Cardiovascular Responses to Hypoxic Stimulation of the Carotid Bodies

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The characteristic cardiovascular responses to systemic hypoxia include tachycardia, hypertension, increased cardiac output, increased total peripheral resistance, venoconstriction, and increased ventricular contractility.1-3 These responses have been inferentially ascribed to stimulation of the aortic and carotid bodies.5-9 However, such a position is not entirely compatible with the observations of Bernthal, Green, and Revzin,10 and more recently Daly and Scott,11 who have shown in the dog that the primary chronotropic response to carotid body hypoxia is not tachycardia as seen in systemic hypoxia, but rather a bradycardia mediated largely by the vagi.

Bernthal14-18 has clearly established that peripheral vasoconstriction mediated by the thoracic-lumbar sympathetic outflow is reflexly induced by carotid body stimulation. From such studies, it might have been anticipated that the heart would also manifest increased sympathetic activity. However, in view of the fact that the primary effect of carotid body stimulation is a negative chronotropic effect,10-12 it seemed worth while to clarify the nature of the primary reflex effect of carotid chemoreceptor stimulation on myocardial performance.

This investigation was designed to study the hemodynamic responses to hypoxic stimulation of the carotid bodies with particular reference to atrial and ventricular contractility. Additional observations were made on other hemodynamic parameters participating in this reflex. A preliminary report on these experiments has been given.19

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Methods

Mongrel dogs, weighing 14 to 30 Kg., were anesthetized with morphine sulfate (2 mg./Kg. I.M.) followed in a half-hour by a warmed mixture of chloralose (60 mg./Kg.) and urethane (600 mg./Kg.), given intravenously. Following an initial dose of 75 mg. heparin intravenously, 10-mg. doses were given hourly to prevent clotting. Intermittent positive pressure respiration was maintained throughout the experiment by a Starling Ideal Pump.

After tracheal intubation, preparation was made for isolated perfusion of both carotid sinus-body regions by ligation of all branches of the common carotid arteries, while preserving the carotid body circulation and the sinus nerves. Inflow cannulae were placed in the common carotid arteries after ligating these vessels proximally. Outflow cannulae were placed in the common carotid arteries after ligating these vessels proximally. Outflow cannulae were placed in the external carotids via a lingual or facial branch.

A double, rotating disc oxygenator system20 primed with 1,500 cc. of thoroughly mixed heparinized donor dog blood was utilized to prepare blood of high and low pO2 values (fig. 1). This was accomplished by passing 5 per cent CO2, 95 per cent O2 through one oxygenator chamber and 5 per cent CO2, 95 per cent Nz through the other. Thus, the pCO2 was about 36 mm. Hg and the pH nearly constant (± 0.02 units) in each chamber. By manipulation of clamps, blood from the desired chamber was pumped with a Dale-Schuster pump through a warm water jacket heat exchanger into the isolated carotid region. The temperature of the perfusate was maintained at 36 C. The pH of the perfusate was continuously measured by a Beckman G pH electrode. Changes in pO2 of the perfusate were continuously monitored by a Clark polarographic electrode which had been shown to have a linear response. Absolute values of pO2 were calculated at frequent intervals from Van Slyke analyses. During perfusion, blood loss from the sinus region was small, about 2 cc./min., ranging from approximately 1 to 5 cc./min.

A transverse thoracotomy transecting the sternum was performed in the fourth or fifth interspace. The aorta was cannulated and total aortic flow measured with a Potter electroturbinometer21 placed in a shunt of tygon tubing (fig. 1). The cephalic portion of the animal was supplied by...
Preparation used for perfusing the isolated carotid region with blood of high or low 
P02 while examining carotidoskeletal responses. Dual, rotating disc oxygenators (Ox); 
heat exchanger (H); modified Dale-Schuster pump (P); Clark polarographic electrode 
P02; Beckman G electrode (pH); Statham pressure transducers (T); Potter electroturbinometer (Pet); common carotid artery (CC); external carotid artery (EC); subclavian artery (S); brachioccephalic artery (B).

a branch from the shunt to the cannulated brachiocephalic and subclavian arteries, these vessels having been ligated near their origin from the aortic arch.22 Thus, the total aortic flow (left ventricular output minus coronary flow) was continuously measured.

