Intracoronary Infusion of Prostaglandin \( \text{I}_2 \) Attenuates Arterial Baroreflex Control of Heart Rate in Conscious Dogs

Maret J. Panzenbeck, Wen Tan, Michael A. Hajdu, and Irving H. Zucker

Prostaglandin \( \text{I}_2 \) (PGI\(_2\)) is known to stimulate ventricular C fiber receptors resulting in a Bezold-Jarisch-like reflex. Also, cardiac receptor stimulation is known to interact with the expression of arterial baroreflexes. Therefore, experiments were performed to determine the effects of left circumflex coronary artery infusion of PGI\(_2\) on the baroreflex control of heart rate in conscious instrumented dogs. Dogs were instrumented chronically with an aortic catheter for the measurement of mean aortic pressure, hydraulic occluder cuffs on the descending aorta and inferior vena cava, a left ventricular catheter for the measurement of left ventricular pressure and heart rate, and a nonocclusive catheter in the left circumflex coronary artery. At the time of experimentation, arterial pressure was altered randomly in steps by partially inflating the occluders. Mean arterial pressure-heart curves (baroreflex curves) were constructed by fitting the data to a logistic curve by nonlinear regression. PGI\(_2\) infused into the left circumflex coronary artery at doses of 10, 20, and 50 ng/kg/min caused significant \((p<0.05)\) inhibition of the maximum heart rate, heart rate range, and maximum slope of the curve compared to the control baroreflex curve obtained during intracoronary infusion of PGI\(_2\) vehicle. PGI\(_2\) had no significant effect on the minimum heart rate during hypertension. Since PGI\(_2\) is known to stimulate left ventricular receptors, these effects were most likely produced via stimulation of cardiac receptors. In additional experiments using \(\beta_1\)-blockade with metoprolol or cholinergic blockade with atropine methyl bromide, it was shown that PGI\(_2\) attenuates baroreflex-mediated tachycardia by preventing parasympathetic withdrawal completely and by attenuating sympathetic stimulation by approximately 50%. Thus, stimulation of cardiac receptors with intracoronary PGI\(_2\) at doses that had no or little effect on resting arterial pressure and heart rate resulted in potent inhibition of baroreflex tachycardia. These results suggest that PGI\(_2\) may cause attenuation of baroreflex control of heart rate during conditions in which there is an elevation of plasma and/or cardiac PGI\(_2\) levels. (Circulation Research 1988;63:860-868)

It is now established that prostaglandin \( \text{I}_2 \) (PGI\(_2\)) can stimulate left ventricular receptors with vagal C fiber afferents.\(^1\) Coronary artery injection of PGI\(_2\) in anesthetized dogs\(^2,3\) and cats\(^4\) and conscious dogs\(^5\) has been shown to result in a Bezold-Jarisch-like reflex bradycardia and hypotension. In those studies, the reflex effects of intracoronary PGI\(_2\) were inhibited after bilateral vagal section, indicating that the afferent pathway is carried in the vagi. Also, severe hypotension and bradycardia have been noted in patients receiving prostacyclin,\(^6\) suggesting that PGI\(_2\) stimulates this reflex in humans.

Stimulation of left ventricular receptors with veratridine has been shown to attenuate the arterial baroreflex control of heart rate\(^7\) and peripheral resistance\(^8\) in conscious dogs, suggesting that ventricular receptors may interact with the expression of the arterial baroreflexes under physiological and/or pathophysiological conditions. Coleridge and Coleridge\(^9\) identified two subpopulations of ventricular receptors with vagal C fiber afferents. One population of receptors, mechanosensitive receptors, is responsive to mechanical stimulation only, and another population, chemosensitive receptors, is only stimulated by certain pharmacological agents (e.g., phenyl diguanide). Whereas veratridine stim-
ulates both types of ventricular receptors.\textsuperscript{10,11} PGI\textsubscript{2} stimulates only the chemosensitive type.\textsuperscript{1} To our knowledge, no study has addressed the question of whether stimulation of chemosensitive ventricular C fibers alone will cause attenuation of baroreflex heart rate control. Nevertheless, previous studies suggest that PGI\textsubscript{2} may also inhibit the arterial baroreflex control of heart rate by augmenting the input from these receptors.

