Reflex Effects of Cephalic Hypoxia, Hypercapnia, and Ischemia Upon Ventricular Contractility

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In the vagotomized dog with deafferented peripheral chemoreceptors, hypoxia, hypercapnia, or ischemia of the central nervous system provokes reflex, positive chronotropic and inotropic effects upon the normally oxygenated heart.1 Bradycardia and depression of myocardial contractility are considered to be the primary reflex effects upon the canine heart elicited by stimulation of the chemoreceptors of the carotid bodies.2-6 Adequate information is not available concerning the effects of hypoxia, hypercapnia, or ischemia of the central nervous system and the carotid bodies conjointly upon the normally oxygenated ventricles. In the present study, this problem has been investigated in an innervated, isovolumetric, left ventricle preparation.

Methods

Thirty-five experiments were performed upon mongrel dogs (average body weight, 8.4 kg) anesthetized with morphine sulfate, 2.2 mg/kg IM, followed 30 min later by iv infusion of urethane, 400 mg/kg, and chloralose, 40 mg/kg. Donor dogs, which were bled in order to fill the perfusion system, were anesthetized with the short-acting anesthetic, thiamyl sodium (Surital, Parke-Davis), 12.5 mg/kg.

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In 26 of these experiments, the carotid sinus regions were denervated bilaterally during the course of the experiment. In 4 animals, the carotid sinus nerves were identified and sectioned; in the remaining 22, the sinus nerves were transected without actually being identified. To accomplish this, loose ligatures were placed about the common and external carotid arteries near the bifurcation of the common carotid artery. By means of the loose ligatures these vessels were retracted ventrally, to permit placing two mass ligatures securely about the tissue which included the carotid sinus nerve and the occipital and internal carotid arteries. Denervation was achieved by cutting between the two mass ligatures. In five of these experiments, the occipital and internal carotid arteries were excluded from the mass ligatures.

Intermittent, positive-pressure breathing was instituted through a tracheal cannula; bilateral thoracotomy and transverse sternotomy were performed in the fourth intercostal space. Heparin, 4.3 mg/kg, was given intravenously, and additional doses were given every 30 minutes. In all experiments, the cephalic portion of the experimental animal was perfused by means of a pump (PB, fig. 1) via a cannula inserted in the brachiocephalic artery (BCA). This pump delivered blood from a rotating-disc oxygenator (OXY A) to an overflow reservoir (RES 1), which permitted cephalic perfusion pressure to be held constant. The left subclavian artery (SCA) was also perfused in 20 experiments, but was ligated in the remaining experiments. The blood in oxygenator A was exposed to 95% O2, 5% CO2. The cephalic venous blood was returned to the oxygenator by means of a large cannula inserted in the superior vena cava (SVC). The coronary vascular bed was also perfused with blood from oxygenator A by means of a second pump (PA). Blood was pumped to overflow reservoir 2 (RES 2), from which the blood was conducted to a cannula inserted retrograde into the descending thoracic aorta just distal to the origin of the left subclavian artery. The overflow arrangement permitted coronary perfusion pressure to remain con-
The temperature of blood perfusing the head and heart was maintained at 37°C by means of heating tapes (H). Coronary venous blood was returned to the oxygenator through a cannula with multiple side holes, which was inserted through the right atrial appendage into the right atrium and ventricle. The inferior vena cava and the hila of the lungs were ligated.

Through an incision in the apex of the left ventricle, a latex balloon, attached to the tip of a rigid cannula, was introduced into the left ventricular cavity and was fixed to the apical myocardium by means of a purse-string suture. The balloon was filled with 2 to 15 (usually 3 to 5) cc of saline, a quantity which was always less than the volume of the unstretched balloon. A cannula with multiple side holes near the tip was inserted through the same incision, in order to prevent accumulation of blood (Thebesian drainage) in the left ventricle. Drainage usually amounted to one drop of blood every three to five seconds, and did not vary perceptibly during control and experimental procedures. Coronary perfusion pressure was always kept higher than left ventricular systolic pressure to prevent bulging of the balloon through the aortic valves. Heart rate was kept constant by simultaneous electrical pacing of the right atrium and ventricle. Pressures in the balloon and in the cephalic and coronary perfusion systems were recorded by means of Statham strain gauges on a Sanborn direct-writing recorder.