The pericardium was incised widely and secured to the chest wall. Short, wide bore, metal cannulas were inserted into the left atrium through the atrial appendage and into the left ventricle through the apical dimple for pressure measurements in the respective chambers. Bipolar electrodes were sutured to the left atrium for electrical control of heart rate during the inscription of ventricular function curves. Heart rate was continuously measured with a Waters carotidostatometer. Aortic pressure and carotid perfusion pressure were also measured. All values were simultaneously recorded on a Sanborn multichannel direct writing oscillograph.

A femoral artery and vein were cannulated and connected to a reservoir of heparinized blood which was thoroughly mixed with that of the experimental animal by infusion and withdrawal of blood. Variation in left ventricular end-diastolic pressure was obtained by stepwise infusion of blood. Ventricular function curves were drawn from data obtained in this manner and served to indicate changes in ventricular contractility.23-24 Total body pressure-flow curves were plotted from the same data. Observations were made on the hemodynamic responses to carotid body hypoxia prior to and following bilateral cervical vagotomy or atrope administration.

The effect of total body hypoxia on ventricular contractility was measured in three animals in which baroreceptor and chemoreceptor mechanisms were left intact. This was accomplished by connecting the inlet of the Starling respiratory pump to a Douglas bag containing nitrogen or 7 per cent O2 in nitrogen and respiring the animal with the mixture for 1½ minutes. These preparations were as previously described, except that the carotids were not separately perfused and the vagi were left intact. Ventricular function curves obtained during hypoxia were compared with those obtained when the animal was breathing room air.
Results

EFFECTS OF CAROTID BODY HYPOXIA ON HEART RATE

The hemodynamic effects of introducing hypoxic blood into the isolated carotid segment are demonstrated in figure 2. In the left panel, when the pO₂ of the blood perfusing the carotid bodies fell to about 30 mm. Hg, a large reduction of heart rate (134 to 81/min.) and a small reduction of cardiac output were observed. Little alteration of aortic pressure occurred. The left atrial and left ventricular diastolic pressures rose slightly. These changes were reversible.

Following bilateral cervical vagotomy (right panel) cardiac slowing, although less marked (150 to 131/min.), still occurred. The aortic pressure rose while aortic flow remained the same. While the heart rate fell, presumably in response to sympathetic withdrawal, an increase of total peripheral resistance was still observed.

The pooled data from 27 observations in nine animals prior to vagotomy (fig. 3) showed that carotid body hypoxia produced an average reversible slowing of 27.4 beats per minute (16.4 per cent, range 4 to 50 per cent). This was not associated with a significant rise in blood pressure. Tachycardia was never observed. In 10 sets of observations in six animals following bilateral cervical vagotomy, cardiac slowing was still present although much reduced to 13 beats per minute (8 per cent, range 3 to 13 per cent). These values are highly significant (P < 0.005).

Figure 4 (upper) demonstrates the bradycardia response to carotid body hypoxia in four animals immediately before and immediately after vagotomy, and in two additional
animals immediately before and immediately after atropine administration. Before vagotomy, the bradycardia observed was an average of 35 beats/min. (24 per cent), and after vagotomy it was 15 beats/min. (10 per cent). In one animal, the bradycardia observed prior to atropine was 21 beats/min. (14 per cent), and 15 beats/min. (10 per cent) after atropine. In the second animal given atropine, the small 16 beats/min. bradycardia was abolished by the atropine.

Figure 4 (lower) shows the effect of vagotomy and ganglionic blockade with hexamethonium chloride on the bradycardia response to carotid body hypoxia in two animals. There was an average initial slowing of 35 beats per minute (18 per cent). Following bilateral cervical vagotomy, the average slowing was reduced to 18 beats per minute (10 per cent). However, after the administration of 25 mg. of hexamethonium chloride, cardiac slowing attributable to carotid body hypoxia was not observed.

