Reflex Tachycardia Due to Temporary Coronary Occlusion in the Conscious Dog

By D. Fred Peterson, Robert L. Kaspar, and Vernon S. Bishop

ABSTRACT

Reflex increases in heart rate which occurred during 1-minute occlusions of the left circumflex coronary artery were studied in conscious dogs. The results indicated that occlusion produced tachycardia (latency to onset 8.5 seconds) preceded by a rise in left atrial pressure (7.2 seconds) and followed by a small fall in arterial pressure (19.5 seconds). Bilateral baroreceptor denervation indicated that the onset of the changes in heart rate could not be accounted for by subtle baroreceptor sensitivity, although the peak response was much reduced (from 34.0 beats/min to 17.5 beats/min), indicating that the magnitude of the response did depend on intact baroreceptors. Beta-receptor blockade with propranolol or cardiac sympathectomy reduced the peak response from 34.0 beats/min to 16.1 beats/min or 12.2 beats/min, respectively. Vagal blockade with atropine reduced the response to 5.3 beats/min, indicating that the remainder of the response was carried in the vagus. Responses were much reduced after baroreceptor denervation plus β-receptor blockade (5.2 beats/min), indicating that the efferent vagal branch of the reflex originated primarily in the arterial baroreceptors. Tachycardia during coronary occlusion, then, is initiated by receptors in or near the heart, and the magnitude of the response is a combination response from these receptors and the arterial baroreceptors.

KEY WORDS propranolol atropine vagus cardiac sympathetic nerves left atrial receptors left circumflex coronary artery arterial baroreceptors

Tachycardia occurs as a result of temporary coronary occlusion in the conscious dog (1, 2). The source of this tachycardia has not yet been determined, although chemoreceptors in the coronary vascular bed, mechanoreceptors in the left atrium or the left ventricle, and arterial baroreceptors are all potential sites of origin. Neural recordings indicate that myocardial ischemia due to coronary occlusion in anesthetized animals activates numerous reflex responses which originate in the coronary vascular bed (3–7); moreover, some receptors in this region have been shown to modify heart rate (7). In addition, numerous dynamic changes take place due to compromise of left ventricular performance during coronary occlusion, and these changes might implicate potential sources of cardiovascular reflexes. Decreases occur in aortic flow and left ventricular end-diastolic pressure, but left ventricular end-diastolic pressure and mean left atrial pressure rise (1, 2). Mechanoreceptors possibly affected by these changes are known to modify heart rate. Arterial baroreceptors reflexly alter heart rate due to changes in arterial pressure (8). Distention of the left ventricle produces bradycardia (9). Balloon inflation of the left atrial–venous junction (10–12) or of the right atrial–venous junction (13) or stretch of the left atrial wall (14) causes tachycardia. Intravenous infusions stimulating receptor areas in the heart and the pulmonary circulation have been reported by Bainbridge to cause tachycardia (15), but others have observed bradycardia (8, 16). More recently, right atrial infusion of Ringer’s solution, elevating both right and left atrial pressure, has been shown to produce tachycardia (17). Thus, receptors in or near the heart cause reflex modification of heart rate, and acute myocardial ischemia might stimulate these receptors either directly or indirectly.

In the present study, heart rate responses were observed during acute (1-minute) occlusions of the left circumflex coronary artery in conscious dogs. The results implicated the left atrium as the site of origin of reflex tachycardia, and arterial baroreceptors were also shown to contribute to the total response. The right cardiac sympathetic nerves appeared to be the primary efferent pathway from...
the left atrial receptors, although the response originating in the arterial baroreceptors had most of its efferent pathway in the vagus.

Methods

CHRONIC SURGERY

Twenty-two mongrel dogs (10–25 kg) were chronically instrumented under sterile surgical conditions using halothane anesthesia. A left thoracotomy was performed through the third 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 artery just beyond its origin. A 6- to 10-mm length of the artery was separated from surrounding tissue, and a balloon type of polyethylene catheter cuff similar to that used by Chimoskey et al. (18) was placed around the vessel. The catheter was then sutured to the wall of the ventricle, thus immobilizing it. A saline-filled syringe was used to verify occlusion. Both the volume and the pressure required for occlusion were determined.