Blood in a second oxygenator (OXY B) was exposed to gas mixtures containing 95% N₂ and 5% CO₂ (hypoxia), 85 to 90% O₂ and 10 to 15% CO₂ (hypercapnia), or 85% N₂ and 15% CO₂ (asphyxia). By appropriate manipulation of four stopcocks (SC 1, 2, 3, and 4), the cephalic portion of the experimental animal could be perfused with hypoxic, hypercapnic, or asphyxic blood. Cerebral ischemia was produced by clamping the tubing connected to the inflow cannula for cephalic perfusion.

From a side-arm of the cephalic perfusion system, blood was pumped at a constant rate of 20 to 25 cc/min through a Gilford cuvette densitometer, the output of which was registered on the Sanborn recorder. The curves obtained were calibrated in terms of oxygen saturation by periodic blood-gas analyses, according to the manometric method of Van Slyke and Neill. In 25 experiments, the blood drawn through the densitometer passed subsequently through a small chamber in which the tip of a pH electrode (radiometer) was immersed. The output of the pH meter was registered continuously on the oscillographic recorder. Respiratory movements were recorded in 13 experiments by means of a Statham force transducer which was connected by an elastic string to the rib cage or larynx of the experimental animal. Heart rate was recorded in all experiments by means of a tachometer which was triggered by the left ventricular pressure tracing. Phasic left ventricular pressure, respiratory movements, and the outputs of the densitometer and the pH meter were also recorded on tape (Honeywell, model LAR 7400).

**Results**

**CEPHALIC HYPOXIA**

A. Carotid Sinus Nerves and Vagi Intact

In 29 dogs, the oxygen saturation of the blood perfusing the cephalic portion of the animal was lowered to 31.5 ± 11.7% (sd) from
a control value of 95.0 ± 2.1% for a mean period of 96 sec. Heart rate was kept constant in each experiment; the mean value for the series was 164 ± 44 (SD) min⁻¹. The pH of the blood perfusing the head during the control period was 7.34 ± 0.17 (SD) and rose significantly (P < 0.001) during hypoxia by 0.046 ± 0.004 (SE) units.

Several types of responses of left ventricular systolic pressure (LVSP) were manifest during hypoxia of the head, but most of the observations in these 29 experiments could be classified in one of two groups. In the first group, consisting of 15 experiments (28 observations), LVSP changed in a biphasic fashion. There was an initial reduction of LVSP, which persisted for a mean period of 61 sec. The maximal decrease of LVSP was 9.0 ± 7.9% (SD) of the control pressure level. After this initial decrease, LVSP rose above control values, and reached a maximal increase of 19.9 ± 15.6% of control. LVSP began rising during hypoxia, but the peak value was usually attained shortly after resumption of cephalic perfusion with fully oxygenated blood. Characteristically, respiration rate increased during the initial phase, and diminished during the later phase of the left ventricular response. Representative examples are displayed in the left panels of figures 2 and 3.

In a second group, consisting of 6 experiments (15 observations), an initial decrease of LVSP was not observed. LVSP started to rise during hypoxia.
rise shortly after the onset of hypoxia, and reached a maximal increase of 53.5 ± 11.7% (SE) above control (P < 0.001). The left half of the left panel of figure 4 shows a typical example. The second peak in the left ventricular pressure tracing in this panel is the response to cerebral ischemia, which will be described below.