EFFECTS OF CAROTID BODY HYPOXIA ON ATRIAL DYNAMICS

In view of the fact that the bradycardia of carotid body hypoxia is in large measure a result of efferent vagal activity, it seemed likely, on the basis of prior experience, that the vigor of atrial contraction would be affected. As illustrated in figure 5, when the heart rate was held constant by electrical pacing (131/min.), the atrial a waves were nearly abolished by carotid body hypoxia and reappeared when well-oxygenated blood was returned to the carotid body.

Varying degrees of heart block, a feature commonly associated with increased vagal activity to the heart, was frequently seen during carotid body hypoxia in these preparations. An example of second-degree heart block is shown in figure 6. With well-oxygenated blood in the carotid body (fig. 6 upper), the a waves occurred at regular intervals, and the time from the onset of atrial systole to the onset of ventricular contraction was
FIGURE 5
Aortic pressure in mm. Hg (AP); left ventricular pressure from 0 to 40 cm. H₂O (LVP); left atrial pressure in cm. H₂O (LAP); directional changes in partial pressure of oxygen in perfusate—downward deflection indicates a decreasing pO₂ (pO₂). Atrium electrically paced. Chart speed 100 mm./sec. Arrows indicate atrial a waves. (See text.)

the same in each cycle. With hypoxic stimulation of the carotid bodies (fig. 6, lower), the a waves still occurred at regular intervals, but the time to ventricular contraction progressively increased until there was no succeeding ventricular beat for the atrial contraction labeled "P."

EFFECTS OF CAROTID BODY STIMULATION ON VENTRICULAR CONTRACTILITY AND PERIPHERAL RESISTANCE: COMPARISON WITH THE EFFECTS OF CAROTID SINUS STIMULATION

Following bilateral cervical vagotomy, simultaneous ventricular function and pressure flow curves were obtained during perfusion of the carotid bodies with well-oxygenated and hypoxic blood. The heart rate was maintained constant by electrical pacing. Figure 7 shows an example of the results obtained. When the carotid body was perfused with hypoxic blood, the ventricular function curve shifted to the right, indicating a decrease of left ventricular contractility, i.e., less external stroke work from any given left ventricular end-diastolic pressure. Simultaneously, a large shift to the left of the pressure flow curve was evident (right panel) indicating an increased total peripheral resistance.

An increase of total peripheral resistance occurred in 11 of 13 sets of observations on seven animals during carotid body hypoxia; in the other two, there was no change. At the same time, a decrease of ventricular contractility as measured by ventricular function curves occurred in 8 of these 13 tests. No change was seen in the remaining 5 tests. An increase of ventricular contractility or a decrease of peripheral resistance was never observed.

Similar measurements were made during high and low carotid sinus pressure. As illustrated in figure 8, carotid sinus hypotension produced a shift to the left of the pressure-flow curve indicating an increased peripheral resistance comparable to that seen in carotid body stimulation. However, this was accompanied by a large shift to the left of the ventricular function curve, indicating an increase of ventricular contractility. This evidence for simultaneously increased sympathetic outflow to both the heart and peripheral vasculature was in contrast to the dichotomous response resulting from carotid body hypoxia.

EFFECTS OF TOTAL BODY HYPOXIA ON CARDIOVASCULAR DYNAMICS

In three dogs with intact baroreceptor and chemoreceptor reflexes, the administration of pure nitrogen or 7 per cent O₂ for brief periods produced the expected tachycardia, hypertension, and increased cardiac output. With the heart rate maintained constant,
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FIGURE 6
(Upper) Aortic pressure in mm. Hg (AP); left ventricular pressure from 0 to 40 cm. H$_2$O (LVP); left atrial pressure in cm. H$_2$O (LAP). Width of lettered boxes indicates the time interval between the onset of atrial systole and the onset of ventricular systole. Well-oxygenated blood in carotid body. Chart speed 50 mm/sec. (Lower) Same experiment after introduction of hypoxic blood into carotid bodies. No ventricular contraction follows atrial systole labeled F.

ventricular function curves demonstrated a considerable increase of left ventricular stroke work from any given left ventricular end-diastolic pressure during total body hypoxia (fig. 9, left panel). The increased ventricular contractility was associated with a simultaneous increase of total peripheral resistance, as shown in figure 9 (right panel).