Eighteen-gauge polyvinyl catheters were placed in the left atrial appendage for measurement of pressure or infusion of drugs. Also an 18-gauge polyvinyl catheter was placed in the internal mammary artery at the time of thoracotomy or in a carotid artery through a cervical incision several days later. In some dogs, a piece of surgical suture (Tevdek) was looped around the left ansa subclavia for later left cardiac sympathectomy. All catheters, the thread, and the occlusive device were exteriorized at the back of the neck. Approximately 2 weeks were allowed for recovery; at the time when coronary occlusions were performed, body temperature and electrocardiogram (ECG) were normal.

CARDIAC SYMPATHECTOMY

Sterile surgery was performed a second time in six dogs. Through a right thoracotomy, a loop of thread was placed around the right ansa subclavia 10–15 mm distal to the stellate ganglion, and the thread was exteriorized through the back of the neck. This thread, as well as the one previously placed on the left side, could later be pulled to cut the sympathetic nerves to the heart, thereby eliminating sympathetic innervation of the heart (19). The sympathectomy was performed either when the dog was anesthetized or after injection of morphine sulfate (0.5 mg/kg).

BARORECEPTOR DENERVATION

Sterile surgery was performed on eight other dogs to denerve their arterial baroreceptors. A midcervical incision was made, the carotid sinus was located bilaterally, and all vessels above the bifurcation of the common carotid arteries except the external carotid arteries were ligated. All tissue was then stripped from above the bifurcation of the common carotid arteries. Occlusion of the common carotid arteries verified that reflex heart rate and blood pressure influences from the carotid sinus had been abolished (Fig. 1). The aortic nerves were located near the junction of the vagus and the cranial laryngeal nerves and were sectioned. Whenever identification of the aortic nerve was in doubt, all branches of the vagus within 2 cm below the cranial laryngeal nerve were sectioned. Baroreceptor-denervated dogs became hypertensive, and bradycardia resulting from a large transient rise in blood pressure after injection of phenylephrine (10 μg) was abolished or drastically reduced. After several days of recovery, the baroreceptor-denervated dogs were again subjected to coronary occlusions.

EXPERIMENTAL PROTOCOL

ECG, blood pressure, heart rate, and left atrial pressure were recorded simultaneously on a Beckman type R Dynograph, using appropriate transducers, couplers, and amplifiers. Coronary 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 artery did not produce extrasystolic beats. All experiments were performed while the dog was conscious, lying on his right side, and lightly restrained.

DRUG ADMINISTRATION

Propranolol hydrochloride (0.5–1.0 mg/kg) was administered intravenously to block β-receptor sites. The effectiveness of blockade was tested with isoproterenol (4 μg, iv) before and after propranolol administration. Atropine sulfate (0.1 mg/kg, iv) was administered to block vagal efferent influences on the heart.

Results

The characteristic response to a 1-minute coronary occlusion in a conscious dog was a rise in left atrial pressure, an increase in heart rate, and a slight fall in arterial pressure (Fig. 2). Sixty-six trials in 22 dogs indicated that all responses were qualitatively similar to those illustrated. The preclosure mean left atrial pressure was 3.1 mm Hg (range 0 to 5.5 mm Hg), the mean arterial blood pressure was 95.2 mm Hg (range 72 to 135 mm Hg), and the mean heart rate was 111.4 beats/min.
Typical responses to a 1-minute occlusion of the left circumflex coronary artery. Responses include a rise in mean left atrial pressure (MLAP), a very slight fall in mean arterial pressure (MAP), and a substantial rise in heart rate (HR). The first arrow represents the onset of occlusion, and the second arrow represents the release of occlusion.