PGI\textsubscript{2} is an endogenous substance that is synthesized by the coronary vasculature,\textsuperscript{12} pericardium, and related structures.\textsuperscript{13,14} Cardiac prostaglandin synthesis has been shown to be increased by myocardial ischemia,\textsuperscript{15} heart failure,\textsuperscript{13} increases in sympathetic nerve stimulation,\textsuperscript{16} and by angiotensin.\textsuperscript{14} It is important, therefore, to determine the action of PGI\textsubscript{2} on left ventricular afferents and any consequent interactions with the baroreflexes. It is important to conduct these studies in conscious dogs because anesthesia and acute surgical trauma are known to inhibit cardiovascular reflexes\textsuperscript{17} and to increase circulating prostaglandins levels,\textsuperscript{18} respectively. Therefore, in the present study, we wished to determine if intracoronary infusion of PGI\textsubscript{2} inhibited the arterial baroreflex control of heart rate in conscious dogs. Also, we wished to determine the autonomic components of any heart rate changes we observed.

\section*{Materials and Methods}

These experiments were performed in accordance with the guidelines of the National Institutes of Health as set forth in "Guide for the Care and Use of Laboratory Animals" and in accordance with institutional guidelines. Eleven dogs of either sex with a mean body weight of 25.6±4.47 kg were used in this study. Although not all dogs were used for every experiment, whenever possible the same dogs were used throughout the different experimental protocols (see below).

\subsection*{Surgical Preparation}

After pretreatment with acepromazine maleate (15 mg s.c.), each dog was anesthetized with sodium pentobarbital (30 mg/kg i.v.). Additional pentobarbital was administered as was necessary to maintain a proper level of surgical anesthesia. Each dog was intubated and mechanically ventilated with a positive pressure respirator (Harvard Apparatus, South Natick, Massachusetts). A left thoracotomy was performed with standard sterile surgical technique. The descending thoracic aorta was wrapped with Dacron for approximately 3 cm, and a hydraulic occluder cuff was then positioned over this area. Frequently, this procedure necessitated tying off and cutting three to six intercostal vessels at their origin on the aorta. A hydraulic occluder cuff was also placed around the inferior vena cava just outside the pericardium. A Tygon catheter for the measurement of aortic pressure was placed into the aorta through a stab wound just proximal to the aortic occluder cuff. The pericardium was incised parallel to the phrenic nerve, and a pericardial cradle was formed. A Tygon catheter was placed through a stab wound in the apex of the left ventricle for the measurement of left ventricular pressure. A silastic catheter (0.025 in. o.d.) was placed into the left circumflex coronary artery by the method of Herd and Barger.\textsuperscript{19} This catheter was nonocclusive and was held in place by suturing an attached Dacron patch to the adjacent myocardium. All catheters and occluder tubings were tunneled subcutaneously and exited from the midscapular area. The chest was closed in layers and evacuated. Postoperatively, the dog was placed on an antibiotic regimen (penicillin procaine and dihydrostreptomycin). In addition, each dog was treated with acepromazine the day after surgery. Each dog was allowed to recover for at least 2 weeks after surgery and was not used unless determined to be nonfebrile and to have a resting heart rate of less than 100 beats/min. During the recovery period, the dogs were brought to the laboratory and trained to lie quietly and unrestrained on a table.

\subsection*{Experimental Protocol}

In these experiments, arterial pressure–heart rate curves were constructed under various experimental conditions. The baroreflex function curves were constructed by changing arterial pressure in 10 to 20 random steps. Arterial pressure was varied by partial occlusion of the aortic occluder cuff (increased arterial pressure) or vena caval occluder cuff (decreased arterial pressure). The partial occlusions were performed in random order and each partial occlusion was held until a new steady-state arterial pressure and heart rate response was obtained. Typically, each occlusion was held for 30 to 60 seconds. Thus, by performing these maneuvers, a series of mean arterial pressure/heart rate points were obtained over a range of arterial pressures. Between each step change in arterial pressure, pressure and heart rate were allowed to return to baseline and stabilized for 3 to 5 minutes.

