Reflex Blood Pressure Control during Acute Myocardial Ischemia in the Conscious Dog

By D. Fred Peterson and Vernon S. Bishop

ABSTRACT
Occlusions of the left circumflex coronary artery were performed before and after surgical denervation of sinoaortic baroreceptors in conscious, resting dogs. The removal of baroreceptors dramatically compromised arterial blood pressure maintenance. Mean pressure fell 9.1 mm Hg before denervation and 33.0 mm Hg after denervation. Aortic flow was reduced somewhat more without baroreceptors, and calculated total peripheral resistance fell 15% at the peak of occlusion in denervated dogs compared with a 2% increase in intact dogs. Flow studies indicated that femoral resistance was maintained or increased under the influence of active arterial baroreceptors but that femoral resistance fell dramatically in their absence. Renal resistance fell during coronary occlusion whether or not arterial baroreceptors were functional. Under both conditions, renal flow was maintained near its resting level. Results of this study suggest an important function in the maintenance of perfusion pressure by arterial baroreceptors during left circumflex coronary artery occlusion. The elimination of the arterial baroreceptors unmasked a dilatory response that reduced total peripheral resistance and, consequently, arterial blood pressure. Vessels which supply skeletal muscle and skin collectively were critically involved, but flow to the kidneys did not appear to play an important role.

KEY WORDS
renal flow peripheral resistance coronary occlusion femoral flow autoregulation arterial baroreceptors

Dramatic cardiovascular changes result from acute coronary artery occlusion in anesthetized and conscious dogs (1–6). Among the changes observed, however, only tachycardia (4) and alterations in peripheral vascular resistance (2, 3, 6) have been shown to be reflexive. There is disagreement about the direction of change in peripheral resistance. Some investigators have observed increased resistance during coronary artery occlusion (6), some have observed decreased resistance (2), and still others have found different responses in specific vascular beds (3).

Changes in cardiovascular dynamics that are rapid and dramatic during coronary artery occlusion suggest the possible stimulation of both arterial and cardiopulmonary baroreceptors (4). A slight fall in arterial blood pressure, a rise in left atrial pressure, and an enlargement of the left ventricle accompany left circumflex occlusion in conscious dogs (1, 4, 5). Such responses could produce antagonistic reflex effects on peripheral resistance change due to increased stretch of cardiopulmonary mechanoreceptors and decreased stretch of sinoaortic mechanoreceptors (7).

The present experiments describe a subtle role of the arterial baroreceptors in maintaining arterial blood pressure during 1 minute of left circumflex coronary artery occlusion in conscious dogs and the subsequent unmasking of a peripheral dilatory effect in the absence of arterial baroreceptors. Reflex influences on total peripheral resistance and selective influences on femoral and renal resistance were investigated as mechanisms for regulating perfusion pressure.

Methods

CHRONIC SURGERY
A total of 23 mongrel dogs (10–25 kg) was chronically instrumented under sterile surgical conditions and halothane anesthesia. A left thoracotomy was performed through the fifth intercostal space exposing the anterior half of the heart and the great vessels coursing cranially. The pericardium was opened, and blunt dissection was used to expose the left circumflex coronary artery just beyond its origin. A 6–10-mm length of the artery was separated from the surrounding tissue, and a balloon-type polyethylene catheter cuff, similar to one pre-
BARORECEPTOR DENERVATION

Sterile surgery was performed on all dogs to denervate their arterial baroreceptors. The dogs were anesthetized with sodium pentobarbital (30 mg/kg, iv), and a midcervical incision was made. The carotid sinuses were located bilaterally, and all vessels above the bifurcation of the common carotid arteries except the external and internal carotid arteries were ligated. All tissue was then stripped from the vessels originating near the common carotid bifurcation. Occlusion of the common carotid arteries verified that reflex heart rate and blood pressure influences from the carotid sinus had been abolished (4). The aortic nerves were located near the junction of the vagus and the superior laryngeal nerves and sectioned. Whenever identification of the aortic nerve was in doubt, all branches of the vagus within 2 cm below the superior laryngeal nerve were sectioned. Baroreceptor-denervated dogs immediately became hypertensive, and their heart rate response to an injection of phenylephrine (10 μg) was abolished or drastically reduced (4). In seven dogs, using sterile techniques and light surgical anesthesia, an electromagnetic flow probe and an occlusive device were placed on the right femoral artery prior to baroreceptor denervation. Coronary artery occlusions were then performed before and after baroreceptor denervation. Zero femoral flow was determined by inflation of the occlusive device, and then both the flow probe and the occluder were removed before recovery from the anesthesia. After several days of recovery, the baroreceptor-denervated dogs were again subjected to coronary artery occlusions.