(97.2 ± 0.5) seconds, but the onset of the fall in arterial pressure was much later (19.5 ± 1.8 seconds). The onset of the rise in heart rate occurred 8.5 ± 0.8 seconds after the beginning of coronary occlusion. Thus, the change in heart rate occurred after the change in left atrial pressure but before the change in arterial pressure. Peak changes in response indicated that mean left atrial pressure rose 4.8 ± 0.6 mm Hg (range 1.5 to 11.5 mm Hg), mean arterial pressure fell 9.9 ± 1.6 mm Hg (range 2 to 22 mm Hg), and heart rate rose 34.0 ± 2.0 beats/min (range 17 to 49 beats/min).

To investigate the reflex nature of the observed changes in heart rate, pharmacologic blocking agents were used to selectively denervate the sympathetic and the vagal innervation to the heart. Administration of propranolol reduced the heart rate response to 16.1 ± 1.8 beats/min (Fig. 3). The subsequent addition of atropine sulfate, which blocked efferent vagal influences on the heart, further reduced the heart rate response to 5.3 ± 0.6 beats/min (Fig. 3). Seven dogs were given atropine initially. Only small changes in heart rate (7.3 ± 1.7 beats/min) were observed in these dogs, and it was presumed that the high initial heart rate (185.4 beats/min) attenuated that part of the response mediated via the cardiac sympathetic nerves. Reduction in purely sympathetic responses after atropine administration has been previously observed in conscious and anesthetized dogs (20). The administration of propranolol had no significant effect on the onset or the magnitude of the rise in atrial pressure or the fall in arterial pressure. The combination of propranolol plus atropine did not affect the magnitude of the change in left atrial pressure but did significantly shorten the latency to onset (P < 0.01, Table 1). In addition, the fall in arterial pressure was significantly greater (P < 0.05, Table 2), and the latency to onset was significantly shorter (P < 0.001, Table 1).

To circumvent possible interfering side effects of propranolol, surgical cardiac sympathectomies were performed in six dogs. Responses to 1-minute coronary occlusions after section of the right ansa subclavia in three dogs indicated that the average heart rate response was reduced from 20.6 beats/min to 7.1 beats/min. Section of the left ansa subclavia did not further reduce the response (7.7 beats/min). In three dogs, section of the left ansa subclavia initially did not significantly reduce the heart rate response compared with control values (36.1–34.6 beats/min). Subsequent section of the right ansa subclavia reduced the heart rate response from 34.6 beats/min to 16.2 beats/min. Administration of atropine sulfate after bilateral cardiac sympathectomy in three dogs reduced the response to less than 1 beat/min and, in effect, abolished it. Thus, surgical sympathectomy appeared to be a more effective means of eliminating reflex effects than was β-receptor blockade. Also, the preceding procedures revealed that most of the efferent limb of the tachycardia observed during coronary occlusion was carried in the right cardiac sympathetic nerves and that the remainder was in the vagus.
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TABLE 1

<table>
<thead>
<tr>
<th>Latencies (seconds) to Onset of Changes Due to Coronary Occlusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (N = 22)</td>
</tr>
<tr>
<td>Heart rate</td>
</tr>
<tr>
<td>Mean left atrial pressure</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
</tr>
</tbody>
</table>

Values are means ± se. Heart rate changes after administration of propranolol and atropine were too slight to estimate onset. Statistical significance was determined using Student’s t-test, and comparisons under each condition were made with their own controls. N = number of dogs tested.

*P < 0.001.
†P < 0.01.

Initial heart rate was not a factor in the magnitude of the response in these dogs when the nervous system was intact. There was no indication that when heart rate changed it sought the intrinsic value reported in the literature to be between 130 and 150 beats/min for dogs (12, 21, 22). One dog had an initial heart rate of 153 beats/min, and the rate increased to 197 beats/min during occlusion. Six other dogs with resting rates below 150 beats/min had rates above 150 beats/min (mean change 129.8 beats/min to 167.0 beats/min).