\subsection*{Dose Response Experiments}

This experiment was performed to determine the effects of intracoronary infusion of PGI\textsubscript{2}, at three dose levels, on the arterial baroreflex control of heart rate. Four separate mean arterial pressure–heart rate curves were obtained for each dog on a single day. The curves were constructed by performing aortic occlusion and vena caval occlusion to obtain a full range of arterial pressure–heart rate responses. The first curve was a control and was obtained during intracoronary infusion of 50 mM Tris (pH 8.4, 0.5 ml/min). The subsequent curves were obtained during intracoronary infusions of PGI\textsubscript{2} at increasing doses of 10, 20, and 50 ng/kg/min. In all cases, PGI\textsubscript{2} or buffer was infused for 5 minutes before and for the duration of construction of each mean arterial pressure–heart rate curve.
To ensure that the effects of an infusion did not influence the effects of a subsequent infusion, between construction of each mean arterial pressure–heart rate curve the coronary infusion was terminated and time was allowed for the return of baroreflex function. This was tested for by performing a veno caval occlusion and observing the heart rate response since the most pronounced effect of PG12 was to inhibit the tachycardia during hypotension. The effects of PG12 were short-lasting; control heart rate responses to hypotension returned within 5 to 10 minutes after terminating the PG12 infusion.

Sympathetic Blockade

The purpose of this experiment was to determine the contribution of the sympathetic nervous system to the observed changes in heart rate and to determine which components of the autonomic nervous system were affected by PG12 infusion. Since we had found that PG12 infusion attenuated the tachycardia evoked by hypotension but had no effect on baroreflex bradycardia, we studied only baroreflex tachycardia in these experiments. A random series of veno caval occlusions were performed to determine the maximum heart rate response in each dog. Eight to 10 occlusions were performed under conditions that the plateau of the arterial pressure–heart rate curve was identified. This was done under four conditions: 1) during intracoronary infusion of vehicle (see above), 2) during infusion of PG12 (20 ng/kg/min), 3) following administration of metoprolol (1.0 mg/kg i.v.), and 4) during intracoronary infusion of PG12 after administration of metoprolol. Blockade of β1-receptors was tested for by observing the elimination of the tachycardia induced by intracoronary injection of isoprotanol (1 μg). Additional metoprolol (0.5 mg/kg/hr) was administered as necessary.

Parasympathetic Blockade

These experiments were performed in a manner similar to the experiments with sympathetic blockade. In each dog, a series of veno caval occlusions were performed to determine the maximum heart rate response. These maneuvers were repeated under four conditions: 1) during intracoronary infusion of vehicle (see above), 2) during infusion of PG12 (20 ng/kg/min), 3) following administration of atropine methyl bromide (0.1 mg/kg i.v.), and 4) during intracoronary infusion of PG12 after administration of atropine methyl bromide. Blockade of muscarinic receptors was tested for by observing the elimination of the effect on heart rate of an intracoronary injection of acetylcholine (1 μg/kg). Additional atropine methyl bromide was administered as necessary (0.1 mg/kg/hr).

Data Analysis and Statistics

Phasic and mean arterial pressure, left ventricular pressure, ECG, and heart rate were recorded continuously on a strip chart recorder (Hewlett-Packard Co, Palo Alto, California). Heart rate was derived electronically by feeding the output of the ECG or left ventricular pressure channel into a biotachometer. During generation of the pressure–heart rate curves, data were recorded on a Vetter multi-channel tape recorder and were sampled by a computer (Compac) equipped with a Tecmar A/D interface (Cleveland, Ohio). Data were sampled by the computer at a rapid rate and averaged over the sampling period. Thus, arterial pressure was changed with the occluder cuffs until a new steady-state level was reached, the computer was activated to sample mean arterial pressure and heart rate for 10 to 20 seconds and the occlusion was released. Mean arterial pressure/heart rate data pairs obtained during any given experimental condition were fitted to a sigmoid logistic function similar to that described by Kent et al20 (see below and Figure 1). Data were fitted to the logistic function using a nonlinear regression program (SAS, PROC NLIN)21 run on an IBM mainframe computer. This logistic model yields four parameters (A1, A2, A3, and A4) derived from the following equation:

\[
HR = A1/[1 + \exp(A2(MAP - A3))] + A4
\]

where HR is heart rate and MAP is mean arterial pressure.