EXPERIMENTAL PROTOCOL

ECG, blood pressure, heart rate, aortic flow, and renal or femoral flow were recorded simultaneously on a dynograph (Beckman type R) using appropriate transducers, couplers, and amplifiers. Coronary artery occlusions were performed by inflating the coronary cuff with saline, and occlusions were maintained for approximately 1 minute. In our experiments, 1-minute occlusions of the left circumflex coronary artery did not produce extrasympathetic beats.

All experiments except those involving femoral flow were performed while the dog was conscious and lying on its right side unrestrained. Dogs used for femoral flow studies were maintained under light surgical anesthesia while responses to coronary artery occlusion were obtained prior to sinoaortic baroreceptor denervation. After denervation surgery and closure of the cervical incision, femoral flow responses were again studied when the dog had partially recovered from the surgical anesthesia.

Total peripheral resistance expressed in peripheral resistance units (PRU) was calculated:

\[
PRU = \left( \frac{\text{Mean arterial blood pressure (mm Hg)}}{\text{Mean aortic flow (ml/min)}} \right) \times 60 \text{ (sec/min)}.
\]

This formula is oversimplified, since the value for pressure is ordinarily calculated as the difference between arterial pressure and venous pressure (10). However, in three dogs, mean right atrial pressure was near zero at rest and did not rise more than 2 mm Hg during coronary artery occlusion. Therefore, we disregarded venous pressure as have other investigators (11, 12) when calculating the peripheral resistance. Changes in femoral and renal resistance were expressed simply as a percent change in the ratio of pressure to flow.

Phenylephrine was infused slowly into nine dogs to elevate their arterial blood pressure temporarily by about 15 and 30 mm Hg before coronary artery occlusion.

Results

The characteristic response to 1-minute occlusions of the left circumflex coronary artery was a rise in heart rate (+27 beats/min) and left atrial pressure (+57 mm Hg) and a slight fall in mean arterial blood pressure (–9.1 mm Hg); these values are similar to those previously reported (4). Systolic arterial blood pressure fell somewhat further (–18.5 mm Hg), and there was a small but significant fall in aortic flow (–359 ml/min) resulting in no significant change in calculated total peripheral resistance (0.04 PRU, Table 1).

Baroreceptor denervation itself produced physi-
TABLE 1
Pressure, Flow, and Resistance Responses Due to Coronary Artery Occlusion

<table>
<thead>
<tr>
<th></th>
<th>Mean blood pressure (mm Hg)</th>
<th>Cardiac output (ml/min)</th>
<th>Peripheral resistance (PRU)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Resting</td>
<td>Δ</td>
<td>Resting</td>
</tr>
<tr>
<td>Intact dogs</td>
<td>84.6±3.5</td>
<td>−9.1±3.1</td>
<td>2545±206</td>
</tr>
<tr>
<td>Sinoaortic-denervated dogs</td>
<td>100.8±3.2*</td>
<td>−33.0±4.3†</td>
<td>2250±235</td>
</tr>
</tbody>
</table>

Values are means ± SE. All results represent the average for 13 conscious dogs. Resting values were taken 5 seconds before occlusion. Δ represents absolute change from resting value as a result of coronary artery occlusion, and PRU stands for peripheral resistance units. Statistical significance was obtained by a comparison of sample differences using paired observations between intact and sinoaortic denervation trials.

*P<0.05.
†P<0.001.
‡P<0.01.

ological changes. Immediate responses under anesthesia included a dramatic increase in arterial blood pressure and a fall in aortic flow resulting in greatly increased total peripheral resistance. After recovery from denervation surgery (24-48 hours), aortic flow was usually lower, but not significantly different from the presurgery level, although arterial blood pressure was higher (+16.2 mm Hg) and total peripheral resistance was increased (+0.88 PRU) (Table 1). Thus, the dogs remained significantly hypertensive, although the hypertension was not nearly so pronounced as it was in the anesthetized condition immediately after denervation and in the first 24 hours postoperative.