The possibility that arterial baroreceptors played a role in this heart rate response was investigated by surgical denervation of the carotid sinus and the aortic arch regions after control values had been obtained from conscious dogs. Dogs were permitted to recover from denervation surgery for 2-3 days before responses to coronary occlusion were studied. Data were collected from eight dogs. Baroreceptor denervation had no significant effect on the change in mean left atrial pressure due to coronary occlusion (Tables 1 and 2). Most dogs became hypertensive immediately as indicated by their higher initial blood pressure (mean change 103.6 mm Hg to 143.3 mm Hg) (Fig. 1). Blood pressure was inconsistent from day to day and occasionally varied considerably during an experiment. In addition, mean arterial pressure fell much further in response to coronary occlusion in baroreceptor-denervated dogs, indicating baroreceptor maintenance of blood pressure in the normal dog (Table 2). These results indicated that the baroreceptors played a significant role in the tachycardia accompanying coronary occlusion (Figs. 4 and 5). The average heart rate response was reduced to 17.5 beats/min (Table 2) during occlusion in baroreceptor-denervated dogs. The arterial baroreceptors did not appear to be involved in the onset of the response but rather in its magnitude. Figure 4 represents a typical response to coronary occlusion in a baroreceptor-denervated dog. Note that mean and pulsatile arterial pressures were maintained until after the heart rate rose. Comparing the development of tachycardia in control, baroreceptor-denervated, and cardiac sympathectomized dogs (Fig. 5) showed that loss of baroreceptor control did not interfere with the magnitude of the response 15 seconds after onset of occlusion. Loss of cardiac sympathetic innervation

TABLE 2

Peak Responses to Coronary Occlusion

<table>
<thead>
<tr>
<th>Control (n = 22)</th>
<th>Propranolol (n = 20)</th>
<th>Bilateral ansa section (n = 6)</th>
<th>Propranolol + atropine (n = 15)</th>
<th>Baroreceptor denervation (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate increase (beats/min)</td>
<td>34.0 ± 2.0</td>
<td>16.1 ± 1.8*</td>
<td>12.2 ± 3.5*</td>
<td>17.5 ± 1.8*</td>
</tr>
<tr>
<td>Mean left atrial pressure rise (mm Hg)</td>
<td>4.8 ± 0.6</td>
<td>6.3 ± 0.7</td>
<td>3.1 ± 1.0</td>
<td>4.2 ± 0.6</td>
</tr>
<tr>
<td>Mean arterial pressure fall (mm Hg)</td>
<td>9.9 ± 1.6</td>
<td>13.8 ± 1.9</td>
<td>11.2 ± 4.0</td>
<td>16.4 ± 2.1†</td>
</tr>
</tbody>
</table>

Values are means ± se. Statistical significance was determined using Student’s t-test, and comparisons under each condition were made with their own controls. N = number of dogs tested.

*P < 0.001.
†P < 0.01.

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Responses to coronary occlusion after baroreceptor denervation. The top trace represents mean left atrial pressure (MLAP), the second trace represents pulsatile arterial pressure (AP), the third trace represents heart rate (HR), and the bottom trace is an electrocardiogram (ECG). Occlusion began at the first arrow and ended at the second arrow. Note that the onset of the fall in mean and pulsatile arterial pressure was considerably slower than the onset of tachycardia.

Heart rate (HR) responses as a function of time after onset of coronary occlusion. Control response (triangles); response after bilateral aortic and carotid sinus denervation (open circles); response after bilateral cardiac sympathectomy with baroreceptors intact (closed circles). At 15 seconds after initiation of coronary occlusion, dogs without baroreceptors demonstrated responses that were not significantly different from control ($P > 0.10$). Dogs without efferent sympathetic nerves to the heart displayed responses significantly reduced in magnitude compared with control at 15 seconds ($4.2$ vs. $11.9$ beats/min, $P < 0.01$). Responses 30, 45, and 60 seconds after either cardiac sympathectomy or arterial baroreceptor denervation were all significantly lower than control. Note that any time after the onset of coronary occlusion the sum of the average responses under the two operative conditions approaches the control response.