Several types of deviations from these more characteristic responses were also obtained. Three experiments (6 observations) exhibited a response as in the first group during one observation, but during another, similar exposure of the head to hypoxia, the initial depression of peak pressure was absent, and only monophasic increases of pressure were observed, as in the second group. A monophasic decrease in LVSP was elicited in 2 other experiments (3 observations). Finally, in 3 experiments (5 observations), there was a brief, moderate increase initially, followed by a late decrease in LVSP.

B. Carotid Sinus Nerves Sectioned; Vagi Intact

After bilateral denervation of the carotid sinuses, in 22 experiments (41 observations) the oxygen saturation of the blood perfusing the head was lowered to 22.9 ± 8.4% (SD) from a control level of 94.4 ± 3.4% for a mean period of 112 sec. During hypoxia, the blood pH rose by 0.074 ± 0.01 (SE) units from a control level of 7.30 ± 0.01 (SD). Heart rate was constant in each experiment; the mean value was 201 ± 31 (SD) min⁻¹ for the series. In the 5 experiments of this group in which respiratory movements were recorded, the
respiratory rate did not change significantly during the first 30 sec of hypoxia, and then decreased by 4.0 ± 0.9 (se) min⁻¹ (P = 0.005) during the remainder of the hypoxic period.

In 18 of these 22 experiments (31 observations), no initial depression of LVSP was detectable, but LVSP rose monophasically beginning 18 sec after the onset of hypoxia, and reached a maximal increase of 22.6 ± 3.1% (se) (P < 0.001) after 72 sec. Of these 18 experiments, 6 were those which showed the first type of response (biphasic response) prior to denervation (fig. 2); 5 were experiments which showed the second type of response (monophasic increase) before denervation (fig. 4); and 4 were experiments which showed the less characteristic types of responses prior to denervation. In the remaining experiments of this group the carotid sinus nerves were sectioned during the preliminary surgical procedures, before any responses to cephalic hypoxia were recorded.

In 3 other experiments (7 observations), a delayed depression of LVSP followed either no initial change or a slight rise in LVSP. In 1 experiment (3 observations), a biphasic response was obtained which was similar to the first type of response before denervation (fig. 2); 5 were experiments which showed the second type of response (monophasic increase) before denervation (fig. 4); and 4 were experiments which showed the less characteristic types of responses prior to denervation. In the remaining experiments of this group the carotid sinus nerves were sectioned during the preliminary surgical procedures, before any responses to cephalic hypoxia were recorded.

C. Carotid Sinus Nerves Intact; Vagi Sectioned
A bilateral, high, cervical vagotomy was performed in 5 experiments immediately after the observations described under section A above were made. In a sixth experiment, the vagi were sectioned before any experimental observations were recorded. For a period of 90 sec, the oxygen saturation of the blood perfusing the head was lowered from 95.0 ± 2.9 (sd) to a level of 27.6 ± 6.0%. In all instances, LVSP started to rise shortly after the beginning of hypoxia and reached a maximal increase of 32.7 ± 9.0% (se) above control (P = 0.003). The right panel of figure 3 shows a representative example. In no instance was an initial depression of LVSP detected after bilateral vagotomy, even though an initial or a sustained depression of LVSP had been obtained in 4 of these 6 experiments prior to vagotomy.

D. Carotid Sinus Nerves and Vagi Sectioned
In this group of 15 experiments (20 observations) in which bilateral carotid sinus denervation and cervical vagotomy were both performed, the oxygen saturation of the blood to the head was decreased for 98 sec from a control value 95.7 ± 1.7 (sd) to a level of 25.7 ± 9.1%. LVSP started to rise shortly after the onset of hypoxia, and attained a maximal increase of 26.3 ± 9.1% (se) (P < 0.001) above control. No instances of either initial or sustained reduction of LVSP were observed in response to cephalic hypoxia. Most animals showed only a very slow respiration rate, which ceased completely during hypoxia of the head.