Using the above four parameters, the following descriptors of the baroreflex function curve were derived: Heart rate range = A1; maximum heart rate = A1 + A4; minimum heart rate = A4; and maximum sensitivity = (A1 × A2)/4.

Unless otherwise noted, all data are expressed as the mean ± SEM. Comparisons made within experimental protocols were done using a repeated measures analysis of variance (SAS, PROC GLM).21 Mul-
Table 1. Mean Baseline Values

<table>
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<tr>
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<th>MABP (mm Hg)</th>
<th>HR (beats/min)</th>
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<tr>
<td>Dose-response experiments (n=10)</td>
<td></td>
<td></td>
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<tr>
<td>Control</td>
<td>96±2.28</td>
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<td>PGI2 20</td>
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<td>Sympathetic blockade (n=9)</td>
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<tr>
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<td>90±2.77</td>
<td>73±3.36</td>
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<tr>
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<td>82±1.82*†</td>
<td>86±5.39*†</td>
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<tr>
<td>MET</td>
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<tr>
<td>Parasympathetic blockade (n=9)</td>
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<tr>
<td>Control</td>
<td>90±2.42</td>
<td>71±3.41</td>
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<tr>
<td>PGI2 20</td>
<td>81±2.49*†</td>
<td>78±5.43*†</td>
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<td>104±3.09*</td>
<td>153±7.31*</td>
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<tr>
<td>ATR+PGI2</td>
<td>87±3.37†</td>
<td>158±9.23*</td>
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Shown are the mean±SEM for the baseline arterial pressure (MABP) and heart rate (HR) during the various experimental protocols. Control is the baseline values during intracoronary infusion of 50 mM Tris buffer. Numbers following PGI2 are intracoronary infusion rates in ng/kg/min. MET, metoprolol. ATR is atropine methyl bromide. *Significantly (p<0.05) different from control. †Significantly (p<0.05) different from the respective autonomic blockade alone.

Multiple comparisons between individual means were performed using the REGWF test (SAS). Differences with a statistical probability of less than 0.05 were considered significant.

Drugs Used

PGI2 was dissolved initially to a concentration of 1 mg/ml in 50 mM Tris (pH 10). Just before use, PGI2 was further diluted with 50 mM Tris (pH 8.4). All other drugs were dissolved in lactated Ringer’s solution.

Results

Effects of Intracoronary PGI2 Infusion on Baseline Parameters

PGI2 infusion had only small effects on baseline arterial pressure and heart rate, although these effects were somewhat variable. As stated above, PGI2 or its vehicle was infused for 5 minutes before generation of the baroreflex curves, and the infusion was maintained for the duration of the curve generation. PGI2 infusion generally caused an initial moderate decrease in arterial pressure; however, arterial pressure gradually returned toward baseline within the first 5 minutes of infusion. The initial effect of PGI2 infusion on heart rate was a small tachycardia, which also tended to return toward baseline. A decrease in heart rate was occasionally, but not consistently, observed.

Table 1 shows the mean data for resting mean arterial blood pressure and heart rate during vehicle infusion (control), during infusion of three doses of PGI2, and during PGI2 infusion following autonomic blockade with metoprolol or atropine methyl bromide. The baseline values shown in Table 1 were obtained during generation of the baroreflex curves, that is, after 5 minutes of infusion. Thus, the values shown represent the steady-state effects of intracoronary infusion.

As stated previously, PGI2 infusion tended to result in a decrease in mean arterial pressure and an increase in heart rate. These effects were small and were not statistically significant in every protocol. In the dose-response experiments, there were no significant differences in baseline mean arterial pressure or heart rate when the values 5 minutes after the start of Tris infusion (control) were compared with the values 5 minutes after beginning intracoronary infusion of any of the doses of PGI2. However, in the sympathetic blockade and parasympathetic blockade experiments, PGI2 infusion did cause small
DOSE RESPONSE

**Figure 3.** The actual data points and regression curves during intracoronary infusion of vehicle (CONTROL) and during infusion of the three doses of prostaglandin I₂ (PGI₂). Data are from one dog. HR, heart rate; MABP, mean arterial pressure.

statistically significant decreases in mean arterial pressure compared with vehicle infusion (control). PGI₂ infusion caused a significant increase in heart rate in the sympathetic blockade experiment before administration of metoprolol only. In all other protocols, PGI₂ infusion was not associated with significant changes in heart rate.