When baroreceptors were intact, however, significantly reduced the early response at 15 seconds. At 30, 45, and 60 seconds after onset of coronary occlusion, increases in heart rate in both baroreceptor-denervated and cardiac sympathectomized dogs were significantly lower than they were in controls (Fig. 5). Such results suggest that receptors other than arterial baroreceptors are responsible for the initiation of the tachycardia due to coronary occlusion and that the arterial baroreceptors contribute to the total magnitude of the response. The administration of propranolol after baroreceptor denervation reduced the heart rate response to 5.2 beats/min. Subsequent administration of atropine sulfate reduced the response to 1.9 beats/min. Thus, a small component of the total response might be mediated by the efferent vagus nerve.

After baroreceptor denervation, heart rate during coronary occlusion tended to go toward the so-called intrinsic value (12, 21, 22). When the initial heart rate was below 150 beats/min, it never exceeded 154 beats/min during occlusion. Three dogs had high initial heart rates during the first trial day after denervation. They demonstrated bradycardia during occlusion (mean change 154.5 beats/min to 138.3 beats/min). Several days later when resting heart rate had fallen, the response of these three dogs to coronary occlusion was reversed (mean change 110.0 beats/min to 130.7 beats/min). One of these three dogs showed an average change in heart rate before denervation (three trials) from 133 beats/min to 179 beats/min. Thus, intact arterial baroreceptor reflexes might be important in generating a tachycardia which exceeds the so-called intrinsic value.

**Discussion**

Cardiovascular changes which have been shown to occur during 1-minute coronary occlusions in conscious dogs include decreased aortic flow, decreased peak left ventricular pressure, increased ventricular diastolic pressure, increased left atrial pressure, decreased arterial pressure, and increased heart rate (1, 2). Our results demonstrated that the tachycardia was reflex in nature but that the other changes might well have been the direct result of myocardial failure (1, 2). These changes suggest that the initiation of tachycardia might originate from the arterial baroreceptors, the left ventricle, the coronary arterial bed, the pulmonary venous bed, or the left atrium.

The delayed onset of the fall in blood pressure suggests that arterial high-pressure baroreceptors...
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do not play a significant role in the initiation of the rise in heart rate. This suggestion is supported by the persistence of the onset of tachycardia when mean and pulsatile arterial pressure is unchanged in baroreceptor-denervated dogs.

Left ventricular mechanoreceptors have been described (9, 23). Such receptors respond only to extreme distention of the left ventricle to produce bradycardia and normally have very low tonic activity (24). Aviado and Schmidt (9) have reported tachycardia resulting from reduction or interruption of inflow into the left ventricle; however, this maneuver produces cerebral anoxia, and the response is delayed 30 seconds. Thus, a small reduction in left ventricular pressure probably would not cause the rapid onset of tachycardia that we observed.

Another possible site of origin of tachycardia during coronary occlusion is the coronary vascular bed. Ample evidence exists for reflexes initiated by mechanical stimuli, ischemia, hypoxia, and hypercapnia of coronary receptors (3, 4). Such reflexes have been shown to have their efferent limb in the cardiac sympathetic nerves (6), although some might have an afferent limb in the vagus (25) and others an afferent limb in the cardiac sympathetic nerves (5). Increased efferent discharge in cardiac sympathetic nerves has been demonstrated during cessation of flow in the main left coronary artery of the anesthetized cat (5); however, no relationship between this reflex and changes in heart rate has been established. Furthermore, reflexes from the coronary vascular bed are carried primarily in the left sympathetic nerves (5). In our experiments, section of the left ansa subclavia did not affect the heart rate response. Thus, these coronary receptors are probably not responsible for the tachycardia we observed.

Since communication between the left atrium and the great pulmonary veins is patent (26), it is not possible to selectively stimulate each of these sites physiologically to determine which may contain receptors involved in changes in heart rate. However, it has been shown that the majority of the receptors in the pulmonary venous-left atrial system are situated in the subendocardial tissue at the junctions of the pulmonary veins and the left atrium (27). It seems likely then that, as observed by Ledsome and Linden (10), elevation of atrial pressure would primarily affect this junctional region.

