

Reflex Inhibition of Renal Sympathetic Nerve Activity during Myocardial Ischemia Mediated by Left Ventricular Receptors with Vagal Afferents in Dogs

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ABSTRACT The major goal of this investigation was to determine if activation of cardiac receptors during coronary artery occlusion could inhibit efferent renal sympathetic nerve activity. In nine chloralose anesthetized dogs with only carotid ($n = 3$) or with sinoaortic ($n = 6$) baroreceptors operative, anterior descending coronary artery (LAD) occlusion resulted in a small decrease in mean arterial pressure (-9.8 ± 5.1 mm Hg, NS) and in a significant ($P < 0.05$) increase in renal nerve activity ($24.0 \pm 4.1\%$). In these dogs, circumflex coronary artery (Cx) occlusion resulted in greater hypotension (-18.4 ± 4.0 mm Hg), and yet no change ($1.1 \pm 9\%$) in renal nerve activity was noted. Changes in left atrial pressure during LAD and Cx occlusion were not different. In seven dogs with carotid sinus denervation, coronary occlusions resulted in decreases both in arterial pressure and in renal nerve activity which were consistently greater during Cx occlusion. The responses to coronary occlusion in six dogs after sinoaortic deafferentation were similar to those observed with only carotid sinuses denervated. In all experiments, vagotomy abolished the difference in the blood pressure responses and the decreases in renal sympathetic nerve activity during Cx occlusion. Vagotomy also abolished the decrease in nerve activity during LAD occlusion in dogs with carotid or sinoaortic denervation. These data show that Cx occlusion and, to a lesser degree, LAD occlusion resulted in reflex withdrawal of renal sympathetic nerve activity mediated by left ventricular receptors with vagal afferents. The

reflex withdrawal of renal nerve activity during Cx occlusion occurred in spite of hypotension and the presence of functioning sinoaortic baroreceptors.

INTRODUCTION

Occlusion of the coronary artery supplying the inferior wall of the heart in man has been frequently observed to result in bradycardia and hypotension (1). Although the hypotension may be due in part to the myocardial ischemia and thus to reduced ventricular function, there is evidence which supports the view that these cardioinhibitory and vasodepressor responses may be in part reflexly mediated via sensory endings in the heart which are activated during myocardial ischemia (2-4).

Although changes in systemic arterial pressure and heart rate during myocardial ischemia are of great interest, they provide little insight into the regional circulatory adjustments which occur during myocardial ischemia. The responses of different vascular beds during coronary occlusion are the result of the integrated influence of sinoaortic and cardiopulmonary receptors on the vasomotor center and thus on the sympathetic outflow to each vascular bed. With the carotid baroreceptors operative, coronary occlusion and its attendant hypotension results in reflex vasoconstriction in skeletal muscle beds (3-5). With the common carotids occluded (4) or the sinoaortic baroreceptors deafferented (3, 5), coronary occlusion results in frank reflex vasodilatation in skeletal muscle which is mediated by left ventricular receptors with vagal afferents (3, 4). This observation is consistent with other evidence that the sinoaortic baroreceptors exert a greater influence on the vasomotor outflow to skeletal muscle than do the cardiopulmonary receptors (6-8).

The influence of the cardiopulmonary receptors on the vasomotor outflow to other vascular beds, par-

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ticularly to the renal (9) and splanchnic circulation (8), appears to be equal to, if not exceed, the influence of the carotid baroreceptors (10). Thus, it has been shown that other vascular beds behave differently from skeletal muscle during myocardial ischemia than has been previously observed for skeletal muscle beds (5, 11). In this regard, it has recently been reported that patients with acute myocardial infarction and evidence of elevated left-sided filling pressures have higher creatinine clearance, urine volume, and sodium excretion than do patients with myocardial infarction and normal filling pressures (12). It is possible that this acute elevation of cardiac filling pressure may have activated sensory endings in the left atrium and left ventricle. Activation of these cardiac receptors could have reflexly mediated withdrawal of renal sympathetic nerve activity resulting in renal vasodilatation, increased glomerular filtration rate, and augmented sodium and water excretion. The major goal of this study was to determine if activation of cardiac receptors during coronary artery occlusion could inhibit efferent renal sympathetic nerve activity and thus account for the changes in renal function previously observed during myocardial infarction.

We have recently shown that inhibitory cardiac receptors with vagal afferents are located mainly in the inferoposterior left ventricle of the dog (3, 13); it was, therefore, an additional goal of this study to determine if circumflex occlusion resulted in greater inhibition of renal sympathetic nerve activity than did anterior descending occlusion.

The data show that circumflex occlusion and, to a lesser extent, left anterior descending occlusion result in reflex withdrawal of renal sympathetic nerve activity. Moreover, this withdrawal of renal sympathetic nerve activity during circumflex coronary occlusion and its attendant hypotension can occur even in the presence of functioning sinoaortic baroreceptors.

