The Circulatory Influences of Vagal Afferents at Rest and during Coronary Occlusion in Conscious Dogs

Vernon S. Bishop and D. Fred Peterson

SUMMARY We studied the role of cardiopulmonary vagal afferents in the cardiovascular responses to coronary artery occlusion in conscious dogs with intact carotid sinuses and following functional denervation of the arterial baroreceptors. The contributions of vagal afferents were determined by cold blocking the vagi. In dogs with intact carotid sinuses, coronary artery occlusion produced small decreases in mean cardiac output and arterial pressure, whereas heart rate increased by 35 beats/min. In dogs with intact carotid sinuses, vagal cold block increased mean arterial pressure by 22 ± 2 (mean ± SE) mm Hg and heart rate by 90 ± 6 beats/min. Mean cardiac output increased by 505 ± 90 ml/min. With the exception of heart rate, responses to coronary occlusion during vagal cold block were similar to the occlusion response prior to vagal cold block. Furthermore, prior occlusion of the coronary artery did not significantly influence the responses to vagal cold block. After arterial baroreceptor denervation, coronary artery occlusion resulted in a substantially greater fall in systemic arterial pressure (~52 mm Hg as compared to ~8 mm Hg, with intact carotid sinuses) and peripheral resistance decreased by ~0.49 peripheral resistance units (PRU). Vagal cold block following denervation increased the arterial pressure by 49 ± 10 mm Hg and peripheral resistance by 0.59 ± 0.13 PRU. Both values were significantly greater than those observed during vagal cold block prior to denervation. In arterial baroreceptor-denervated dogs, vagal blockade significantly attenuated the response to coronary occlusion. Therefore, in conscious dogs, vagal afferents from cardiopulmonary receptors exert a significant inhibitory influence on the peripheral vascular tone. When the carotid sinuses are intact, this inhibitory influence appears to be marked during myocardial ischemia. In the absence of functional arterial baroreflexes, vagal afferent activity contributes to the depressor responses observed during ischemia.

RECENT evidence indicates that cardiopulmonary receptors mediated via vagal afferent fibers play a significant role in circulatory control. However, little is known regarding the normal role of these receptors in the conscious animal. Likewise, the influence of cardiac vagal activity on the circulatory adjustments to coronary occlusion has not been studied in conscious animals. In anesthetized dogs, left circumflex coronary occlusion results in hypotension, bradycardia, and a decrease in cardiac sympathetic efferent activity. A similar response has been observed in chloralose-anesthetized cats during left anterior descending occlusion. These are responses which can be abolished by vagotomy and are similar to effects of direct electrical stimulation of the nonmyelinated vagal afferents. Recent studies also have shown an increase in nonmyelinated vagal afferent activity from ventricular receptors during coronary occlusion.

In contrast to the responses observed in anesthetized cats and dogs, both arterial pressure and peripheral resistance are well maintained during coronary occlusion in the conscious dog. However, after sinoaortic denervation, coronary occlusion in the conscious dog results in a drastic fall in arterial pressure and systemic resistance, indicating that functional sinoaortic baroreceptors are essential for the maintenance of arterial pressure and vascular tone. In those studies, the vagi remained intact; hence, their role in mediating observed responses could not be determined.

The purpose of this study was to evaluate, in the conscious dog, the role of vagal afferent activity on the cardiovascular responses to coronary artery occlusion before and after sinoaortic denervation. Circulatory adjustments regulated by vagal afferent activity were determined by blocking the vagi with cold. Results suggest that vagal afferent activity exerts a restraining influence on the vasomotor center at rest and during coronary occlusion, but that intact functional arterial baroreceptors strongly oppose these influences mediated by the vagi. In the absence of functional arterial baroreceptors, the drastic fall in arterial pressure and peripheral resistance during coronary occlusion can be abolished partially by vagal cold block, indicating the potential of these vagal afferents for regulating the cardiovascular responses to coronary occlusion.
Methods

Twenty-one mongrel dogs were anesthetized with halothane and, under sterile procedures, a left thoracotomy was performed through the 5th intercostal space. An electromagnetic flow transducer was placed around the ascending aorta. An 18-gauge polyvinyl catheter was placed in the left atrial appendage to measure left atrial pressure. A second catheter was placed in the descending aorta to measure systemic arterial pressure.