**Dose-Response Experiments**

These experiments were performed to determine the effects of intracoronary infusion of PGI₂ at three doses on the baroreflex control of heart rate. Figure 2 depicts succinctly the results of these experiments by showing the effects of a vena caval occlusion and an aortic occlusion on arterial pressure and heart rate in a single conscious dog. During vehicle infusion (upper left panel), partial occlusion of the inferior vena cava resulted in hypotension and the expected reflex tachycardia. During intracoronary infusion of PGI₂ (upper right panel), a similar degree of hypotension induced by vena cava occlusion was accompanied by a greatly attenuated heart rate response. On the other hand, partial occlusion of the descending aorta during vehicle infusion (lower left panel), resulted in hypertension and reflex bradycardia. However, unlike the response to baroreceptor unloading, infusion of PGI₂ (lower right) had no effect on the baroreflex-mediated bradycardia induced by hypertension.

Shown in Figure 3 are the actual data points obtained from a series of occlusions and the associated regression curves from a single dog. The curves were obtained during control conditions (Tris infusion) and during infusion of PGI₂ at 10, 20, and 50 ng/kg/min. As can be seen, PGI₂ attenuated the tachycardia at hypotensive pressures but had little effect on the bradycardia at hypertensive pressures. PGI₂ also attenuated the maximum slope of the curve obtained from the regression of the data points. Summarized in Figure 4 are the mean data for these dose-response experiments. At all doses, PGI₂ significantly attenuated the heart rate range, the maximum heart rate, and the maximum slope of the baroreflex function curve. These effects were dose-related for the 10 and 20 ng/kg/min infusions. However, there were no significantly greater effects on the baroreflex parameters at the 50 ng/kg/min infusion compared with the 20 ng/kg/min infusion. Also, there was no significant effect with any of the doses of PGI₂ on the minimum heart rate, that is, the maximum bradycardia during hypertension.

**Effects of Autonomic Blocking Agents and PGI₂ on Baroreflex Tachycardia**

Inasmuch as PGI₂ affected primarily baroreflex mediated tachycardia, we examined further the contribution of the two components of the autonomic nervous system to baroreflex tachycardia. Therefore, two sets of additional experiments were performed. In these experiments, the maximum tachycardiac response to baroreceptor unloading was determined in each of four conditions: 1) under control conditions with intracoronary infusion of vehicle (Tris buffer), 2) during infusion of PGI₂ (20 ng/kg/min), 3) after autonomic blockade with either metoprolol or atropine methyl bromide, and 4) after autonomic blockade and infusion of PGI₂. These experiments allowed us to determine to what extent the tachycardia was a result of sympathetic stimulation and to what extent it was a result of parasympathetic (vagal) withdrawal. Secondly, these experiments allowed us to determine the extent to which infusion of PGI₂ selectively interfered with each autonomic component of the tachycardia.

The experiment with atropine methyl bromide is summarized in Figure 5. The experiment with metoprolol is summarized in Figure 6. Both figures show the mean maximum changes in heart rate from baseline in response to baroreflex unloading during the various experimental conditions. As shown in
Table 1. Metoprolol administration had no significant effect on baseline mean arterial pressure or heart rate. Atropine methyl bromide administration caused a small significant increase in arterial pressure and a significant increase in heart rate.

As can be seen in Figures 5 and 6, the maximum tachycardia to baroreceptor unloading under control conditions was approximately 115 beats/minute in both experiments. Also, in both experiments, PG1 infusion alone attenuated the maximum tachycardia by approximately 70%. Following administration of atropine methyl bromide, the maximum increase in heart rate during hypotension was 66% ± 5.8% of the control response. PG1 administration after atropine methyl bromide inhibited by 51% ± 8.4% the heart rate response compared with atropine alone. Thus, inasmuch as changes in heart rate after atropine methyl bromide administration result only from changes in sympathetic activity, PG1 infusion prevented approximately one half the sympathetic stimulation that normally accompanies baroreflex steady-state hypotension. On the other hand, after metoprolol administration, the maximum increase in heart rate was only 30% ± 6.3% of the respective control response. Infusion of PG1 after metoprolol blocked 91% ± 6.2% of the heart response compared with metoprolol alone. Thus, inasmuch as tachycardia after metoprolol administration is a result of vagal withdrawal, PG1 infusion essentially abolished the baroreflex mediated vagal withdrawal during steady-state hypotension.