METHODS

16 mongrel dogs weighing 14–24 kg were anesthetized with thiopental sodium (30 mg/kg i.v.) and alpha chloralose (80 mg/kg i.v.). Supplemental doses of chloralose (10 mg/kg) were given hourly. A cuffed endotracheal tube was inserted and the dogs were artificially ventilated with air supplemented with oxygen (2–3 liters/min) at a frequency of 12 cycles/min and a tidal volume determined by a nomogram based on body weight. Arterial PO_2 , PCO_2 , and pH were measured at intervals and the respiratory frequency was adjusted to maintain PCO_2 at 30–40 mm Hg. When necessary, sodium bicarbonate (2–5 ml of a 7% solution) was given intravenously to maintain pH between 7.3 and 7.4. During the protocol, muscle movement was prevented with decamethonium bromide (0.3 mg/kg i.v.). Body temperature was maintained between 37° and 39°C by external warming.

Preparation of the animal. A midline incision was used to expose both vagi in the mid-cervical region. In six dogs the aortic nerves on each side were dissected free caudal to the

nodose ganglion and identified by recording afferent traffic. The aortic nerve was traced distally to its junction with the vagus or sympathetic nerve and sectioned. This procedure has been shown to acutely abolish the baroreflex and chemoreflex from the aortic arch and the baroreflex from the major intrathoracic arteries (14).

In 13 dogs the carotid bifurcations were exposed so as to permit carotid sinus denervation before or during the course of the experiment. Carotid sinus denervation was carried out by sectioning the carotid sinus nerves and by stripping the adjacent vessels of all visible innervation. The carotid regions were considered denervated when bilateral common carotid occlusion failed to change heart rate or arterial pressure.

Through a left thoracotomy the pericardium was opened and the margins of the pericardium were attached to the thoracotomy margins to fashion a cradle for the heart. A short segment of the proximal anterior descending coronary artery (LAD)¹ and of the circumflex coronary artery (Cx) were exposed for placement of snare occluders on each vessel. Care was taken to avoid damaging the nerves which course near these arteries.

The left flank was opened between the iliac crest and the costovertebral angle and the left renal artery was then exposed.

Recording of nerve activity. A small branch of the renal sympathetic nerves was cut distally and dissected free from the renal artery and surrounding connective tissue. The nerve sheath was removed, and the nerve was covered with mineral oil and placed on bipolar platinum electrodes for recording of sympathetic efferent nerve activity. Multifiber activity was recorded from the intact nerve branch or, in some instances, from thin filaments obtained from this nerve. The signal was amplified by a Grass band-pass amplifier (P511; Grass Instruments Co., Quincy, Mass.) with the high frequency cutoff at 300–3,000 Hz and the low frequency cutoff at 30 Hz. The output of the amplifier was viewed with a Tektronix oscilloscope (Tektronix, Inc., Beaverton, Oreg.). The output of the amplifier also was fed into a loudspeaker and into a Beckman resetting integrator (Beckman Instruments, Inc., Fullerton, Calif.) whose reset interval was a function of the recorded activity. The resetting integrator integrated the voltages of all recorded spike activity whose amplitudes exceeded the noise level. A DC offset permitted the elimination of the noise from the integrated activity. The integrator was calibrated over a wide range of frequencies (from 0.25 to 100 Hz) with a square-wave generator using input voltage and duration similar to those of the recorded spikes. The degree to which the output of the integrator accurately reflected the changes in recorded activity was validated by the close agreement between the values of nerve activity obtained with this device and those measured with a nerve traffic analyzer employed in a previous study (15). The values for nerve activity are reported in hertz and represent the average discharge frequency over 30–60 s during the control period and over 10–30 s of the peak change which occurred during coronary artery occlusion.

Hemodynamic measurements. Arterial pressure was measured via a cannula in the right femoral artery connected to a Statham P23dB transducer (Statham Instruments, Inc., Oxnard, Calif.). Mean arterial pressure was obtained by electrical averaging. Heart rate was measured with a cardiometer preamplifier which was triggered by the arterial pressure wave. In 13 experiments, mean left atrial pressure was measured via a left atrial cannula passed through the appendage and connected to a Statham P23dB transducer.

¹ Abbreviations used in this paper: Cx, circumflex coronary artery; LAD, anterior descending coronary artery.

Protocol for coronary occlusions. The protocol was started for the 16 dogs 1 h after completing the surgical preparation. After establishing the control steady state, the LAD or Cx was occluded for 60–120 s and the parameters indicated above were monitored. After the release of the occlusion and the return of all measured variables to control, the other coronary artery was occluded. The order in which the coronary arteries were occluded was randomized. After occluding each vessel the vagal nerves were sectioned and after 30 min the protocol was repeated. This protocol was used to study dogs with sinoaortic baroreceptors intact ($n = 6$) or with carotid sinuses undisturbed but aortic nerves sectioned ($n = 3$) (group I), dogs with carotid sinus denervation but with aortic depressor nerves undisturbed ($n = 7$) (group II), and dogs with sinoaortic deafferentation ($n = 6$) (group III). In four experiments, coronary occlusions were carried out first with carotid and aortic baroreceptors intact and subsequently after carotid sinus denervation so that data from these dogs are included in both groups I and II. In two experiments coronary occlusions were carried out first with aortic nerves sectioned and again after carotid sinus denervation so that data from these dogs are included in both groups I and III. In five dogs with carotid sinus denervation (group II) and six dogs with sinoaortic deafferentation (group III), LAD and Cx occlusion were repeated (before vagotomy) after expansion of the blood volume with 6% dextran in normal saline (15 ml/kg i.v.). A minimum of 30 min was interposed between paired coronary occlusions.