The left circumflex coronary artery was exposed near its origin by blunt dissection. A 6 to 10-mm length was separated and a hydraulic occluder, similar to that previously described, was placed around the vessel. The volume and pressure required for complete occlusion of the circumflex coronary artery were determined.

At the time of the instrumentation, the aortic baroreceptor was denervated by stripping the nerves and adventitia from the aortic arch and applying isopropyl alcohol to the region. All catheters and leads were exteriorized from the back of the neck. Two weeks after recovery from the initial surgery, when each animal appeared healthy, it was anesthetized with intravenous sodium pentobarbital (30 mg/kg). A midline cervical incision was made, and a 6-cm length of both right and left vagosympathetic nerve trunks was dissected free from the common carotid artery. A stainless steel coil made of 10-gauge stainless steel tubing was placed around each nerve trunk, and a Silastic tube connected to each coil was exteriorized through the skin. Each coil was then insulated from the surrounding tissue with a jacket fashioned from medical grade Silastic rubber. The carotid arteries were isolated from the coil by suturing a layer of muscle over the arteries. The details of the vagal cold block technique have been published previously. To monitor temperature of the tissue encompassed by the stainless steel coil wire, thermocouple wires were placed inside each coil near the nerve, and lead heads from the thermocouples were exteriorized at the back of the neck so the temperature within the coils could be monitored continuously either on the pen recorder or the oscilloscope. When the dogs were killed, gross and microscopic examinations of the vagus nerve trunk verified that no pathological changes in the nerve trunk occurred during the course of instrumentation. After implantation of the cooling coils, the dogs were allowed to recover for several days, during which time ECG, heart rate, arterial and left atrial pressure, and cardiac output were monitored daily, on a Beckman Type R Dynograph and an Ampex tape recorder, using appropriate transducers, couplers, and amplifiers.

Experimental Protocol

All experiments were performed while the dog was conscious, lying unrestrained. First, the left circumflex coronary artery was occluded for 1 minute in each animal to determine the characteristic response. As in previous reports, the maximum response to the occlusion always occurred within this interval. Usually, three occlusions were performed, separated by 10-15 minutes. Subsequently, the vagi were blocked by circulating cooled alcohol through each coil while continuously monitoring the temperature of the medium inside the coil; vagal blockade was assumed to be complete when temperature reached 2°C to 0°C. At this temperature, heart rate was elevated and respiration became slower and deeper. The block was reversed by circulating warm alcohol through each coil. Additional vagal blocks were performed to verify the reproducibility of the responses. In six days, the heart rate, cardiac output, and mean arterial pressures were monitored at tissue temperatures from 16°C to 0°C (Fig. 1). Blood PaO₂, PaCO₂, and pH were monitored on an Instrumentation Laboratory model 113 blood gas system, and no changes were observed during vagal blockade or coronary occlusion.

After the above responses had been obtained, coronary occlusions were performed during blockade of the vagi, and the block reversed while the occlusion was maintained.

In seven dogs, responses to coronary occlusions of 2-4 minutes were determined. The maximum changes due to the occlusion occurred within 60 seconds and remained constant during the occlusion. The responses to occlusions of this duration were not different from those to 1-minute occlusions. Subsequently, the effects of vagal blockade on the response to coronary occlusion was obtained by cold block of the vagi after 60 seconds of occlusion. The vagi then were rewarmed and the occlusion released. To determine the heart rate effects resulting from blockade of the vagal efferent nerves, the effects of atropine (0.1-0.2 mg/kg, iv) and cold block were compared in five dogs (Table 1). In six
dogs, vagal cold block was performed after atropine administration (Table 2).

The dogs again were anesthetized (intravenous pentobarbital, 30 mg/kg) after the above protocols had been completed. Anterior cervical incision was made and the carotid sinuses were denervated by removal of all tissue from the area of the carotid sinus bifurcation. Verification of denervation was obtained by lack of a heart rate response to bilateral carotid occlusion prior to closure of the incision. Completeness of total baroreceptor denervation was tested after at least 5–7 days following surgery, using a bolus injection of phenylephrine (2 µg/kg). Postoperatively, arterial baroreceptor denervation was assumed to be complete when the reflex heart rate response to the intravenous injection of nitroglycerin (12 µg/kg) or phenylephrine was attenuated (−6 beats/min, or less).