Ledsome and Linden (10) have reported reflex tachycardia due to stretch of the left atrial-pulmonary venous junction. They have located the efferent limb of the reflex in the cardiac sympathetic nerves. Numerous subsequent studies have generally supported their findings in the anesthetized dog (11, 13, 28). Coronary occlusion in the conscious dog causes a rise in left atrial pressure which precedes the increase in heart rate and, thus, undoubtedly produces stretch of the left atrial receptors, which could, in turn, produce tachycardia. If so, our results present the first evidence of a physiological stimulus that affects these junctional receptors.

The reflex efferent pathway of the heart rate response in the baroreceptor-intact dog was partially in the right cardiac sympathetic nerves and partially in the vagus. Sympathetic efferent blockade with propranolol reduced the response to about 50% of control, and the addition of atropine (vagal blockade) nearly abolished the tachycardia due to coronary occlusion. Our results indicated that surgical sympathectomy was a more effective method of eliminating the response than was propranolol blockade; our study also confirmed the evidence that not all of the tachycardia was due to activity in the efferent cardiac sympathetic nerves. Since section of the left ansa subclavia did not affect the response, neither afferent nor efferent pathways appear to be carried in the left sympathetic nerves. Afferent pathways in our study were not established, although previous studies of left atrial receptors have implicated the vagus (10-12). The potential, however, for a right sympathetic afferent pathway cannot be discounted, although, in view of the work of others (10-12), it certainly seems less likely than the vagal pathway.

Dogs were less responsive to coronary occlusion after baroreceptor denervation than they were during control conditions. Loss of baroreceptor input caused diminution of the total magnitude of the response; nevertheless, baroreceptor removal and its associated trauma in the chronic dog did not abolish the tachycardia induced by acute coronary occlusion, nor did it interfere with the latency to onset or the early magnitude of the response, suggesting that arterial baroreceptors are not critical in generating the tachycardia. Edis et al. (12) have found that when baroreceptor activity is controlled animals whose initial heart rate exceeds 150 beats/min demonstrate bradycardia when the left atrial junction is stretched. Our results, although only for three dogs, tended to support this finding for baroreceptor-denervated animals. Fournival et al. (28) have challenged this possibility on

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the grounds that their work and that of others (29) always results in tachycardia even when initial heart rate is as high as 202 beats/min and carotid sinus pressure is controlled. A possible explanation for the apparent inconsistency might lie in the fact that Carswell et al. (29) did not eliminate aortic baroreceptor input, whereas an effort was made to section the aortic nerve by Edis et al. (12) as well as in the present study. Administration of propranolol after baroreceptor denervation drastically reduced the observed tachycardia. This finding supports the evidence of Furnival et al. (28) that the reflex originating in or near the heart has its primary efferent limb in the cardiac sympathetic nerves and implies that the response seen in the intact dog during β-receptor blockade originates primarily in the arterial baroreceptors. A small response (5.2 beats/min) did appear to originate exclusive of the arterial baroreceptors and after β-receptor blockade, suggesting a minor efferent pathway in the vagus nerve. Tachycardia produced by infusion of saline into the right atrium has been shown to have a predominant efferent pathway in the vagus (17). The response in that study might have involved the receptors producing the response we reported, but it must have also involved receptors in the cardiopulmonary region not affected by our stimulus.

In our study some important questions concerning reflex regulation of blood pressure were raised. Although propranolol or ansa subclavia section alone did not significantly alter either latency to onset or magnitude of blood pressure changes during coronary occlusion, the combination of propranolol plus atropine markedly shortened latency to onset of the blood pressure decline and increased the magnitude of the response (Table 1 and 2). This finding implicates either blockade of the efferent vagal pathway of a cardiocardiac reflex important in maintenance of blood pressure or inability of the heart to maintain its output at a high (171.5 beats/min) or constant heart rate during regional myocardial ischemia. A second reflex most important in maintaining pressure but less significant in prolonging the onset of the fall in arterial pressure during coronary occlusion originates in the arterial baroreceptors. Baroreceptor denervation resulted in a slightly significant decrease in latency to onset of change and a large maximum fall in mean pressure (35.0 mm Hg, Tables 1 and 2). Such results imply an important function in maintenance of arterial pressure but do not indicate the efferent mechanism.

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References


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