Data analysis. Peak mean arterial pressure, heart rate, mean left atrial pressure, and renal nerve activity responses to coronary artery occlusion were measured. The observations were summed to obtain mean and standard error for each group. The statistical significance of the difference in means was evaluated by Student's t test for paired observations (16). The difference in means was considered significant for $P < 0.05$.

RESULTS

Group I, sinoaortic ($n = 6$) or carotid ($n = 3$) baroreceptors intact. Fig. 1 summarizes the changes in mean arterial pressure, mean left atrial pressure, heart rate, and the percentage of change in renal nerve activity

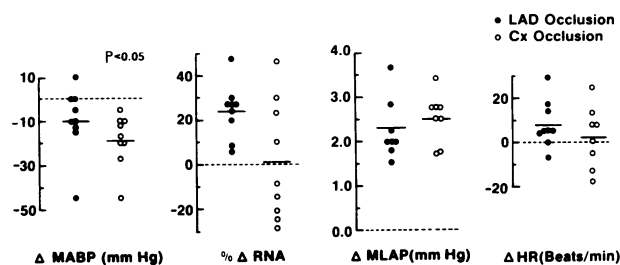


FIGURE 1 Changes in mean arterial pressure (Δ MABP), mean left atrial pressure (Δ MLAP), heart rate (Δ HR), and the percentage of change in renal nerve activity ($\% \Delta$ RNA) resulting from occlusion of the Cx (open symbols) or LAD (solid symbols) in dogs with sinoaortic ($n = 6$) or carotid ($n = 3$) baroreceptors intact (group I). Mean values are indicated for each parameter by horizontal lines. Standard errors for these data are shown in Figs. 2 and 6. Only the Δ MABP and Δ MLAP were significant during Cx occlusion, whereas only the $\% \Delta$ RNA and Δ MLAP were significant during LAD occlusion. Significant differences between LAD and Cx responses are so indicated.

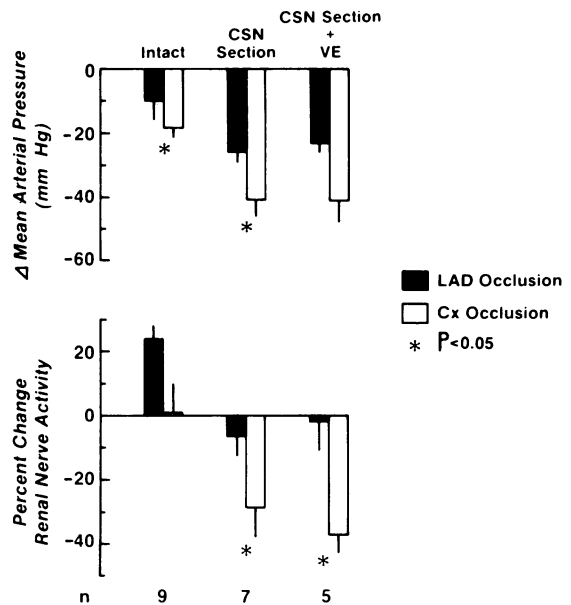


FIGURE 2 Changes in mean arterial pressure and percentage of change in renal sympathetic nerve activity resulting from occlusion of the Cx (open bars) or LAD (solid bars) in dogs with carotid sinus baroreceptors denervated (CSN section, group II) before and after expansion of the blood volume (VE) with 15 ml/kg of 6% dextran in normal saline. Group I data (indicated as Intact) are shown for comparison. The decrease in renal nerve activity during Cx occlusion and the decreases in mean arterial pressure during LAD and Cx occlusion were significant in dogs with carotid sinus denervation. Significant differences between LAD and Cx responses are so indicated. Mean values (\pm SE) are shown.

tivity that resulted from LAD and from Cx occlusion in these dogs. During LAD occlusion, mean arterial pressure fell from 122.3 ± 8.2 to 112.6 ± 15.1 mm Hg (NS) and renal nerve activity increased significantly from 21.6 ± 2.5 to 25.9 ± 2.8 Hz. Even though there was a greater fall in arterial pressure during Cx occlusion (from 124.0 ± 7.3 to 105.6 ± 4.0 mm Hg; $P < 0.05$), there was no change (mean data) in renal nerve activity (19.1 ± 2.9 to 19.8 ± 3.9 Hz). In fact, five of nine dogs exhibited frank reductions in nerve activity during Cx occlusion and its attendant hypotension. LAD and Cx occlusions were accompanied by small increases in heart rate which were significant only for LAD occlusions. Significant increases in left atrial pressure of similar magnitude were noted during LAD and Cx occlusion. Although not shown in this or subsequent figures, all measured variables returned to control within 1–3 min after release of the occlusions.

Group II, carotid sinus denervation. Because arterial baroreflexes may have partially masked the inhibitory influence of the cardiac receptors, we performed LAD and Cx coronary occlusions in dogs with bilateral carotid sinus denervation (Fig. 2). For ease of comparison group I data are also shown in Fig. 2. After

carotid sinus denervation Cx occlusion resulted in significant decreases in arterial pressure (134.1 ± 9.9 to 94.9 ± 13.3 mm Hg) and renal nerve activity (30.8 ± 5.7 to 22.8 ± 5.4 Hz) despite the presence of functioning aortic baroreceptors (Fig. 2). LAD occlusion resulted in a significant but smaller decrease in arterial pressure (136.0 ± 12 to 110 ± 11 mm Hg) and in an insignificant decrease in renal nerve activity. Fig. 3 shows the typical responses to LAD and Cx occlusion in a dog with carotid sinus denervation. After expansion of the blood volume (6% dextran in normal saline, 15 ml/kg) the arterial pressure and renal nerve activity responses to LAD and Cx occlusion were similar to those observed before volume expansion (Fig. 2). Heart rate and mean left atrial pressure responses to LAD and Cx occlusion before and after volume expansion in these group II experiments and for the remainder of the coronary occlusion experiments are summarized separately at the end of Results.