E. Control Observations
In 9 experiments, 95% O₂ and 5% CO₂ were passed through oxygenator B (fig. 1) as well as oxygenator A, in order to determine whether blood, that was not being circulated continually through the animal, exerted reflex effects due to causes other than those arising from changes of blood gas composition. When the head of the experimental animal, which otherwise was supplied from oxygenator A, was perfused for 90-sec intervals with blood from oxygenator B, a small but significant (P = 0.05) increase of 1.9 ± 0.7 (se) mm Hg was observed, which represented 2.2% of the control value. These changes were so small in comparison with the effects of cephalic hypoxia that they did not complicate the interpretation of the data.

CEPHALIC HYPERCAPNIA
In 15 experiments (23 observations), the CO₂ content of the blood perfusing the head was gradually increased by raising the fraction of CO₂ in the gas mixture passing through the appropriate oxygenator. In 4 experiments, the carotid sinus nerves were intact and the vagi were cut; in 5 experiments, the carotid sinus areas were denervated and the vagi were intact; and in the remaining 6
experiments, the carotid sinuses were de-nervated and the vagi were cut. No observations were made with both carotid sinus nerves and vagi intact. From a control value of 7.28 ± 0.13 (SD), the blood pH was reduced to a mean level of 6.93 ± 0.15; it was then allowed to return to control levels. These episodes of hypercapnia lasted approximately 6.5 min. The oxygen saturation during the control period was 96.7 ± 3.0%; during hypercapnia, 96.6 ± 3.2%. The heart was paced at a constant rate in each experiment; the average value for this series was 214 ± 30 min⁻¹.

The results were directionally similar under all conditions. There was a maximal increase in LVSP of 46.3 ± 8.5% (SD) above control (P< 0.001). Figure 5 shows a representative example. The rhythmic variations of peak left ventricular pressure in this figure are associated with respiratory center activity, as will be discussed in a subsequent publication.

**CEPHALIC ASPHYXIA**

After bilateral cervical vagotomy and de-nervation of the carotid sinuses in 4 experimental animals (5 observations), the oxygen saturation of the blood perfusing the head was lowered for a period of 90 sec from a control level of 95.1 ± 4.9% (SD) to a level of 31.0 ± 8.6%. Simultaneously, by adding CO₂ to the gas mixture, the pH was lowered from 7.29 ± 0.06 (SD) to 7.01 ± 0.12. Heart rate was constant in each experiment; the mean value for this series was 226 ± 11 min⁻¹. LVSP showed a maximal increase of 43.7 ± 9.6% (SE) above control (P = 0.01). The increase of LVSP during asphyxia of the head was greater than the sum of the individual effects of hypoxia and hypercapnia under similar circumstances (P = 0.02). The levels of the control and test O₂ saturation during hypoxia and asphyxia, and of the control and test pH during hypercapnia and asphyxia, were not significantly different in the 4 experiments.

**CEPHALIC ISCHEMIA**

In each of 10 experiments, ischemia of the head for a period of 43 sec evoked a maximal increase of LVSP of 57.7 ± 9.0% (SE) above control (P< 0.001). The second elevation of LVSP in the left panel of figure 4 shows a representative example. In this experiment, in which the carotid sinus nerves and vagi were still intact, after recovery from a period of cephalic hypoxia, the blood supply to the head was interrupted during the 34-sec interval indicated by the black bar at the top of the tracing. About 15 sec after cessation of blood flow, LVSP increased abruptly from 60 mm Hg to a maximum level of 99 mm Hg, which was attained 16 sec after resumption of circulation. The type of response elicited by cephalic ischemia was similar in animals with the carotid sinus nerves and vagi intact and in those with various combinations of vagotomy and carotid sinus denervation.

