Cardiovascular Reflexes from Stretch of Pulmonary Vein-Atrial Junctions in the Dog


ABSTRACT

The reflex cardiovascular response to stretch of left pulmonary vein-atrial junctions was studied in anesthetized dogs in which both aortic nerves were cut and the carotid sinuses were isolated vascularly. After thoracotomy, the root of the left lung was tied and a small Silastic balloon (1.5-cm long), attached to a nylon catheter, was inserted into each of the three left pulmonary veins and tied so that its tip lay at the junction of the vein with the left atrium. In six dogs, heart rate response to balloon distension of 2.0 ml was studied over a range of initial heart rates (75 to 240 beats/min) achieved by varying the carotid sinus pressure. On distension of the balloons, slowing occurred if the initial heart rate was > 140 to 150 beats/min and acceleration if it were less. In eight dogs, aortic blood pressure and cardiac output measured before, during, and after balloon distension (0.25 to 2.0 ml) demonstrated a hyperbolic relationship between balloon volume and decrease in calculated systemic vascular resistance. All responses were abolished by vagotomy. The reflex vasodilatation was sustained and caused by decreased adrenergic activity; the reflex bradycardia or tachycardia was due to interplay of vagal and sympathetic cardiac efferents.

ADDITIONAL KEY WORDS

intrinsic heart rate low-pressure receptors
After induction of anesthesia, the trachea was intubated and artificial ventilation with oxygen was begun. When the chest was opened, resistance to expiration was provided by placing the expiratory outlet under 3 cm of water. Blood samples were taken anaerobically from an aortic catheter, and arterial Po$_2$, PCO$_2$, and pH were measured (Instrumentation Laboratory Inc., Lexington, Mass.) periodically throughout the experiment. Po$_2$ was always greater than 300 mm Hg; PCO$_2$ was maintained between 30 and 40 mm Hg by adjusting tidal volume. Progressive acidemia was prevented by repeated intravenous infusions of 10 to 20 mEq of NaHCO$_3$ (7.5% solution; Abbott Laboratories) to maintain pH between 7.30 and 7.40.

The carotid sinuses were vascularly isolated according to the Moissejeff technique (6), and the aortic nerves were severed where they separate from the vagosympathetic trunks near the nodose ganglia. With the carotid sinus area excluded from the systemic circuit, abolition of the hypertensive response to sodium cyanide by aortic nerve section was taken to indicate aortic chemoreceptor and, by implication, baroreceptor denervation (6a). The mean change in aortic blood pressure in response to sodium cyanide (0.1 mg/kg) injected into the aortic root was $+18 \pm 3$ mm Hg (sx) before section and $-3 \pm 2$ mm Hg after section.

**Balloon Study.**—The chest was opened in the fifth left intercostal space and the roots of the lobes of the left lung, excluding the pulmonary veins, were tied. A small Silastic balloon, 1.5-cm long and attached to a nylon catheter, was inserted into each of the three left pulmonary veins and tied so that its tip lay at the junction of the vein with the left atrium. The pulmonary vein-atrial junctions were distended simultaneously by injecting each balloon with 0.25 to 2.0 ml of saline.

Heart rate was calculated from the electrocardiogram. Aortic blood pressure was measured via a catheter inserted into the right carotid artery and connected to a Statham strain-gauge transducer. Cardiac output was determined by injecting indocyanine green (Hynson, Westcott & Dunning, Inc., Baltimore, Md.) into the right atrium and recording the changes in indicator concentration at the aortic root via a catheter and cuvette densitometer (X-250, Waters Co., Rochester, Minn.). In two dogs a noncannulating flow transducer (Carolina Medical Electronics, Inc., King, N. C.) was placed on the descending thoracic aorta to monitor continuously the blood flow to the lower trunk and hind limbs. Recordings were made on a Honeywell Visicorder.

**Left Atrium-Pulmonary Vein Pouch.**—In three dogs an extracorporeal circuit utilizing an isolated heart-lung preparation was used to maintain the systemic circulation. With the heart bypassed in this manner, it was possible to isolate the proximal portions of the pulmonary veins and the left atrial chamber by ligation of the former at the level of their first-order branches and by securing a firm, constricting ligature around the atrioventricular groove. The pericardium was incised widely and each lung was amputated at its hilus. Pressure within the blood-filled left atrium-pulmonary vein pouch was then controlled via a catheter inserted through the atrial appendage.