Group III, sinoaortic deafferentation. When only the carotid sinus baroreceptors were denervated, the aortic baroreceptors were still intact and could have attenuated the influence of cardiac receptors on renal sympathetic nerve activity. Thus, we studied the responses to coronary occlusions in dogs with sinoaortic deafferentation. With carotid sinus and aortic depressor nerves sectioned Cx occlusion resulted in decreases both in arterial pressure (144 ± 6.5 to 101.2 ± 12 mm Hg) and in renal nerve activity (18.4 ± 1.9 to 14.0 ± 1.5 Hz) (Fig. 4). LAD occlusion in these experiments resulted in a smaller decrease in renal nerve activity. After expansion of the blood volume the de-

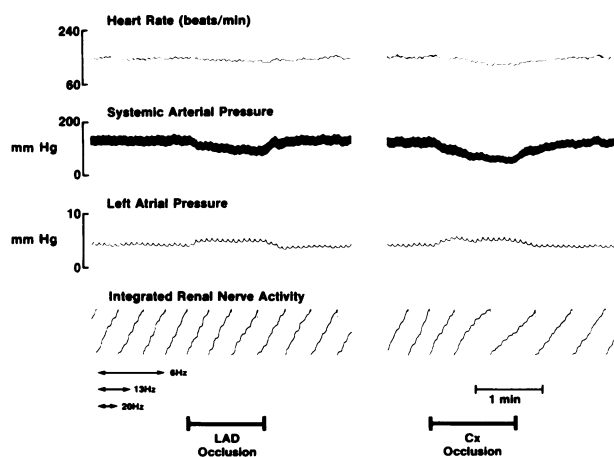


FIGURE 3 Original records showing heart rate, systemic arterial pressure, left atrial pressure, and integrated nerve activity responses to LAD (right half) and Cx (left half) occlusion in a dog with carotid sinus baroreceptors denervated but with aortic baroreceptors intact. Note that Cx occlusion resulted in greater cardiac slowing, hypotension, and withdrawal of renal nerve activity. The changes in left atrial pressure were small and similar in magnitude.

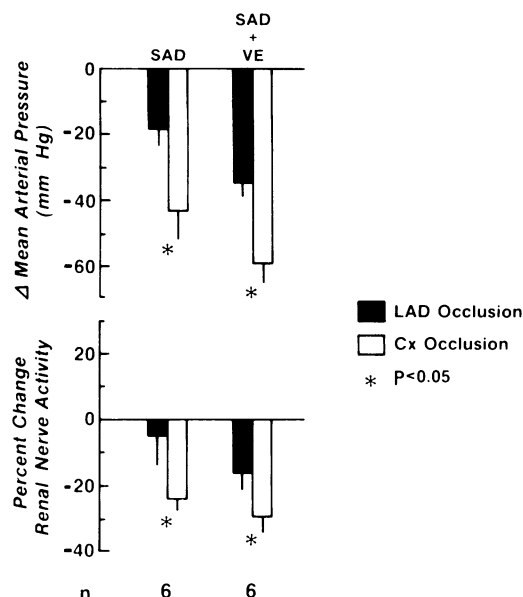


FIGURE 4 Changes in mean arterial pressure and the percentage of change in renal nerve activity during occlusion of the Cx (open bars) or LAD (solid bars) in dogs with sinoaortic deafferentation (SAD, group III) before and after expansion of the blood volume (VE) with 15 ml/kg of 6% dextran in normal saline. All changes were significant except for the decrease in nerve activity during LAD occlusion before volume expansion. Significant differences between LAD and Cx responses are so indicated. Mean values (\pm SE) are shown.

creases in arterial pressure and renal nerve activity were augmented both for LAD and Cx occlusion. However, the decreases in nerve activity and arterial pressure after volume expansion were greater during Cx occlusion. This was the only circumstance in which a significant reduction in renal nerve activity was observed during LAD occlusion.

Influence of vagotomy. Fig. 5 shows the responses to LAD and Cx occlusion in 13 dogs after volume expansion and section of the carotid sinus, aortic depressor, and vagal nerves. Results from volume-expanded dogs with sinoaortic deafferentation (group III) are shown for comparison. After vagotomy, both LAD and Cx occlusion resulted in similar decreases in arterial pressure and in similar and significant increases in renal nerve activity. In three of these experiments nitroglycerin-induced hypotension did not change renal nerve activity or heart rate, whereas coronary occlusion (LAD or Cx) increased the recorded activity, thus indicating that the increased nerve activity observed during coronary occlusion after vagotomy was not mediated by arterial baroreceptors. In another dog with vagi sectioned but carotid sinus nerves intact, renal nerve activity increased 20% during Cx occlusion and 25% during LAD occlusion. No postvagotomy data were obtained in two dogs because of the development of arrhythmias and resulting hemodynamic instability.