Discussion
The early observations of Bernthal$^{14}$-$^{18}$ that hypoxic stimulation of the carotid bodies produces a pronounced vasoconstriction in the innervated perfused limb, and the observations of others that hypertension usually, and tachycardia not infrequently, accompanied carotid body stimulation, led to the view that the responses observed in total body hypoxia were ascribable to activation of the peripheral chemoreceptors. However, it was
found that when the respirations were mechanically controlled, hypoxic stimulation of the carotid chemoreceptors did not produce tachycardia but bradycardia.\textsuperscript{10} - \textsuperscript{13} It appeared, then, that the primary chemoreceptor reflex response is not the same as that seen in total body hypoxia.

This study fully confirms the observations that significant cardiac slowing, never tachycardia, results from carotid body hypoxia when the respiratory component of the reflex is not permitted to override the primary effect.\textsuperscript{10, 11} Although the average per cent slowing was less than that observed by Daly and Scott,\textsuperscript{11} a slowing of 40 to 50 per cent was not uncommonly seen. In studies in which the perfusate is obtained from an hypoxic donor animal, other factors in addition to low PO_{2} may be stimulating the chemoreceptor tissue. It should be pointed out, in this regard, that by utilizing a mechanical oxygenator system the PO_{2}, PCO_{2}, and pH could be quite closely controlled. The possibility must be considered, however, that minute fibrin emboli forming in such a system may partially obstruct the glomus circulation and thus reduce the relative response.

Cardiac slowing in response to carotid body hypoxia still persisted, although reduced, following bilateral vagotomy or atropine administration and was abolished by hexamethonium. This indicates a reduction of cardiac sympathetic discharge and is in sharp contrast to the concomitant increase of sympathetic discharge to the peripheral vascular bed manifested by an increase of total peripheral resistance.

Atrial contractility is reduced by carotid body hypoxia (fig. 5). This response is dependent upon the integrity of the vagi and is consonant with the fact that increased vagal activity to the heart diminishes atrial contractility.\textsuperscript{25} The observation that the atrial a wave may be nearly obliterated by a chemoreceptor reflex while the atrium is being electrically paced is of considerable interest. It has been shown also that varying degrees of atrioventricular conduction block can be produced by increased vagal activity to the heart.\textsuperscript{26, 27} Hence, the finding during carotid body hypoxia of a partial block of atrioventricular conduction, similar to the well-known Wenckebach phenomenon seen electrocardiographically, is further evidence for increased vagal discharge to the heart.

Carotid body hypoxia usually caused a reduction of ventricular contractility as measured by ventricular function curves (fig. 7). This was associated with a simultaneous increase in total peripheral resistance. In about one-third of the trials, no alteration of ventricular contractility was discernible, although these were also associated with an increased total peripheral resistance. An increase of ventricular contractility in response to carotid body hypoxia was never seen. It seems likely that the sympathetic withdrawal associated with postvagotomy cardiac slowing in these preparations was also responsible for the observed reduction in ventricular contractility.

In this regard, it is well to consider the likelihood that the level of circulating catecholamines was increased,\textsuperscript{28} and also that an increased resistance to ventricular ejection is known to increase ventricular contractility per se.\textsuperscript{29} It is, therefore, reasonable to assume that, had these two factors tending to produce an increased ventricular contractility not been operative, there would have been a more consistent and even more pronounced decrease...
of contractility than was actually observed. Hypoxic stimulation of the carotid bodies produces an increased sympathetic discharge to the peripheral blood vessels, a concomitant vagal slowing of the heart, and general cardiac sympathetic withdrawal. Thus, a dichotomous response of the sympathetic nervous system associated with increased vagal discharge to the heart results from carotid body hypoxia. This sets the primary consequences of carotid body hypoxia in sharp contrast to the heart results from carotid sinus hypoxia. Further, the finding of a depressed atrial contractility as a primary result of carotid body hypoxia is important in the light of the recent work on the transport function of the atrium.