Discussion

The present study has shown that stimulation of cardiac receptors with intracoronary infusion of PG1 at doses that had no or only small effects on resting arterial pressure and heart rate resulted in a potent attenuation of baroreflex-mediated tachycardia in conscious, instrumented dogs. Intracoronary infusion of PG1 attenuated the sensitivity of the baroreflex as measured by the maximum slope of the curve relating heart rate to arterial pressure. PG1 also attenuated the heart rate range and maximum heart rate of the baroreflex curve but had no significant effect on the magnitude of the maximum bradycardia attained. Furthermore, the present study has shown that intracoronary infusion of PG1 (20 ng/kg/min) attenuated the maximum baroreflex mediated tachycardia by 1) inhibiting vagal withdrawal and 2) attenuating by approximately 50% the sympathetic activation normally associated with baroreceptor unloading.

Inasmuch as PG1 is known to stimulate cardiopulmonary reflexes with vagal afferents, it is likely that the effects observed in the present study were mediated by cardiac afferent nerves. Direct evidence for involvement of cardiopulmonary afferents has not been demonstrated in the present study. However, work from our laboratory has shown that intracoronary infusion of PG1 in anesthetized dogs inhibited baroreflex-mediated increases in renal nerve activity in response to nitroprusside-induced hypotension. In the latter study, the inhibitory effect of PG1 on baroreflex control of efferent sympathetic nerve activity was abolished by vagotomy or pericoronary nerve block with lidocaine, thus demonstrating that PG1 had acted via an afferent vagal pathway.

The present experiments with the autonomic blocking agents demonstrated that under control conditions, the maximum tachycardia induced by steady-state unloading of the baroreceptors was mediated primarily by sympathetic stimulation of the sinoatrial node and to a lesser extent by vagal withdrawal. The latter conclusion is based on the observation that under control conditions (without
PGI₂ metoprolol administration attenuated the maximum heart rate response to a greater extent (approximately 70%) than did administration of atropine methyl bromide (approximately 34%). By comparison with the effects of autonomic blockade alone, PGI₂ infusion attenuated the maximum tachycardia by inhibiting vagal withdrawal and by attenuating sympathetic stimulation by approximately 50% of that obtained under control conditions of steady-state hypotension. This apparent inhibition of the baroreflex most likely occurred through an interaction within the brainstem between the arterial baroreflex pathways and input from ventricular receptors with vagal afferents.

It is noteworthy that in the present study, heart rate changes were measured during steady-state unloading of the baroreceptors. Under these conditions, we have found that the tachycardia results from sympathetic stimulation primarily and to a smaller extent from vagal withdrawal. The relative contributions of the sympathetic and parasympathetic nervous systems to baroreflex tachycardia under the present control conditions is the opposite of what has been observed in conscious dogs during acute dynamic changes in arterial pressure, such as occurs on injection of nitroglycerin. In conscious dogs, the baroreflex tachycardia evoked by acute dynamic changes in arterial pressure has been shown to be mediated primarily by vagal withdrawal, with a smaller contribution of the sympathetic nerves. Similarly, the balance of sympathetic and parasympathetic components of baroreflex tachycardia vary, depending on whether the hypotensive event is static or dynamic. Parasympathetic withdrawal may represent a mechanism for producing rapid tachycardia in response to sudden baroreceptor unloading, whereas sympathetic activation may be a slower, yet more sustainable, mechanism for increasing heart rate.