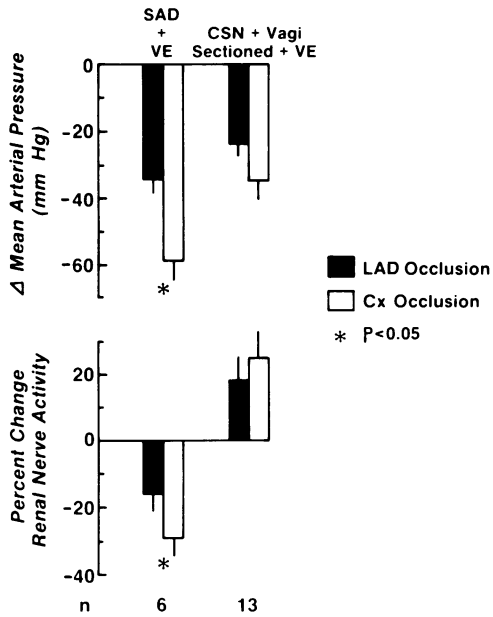


FIGURE 5 Changes in mean arterial pressure and the percentage of change in renal nerve activity during occlusion of the Cx (open bars) or LAD (solid bars) in dogs with sinoaortic denervation (SAD) and volume expansion (group III) and in dogs with carotid sinuses denervated (CSN), vagi sectioned, and blood volume expanded (VE, 15 ml/kg of 6% dextran in normal saline). All changes were significant. Significant differences between LAD and Cx responses are so indicated. Mean values (\pm SE) are shown.

Summary of heart rate and left atrial pressure responses. Fig. 6 summarizes the heart rate and mean left atrial pressure responses for all experiments. As previously noted, with sinoaortic or carotid baroreceptors operative (group I), LAD and Cx occlusion resulted in modest increases in heart rate which were significant only for LAD occlusion. After carotid sinus denervation (group II), occlusion of either vessel resulted in insignificant decreases in heart rate. Similar responses were observed after sinoaortic denervation (group III). After volume expansion the decreases in heart rate in response to Cx occlusion were significant in both groups II and III. Vagotomized dogs with sinoaortic denervation failed to alter their heart rate in response to LAD or Cx occlusion.

Changes in left atrial pressure during both LAD and Cx occlusion were significant in groups I, II, and III, and postvagotomy. The changes were similar in all groups except for the dogs with vagotomy and sinoaortic denervation in which Cx occlusion resulted in a significantly greater increase (2.8 ± 0.5 mm Hg) than did LAD occlusion (2.5 ± 0.2 mm Hg). In addition, volume expansion significantly increased control left atrial pressure from 3.3 ± 0.5 to 4.7 ± 0.9 mm Hg in carotid sinus denervated dogs and from 4.3 ± 0.7 to 5.2 ± 0.6 mm Hg in dogs with sinoaortic deafferentation.

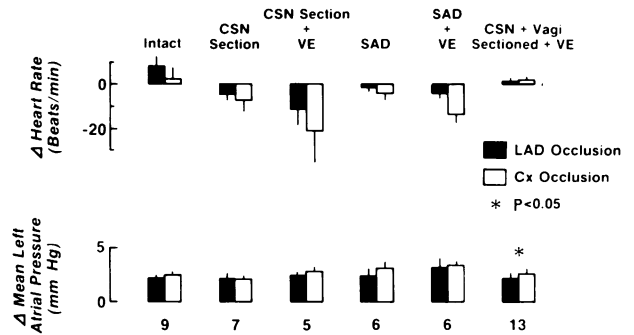


FIGURE 6 Changes in heart rate and mean left atrial pressure during occlusion of the Cx (open bars) or LAD (solid bars) for group I (Intact), group II (CSN section), group III (SAD), and for dogs with carotid denervation and vagotomy. VE indicates expansion of the blood volume with 15 ml/kg of 6% dextran in normal saline. See Results for discussion of data. Mean values (\pm SE) are shown.

DISCUSSION

Coronary artery occlusion results in decreases in cardiac output and arterial pressure and in increases in cardiac-filling pressure, particularly in the left ventricle and left atrium. Under these circumstances the tonic inhibition of the vasomotor center exerted by sinoaortic baroreceptors is diminished, whereas the inhibitory influence of the cardiopulmonary receptors, particularly those in the left heart, is augmented. Thus, the change in sympathetic outflow to a particular regional vascular bed will depend on the central interaction between the inputs from these two reflexogenic areas. The present data show that in the absence of the sinoaortic baroreceptors, Cx occlusion, and to a lesser extent LAD occlusion, resulted in reflex cardiac slowing and withdrawal of renal nerve activity and in hypotension which was in part reflexly mediated. Similar responses were observed in dogs with aortic baroreceptors intact but carotid baroreceptors denervated. With the sinoaortic or carotid baroreceptors intact, LAD occlusion resulted in cardiac acceleration and increases in renal sympathetic nerve activity and in small decreases in arterial pressure. In contrast, Cx occlusion resulted in significantly greater hypotension and yet there was no net change in renal nerve activity or heart rate. These data indicate that activation of receptors in the inferoposterior wall of the left ventricle by Cx coronary occlusion can interfere with the baroreceptor-mediated increases in renal sympathetic nerve activity which normally occur during systemic hypotension (17, 18) and which were consistently observed during LAD occlusion. The findings are consistent with other results from our laboratory that indicate that the inhibitory cardiac receptors responsible for these effects are located mainly in the Cx distribution (3, 13).