Responses to coronary artery occlusion after denervation were dramatically different from responses before denervation. Systolic and mean arterial blood pressure fell much more than they did before denervation (−33.9 and −33.0 mm Hg, respectively). The fall in aortic flow was slightly greater (−541 ml/min after denervation compared with −359 ml/min before denervation). Instead of total peripheral resistance being maintained during occlusion as it was in the intact dogs, it fell sharply and was 15% lower than the resting, preocclusion value (Fig. 1, Table 1). The earliest indication of pressure changes before denervation was the onset of reduced systolic pressure 14.3 seconds after the beginning of the occlusion. After denervation, systolic pressure began to fall significantly earlier (7.7 seconds, P<0.001).

The possibility that hypertension was directly responsible for the highly significant fall in blood pressure after denervation was investigated in nine dogs. Phenylephrine was infused to selectively constrict peripheral vessels prior to denervation (13). Peripheral resistance and, consequently, blood pressure were elevated to two different levels by

FIGURE 1
Comparison of aortic flow, arterial blood pressure, and total peripheral resistance responses due to coronary artery occlusion before (A) and after (B) sinoaortic baroreceptor denervation. The top trace in each section represents pulsatile flow, the second trace represents mean flow, the third trace represents arterial blood pressure, and the bottom trace represents calculated total peripheral resistance. Coronary artery occlusion begins at the first arrow and ends at the second arrow.
the infusion of phenylephrine. Blood pressure responses to coronary artery occlusion, however, were identical to control responses (Table 2). This finding indicated that hypertension alone was not responsible for the greater fall in arterial blood pressure after baroreceptor denervation. Table 2 demonstrates that baroreceptors in these dogs were functional, since heart rate was reduced as arterial blood pressure rose, and that the heart rate response to coronary artery occlusion was not significantly altered by a 30-mm Hg increase in resting arterial blood pressure or a 17-beat/min reduction in resting heart rate.

FEMORAL VASCULAR RESPONSE

In seven lightly anesthetized dogs instrumented with femoral flow probes, maximal decreases in blood pressure during occlusion were not significantly different from those observed in experiments on conscious dogs (−13.6 ± 3.3 mm Hg intact, −33.0 ± 5.6 mm Hg baroreceptor denervated). In these dogs with baroreceptors intact, femoral flow fell an average of 19.6% below its resting level and femoral resistance rose 11.5% (Fig. 2). After baroreceptor denervation, femoral flow changes were extremely erratic: two dogs showed dramatic increases and five dogs showed decreases. In all cases, however, calculated femoral resistance was much reduced due to coronary artery occlusion after baroreceptor denervation. The mean response in flow was a slight increase of 4.9%. At peak occlusion, flow change ranged between −37% and +74% of its resting value. Thus, large differences in femoral flow from dog to dog probably depended on differences in total distribution in flow. Dogs that showed increases in femoral flow during occlusion had the least fall in arterial blood pressure (−18 mm Hg, mean for two dogs). Dogs whose femoral flow decreased showed greater falls in arterial blood pressure (−39 mm Hg, mean for five dogs).

RENAL VASCULAR RESPONSE

Chronically implanted flow probes indicated that, in six dogs with functional arterial baroreceptors, renal flow was maintained well during coronary occlusion (97.5% of control value) (Fig. 2). Renal resistance was down an average of 10.5% in the six dogs studied. In three of these dogs, renal responses to coronary occlusions were noted after baroreceptor denervation. Renal flow was not greatly altered (−5.5%) in these three dogs. Likewise, renal resistance changes were not significantly different from control values (−15.2%, Fig. 2).

### Table 2

<table>
<thead>
<tr>
<th></th>
<th>Mean blood pressure (mm Hg)</th>
<th>Heart rate (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Resting</td>
<td>Peak response</td>
</tr>
<tr>
<td>Control</td>
<td>93.9 ± 4.0</td>
<td>−11.7 ± 2.0</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>110.5 ± 5.5</td>
<td>−11.4 ± 1.5</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>124.7 ± 4.1</td>
<td>−11.2 ± 1.9</td>
</tr>
</tbody>
</table>

Values are means ± se. Results represent the average for nine conscious dogs. Amount of phenylephrine injected was that required to raise arterial blood pressure to levels 15 and 30 mm Hg above resting for each respective trial. Peak response represents the change observed during coronary artery occlusion.