To study changes in vascular resistance during distention of the left atrial pouch, one hind limb was perfused at constant flow. Blood taken from the main extracorporeal arterial line was fed by a roller pump into the femoral artery. A heat exchanger maintained the perfusate at 37°C. The pump speed was adjusted to give an initial perfusion pressure similar to the mean aortic pressure. The perfusion pressure of the limb measured by a Statham strain gauge was used as an index of vascular resistance.

Even in the presence of a clamp across the aortic root, the atrium continued to beat regularly for an hour or so; in one experiment, coronary perfusion to the left atrium was provided by retrograde cannulation of the anterior descending branch of the left coronary artery. All measurements were made within the first 30 minutes of cross clamping the aortic root, in the presence of spontaneous, rhythmic atrial contractions. The aortic and carotid reflexogenic areas were vascularly isolated from the systemic circuit to prevent them from buffering the reflex vascular response to left atrial distention.

**Drugs.**—The following drugs were used: sodium cyanide (Mallinckrodt Chemical Works), atropine sulfate (Eli Lilly and Company), propranolol hydrochloride (Inderal, Ayerst Laboratories), acetylcholine chloride (Hoffmann-La Roche, Inc.), isoproterenol hydrochloride (Isuprel, Winthrop Laboratories), and phenoxybenzamine hydrochloride (Dibenzyline, Smith-Kline & French Laboratories). In all experiments, coagulation of the blood was prevented by heparin (Fellows-Testag), given when the operative procedures had been completed.

The effect of drugs on the reflex vascular response to pulmonary vein-atrial junction distention was specifically examined in four dogs. These animals were anesthetized and surgically prepared as for the balloon studies; in addition, one hind limb was perfused with autologous arterial blood through the femoral artery by a constant-flow roller pump. Changes in perfusion pressure were used as an index of changes in limb vascular resistance.
Results

It was important to establish at the start of recording that each dog was capable of a known reflex cardiovascular response. Accordingly, the response to a decrease in carotid sinus pressure from control systemic arterial pressure to static 40 mm Hg was tested. Some animals had an inadequate response to this maneuver (blood pressure increase, <16 mm Hg; heart rate increase, <6 beats/min) and were consequently rejected. The mean (±SE) blood pressure response recorded in the 16 dogs accepted for study was +55 ± 5 mm Hg, and the heart rate response was +19 ± 3 beats/min.

Balloon Distension of Pulmonary Vein-Atrial Junctions.—Inflation of the three balloons in eight dogs (13.5 to 18 kg) caused systemic hypotension (Figs. 1 and 2). The temporal features of the decrease in aortic blood pressure were as follows. After a latent period of 3 to 6 seconds, the aortic pressure decreased rapidly to reach its nadir in 20 to 22 seconds. In 26% of cases there was no subsequent recovery until deflation of the balloons 2 minutes later. In the remainder, partial recovery of blood pressure began at 22 seconds and reached a steady state value at 40 seconds (average values); though it varied in each dog, the degree of recovery during balloon distension was similar to that during increased pressure in the isolated carotid sinus (Fig. 1, bottom left). The decrease in aortic blood pressure with balloon inflation was maximal when the carotid sinus pressure was set at 40 mm Hg, became less as the latter pressure was increased and, although small, was still discernible at carotid sinus pressures at or above 200 mm Hg (Fig. 2). Table 1 compares, in the eight dogs, the maximal decrease in aortic blood pressure in response to a 2-ml balloon inflation with that evoked by increasing carotid sinus pressure from 40 to 200 mm Hg.

In these eight dogs, simultaneous measurements were made of aortic blood pressure and cardiac output (indicator-dilution technique) in the control period before balloon inflation, during the steady-state response to inflation, and 2 minutes after deflation. Thus, the values for aortic blood pressure during inflation which were used in the calculation of systemic...
vascular resistance were not usually the lowest values. Measurements made during inflation were compared with the average of the measurements during the two control periods. Significant (P < 0.05) decrease in calculated systemic vascular resistance was seen at all balloon volumes (0.25 to 2.0 ml), and the mean maximal decrease, at a balloon volume of 2.0 ml, was 22% (Fig. 3). The percent decrease in cardiac output was not statistically significant at any balloon volume; blood pressure decreases were significant with balloon volumes in excess of 0.25 ml. Stimulus-response curves relating balloon volume to percent decreases in cardiac output, aortic blood pressure, and calculated systemic vascular resistance are depicted in Figure 3 (left panel). Section of both vagal trunks in the neck abolished the blood pressure response to inflation.