Maintained ischemia of the head in 14 experiments, without subsequent resumption of cephalic blood flow, was accompanied by a pronounced increase in LVSP. A maximum value of 95.9 ± 19.7% (SE) above control (P < 0.001) was attained 60.7 ± 37.1 (SD) sec after the onset of ischemia. LVSP subsequently declined, and after 4 min reached a new, stable level which was 15.0 ± 5.0 (SE) mm Hg (P = 0.01) lower than the original control level of 58.8 ± 22.3 (SD) mm Hg. Figure 6 shows a typical example.
**Discussion**

**SIGNIFICANCE OF THESE RESULTS**

In an isovolumetric left ventricle preparation, that provides constancy of heart rate, coronary perfusion pressure, and left ventricular volume, any change in left ventricular systolic pressure indicates a corresponding change of left ventricular contractility. After bilateral cervical vagotomy and carotid sinus denervation, LVSP usually increased during hypoxia, hypercapnia, or ischemia of the central nervous system. This augmentation of contractility confirms the work of Downing et al., and parallels the effects of these stimuli upon blood pressure and peripheral arteriolar resistance. The effects of cerebral asphyxia upon ventricular contractility in dogs with all peripheral chemoreceptors deafferented revealed a definite interaction between the effects of hypoxia and of hypercapnia on the central nervous system. This augmentation of contractility confirms the work of Downing et al., and parallels the effects of these stimuli upon blood pressure and peripheral arteriolar resistance.

When the carotid sinus nerves and the vagi were intact, the changes of LVSP in the paced heart were variable during cephalic hypoxia, but two principal patterns predominated. The most frequent reaction was biphasic; LVSP decreased during the initial phase of hypoxia, with a subsequent rise during the later stage. The second most frequent response consisted of a monophasic rise of LVSP, which persisted during the entire period of hypoxia. After denervation of the carotid sinuses or after bilateral cervical vagotomy, cephalic hypoxia usually evoked only a monophasic increase in LVSP. This suggests strongly that in the large group of experimental animals which evinced the biphasic response when the vagi and carotid sinus nerves were intact, the initial depression of LVSP was elicited by reflexes which originated in the carotid chemoreceptors and in which the vagi comprised the efferent limb. These observations are in full accord with a concurrent study which shows that the primary reflex effect upon the ventricular myocardium of stimulation of the carotid chemoreceptors is inhibitory, and is mediated mainly by the vagi. It seems likely, therefore, that in this group which exhibited the biphasic response, the carotid chemoreceptors were principally responsible for the reflex changes in left ventricular contractility during the early stages of acute cephalic hypoxia. The direct effects of hypoxic stimulation of the central nervous system, therefore, were masked in the initial stages, but became manifest as the secondary increase in LVSP during hypoxia (e.g., left panels of figs. 2 and 3).

In the second largest group of experimental animals, in which hypoxia produced a monophasic increase in LVSP with intact vagi and carotid sinus nerves (fig. 4, left panel), the absence of an initial depression of left ventricular contractility during cephalic hypoxia could be accounted for by postulating (a) an effect of chemoreceptor hypoxia upon ventricular contractility contrary to the usual response, or (b) a prepotent influence of central nervous system stimulation over chemoreceptor excitation even in the early phases of hypoxia. In a concurrent study, it was found that in a few experimental animals before vagotomy, hypoxia of the isolated carotid sinus elicited a positive rather than a negative inotropic effect upon the ventricular myocardium. This was attributed to a stimulation of the cardiac sympathetic centers by the markedly increased activity of the respiratory center during chemoreceptor stimulation, thereby reversing the primary reflex effects of hypoxia of the carotid chemoreceptors upon the heart. If we postulate that in this group the ultimate reflex effect

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of chemoreceptor stimulation on the myocardium is an increase in contractility, a reason for the absence of the initial depression of LVSP becomes apparent. In only a few experiments of this group was respiration rate recorded; in such experiments, however, only a small increase in rate was observed during the early stages of hypoxia, followed by a decrease. This suggests, therefore, that the primary reflex effects of carotid chemoreceptor activation were overwhelmed by the more potent effects of hypoxia directly upon the central nervous system, even during the earliest phases of hypoxia.