The receptors that mediated the vasodepressor responses we observed were subserved by afferents which traveled in the vagus. This is supported by the observation that vagotomy abolished the withdrawal of renal sympathetic nerve activity and the cardiac slowing, and decreased the magnitude of the hypotension that resulted from Cx occlusion. In fact, with sinoaortic and vagal denervation, LAD and Cx occlusion each resulted in increases in renal sympathetic nerve activity. Although we did not repeat the occlusions after interruption of cardiac sympathetic nerves, it can be suggested that the postvagotomy increases in renal nerve activity were mediated by cardiac receptors subserved by afferents that travel in the sympathetic nerves (19). Activation of these excitatory receptors may have partially masked the inhibitory influence of cardiac receptors with vagal afferents during coronary artery occlusion. It is unlikely that activation of excitatory sympathetic afferents could have accounted for the differential reflex inhibitory responses observed during LAD and Cx occlusion with vagi intact. To account for the differences, larger excitatory responses would have to result from LAD than from Cx occlusion. However, our data show that the increases in renal nerve activity in dogs with sinoaortic deafferentation and vagotomy during Cx occlusion were not different from those resulting from LAD occlusion.

Coronary occlusions were carried out before and after the blood volume was expanded so as to augment both the base-line activity of the cardiopulmonary receptors and the increase in their discharge frequency during coronary occlusion (10). Volume expansion caused a significant increase in the heart rate, blood pressure, and renal nerve activity responses to LAD and Cx occlusion in dogs with sinoaortic deafferentation (group III) and in the heart rate responses to Cx occlusion in dogs with carotid sinus denervation (group II). Because no effort was made to replace volume losses incurred during surgery, it can be suggested that the volume expanded responses are more representative of those which might be observed in dogs with normal blood volumes.

Several investigators have recently examined the influence of coronary artery occlusion on the kidney. Peterson and Bishop (5) observed similar decreases in renal vascular resistance during Cx occlusion in dogs with sinoaortic baroreceptors denervated or intact. They suggested that the renal vasodilatation observed under both circumstances was the normal autoregulatory response and thus did not reflect a withdrawal of renal sympathetic nerve activity. Stinson et al. (20) found a decrease in renal vascular resistance in anesthetized dogs during LAD occlusion. Our data shows that LAD occlusion consistently results in increases in renal nerve activity. Thus, the renal vasodilatation observed by Stinson et al. was probably not the result of

sympathetic withdrawal. Although their results suggested that the vasodilatation was cholinergically mediated, atropine administration reduced base-line flow, thus making these results difficult to interpret. The papers of Peterson and Bishop (5) and of Stinson et al. (20) indicate only that coronary artery occlusion (LAD or Cx) does not result in neurally mediated renal vasoconstriction.

The study of Hanley et al. (2) provides clear evidence that coronary artery occlusion can result in reflex renal vasodilatation in spite of systemic arterial hypotension. They occluded LAD, Cx, or both and elicited reflex renal vasodilatation in constant-flow perfused kidneys in 18 of 23 dogs. The afferent pathway for the reflex renal vasodilatation was not investigated but was assumed to be the vagus. Falicov et al. (21) injected metallic mercury into the left main coronary artery in dogs and claimed to show results similar to those of Hanley et al. (2). When the appropriate statistical test is applied to their data (analysis of variance) no significant change in renal flow occurred after mercury embolization. In addition, the validity of their flow measurements is questionable because no occlusive zero was obtained for the flow probes they used. It is likely that the decreases in renal resistance they observed were the result of autoregulation.

Gorfinkel and colleagues (22) compared the systemic and renal hemodynamics and urine volumes of dogs with cardiogenic shock as a result of occlusion of the Cx to those of dogs with hemorrhagic shock. Although arterial pressure and cardiac outputs were similar in the two groups, renal blood flow decreased 90% in the hemorrhaged dogs but only 25% in dogs with cardiogenic shock. In addition, urine output was better maintained in the dogs with cardiogenic shock. These investigators suggested that receptors in the cardiopulmonary area may have played a role in these differential renal responses because cardiac filling pressures were high in cardiogenic shock and low in hemorrhagic shock. In a subsequent study from the same laboratory, Kahl and colleagues (23) investigated the influence of left atrial distention on renal vasomotor tone and suggested that atrial receptors were primarily responsible for the protection of the renal circulation (prevention of renal vasoconstriction) during cardiogenic shock. In our experiments the increases in left atrial pressure during LAD occlusion were similar to those that resulted from Cx occlusion, yet the latter caused greater reflex vasodepressor responses. In addition, it is unlikely that Cx occlusion resulted in left atrial ischemia and thus in left atrial receptor activation. Moore (24) has shown that the left atrial branches of the Cx are two in number. The first arises 3–7 mm from the origin of the Cx and supplies the anterior half of the left atrium, the left auricular appendage, and the anterior half of the interatrial septum. This vessel was consistently

proximal to the point at which the Cx was occluded in this study. The second or distal artery arises near the posterior interventricular sulcus and supplies the remainder of the left atrium. Moore (24) showed that there are abundant collaterals between the distal atrial branch arising from the Cx and atrial branches arising from the right coronary artery. Thus, it is also unlikely that ischemia of the posterior atrial wall resulted from Cx occlusion. Thus, our data are consistent with the view that short-lasting coronary occlusions activated primarily ventricular receptors and that these receptors mediated the reflex vasodepressor and renal nerve activity responses we observed.