In eight cases, the responses to coronary occlusion and vagal blockade were studied in the conscious dogs 1 week following baroreceptor denervation, using the protocol described above. Total peripheral resistance, expressed in terms of peripheral resistance units (PRU), was calculated as the quotient of the mean arterial pressure gradient and mean cardiac output times 60. Statistical evaluation of the data employed Student’s t-test and analysis of variance.

### Table 1  
**Mean Responses to Coronary Occlusion and Vagal Cold Block in Intact Conscious Dogs**

<table>
<thead>
<tr>
<th></th>
<th>Heart rate (beats/min)</th>
<th>Mean cardiac output (ml/min)</th>
<th>Mean left atrial pressure (mm Hg)</th>
<th>Mean arterial pressure (mm Hg)</th>
<th>Peripheral resistance (PRU)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>X</td>
<td>±SEM</td>
<td>X</td>
<td>±SEM</td>
<td>X</td>
</tr>
<tr>
<td>CON</td>
<td>91±5</td>
<td>2798±166</td>
<td>2.5±0.5</td>
<td>97±4</td>
<td>2.13</td>
</tr>
<tr>
<td>CO</td>
<td>129±8</td>
<td>2503±166</td>
<td>7.2±4.7</td>
<td>89±8</td>
<td>2.17±0.04</td>
</tr>
<tr>
<td>CON</td>
<td>96±6</td>
<td>2845±174</td>
<td>1.2±0.8†</td>
<td>4±3†</td>
<td>±0.2±0.04</td>
</tr>
<tr>
<td>VB</td>
<td>177±9</td>
<td>3352±172</td>
<td>2±0.9</td>
<td>120±22</td>
<td>2.19±0.07</td>
</tr>
<tr>
<td>VB+CO</td>
<td>186±9</td>
<td>2967±109</td>
<td>2.5±1.6</td>
<td>115±17</td>
<td>2.42±0.39</td>
</tr>
</tbody>
</table>

Mean values $X ± SEM$ are shown during control states (CON), coronary occlusion (CO), and coronary occlusion plus vagal cold block (CO ± VB). $A = mean differences between CO response and those observed during CO + VB; A = mean difference between CO + VB; $A = mean difference between control values and those observed during CO and CO ± VB. $A = mean difference between control values and those observed during CO and CO + VB.$

$* P < 0.001; †P < 0.05; ‡P < 0.01.$

### Results

Figure 1 illustrates the average changes in heart rate, mean arterial pressure, and cardiac output in response to progressive bilateral cooling of the cervical vagus nerves in six conscious dogs. Arterial pressure increased as the temperature in the medium surrounding the vagus nerves approached 9°C and reached a maximum between 2° and 0°C. Heart rate was significantly elevated at 5°C, and reached a maximum near 0°C.

In 14 dogs, cooling the vagus nerves to 0°C resulted in significant increases in mean cardiac output (507 ± 90 ml/min, $P < 0.001$), arterial pressure (22.0 ± 0.9 mm Hg, $P < 0.001$), and heart rate (82 ± 6 beats/min, $P < 0.001$; Table 1). No significant changes in left atrial pressure were observed, and the ECG was not observably altered. Similar responses have been reported previously during cold block of the right vagus nerve in conscious dogs with the left cervical vagus sectioned. 11

Occlusions of the left circumflex coronary artery were performed at rest and during vagal cold block. At rest, the cardiovascular responses were characterized by small but significant decreases in mean cardiac output (−295 ± 63 ml/min) and mean arterial pressure (−8 ± 3 mm Hg). Heart rate and mean left atrial pressure were significantly elevated (38 ± 5 beats/min and 4.7 ± 0.8 mm Hg, respectiv
Circulatory Influences of Vagal Afferents/Bishop and Peterson

Changes in peripheral resistance were variable and not significant (Table 1).