The absence of significant changes in cardiac output during balloon inflation was confirmed in two dogs in which aortic blood flow was continuously measured by a flow transducer on the descending thoracic aorta. The peak changes in aortic blood flow, aortic pressure, and calculated lower body resistance in one of these dogs are shown in Figure 3 (right panel).

In two dogs the mean decrease in aortic blood pressure in response to distension of the pulmonary vein-atrial junctions was 28% before the intravenous injection of atropine sulfate (0.2 mg/kg) and 30% after. In two dogs the mean reflex decrease in aortic pressure was 30% before treatment with propranolol (1 to 2 mg/kg) and 25% after. In one dog, administration of phenoxycbenzamine (10 mg/kg) intravenously reduced the blood pressure decrease with balloon inflation from 17% before to 6% after. The ability of these drugs to modify the decrease in hind-limb
Effect of distension of pulmonary vein-atrial junctions on aortic blood pressure, cardiac output, and calculated vascular resistance. Left: eight dogs; cardiac output determined by indicator-dilution method (steady-state changes, mean ± SE). Right: one dog; aortic blood flow determined by noncannulating electromagnetic flow transducer on thoracic aorta (peak changes plotted). Magnitudes of blood pressure and vascular resistance changes are proportional to inflation volume of balloons.

Perfusion pressure caused by balloon inflation was specifically examined in four other dogs. The decrease in hind-limb perfusion pressure during balloon inflation was not altered by an intravenous dose of atropine (0.2 mg/kg), sufficient to abolish the vasodilator action of 30 μg of acetylcholine injected into the hind-limb perfusate (mean decrease: 31 mm Hg before and 37 mm Hg after), or by an intravenous dose of propranolol (1 mg/kg) sufficient to block the vasodilator action of 5 μg of isoproterenol injected into the hind-limb perfusate (mean decrease: 18 mm Hg before and 29 mm Hg after). Phenoxybenzamine (10 mg/kg, intravenously) virtually abolished the decrease in hind-limb perfusion pressure evoked by inflation of the balloons (mean decrease: 42 mm Hg before and 4 mm Hg after).

Heart rate responses to balloon inflations of 2-minute duration were specifically examined in an additional six dogs (15 to 17 kg). These studies were necessary because the withdrawal of blood (20 ml/min) during the determination of cardiac output by dye dilution could in itself have been responsible for changes in heart rate. Heart rate was calculated from the electrocardiogram for each consecutive 6-second period. The balloons were not inflated until the heart rate was stable to within three beats over a 30-second interval. The postinflation control rate was taken as the rate after stable values were regained—usually within 30 to 60 seconds after the balloons were deflated. Measurements made during inflation of the balloons were compared with the average of the measurements during the two control periods.
TABLE 1
Comparison of Decrease in Aortic Blood Pressure to Balloon Inflation and Carotid Sinus Hypertension in Eight Dogs

<table>
<thead>
<tr>
<th>Dog</th>
<th>Decrease in aortic pressure (mm Hg)</th>
<th>Carotid sinus hypertension (1) (\times 10^2)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>45</td>
<td>115</td>
</tr>
<tr>
<td>2</td>
<td>46</td>
<td>95</td>
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<tr>
<td>3</td>
<td>60</td>
<td>116</td>
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<td>4</td>
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<td>5</td>
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<td>95</td>
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<td>6</td>
<td>77</td>
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<td>7</td>
<td>60</td>
<td>90</td>
</tr>
<tr>
<td>8</td>
<td>60</td>
<td>73</td>
</tr>
</tbody>
</table>

*2-ml balloon inflation.

