, and 60 minutes.

Heart Rate and ECG Changes.—Table 6 summarizes the effect of acute embolization on heart rate. Significant changes in heart rate did not result from coronary embolization or hypotension except during brief bursts of ventricular arrhythmias in animals with intact vagi. Control and postembolic heart rates in animals vagotomized before embolization were not significantly different from those of nonvagotomized animals, since the animals were presumably already under the vagolytic effect of pentobarbital (20).

The electrocardiograms of 34 animals were examined. There were classical ST segment elevations in leads II and III following embolization in 13 experiments, while ST segment elevation in leads I and precordial leads occurred in 4 experiments. In the remaining 17, there were deep ST segment depressions in precordial and limb leads with high peaked T waves which later inverted.

Discussion

When hypotension was produced by coronary embolization, blood pressure and blood flow in the intact limb fell proportionately. Calculated vascular resistance remained unchanged. However, unchanged vessel caliber in the face of reduced distending pressure indicated that vessel wall tension had fallen.
TABLE 5

Effect of Vagotomy Performed before Embolization on Changes in Blood Pressure and Hindlimb Perfusion Pressure Produced by Coronary Embolization

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Change after injection of microspheres</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>5 min</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vagi intact*</td>
<td>99 ± 4</td>
<td>-48 ± 4</td>
</tr>
<tr>
<td>Vagi cut</td>
<td>120 ± 8 (5)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limb perfusion pressure (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vagi intact*</td>
<td>131 ± 8</td>
<td>+4 ± 3</td>
</tr>
<tr>
<td>Vagi cut</td>
<td>123 ± 7 (5)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Control values were obtained just before embolization. P obtained by grouped t-tests; NS = not significant. Number in parentheses is number of animals.

The values for systemic arterial and perfusion pressures before and after embolization in the nonvagotomized unilateral and bilateral perfusion experiments were pooled, since the values were not significantly different from each other statistically.

On this basis it was anticipated that perfusion pressure would fall following embolization when the limb vessels were perfused at constant flow. Since this did not occur, the fall in vessel wall tension in the variable flow experiments must have been of some other origin than neurogenic, perhaps the result of a local autoregulatory compensation for the fall in distending pressure (21, 22).

It is evident from the present data that compensatory reflex vasoconstriction in the hindlimb of the dog, the expected response to hypotension, failed to occur in the face of a 50% reduction in systemic mean arterial pressure after injection of emboli. Possible explanations considered in the present study for this failure of vasoconstriction to occur included (a) the opposing influence of a circulating vasodilator substance, (b) impaired function or decreased sensitivity of chemoreceptors, (c) impaired transmission of sympathetic impulses through sympathetic nerves, ganglia, or both, or by inhibition of release of the neurotransmitter norepinephrine from nerve endings, (d) diminished responsiveness of vascular receptors to the neurotransmitter norepinephrine, or (e) reflex inhibition of reflex vasoconstriction perhaps mediated by activation of cardiac afferents.

The likelihood that hypotension was associated with release of a circulating vasodilator substance in sufficient quantity to mask reflex vasoconstriction was excluded in the bilateral hindlimb perfusion experiments. If such had been the case, vasodilatation would have been noted in the denervated limb, since the vessels in this limb are presumably responsive only to circulating vasoactive substances. Immediate

TABLE 6

Heart Rate (Beats/Min) in Dogs with and without Vagotomy during Postembolic Hypotension

<table>
<thead>
<tr>
<th>Vagi Status</th>
<th>Min after onset of hypotension</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Control*</td>
<td>137 (21)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>133</td>
</tr>
<tr>
<td>MD ± SE†</td>
<td>7 ± 5</td>
</tr>
<tr>
<td>Vagi cut</td>
<td>130 (4)</td>
</tr>
<tr>
<td>Control*</td>
<td>130</td>
</tr>
<tr>
<td>Hypotension</td>
<td>130</td>
</tr>
<tr>
<td>MD ± SE†</td>
<td>0</td>
</tr>
</tbody>
</table>

*Average value at zero time for animals surviving at each time. Number in parentheses is number of animals. Number decreases because of death of animals.
†Mean difference in heart rates during control and hypotensive periods compared by paired t-tests. Changes were not statistically significant, and there was no significant difference between control values of dogs with, and those without, vagotomy.

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Vasoconstriction and Coronary Embolization

Immediately after the onset of hypotension, no change in hindlimb perfusion pressure occurred in either the innervated or denervated hindlimbs. Thus, there was neither an increased concentration of a humoral vasodilator, nor was there any change in the effect of neurogenic activity to the intact limb. Thirty minutes later, a small but significant increase in perfusion pressure occurred in both hindlimbs. Since the increment in hindlimb perfusion pressure in the denervated hindlimb was equal to that which occurred in the innervated limb, this small rise in resistance probably represents the influence of a vasoconstrictor substance released into the circulation late in the course of hypotension, and not neurogenically-induced reflex vasoconstriction.