As a result of the effects of vagal cold block at rest, the absolute values of heart rate, cardiac output, and arterial pressure, as well as peripheral resistance, were greater during coronary occlusion in the presence of vagal cold block than the corresponding values at rest (Table 1). However, changes in cardiac output, arterial pressure, mean left atrial pressure, and peripheral resistance resulting from coronary occlusion during vagal blockade were qualitatively similar to those observed during occlusion with intact vagi (Table 1, Fig. 2). The increase in heart rate was much less, owing to the rapid heart rate associated with vagal blockade. Vagal blockade alone did not result in a significant increase in peripheral resistance; however, subsequent coronary occlusion increased peripheral resistance over the resting (14.2% higher) and vagal block (10.5% higher levels; Table 1). This finding suggests that, when vagal restraint is blocked, peripheral resistance changes in response to coronary occlusion are enhanced (P < 0.005).

Since myocardial ischemia may activate receptors in the cardiopulmonary region which are subserved by vagal afferents, vagal restraint during coronary occlusion might be increased. To test this possibility, coronary occlusion was initiated in nine dogs. After 60 seconds, when the response to coronary occlusion was constant, the vagi were blocked with cold. As shown in Table 2, the response to coronary occlusion was qualitatively similar to that observed above. Vagal blockade during the occlusion resulted in increases in heart rate (43 beats/min), mean cardiac output (427 mL/min), and arterial pressure (22 mm Hg). The absolute control P < 0.5) and peripheral resistance (0.52 PRU greater than control, P < 0.01) than vagal blockade with intact carotid sinus baroreceptors, but heart rate changes were significantly lower (Table 1 and Table 5).

In dogs with the arterial baroreceptors denervated, coronary occlusion after vagal blockade decreased mean arterial pressure by only 25 mm Hg and had no effect on peripheral resistance, suggesting that receptors subserved by vagal afferents were responsible for the large decline in mean arterial pressure and peripheral resistance during occlusion after arterial baroreceptor denervation.

In four dogs with arterial baroreceptors denervated, vagal blockade during coronary occlusion increased mean arterial pressure by 59 ± 8 mm Hg, supporting the conclusion that intact vagi contribute to the fall in mean arterial pressure and peripheral resistance during coronary occlusion after arterial baroreceptor denervation.

Discussion

In this study, we have observed an increase in mean arterial pressure during vagal cold block which suggests that, in the conscious dog, tonic afferent vagal activity from receptors in the cardiopulmonary region exerts an important restraint on systemic arterial pressure. Since vagal blockade causes a much greater increase in arterial pressure and peripheral resistance following sinoaortic denervation, it appears that, in the conscious dog, arterial baroreceptors can attenuate drastically the systemic vascular response to vagal blockade under normal resting conditions. This is in apparent agreement with results of previous studies in anesthetized animals which have shown that the vagal inhibitory influence on efferent sympathetic outflow, as indicated by changes in arterial pressure during interruption of vagal afferents, varies inversely with the carotid sinus pressure. Hence, the contribution of the vagal receptors in values of these parameters (Table 2) were similar to those observed with vagal blockade at rest prior to occlusion (Table 1). However, peripheral resistance was increased with vagal blockade during occlusion, as opposed to the response observed during vagal blockade at rest.

Chemical blockade of the vagal efferent activity with atropine (0.1-0.2 mg/kg) elicited heart rate responses which were equivalent to those observed with vagal cold block (74 and 84 beats/min, respectively) (Table 3). Increases in mean cardiac output were likewise similar and not significantly different. However, vagal cold block caused a significant increase in arterial pressure (P < 0.001), whereas atropine alone did not. In addition, vagal block following atropine resulted in a significant increase in mean arterial pressure without affecting either heart rate or cardiac output (Table 4). Thus, it is
TABLE 3  Comparison of Responses to Atropine and Vagal Cold Block

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Atropine</th>
<th>Δ</th>
<th>Control</th>
<th>Vagal blockade</th>
<th>Δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean cardiac output (ml/min)</td>
<td>2821 ± 328</td>
<td>3024 ± 238</td>
<td>235 ± 105</td>
<td>2775 ± 574</td>
<td>3173 ± 362</td>
<td>398 ± 108</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>102 ± 7</td>
<td>175 ± 11</td>
<td>74 ± 9</td>
<td>92 ± 8</td>
<td>177 ± 10</td>
<td>84 ± 7</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>104 ± 4</td>
<td>104 ± 4</td>
<td>0</td>
<td>100 ± 4</td>
<td>121 ± 6</td>
<td>21 ± 3</td>
</tr>
</tbody>
</table>