The maximal change in heart rate in response to a 2-ml inflation is plotted against initial (predistension) heart rate in Figure 4. Regression analysis of the plotted points gives an intercept on the line of no heart rate change at 145 beats/min, with a 95% confidence interval of ±5 beats/min. Thus, in the main, with initial heart rates greater than 140 to 150 beats/min, distention caused a slowing; with rates less than 140 to 150 beats/min, distention caused acceleration. The magnitude of the change in heart rate to the same degree of distension (2 ml) was proportional to the difference between the initial rate and 145 beats/min. The intravenous administration of propranolol (1 to 2 mg/kg) to four dogs did not prevent the acceleration of the heart in response to balloon inflation. The mean increase in rate was 15 beats/min before propranolol and 13 beats/min after. In two dogs, intravenous atropine sulfate (0.2 mg/kg) failed to abolish the slowing evoked by distension; the mean control decrease in rate of 16 beats/min was unchanged by the drug. However, in both groups (six dogs), no change in rate was seen after combined administration of atropine and propranolol; this pharmacologic "denervation" of the heart resulted in an average resting rate of 147 beats/min.

If initial heart rates were kept constant at values well in excess of 150 beats/min, by maintaining a low carotid sinuses pressure (40 to 50 mm Hg), the change in heart rate was proportional to the degree of balloon inflation (in this instance, up to 3.0-ml inflation; see Figure 5).

Bilateral cervical vagotomy abolished heart rate responses to inflation.

The time relationships of the heart rate responses are illustrated in Figure 6. The maximal change in rate occurred within the first 20 seconds, but acceleration usually was sustained better than slowing. Recovery usually was some 30 seconds slower in the case of the tachycardia response, and occasionally the rate did not decrease to the pre-inflation value. The latter may have been due to leakage of blood from the carotid sinuses in which pressure was high, leading to a slight but progressive increase in base-line heart rate.
Change in heart rate in response to graded distension of pulmonary vein-atrial junctions in four dogs. In each dog the control heart rate was kept constant and the change in rate has been expressed as percent of maximal change observed.

Distension of Left Atrium-Pulmonary Vein Pouch.—Hind-limb vasodilatation occurred with distension of the pouch; these responses were abolished by bilateral vagotomy. The changes in hind-limb perfusion pressure evoked by distension of the left atrium-pulmonary vein pouch in three dogs are shown in Figure 7.

The alterations in limb perfusion pressure were not accompanied by changes in the rate of left atrial contraction, probably because most cardiac efferent nerves were crushed by the aortic clamp (7). Left atrial afferents probably were not affected by the clamp; Dawes and Widdicombe (8) examined the distribution of left vagal branches in dogs and concluded that the main course of left atrial afferents was cephalad from the posterior surface of the heart behind the left pulmonary artery to join the left recurrent laryngeal nerve as it crosses the aortic arch.
Discussion

Stretch receptors found in the subendocardial tissues of the left atrium and in the terminal portions of the pulmonary veins (9, 10) can be strongly stimulated on distension by small balloons (11). They are subserved by afferents traveling mainly in the cervical vagus (12), and their response to sustained stretch is slowly adapting (13).

In the present study the root of the left lung was firmly ligated behind the pulmonary veins and the balloons were placed so that their distension was unlikely to interfere with blood flow through the left atrium. A significant decrease in calculated systemic vascular resistance was seen on distension with balloon volumes of 0.25 ml, whereas no significant change in cardiac output occurred even with 2.0-ml inflations. Thus, inflation of the balloons in the pulmonary vein-atrial junctions did not interfere mechanically with cardiac hemodynamics.

The receptors stimulated were probably those of the left pulmonary vein-atrial junctions, as demonstrated by Kidd and associates (11). The reflex vasodilator response to distension of the isolated left atrium-pulmonary vein pouch afforded additional support for this contention because in this study each lung was amputated at its hilus, the pericardium was incised widely, and the atrioventricular ring was ligated firmly. In the absence of other histologically recognizable stretch receptors in the walls of the left atrium (12), "effective" distension was probably that occurring at atriovenous junctions.

Denervation of the aortic arch and vascular isolation of the carotid sinuses prevented modification of the reflex responses to junction distension by secondary feedback from these areas. The carotid sinus reflex also provided a control cardiovascular response against which left atrial-pulmonary vein reflex responses could be compared and interpreted. In addition, by using the carotid sinus preparation, it was possible to determine how altering the background level of autonomic nervous activity could modify the pattern of reflex effects: The magnitude of the aortic blood pressure response decreased with decrease in sympathetic activity; the heart rate response was found to depend on the initial heart rate.