The small change in perfusion pressure in the innervated hindlimbs of both unilateral and bilateral autoperfusion experiments indicated that tension in the vessel walls of the arterial vasculature did not change greatly during the hypotensive period after infarction. Since only small changes in vascular resistance occurred in both the innervated and denervated hindlimbs of the bilateral autoperfusion experiments, it may be concluded that normal neurogenic vascular tone is sustained during hypotension after coronary embolization. This view is further supported by data which indicated that in bilaterally autoperfused hindlimbs the degree of vasodilatation produced by sympathectomy was essentially the same whether it occurred before or after embolization.

Failure of peripheral resistance to increase in response to hypotension might be the result of alteration in the integrity of vascular reflexes known to participate in the regulation of peripheral resistance. This possibility was examined in both variable flow and constant flow preparations. Vasoconstrictor reflexes in response to chemoreceptor stimulation were not altered significantly during hypotension. These data therefore indicated that the failure of peripheral resistance to increase during hypotension was not due to any disturbance of the chemoreceptor reflex and further demonstrated that reflex increases in peripheral resistance were possible under the conditions existing following injection of emboli. The chemoreceptor reflex response could have resulted in part from activation of the chemoreceptors by hypotension per se.

Preliminary studies on vasoconstriction produced in the intact hindlimb by electrical stimulation of the preganglionic lumbar sympathetic chain and by local intra-arterial injection of norepinephrine suggested that the postembolization hypotensive state was associated with attenuated responses to these stimuli at a peripheral locus. The increments in calculated vascular resistance produced by these stimuli were less than those observed before embolization. However, femoral blood flow was already reduced from control levels, limiting the magnitude of possible vasoconstriction. It was necessary, therefore, to confirm these findings in the autoperfused hindlimb with flow constant. Diminished vasoconstriction in response to preganglionic stimulation of the sympathetic chain and norepinephrine was also observed in these preparations. The depression of the vasoconstrictor response to sympathetic stimulation appeared to be twice as great as the reduction in response to intra-arterial norepinephrine. Since the decrement in vasoconstrictor response to intra-arterial norepinephrine was insufficient to explain the larger decrement in response to stimulation of the sympathetic chain, mechanisms which operate to inhibit liberation of norepinephrine from sympathetic terminals or to reduce ganglionic transmission may have been active. This reduction in responsiveness to sympathetic nerve stimulation could have resulted from the effects of sustained hypotension, but was not likely to have been caused by time alone or by respiratory or metabolic alterations since (1) no reduction in vasoconstriction in response to these stimuli occurred in identically prepared sham-embolized control animals and (2) arterial blood gas and pH values during the postembolization period were not altered significantly. These findings suggest that impaired sympathetic transmission, involving both sympathetic nerves and blood vessels, is
perhaps involved in the lack of reflex vasoconstriction observed during hypotension induced by coronary embolization. However, as will be seen, this mechanism does not appear to play a primary role.

One of the questions considered was whether, under the conditions of these experiments, reflex constriction would have occurred in the face of hypotension induced by other means. In nonembolized animals an appropriate large immediate increase in hindlimb vascular resistance occurred when hypotension equivalent to that resulting from coronary embolization was produced by electrical stimulation of the distal segment of the sectioned right vagus nerve. The lack of such an immediate response during hypotension due to emboli suggested that inhibition of the normal reflex vasoconstrictor mechanism had occurred.

Normal reflex vasoconstrictor responses produced by hypotension occurred following bilateral cervical vagotomy. Animals vagotomized prior to coronary embolization responded to a 40% reduction in mean arterial pressure by an appropriate large immediate increase in hindlimb vascular resistance similar to that which resulted from hypotension induced by electrical stimulation of the vagus. Bilateral cervical vagotomy during the course of postembolic hypotension also allowed normal reflex vasoconstriction to proceed. These data indicate that the normal baroreceptor reflex, which promotes vasoconstriction during systemic hypotension, is reflexly inhibited immediately following coronary embolization, perhaps by activation of cardiac vagal afferents. It is of interest to note that this inhibitory mechanism appears to be quite specific for the vasoconstrictor reflex activated by hypotension (low pressure on the baroreceptors) since vasodilator baroreceptor reflexes were unaltered by hypotension associated with coronary embolization.

In experiments involving stimulation of the distal end of the sectioned right vagus, reflex vasoconstriction occurred during the hypotensive period. It might be argued that this vasoconstriction occurred only because afferents which inhibit vasoconstriction and are carried in the right vagus were removed. This possibility seems remote because we demonstrated in these experiments that reflex vasoconstriction mediated through the baroreceptors occurred in the presence of intact vagi (carotid occlusion response prior to embolization). By comparison, no early reflex vasoconstrictor response occurred after embolization when vagi were intact. In addition, the increase in pulse pressure associated with bradycardia produced by vagal stimulation would have tended to reduce rather than increase the magnitude of reflex vasoconstriction, i.e., for the same reduction in mean pressure produced by embolization and by vagal stimulation, greater activation of the baroreceptors, and thus less vasoconstriction, would have been anticipated with the larger pulse pressure found during vagal stimulation. The validity of the experiments using vagal stimulation as an means of testing for the effects of hypotension appears to be reinforced by this argument.