Values = mean ± SEM. Control values were determined prior to the administration of atropine (0.2 mg/kg) or vagal cold block. P values are for paired t-test between control and experimental response (P < 0.05, n = 5).

not likely that the increases in mean arterial pressure and peripheral resistances observed in the above studies are the result of changes in heart rate due to blockade of the vagal efferent activity. Others have shown that, in anesthetized dogs with experimental infarction, atropine increases heart rate but fails to reproduce the effects of vagotomy on systemic arterial pressure.14

Denervation of the carotid baroreceptors resulting in total arterial baroreceptor denervation increased mean cardiac output (840 ml/min, P < 0.05), heart rate (30 beats/min, P < 0.001), and mean arterial pressure (30 mm Hg, P < 0.05). Coronary occlusion following arterial baroreceptor denervation resulted in a significant fall in mean arterial pressure (−52 mm Hg, P < 0.001). In contrast to the responses to occlusion observed in the control state, peripheral resistance fell significantly during coronary occlusion after arterial baroreceptor denervation (P < 0.001) (Table 5, Fig. 3).

Vagal cold block after arterial baroreceptor denervation caused a significantly greater increase in mean arterial pressure (27.1 mm Hg greater than the regulation of the circulation appears to depend on the existing arterial baroreflex activity.

The influence of intact carotid sinus baroreceptors and their interaction with vagal reflexes was demonstrated clearly during coronary occlusion before and during vagal cold block. Coronary occlusion elicited changes in cardiac output and mean arterial pressure which were qualitatively similar, whether or not the vagi were blocked. However, in the absence of vagal afferents, coronary occlusion elicited an increase in peripheral resistance, suggesting that interruption of vagal afferents unmasks a vasoconstrictor response to coronary occlusion which presumably is initiated by the carotid sinus. This result is consistent with results of studies in anesthetized cats in which resistance in the isolated, perfused calf muscle was increased during coronary occlusion, after vagal cold block.7

In the present study, the aortic arch was denervated at the time of instrumentation. Subsequent carotid sinus denervation resulted in a functional denervation of the arterial baroreceptors as judged by the abolition or the marked attenuation of the reflex heart rate response to a pressor agent in all animals studied. It is unlikely that the initial denervation of the aortic baroreceptors influenced our results, because these receptors have been shown to have a higher threshold pressure than the carotid sinuses.15 Also, the responses to coronary occlusion following aortic denervation were not different from results of earlier studies on normally innervated animals in this laboratory.12, 13 This is further substantiated by the observation that vagal cold block in dogs with intact aortic nerves results in increases in arterial pressure that are similar to those in this study.15 Coronary occlusion following carotid sinus denervation caused a substantially greater fall in mean arterial pressure (−41%) and peripheral resistance (−23%) as compared to the responses prior to the denervation of the carotid sinuses (−6% and no change, respectively). These changes are similar qualitatively to those previously reported from our laboratory and support our original conclusions concerning the importance of the arterial baroreceptors in the maintenance of the systemic pressure during coronary occlusion.10 In the present study, however, the fall in both arterial pressure and peripheral resistance during coronary occlusion in sinoaortic-denervated dogs was greater, quantita-

Table 4  Responses to Vagal Cold Block in Dogs That Received Atropine

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Atropine</th>
<th>Atropine and vagal cold block</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial pressure (mm Hg)</td>
<td>98 ± 4</td>
<td>101 ± 1.9</td>
<td>119 ± 7*</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>90 ± 10</td>
<td>183 ± 14</td>
<td>189 ± 19</td>
</tr>
<tr>
<td>Mean cardiac output (ml/min)</td>
<td>3001 ± 476</td>
<td>3165 ± 430</td>
<td>3284 ± 372</td>
</tr>
</tbody>
</table>

Values = mean ± SEM. * P < 0.01; n = 6.
TABLE 5  Mean Responses to Coronary Occlusion and Vagal Cold Block in Sinoaortic-Denervated Dogs