Circulation Research, Vol. XXXIV, February 1974
Discussions

We found that in the face of myocardial compromise the sinoaortic baroreceptors functioned to maintain arterial perfusion pressure even though the initial change in arterial blood pressure, which initiated the baroreflex, was too subtle to be identified on the recording traces. This finding suggests that the arterial baroreceptors may play a much keener role in beat-to-beat blood pressure regulation than has been suspected previously. It has been reported (4) that with arterial baroreceptors intact mean pressure does not begin to fall until 19.5 seconds after the onset of occlusion. In the present study, without functional sinoaortic baroreceptors, systolic pressure began to fall in 7.7 seconds, although the initial reduction in systolic arterial blood pressure in intact dogs could not be detected until 14.3 seconds after the onset of occlusion. It is clear that detectable, consistent changes in arterial blood pressure did not precede the reflex adjustments that maintained aortic pressure. Thus, efficiently functioning sinoaortic baroreceptors in the conscious dog appear to regulate arterial blood pressure on a beat-to-beat basis. Drastic, sudden reduction in arterial blood pressure in the conscious dog has been shown to affect heart rate on the next beat (14). Beat-to-beat heart rate reduction has been demonstrated following a phenylephrine-induced blood pressure increase in conscious man (15). This finding is supported by recent evidence that heart rate can be modified when electrical stimulation of the aortic nerve is confined to one cardiac cycle (16). However, none of these studies have revealed the profound capacity of the arterial baroreceptors to regulate peripheral resistance to maintain arterial blood pressure when the stimulus to the baroreceptors is subtle. In our study, this capacity was revealed after sinoaortic denervation. Thus, the lack of measurable changes in systemic arterial blood pressure did not preclude functional baroreflex adjustments.

Persistent increases in peripheral resistance and arterial blood pressure were due to the denervation itself. However, our blood pressure values generally agreed with those reported by Cowley et al. (11) and supported their belief that previously reported chronic neurogenic hypertension (17) was undoubtedly exaggerated. The higher peripheral resistance changes and the slightly higher blood pressure values determined in the present experiments could possibly be due to handling of the dogs in the laboratory or to the time of day values were obtained. Our data were collected between 9 AM and 5 PM. Cowley et al. (11) usually made their observations when each dog was isolated from the experimenters, and values were usually the averages of 24 hours of continuous observations. However, since our dogs were preconditioned to the laboratory and often slept during an experiment, it is unlikely that they were excited. It may be significant that all of our values represent resting dogs and that Cowley et al. (11) averaged data from dogs performing all of the normal activities of a caged animal over a 24-hour period.

Since after sinoaortic denervation coronary artery occlusion did not reduce peripheral resistance below presurgical control levels (Table 1) nor did it dramatically reduce blood pressure below intact response levels, the changes in responses might have resulted from the hypertension produced rather than from the loss of baroreceptor function. However, the responses of intact dogs made acutely hypertensive with infused phenylephrine demonstrated that this theory was not the case. The arterial blood pressure responses to coronary artery occlusion were not significantly different from those in the normotensive control dogs, even though resting blood pressure was increased by approximately twice the observed increase in the conscious denervated dogs.