Distension of the pulmonary vein-atrial junctions caused a sustained reflex decrease in arterial blood pressure and systemic vascular resistance proportional to the degree of distension. The dilatation in the peripheral vasculature effected through this reflex compares favorably with that evoked from the carotid sinus. If the vein-atrial reflex were operant in the normal dog, the threshold of activation should lie within the physiologic range of left atrial pressure. While a significant reflex decrease in systemic vascular resistance was evoked by balloon distensions with only 0.25 ml, data are not available to correlate this degree of junction distension with that evoked by pressure-volume changes within the physiologic range. Preparation of the pulmonary vein-atrial pouch so distorted the normal anatomy of the region that no inferences can be drawn from these experiments regarding the threshold pressure for the reflex in the normal dog.

The above findings are contrary to the conclusion reached by Carswell and associates (4) that no significant reflex vasomotor changes occurred with stimulation of pulmonary vein-atrial receptors in the dog.

In keeping with the neurophysiologic evidence of slow adaptation of the left atrial receptors, pressure responses were sustained over a 3-minute period, often following an initial greater depression lasting about 30 to 40 seconds. The initial response may have been due to rate sensitivity of the reflex, as has been described for the carotid sinus reflex (14), but one cannot exclude the possibility that despite restraint by the nylon catheters, the balloons may have slipped partly into the atrial chamber after their initial inflation.

The decrease in systemic vascular resistance was prevented by phenoxybenzamine and not abolished by atropine. Therefore it was due to decreased activity in adrenergic nerves rather than to activation of the cholinergic sympathetic outflow (15). The afferent pathway for
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the reflex was in the cervical vagus because blood pressure responses were no longer obtained after section of both vagus nerves in the neck.

Analysis of the heart rate data yielded a range of initial heart rate (140 to 150 beats/min) above which there was reflex bradycardia and below which there was reflex tachycardia with distension of the pulmonary vein-atrial junctions. It is of interest to note that an intrinsic frequency of 140 beats/min results from complete surgical denervation of the heart in dogs (16). In our study, pharmacologic denervation of the heart produced an average resting rate of 147 beats/min. Either cardiac slowing or cardiac acceleration was reported by Daly and associates (1) to accompany the decrease in systemic blood pressure occurring after pulmonary venous distension caused by an increase in pulmonary blood flow. Acceleration of the heart was seen only in preparations with a "high vagal tone"—that is, a slow initial heart rate. Subsequent workers have not observed this phenomenon of duality, and in a recent study by Carswell and associates (4) in which initial rate was altered by controlled carotid perfusion (range, 54 to 207 beats/min), it was found that distension of the pulmonary vein-atrial junctions always caused an increase in rate. It is difficult not to draw a parallel between our observations and those of Coleridge and Linden (17) concerning the heart rate response to intravenous infusions in dogs (Bainbridge reflex). These workers found that intravenous infusions in dogs produced bradycardia when the initial rate was 150 beats/min or more, tachycardia occurring only at slower initial heart rates. The mechanisms by which distension of the pulmonary vein-atrial junctions causes either cardiac acceleration or slowing at particular heart rates remain obscure, but the inability of either atropine or propranolol alone to abolish the heart rate response and the effectiveness of combined administration of these drugs would suggest that both responses are the result of a reciprocal interplay of vagal and sympathetic cardiac efferents.

The observation that the change in heart rate produced by left atrial distension is related to the initial rate suggests some explanation for the apparently conflicting results obtained by previous workers who have investigated left atrial reflexes.

The magnitude of the heart rate responses was proportional to the degree of junction distension when initial rates were similar and to the difference between the initial rate and 145 beats/min when the degree of distension was the same. Tachycardia was always well maintained during sustained distension, but rate usually recovered partially toward control values during the bradycardia response. We do not have an explanation for this. The cervical vagi provide the afferent pathway for the reflex since heart rate responses were no longer seen after section of both vagus nerves in the neck.

Evidence has been presented to show that distension of the pulmonary vein-atrial junctions evokes sustained reflex peripheral vasodilation, due to a decrease in adrenergic nervous activity, and concomitant reflex bradycardia or tachycardia, due to an interplay of vagal and sympathetic cardiac efferents.

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ANTHONY J. EDIS, DAVID E. DONALD and JOHN T. SHEPHERD

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