<table>
<thead>
<tr>
<th></th>
<th>Heart rate (beats/min)</th>
<th>Mean cardiac output (ml/min)</th>
<th>Mean left atrial pressure (mm Hg)</th>
<th>Mean arterial pressure (mm Hg)</th>
<th>Peripheral resistance (PRU)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>X ± Δa ± Δav</td>
<td>X ± Δa ± Δav</td>
<td>X ± Δa ± Δav</td>
<td>X ± Δa ± Δav</td>
<td>X ± Δa ± Δav</td>
</tr>
<tr>
<td>CON</td>
<td>134 ± 8 3638 ± 8</td>
<td>1.3 ± 0.3 6.8 ± 247*</td>
<td>127 ± 8 52.1 ± 6.4</td>
<td>2.10 ± 0.25</td>
<td></td>
</tr>
<tr>
<td>CO</td>
<td>130 ± 4 2956 ± 4</td>
<td>6.5 ± 5.2 75 ± 10.1</td>
<td>1.62 ± 0.22 0.49</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VB</td>
<td>134 ± 8 3387 ± 8</td>
<td>1.1 ± 1.6 5.8 ± 5.1†</td>
<td>2.01 ± 0.23 0.7†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VB + CO</td>
<td>153 ± 19 3583 ± 19</td>
<td>3.6 ± 1.4 159 ± 49</td>
<td>2.60 ± 0.59 0.59</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mean values X ± SEM are shown during control states (CON), coronary occlusion (CO), vagal cold block (VB), and during vagal cold block and coronary occlusion (VB + CO). Δa = mean difference between control values and those observed during CO, VB, and VB + CO. Δav = mean difference between VB responses and those observed during VB and CO.

* P < 0.05; † P < 0.01; ‡ P < 0.001.


tively, than in our previous report, suggest that the denervation technique now used is more selective than the former method. Formerly, the aortic arch denervation was accomplished in the cervical region by the method of Edis and Shepherd,16 which included removal of part of the left vagus. The risk of cutting vagal cardiac fibers or leaving some aortic fibers intact would be less likely by denervating the aortic arch.17

In sinoaortic-denervated dogs, the dramatic fall in arterial pressure and peripheral resistance observed during coronary occlusion was attenuated significantly when vagal afferents were interrupted prior to the occlusion. This suggests that at least part of the hypotensive response to myocardial ischemia results from an inhibitory influence on the vasomotor center that is mediated through vagal afferents. However, vagal blockade resulted in a substantially larger increase in mean arterial pressure in sinoaortic-denervated dogs. Accordingly, it could be argued that this large increase in mean arterial pressure resulting in increased coronary perfusion pressure, sustained myocardial function during coronary occlusion, thereby inhibiting the fall in arterial pressure. Earlier work, in which arterial pressure was elevated by phenylephrine infusion does not support this possibility.10 In that study, the blood pressure response to coronary occlusion was quantitatively similar at resting blood pressures over a 30 mm Hg range. In the present study, it seems unlikely that differences in myocardial function affected the response, since coronary occlusion caused similar reductions in cardiac output, whether the vagi were intact or not. The differences in arterial pressure changes were more likely secondary to peripheral resistance changes. Vagal blockade prior to coronary occlusion prevented the fall in peripheral resistance that always was observed during coronary occlusion following arterial baroreceptor denervation in dogs with intact vagi. Nevertheless, the hypotension observed during coronary occlusion after arterial baroreceptor denervation was not completely abolished by vagal cold block. This suggests that part of the response was related to the fall in cardiac output due to a direct depressant effect of myocardial ischemia on cardiac function. Thus, not only does the carotid sinus reflex buffer the blood pressure...
fall due to depressed cardiac function, but it inter-
acts with the vagal inhibitory influences on the
vasomotor neurons controlling sympathetic efferent
discharge to the periphery. Apparently, during
acute activation, the arterial baroreflex overrides
the cardiopulmonary reflex, preventing the fall in
systemic arterial pressure. Previous studies by Con-
stantin and Thoren also showed that coronary
occlusion produces reflex hypotension in anesthe-
tized dogs and cats. Interruption of the vagus re-
duces or abolishes the hypotension. In both of these
studies, the magnitude of the hypotension was in-
fluenced by the arterial baroreceptors. Our results
in the conscious dog, following arterial baroreceptor
denervation, agree with results of those studies, in
that vagotomy reduced the hypotensive response to
coronary occlusion in anesthetized dogs and cats.
However, unlike the anesthetized animal, arterial
pressure was well maintained in the conscious dog
with intact carotid sinuses during coronary occlu-
sion, and the presence or absence of vagal afferents
did not influence the arterial pressure response. A
number of studies have shown that cardiac
receptors, with both myelinated and nonmyelinated
fibers traveling in the vagus, can exert reflex influ-
ences on the cardiovascular system. Some of these fibers originate from ventricular receptors.
Other studies have shown that receptors in the atria, ventricle, and lungs also exert a tonic
inhibition of the vasomotor center. Thus, the
response observed during interruption of vagal af-
ferents undoubtedly represents a summation of in-
puts from different receptors located in the cardio-
pulmonary region. In the present study, we have no way of knowing the relative contribu-
tion of ventricular receptors vs. atrial or pulmonary
receptors. However, in anesthetized animals, elec-
trical stimulation of nonmyelinated afferent cardiac
nerve fibers from ventricular receptors, as well as
coronary occlusion and coronary sinus occlusion,
have been shown to produce bradycardia and hy-
potension. Furthermore, neural activity in nonmye-
linated afferent vagal nerve fibers from ventricular
receptors increases in concert with systolic bulging.
In the conscious dog, coronary occlusion produces
a reflex tachycardia, unless the heart rate is near
the intrinsic rate (130–150 beats/min). As noted in
this study, bradycardia sometimes is observed dur-
ing coronary occlusion in sinoaortic-denervated
dogs. The difference in heart rate response, com-
paring the anesthetized cat and dog and the con-
scious dog, may be related to the initial heart rate
which, no doubt, reflects a different level of neural
regulation. Anesthesia is known to alter the
reflex regulation of the cardiovascular system. Ad-
ditionally, in the cat, there could be a species-de-
pendent difference.