Kezdi et al. (25) reported that coronary occlusion resulted in activation of cardiac vagal afferents and in reflex suppression of renal nerve activity. They showed that 3 h after the injection of metallic mercury into the Cx of closed chest anesthetized dogs there was still a modest tonic inhibitory influence on the sympathetic outflow to the kidney, as indicated by the increases in renal nerve activity that followed vagotomy. It is likely that this inhibition observed 3 h after coronary occlusion by Kezdi et al. (25) was mediated primarily via cardiopulmonary receptors outside the ventricle (e.g., left atrium, pulmonary artery, etc.) because left atrial pressure has been shown to be markedly elevated 3 h after Cx occlusion (22). In addition, the data of Thorén (26) indicate that left ventricular receptors with non-myelinated vagal afferents, whose discharge frequency is augmented during the first few minutes of coronary artery occlusion, fail to sustain much of an increased firing frequency beyond 5–10 min.

Finally, Uchida and Sakamoto (27) injected air into the LAD and Cx coronary arteries in dogs and found that during myocardial ischemia, cardiac receptors with vagal afferents reflexly suppressed renal nerve activity when blood pressure did not decrease by >34% of control. Because their study did not examine the responses to coronary occlusion after eliminating the influence of the sinoaortic baroreceptors, they could only suggest an interaction between carotid and cardiac receptors in the control of renal nerve activity during myocardial ischemia. The present data provides systematic evidence that this interaction is the major determinant of the integrated renal nerve response to myocardial ischemia. Uchida and Sakamoto's study (27) also suggested that there was a difference in the response to LAD as opposed to Cx air embolization. They were unable to explain the mechanism for this difference as their study did not determine the relative roles of cardiac receptors with sympathetic (excitatory) as opposed to vagal (inhibitory) afferents in this differential response. This study shows that the differences in response to Cx as opposed to LAD occlusion are a result of inhibitory cardiac receptors with vagal afferents which are located mainly in the Cx distribution.

The renal nerve responses we observed were quite different from the skeletal muscle vascular responses to coronary occlusion that have been previously reported (2, 3, 5, 13, 26). With the carotid baroreceptors operative, we observed vasoconstriction in the gracilis of similar magnitude during LAD and Cx occlusion (3). With only aortic baroreceptors operative there was less vasoconstriction during Cx than LAD occlusion (3). Only in dogs with sinoaortic deafferentation were frank vasodilator responses observed with Cx occlusion eliciting the greater vasodilatation (3). The differences in the gracilis vascular responses and the renal nerve responses to coronary occlusion are consistent with previous studies which indicate that: (a) sinoaortic baroreceptor influence dominates cardiopulmonary receptor influence in the control of skeletal muscle vascular beds (8); and (b) cardiopulmonary receptor influence equals or exceeds that of the sinoaortic baroreceptors in the control of sympathetic outflow to the kidney (9, 10).

The circulatory responses to Cx occlusion in the dog, particularly in the absence of the sinoaortic baroreceptors (3, 5), tend to mimic the cardioinhibitory (bradycardia) and vasodepressor (hypotension) responses to inferior infarction in man (1). Prevention by cardiac receptors of normal baroreceptor-induced increases in renal nerve activity could contribute to the hypotension by three mechanisms. First, ≈ 15 –20% of the resting cardiac output passes through the renal circulation. If, in the face of hypotension, the kidney is not vasoconstricted then it acts as a low-resistance shunt and keeps total peripheral resistance inappropriately low. Second, prevention of increases in renal nerve activity would also prevent the neural release of renin (28) with subsequent generation of angiotensin, a powerful vasoconstrictor. Third, in the absence of an increase in renal nerve activity and renal vasoconstriction, salt and water excretion could continue at inappropriately high levels (29) with cumulative volume losses becoming significant in a brief period.

In conclusion, Cx occlusion activates inhibitory left ventricular receptors with vagal afferents sufficiently to prevent baroreceptor-induced increases in renal nerve activity. Inhibitory responses to LAD occlusion are only evident when the influence of the sinoaortic baroreceptors is abolished, thus indicating that there are fewer inhibitory cardiac receptors in the LAD distribution.