In the present experiment, active maintenance of total peripheral resistance contributed to the maintenance of arterial blood pressure. Our findings demonstrated that, in the conscious dog, functional arterial baroreceptors caused a maintenance of or an increase in femoral vascular resistance that overrode the femoral vasodilatory stimulus which was uncovered after baroreceptor denervation. Because the femoral artery supplies both skeletal muscle and skin, the increase in resistance indicates that maintenance of arterial blood pressure during this period of acute myocardial failure is due to very efficient baroreceptor modulation of sympathetic efferent activity to the periphery. Acute studies have reported conflicting results; one report (7) suggests that, with the vagus intact or cut, femoral vasoconstriction occurs. This finding supports our results that as long as baroreceptors are intact vasoconstriction overrides any other response. Other studies (2, 3) have suggested that when the vagus is intact coronary artery occlusion produces a net vasodilation in the hind limbs during the first minute after occlusion whether or not arterial baroreceptors are functional. A recent study (18) has concluded that, with the vagus cut and the.
sinoaortic regions denervated, the peripheral vasculature autoregulates as cardiac output is altered during coronary artery occlusion. The vasodilator response reported by Costantin (2) occurred in about half of the dogs he tested and became weaker with repeated occlusions. In addition, when carotid sinus pressure was held constant, he found that the dilator response was enhanced, suggesting that the baroreceptors were maintaining peripheral resistance. In the present study, the analysis of responses to the first occlusion on any day compared with the responses to the second and the third occlusions on the same day for all dogs indicated no significant change in response due to repeated occlusion. Hanley et al. (3) have reported differential control of skeletal muscle and skin vessels during coronary ischemia in anesthetized dogs and have suggested that vasodilation in the skin overrides constriction in skeletal muscle to produce a net increase in flow. Their observed decrease in total resistance was slight, however, and was produced in anesthetized animals after drastic surgery. In our femoral flow studies on lightly anesthetized dogs, arterial blood pressure responses to coronary occlusion were not significantly different from those in conscious dogs. Thus, potential differences in experimental conditions complicate the comparison of results of studies on conscious or lightly anesthetized dogs vs. deeply anesthetized dogs. Nevertheless, since baroreceptor denervation unmasked a vasodilatory response to coronary artery occlusion in our experiments, this response could involve autoregulation (18), an active vasodilatory reflex from the cardiopulmonary region (2, 3), or both.

Earlier studies have demonstrated a role for cardiopulmonary receptors in the regulation of peripheral resistance during stretch of the left atrium (19, 20) and during hemorrhage (12, 21). Stretch of the left atrial receptors has been shown to produce systemic vasodilation (20), although not in every dog (19). Vasoconstriction resulting from hemorrhage has been shown to originate from both the arterial and the cardiopulmonary baroreceptors (12, 21). Since coronary artery occlusion causes enlargement of the left ventricle and stretch of the left atrium (1, 4, 5), the fall in femoral resistance after baroreceptor denervation could partly result from a reflex originating from either the atrium or the ventricle.

Whole-body autoregulation in areflexic dogs has been well documented (22, 23). Reduced cardiac output due to coronary occlusions in anesthetized, vagotomized, baroreceptor-denervated dogs has demonstrated autoregulation of peripheral resistance (18). Undoubtedly, much of the fall in peripheral resistance after sinoaortic denervation in our experiments was due to autoregulatory mechanisms. Slopes for the pressure, flow, and resistance relationships in our experiments on baroreceptor-denervated dogs are similar to those of Liedtke et al. (18) over a similar range in values. Nevertheless, because the dogs in our study were conscious with intact vagi and because others have demonstrated reflex peripheral vascular changes with the afferent limb in the vagi (2, 3, 12, 19–21), our experiments cannot discount an active reflex dilatory influence during coronary artery occlusion.

Our results indicate that the renal resistance did not consistently participate in the maintenance of arterial blood pressure in our experiments either in the presence or the absence of functional arterial baroreceptors. Renal flow was maintained nearly constant while renal resistance fell considerably under both sets of circumstances, suggesting a dominant autoregulatory mechanism in the renal vasculature. It appears that maintenance of flow under our experimental conditions is of greater importance to the kidney in spite of compromises made in other regions of the body.

It has previously been shown that functional sinoaortic baroreceptors contribute to the tachycardia observed during 1 minute of coronary occlusion (4). Our findings demonstrated that the maximum fall in cardiac output during coronary artery occlusion when these baroreceptors were not functioning was significantly greater than that when they were functioning. Also, Figure 1 demonstrates that mean flow began to fall earlier after baroreceptor denervation. This observation suggests that tachycardia made an important contribution to the maintenance of arterial blood pressure by inhibiting the fall in cardiac output in the intact conscious dog.

Our results indicate that functional sinoaortic baroreceptors are essential for the maintenance of arterial blood pressure during acute myocardial ischemia, that vessels which supply skeletal muscle and skin as a unit play a major role in the vasoconstrictive response, and that the kidney appears to function independently.

Acknowledgment

The authors wish to thank Linda Fox for her assistance in this project.
References


Reflex Blood Pressure Control during Acute Myocardial Ischemia in the Conscious Dog
D. FRED PETERSON and VERNON S. BISHOP

Circ Res. 1974;34:226-232
doi: 10.1161/01.RES.34.2.226

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1974 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/34/2/226

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/