In summary, we have shown that, in the con-
scious dog, vagal afferents from the cardiopulmo-
nary region exert a significant depressant influence
on the systemic arterial pressure at rest, and that
this effect apparently is not increased by coronary
artery occlusion. However, the presence of the ca-
rotid sinus reflex apparently masks the true blood
pressure-depressing potential of these cardiac vagal
afferents. Following sinoaortic denervation, marked
increases occur in arterial pressure and peripheral
resistance during vagal cold block. The dramatic
hypotension occurring with coronary occlusion after sinoaortic denervation is partially reversed by
vagal cold block, and the decline in peripheral re-
sistance is prevented.

Acknowledgments

We wish to express our gratitude to Linda Fox and Jesse
Rodriguez for their technical skills and assistance during this
research project.

References

1. Guazzi MAL, Brettii L, Zanchetti A: Tonic reflex regulation
of the cat's blood pressure through vagal afferents from the
2. Pillsbury HRC III, Guazzi M, Fries ED: Vagal afferent
depressor nerves in the rabbit. Am J Physiol 217: 768-770,
1969
3. Oberg B, White S: Circulatory effects of interruption and
stimulation of cardiac vagal afferents. Acta Physiol Scand
86: 383-394, 1970
4. Mancia G, Donald DE, Shepherd JT: Inhibition of adrenerg-
ic outflow to peripheral blood vessels by vagal afferents
from the cardiopulmonary region in the dog. Circ Res 33:
713-721, 1973
5. Mancia G, Shepherd JT, Donald DE: Interplay among ca-
rotid sinus, cardiopulmonary and carotid body reflexes in
6. Constantin L: Extra cardiac factors contributing to hypoten-
sion during coronary occlusion. Am J Cardiol 11: 205-217,
1968
7. Thoren P: Evidence for a depressor reflex elicited from left
ventricular receptors during occlusion of one coronary artery
8. Oberg B, Thoren P: Circulatory responses to stimulation in
mediated and non-mediated afferents in the cardiac
9. Thoren P: Activation of left ventricular receptors with non-
mediated vagal afferent fibers during occlusion of a coro-
nary artery in the cat. Am J Cardiol 37: 1046-1051, 1976
10. Peterson DF, Bishop VS: Reflex blood pressure control
during acute myocardial ischemia in the conscious dog. Circ
Res 34: 226-232, 1974
11. Stone HL, Bishop VS: Ventricular output in conscious dogs
following acute vagal blockade. J Appl Physiol 24: 782-786,
1968
12. Peterson DF, Kaspar RL, Bishop VS: Reflex tachycardia
due to temporary coronary occlusion in the conscious dog.
13. Bishop VS, Kaspar RL, Barnes GE, Kardon MB: Left ven-
tricular function during acute regional myocardial ischemia
of vagal afferents in experimental myocardial infarction. Am
J Cardiol 35: 833-840, 1974
15. Pelletier CL, Clement DL, Shepherd JT: Comparison of afferent
activity of the canine aortic and sinus nerves. Circ
Res 31: 557-568, 1972
baroreceptors and chemoreceptors in dogs. J Appl Physiol
30: 294-296, 1971
Inotropic and Toxic Effects of a Polar Cardiac Glycoside Derivative in the Dog