It is unlikely that baroreceptor discharge was significantly altered during perfusion of the carotid sinus with hypoxic blood in these preparations, since the sinus pressure, both systolic and diastolic, and the pump rate remained constant. Electrophysiologic evidence indicates that hypoxia per se does not alter the discharge pattern of the baroreceptors. Further, baroreceptor stimulation sufficient to cause a reduction in heart rate is associated with a reduction of peripheral resistance, not an increase, as was observed during perfusion of the sinus with hypoxic blood.

The results of this study indicate that, with the exception of peripheral vasoconstriction, the hemodynamic responses to systemic hypoxia cannot be ascribed to a primary chemoreceptor reflex originating in the carotid bodies. The aortic chemoreceptor was not investigated in this study, and it should be recalled that Conroe found the blood pressure response in the dog to be more pronounced when this structure was chemically stimulated than when the carotid bodies were similarly stimulated. Although it remains to be demonstrated, it seems unlikely that qualitatively different cardiovascular responses will be found.

Daly and Scott have shown that carotid body stimulation may produce tachycardia if hyperpnea is permitted to develop. This may be abolished by denervation of the lungs. Hence, in systemic hypoxia, the primary cardiac responses to carotid body stimulation may be overridden by reflex effects of the increased respiratory activity, which also results from carotid body hypoxia. However, this does not explain the tachycardia which develops in response to systemic hypoxia when the respiratory activity is mechanically controlled. Thus, other mechanisms appear to be operative in producing the cardiovascular responses seen in systemic hypoxia.

Recent unpublished investigations in this laboratory have shown that hypoxia of the central nervous system causes an increase of heart rate, blood pressure, cardiac output, and ventricular contractility. Furthermore, studies using electroneurographic techniques have shown that total body hypoxia is associated with a large increase of sympathetic discharge to the heart after elimination of all known chemoreceptor reflexes by appropriate nerve sectioning. The findings of Alexander that hypoxia of the spinal cardiovascular centers increases cardiac sympathetic discharge would suggest one possible source for these responses originating within the central nervous system itself. It is, therefore, suggested that the cardiovascular responses to systemic hypoxia are due, at least in part, to direct hypoxic stimulation of the central nervous system.

**Summary**

The hemodynamic responses to hypoxic stimulation of the carotid bodies were investigated in the dog with controlled respiration. A dual, rotating disc oxygenator system was utilized to perfuse the vascularly isolated carotid region alternately with blood of high or low pO2. Perfusion of the carotid bodies with hypoxic blood caused a large reduction of heart rate. The bradycardia response was reduced, but not abolished, by vagotomy. However, the subsequent administration of hexamethonium completely abolished the response. The contractility of the atrium was reduced by carotid body hypoxia, and varying degrees of heart block were frequently ob-
served. These responses were abolished by vagotomy and considered to be due to efferent vagal activity. Ventricular function curves showed that carotid body hypoxia usually caused a reduction, never an increase, of ventricular contractility. This indicates a reduction of sympathetic discharge to the heart. The reduction in heart rate after vagotomy and the reduction in ventricular contractility were associated with a concomitant increase of total peripheral resistance. These findings indicate that hypoxic stimulation of the carotid bodies causes a dichotomous sympathetic response, that is, a reduction of sympathetic discharge to the peripheral vasculature. Systemic hypoxia caused an increase of both ventricular contractility and total peripheral resistance. Consequently, the hemodynamic responses to systemic hypoxia cannot be entirely ascribed to a primary chemoreceptor reflex from the carotid bodies. It is suggested that the cardiac sympathetic responses seen in systemic hypoxia are due, at least in part, to direct hypoxic stimulation of the central nervous system.

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References


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