The experiments with vagotomy, while clearly demonstrating that reflex vasoconstriction can proceed following embolization in the absence of the vagi, leave unanswered many questions about the role and precise nature of the proposed afferents. For example, since the vagosympathetic trunks contain efferent and afferent fibers to and from many parts of the body, the possibility remains open that the afferent inhibitory activity arose from some extracardiac site, perhaps activated by low arterial pressure. The possibilities that all the fibers pass centrally in either the right or left vagus or that the fibers might be identified by differential cooling of the vagosympathetic trunk, or by specific cardiac vagal deafferentation remain unexplored.

The location and nature of the proposed intracardiac receptors is not known. However, the existence of intramural myocardial receptors that influence cardiovascular performance has been established by others (23-27). It is conceivable that more than one kind of receptor exists. It seems unlikely that a baroreceptor-like response to increased intra-
cavitary pressure resulting from heart failure
initiates this reflex since it has been dem-
onstrated by Agress et al. (14) that these
pressures do not increase for several hours
after the onset of postembolic hypotension.
Stretch placed on normal cardiac tissue
adjacent to the injured zone during systole
is an unexplored possibility. Agress et al. (14)
found that occlusion of only right angle
branches of mainstem coronary arteries in the
ventricular myocardium of the dog by micro-
spheres consistently resulted in postembolic
hypotension. Kurland et al. (28), in a
retrospective study of postmortem exami-
nations of patients dying following myocardial
infarction, found that the incidence of shock
was significantly greater when associated with
occlusions of primary branches of the main
coronary arteries or in branches formed after
their terminal bifurcation than in mainstem
occlusion or infarctions without fresh occlu-
sions. These findings suggest that an "injury
receptor" sensitive to damage or to products
released from injured tissue might be opera-
tional in evoking inhibitory reflexes.

It should be mentioned that vagal afferents,
proposed to be fundamentally important for
inhibiting reflex vasoconstriction following
myocardial infarction, may not be the sole
afferent pathway involved. The suggestion has
been made that inhibition of reflex vasocon-
striction (17, 29) or actual vasodilatation (30)
after myocardial infarction could result from
the activation of afferent nerve fibers traveling
in the sympathetic nerves innervating the
heart.

Reflex inhibition of reflex vasoconstriction
during postinfarction hypotension could result in
perfusion of nonvital areas such as skin and
skeletal muscle and underperfusion of heart,
brain and kidney. The influence of such
inhibition of reflex vasoconstriction has not,
however, been studied in other vascular beds
during postembolic hypotension. Although the
data obtained from animal experiments may
not be directly applicable to man, sufficient
data suggesting that failure of vascular
resistance to increase may be contributing to
cardiogenic shock in man (4, 6) and animal
have been accumulated to warrant further inqui-
ry into this possibility.

References
1. LOWN, B., AND SELZER, A.: Coronary care unit.
3. KUHN, L. A.: Treatment of cardiogenic shock:
Part 1: Nature of cardiogenic shock. Amer
4. THOMAS, M., MALMCRONA, R., AND SCHILLING-
ford, J.: Circulatory changes associated with
systemic hypotension in patients with acute
myocardial infarction. Brit Heart J 28: 108,
1966.
5. SMITH, W. W., WIKLER, N. S., AND FOX, A. C.: Hemodynamics studies of patients with myo-
6. GUNNAR, R. M., CONZ, A., BOSWELL, J., CO, S. B.,
PIETRAS, R. J., AND TEBIN, J. R.: Myocardial
infarction with shock. Circulation 33: 753,
1960.
7. GUNNAR, R. M., LOEB, H. S., PIETRAS, R. J., AND
TOBIN, J. R.: Ineffectiveness of isoproterenol in
shock due to acute myocardial infarction.
8. GROOTNICK, A., AND KNOX, F. H.: Management of
shock in acute myocardial infarction. Circula-
tion 7: 511, 1953.
9. ROSS, J.: Left ventricular contraction and the
therapy of cardiogenic shock. Circulation 35:
611, 1967.
10. WENDT, V. E., BALCON, R., RIBEILMA, J., AND
BING, R. J.: Circulatory changes following
experimental myocardial infarction. In Shock
and Hypotension, edited by L. C. Wells and J.
H. Moyer. New York, Grune and Stratton,
1965, p. 492.
response to acute coronary occlusion in the
12. LLUCH, S., MOQUELENSKY, H. C., PIETRA, C.,
SHAFFER, A. B., HIRSCH, L. J., AND FEINAN,
A. P.: Reproducible model of cardiogenic
746, 1962.
14. AGRESS, C. M., GLASSNER, H. F., BINDER, M. J.,
469, 1957.
15. BING, R. J., CASTELLANOS, A., GRADEL, E.,
LOUPION, C., AND SEIDEL, A.: Experimental
myocardial infarction: Circulatory, biochemical
and pathologic changes. Amer J Med Sci 232:
533, 1956.

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