GILBERT H. MUDGE, JR., BRIAN L. LLOYD, DAVID J. GREENBLATT, AND THOMAS W. SMITH

SUMMARY It has been suggested that central nervous system (CNS) neuroexcitation plays an important role in digitalis-induced cardiac arrhythmias. To elucidate further the role of the CNS in digitalis-induced arrhythmias, the inotropic and toxic effects of a highly polar semisynthetic cardiac glycoside, 3β-O-(4 amino-4,6 dideoxy-β-D-galactopyranosyl)-digoxigenin (ASI-222) were compared to those of digoxin and correlated with plasma and cerebrospinal fluid (CSF) concentrations of each drug. Thirteen dogs anesthetized with sodium pentobarbital were given repeated intravenous doses of digoxin or ASI-222. Ventricular tachycardia was elicited at a mean dose of digoxin of 0.12 mg/kg, compared with 0.09 mg/kg for ASI-222 (not significant). Terminal ventricular fibrillation occurred after 0.18 mg/kg of digoxin, a value significantly larger than the ASI-222 dose (0.14 mg/kg, P < 0.05) required to produce lethal arrhythmias. Digoxin produced a 21% increase in LV dP/dt at a plasma digoxin concentration of 20.0 ± 2 ng/ml (mean ± SEM) 30 minutes after 0.05 mg/kg; the CSF digoxin concentration at this time averaged 0.7 ± 0.1 ng/ml. At death, the plasma digoxin concentration was 88 ± 16 ng/ml and CSF SF digoxin concentration was 5.7 ± 1.6 ng/ml. ASI-222 produced a similar 25% increase in LV dP/dt 30 minutes after administration of 0.05 mg/kg, with a plasma concentration of 18 ± 2 ng/ml as determined by a newly developed radioimmunoassay. The plasma ASI-222 concentration at death, 95 ± 18 ng/ml, was similar to that of digoxin. However, CSF samples at 30 minutes and at death showed no detectable levels of ASI-222. Thus, despite similar inotropic and toxic responses and similar plasma drug concentrations compared to digoxin, ASI-222 was demonstrated to have limited if any access to the CNS as judged by CSF concentrations. These findings suggest that direct CNS stimulation does not play a primary part in the genesis of digitalis-induced cardiac arrhythmias in this experimental model, or that CNS effects are mediated by an area or areas lacking an effective blood-brain barrier.

THERAPEUTIC use of cardiac glycosides is complicated by frequent signs and symptoms of cardiac and extracardiac toxicity,1 and the narrow margin between therapeutic inotropic effect and serious cardiac arrhythmias is well known. Recent experimental evidence suggests that digitalis-induced central nervous system (CNS) neuroexcitation contributes to cardiac rhythm disturbances.2-5 Ventricular arrhythmias have been temporally related to enhanced cardiac sympathetic neural activity4-5 or to...
The circulatory influences of vagal afferents at rest and during coronary occlusion in conscious dogs.
V S Bishop and D F Peterson

Circ Res. 1978;43:840-847
doi: 10.1161/01.RES.43.6.840

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1978 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/43/6/840

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/