The present study confirms other recent work in conscious dogs that has shown that stimulation of cardiac receptors with vagal afferents can result in centrally mediated attenuation of the baroreflex. In one study 7 in conscious dogs, intracoronary infusion of veratridine resulted in inhibition of baroreflex-mediated tachycardia without affecting baroreflex bradycardia. Another study 8 in conscious dogs showed that intracoronary infusion of veratridine attenuated the arterial pressure and total peripheral resistance responses to decreases in isolated carotid sinus pressure. Interestingly, in the latter study, veratridine infusion had little effect on the arterial pressure and total peripheral resistance responses to hypertensive levels of carotid sinus pressure. Together, these studies suggest that cardiopulmonary receptors with vagal afferents attenuate baroreflex responses to baroreceptor unloading but do not affect baroreceptor responses to hypertension. In other words, stimulation of these cardiopulmonary receptors will diminish the compensatory mech-
organisms that normally occur in response to hypotension. However, compensatory mechanisms that are called into play in response to hypertension are left intact by stimulation of these receptors.

The present study is unique because prostacyclin is an endogenous substance synthesized in vivo. Previous studies have demonstrated that chemical stimulation of ventricular receptors results in inhibition of baroreflexes. However, these studies have used veratrum alkaloids to stimulate cardiopulmonary receptors. Whereas use of these substances has yielded valuable insights about the function of cardiac receptors with vagal afferents, the veratrum alkaloids do not naturally occur in animal species. As indicated earlier, veratrum alkaloids are relatively nonspecific in stimulating cardiopulmonary sensory endings, whereas PGJ₂ has been shown to preferentially stimulate chemosensitive endings. The present study suggests that stimulation of the chemosensitive type of receptors alone is sufficient to result in attenuation of arterial baroreflexes.

The present findings are important because prostacyclin is synthesized by cardiac tissues and may serve as a physiological and/or pathophysiological mediator of cardiopulmonary receptor stimulation in vivo. Increased prostaglandin synthesis has been shown to occur during myocardial ischemia, during increases in cardiac sympathetic nerve stimulation, in heart failure, and in response to circulating angiotensin and bradykinin.

In the present study, PGJ₂ inhibited baroreflex tachycardia by inhibiting vagal withdrawal and attenuating sympathetic activation. These effects of PGJ₂ were most likely secondary to stimulation of cardiac receptors with vagal afferents. This mechanism could serve as a feedback loop to limit cardiac work in the face of limited oxygen delivery. We hypothesize that increased synthesis and release of prostacyclin occurs during conditions of increased oxygen consumption and cardiac work. The prostacyclin thus released could stimulate cardiac receptors that signal the brainstem to limit baroreflex tachycardia and to limit baroreflex mediated increases in peripheral resistance. These actions could help bring myocardial oxygen demand into closer balance with delivery. Also, it is possible that inhibition of the arterial baroreflexes might occur via prostacyclin-stimulated cardiac receptors in pathophysiological conditions in which plasma prostacyclin levels are elevated. Such states may include congestive heart failure and coronary ischemia, both conditions in which the baroreflex control of heart rate is known to be attenuated.

Increased release of prostaglandins has also been implicated as part of the overall response to various pharmacological agents, including hydralazine, furosemide, and captopril. It is not unreasonable to expect that during administration of these agents increased plasma levels of prostaglandins of cardiac or extracardiac origin might stimulate or sensitize cardiac receptors, which results in attenuation of baroreflex sensitivity and tachycardia. Recently, we have shown that captopril administration in conscious dogs potentiated the reflex effects of intracoronary veratridine injection. The captopril-induced potentiation was reversed after indomethacin administration, which suggests that endogenously released prostaglandins had sensitized ventricular receptors. Thus, prostaglandin interactions with ventricular receptors may play a role in the action of some drugs.

Clearly, more research is required to fully establish the roles that cardiopulmonary receptors play in neural control of the cardiovascular system. The interaction of cardiopulmonary reflexes with arterial baroreflexes as demonstrated by the present study implies that these receptors may play an important role in the regulation of arterial pressure. Also, the exact roles that prostaglandins play in cardiovascular regulation must await further research. These seemingly ubiquitous autacoids not only stimulate ventricular receptors but can have a variety of other actions on the cardiovascular system. As more knowledge is gained about the actions of prostaglandins, a clear picture can emerge of how these substances interact with other locally produced substances to help maintain cardiovascular homeostasis.

Acknowledgments

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References


KEY WORDS • prostaglandin I2 • ventricular reflexes • baroreflexes • heart rate • prostacyclin • cardiac reflexes
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