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REFERENCES

- Webb, S. W., A. A. Adgey, and J. F. Pantridge. 1972. Autonomic disturbance at onset of acute myocardial infarction. *Br. Med. J.* 3: 89-92.
- Hanley, H. G., A. E. Raizner, T. V. Inglesby, and N. S. Skinner, Jr. 1972. Response of the renal vascular bed to acute experimental coronary arterial occlusion. *Am. J. Cardiol.* 29: 803-808.
- Thames, M. D., H. S. Klopfenstein, F. M. Abboud, A. L. Mark, and J. L. Walker. 1978. Preferential distribution of inhibitory cardiac receptors with vagal afferents to the inferoposterior wall of the left ventricle activated during coronary occlusion in the dog. *Circ. Res.* 43: 512-519.
- Thorén, P. 1973. Evidence for a depressor reflex elicited from left ventricular receptors during occlusion of one coronary artery in the cat. *Acta Physiol. Scand.* 88: 23-34.
- Peterson, D. F., and V. S. Bishop. 1974. Reflex blood pressure control during acute myocardial ischemia in the conscious dog. *Circ. Res.* 34: 226-232.
- Koike, H., A. L. Mark, D. D. Heistad, and P. G. Schmid. 1975. Influence of cardiopulmonary vagal afferent activity on carotid chemoreceptor and baroreceptor reflexes in the dog. *Circ. Res.* 37: 422-429.
- Mancia, G., J. T. Shepherd, and D. E. Donald. 1976. Interplay among carotid sinus, cardiopulmonary, and carotid body reflexes in the dog. *Am. J. Physiol.* 230: 19-24.
- Pelletier, C. L., A. J. Edis, and J. T. Shepherd. 1971. Circulatory reflex from vagal afferents in response to hemorrhage in the dog. *Circ. Res.* 29: 626-634.
- Little, R., G. Wennergren, and B. Öberg. 1975. Aspects of central integration of arterial baroreceptor and cardiac ventricular receptor reflexes in the cat. *Acta Physiol. Scand.* 93: 85-96.
- Thorén, P. N., D. E. Donald, and J. T. Shepherd. 1976. Role of heart and lung receptors with nonmedullated vagal afferents in circulatory control. *Circ. Res.* 38: II-2-II-9.
- Hanley, H. G., J. C. Costin, and N. S. Skinner. 1971. Differential reflex adjustments in cutaneous and muscle vascular beds during experimental coronary artery occlusion. *Am. J. Cardiol.* 27: 513-521.
- Bennett, E. D., N. Brooke, Y. Lis, and A. Wilson. Elevated renal function in patients with acute heart failure. ? Homeostatic mechanism. In *Cardiac Receptors*. R. J. Linden, editor. Cambridge University Press, London. In press.
- Walker, J. L., M. D. Thames, F. M. Abboud, A. L. Mark, and H. S. Klopfenstein. 1978. Preferential distribution of inhibitory cardiac receptors in left ventricle of the dog. *Am. J. Physiol.* 235: H188-H192.
- Edis, A. J., and J. T. Shepherd. 1971. Selective denervation of aortic arch baroreceptors and chemoreceptors in dogs. *J. Appl. Physiol.* 30: 294-296.
- Thames, M. D., D. E. Donald, and J. T. Shepherd. 1977. Behavior of cardiac receptors with nonmyelinated vagal afferents during spontaneous respiration in cats. *Circ. Res.* 41: 694-701.
- Steel, R. G., and J. H. Torrie. 1960. Principles and Procedures of Statistics. McGraw-Hill Book Co., New York.
- Ninomiya, I., N. Nisimaru, and H. Irisawa. 1971. Sympathetic nerve activity to the spleen, kidney, and heart in response to baroreceptor input. *Am. J. Physiol.* 221: 1346-1351.
- Kendrick, E., B. Öberg, and G. Wennergren. 1972. Vasoconstrictor fiber discharge to skeletal muscle, kidney, intestine, and skin at varying levels of arterial baroreceptor activity in the cat. *Acta Physiol. Scand.* 85: 464-476.
- Peterson, D. F., and A. M. Brown. 1971. Pressor reflexes produced by stimulation of afferent fibers in the cardiac sympathetic nerves of the cat. *Circ. Res.* 28: 605-610.
- Stinson, J. M., P. J. Mootry, C. G. Jackson, H. O. Gates, and M. T. Scott. 1976. Renal vasodilation in response to coronary artery ligation in the dog. *Clin. Expt. Pharm. Physiol.* 3: 191-194.
- Falicov, R. E., M. J. Christopher, and I. T. Gabe. 1975. The response of the renal and femoral vascular beds to coronary embolization in the dog. *Cardiovasc. Res.* 9: 151-160.
- Gorfinkel, H. J., J. P. Szidon, L. J. Hirsch, and A. P. Fishman. 1972. Renal performance in experimental cardiogenic shock. *Am. J. Physiol.* 222: 1260-1268.
- Kahl, F. R., J. F. Flint, and J. P. Szidon. 1974. Influence of left atrial distention on renal vasomotor tone. *Am. J. Physiol.* 226: 240-246.
- Moore, R. A. 1930. The coronary arteries of the dog. *Am. Heart J.* 5: 743-749.
- Kezdi, P., R. K. Kordenat, and S. N. Misra. 1974. Reflex inhibitory effects of vagal afferents in experimental myocardial infarction. *Am. J. Cardiol.* 33: 853-860.
- Thorén, P. N. 1976. Activation of left ventricular receptors with nonmedullated vagal afferent fibers during occlusion of a coronary artery in the cat. *Am. J. Cardiol.* 37: 1046-1051.
- Uchida, Y., and A. Sakamoto. 1974. Role of autonomic nerves in the pathogenesis of hypotension produced by coronary embolization. *Jpn. Circ. J.* 38: 491-495.
- Bunag, R. D., I. H. Page, and J. W. McCubbin. 1966. Neural stimulation of release of renin. *Circ. Res.* 19: 851-858.
- DiBona, G. F. 1977. Neurogenic regulation of renal tubular sodium reabsorption. *Am. J. Physiol.* 233: F73-F81.