It is well established that a decrease of blood flow through the carotid bodies may stimulate the chemoreceptors, and thereby increase cardiac vagal tone. Furthermore, ischemia of the central nervous system provokes a marked stimulation of the cardiac vagal centers, as manifested by severe bradycardia. It has recently been shown that electrical stimulation of the peripheral end of either sectioned cervical vagus nerve has a negative inotropic effect upon the ventricular myocardium. From the present work, and also from a concurrent study, it is probable that the cardiac vagal centers play a significant role in the reflex control of ventricular contractility. Therefore, vagally mediated depression of ventricular contractility might be anticipated during cephalic ischemia. Nevertheless, in all conditions under which it was studied in the present investigation (including intact carotid sinus nerves and vagi), ischemia of the head even for a few seconds elicited only a marked, positive, reflex, inotropic effect upon the ventricular myocardium (second response, left panel of fig. 4). This suggests the existence of a strong, direct stimulation of the cardiac sympathetic centers by cerebral ischemia, that overwhelmed any inotropic effects which might be elicited by stimulation of the cardiac vagal centers, directly or via the carotid chemoreceptors. The decline of left ventricular performance observed 3 to 4 min after the onset of maintained cerebral ischemia (fig. 6) probably reflects loss of the normally present sympathetic tone to the heart. It is unlikely that this resulted from fatigue of the myocardium, due to the increase in the amount of tension generated by the left ventricle during the initial phases of cerebral ischemia because, in our experimental preparation, heart rate was kept constant and LVSP was rarely permitted to exceed 120 mm Hg.

LIMITATIONS OF THIS STUDY

The observations reported in the present study were made in experimental animals under general anesthesia and subjected to major surgery and extracorporeal perfusion. This experimental preparation was employed in order to limit to a minimum the number of variables which could influence cardiac performance. It permitted rigorous control of coronary and cephalic perfusion pressure and blood gas composition. It therefore precluded the influence of several factors which might also have affected ventricular performance; namely (1) coronary arterial anoxemia and hypercapnia, (2) changes in coronary perfusion pressure, (3) baroreceptor reflexes, and (4) the accelerated secretion of catecholamines elicited by stimulation of the chemoreceptors. This preparation also revealed transient changes of left ventricular contractile force which probably would not be detected by conventional techniques. For example, the typical biphasic responses displayed in figures 2 and 3 could not have been evaluated so readily by means of standard ventricular function curves.

In many of the present experiments, denervation of the carotid sinuses included ligation of the internal carotid and occipital arteries. This procedure probably did not interfere with the cerebral blood supply, since large collateral communications exist between the carotid and vertebral arteries in the dog. Furthermore, there were no obvious differences between the results of such experiments and those in which the sinuses were denervated without ligating these vessels.

In the present study, the reflex effects upon the heart of stimulation of the carotid chemo-
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receptors during hypoxia, hypercapnia, or ischemia of the central nervous system were evaluated by comparing the effects of these stimuli before and after section of the carotid sinus nerves, the vagi, or both. Certain basic difficulties are inherent in such a procedure. Vagotomy or denervation of the carotid sinuses liberates the cardiac autonomic centers from the tonic influence of baroreceptors. Consequently, these denervation procedures profoundly alter the "tuning" of the autonomic centers within the central nervous system. It has been well established that sympathetic or parasympathetic tuning can alter quantitatively, and even directionally, certain reflex cardiovascular responses. The extent to which changes in tuning might have influenced the results of our experiments is difficult to ascertain. However, in an attempt to minimize the magnitude of the changes in tuning, the preparation was perfused at a nonpulsatile pressure of approximately 100 mm Hg. Static pressures at this level cause only a moderate discharge of the baroreceptors. Consequently, bilateral carotid sinus denervation, bilateral vagotomy, or both, probably did not elicit major changes in autonomic tuning. When the vagi and carotid sinus nerves were intact, a rather low vagal tone was present, as shown by a mean value for heart rate of approximately 150 min⁻¹.

Summary

The effects of brief periods of cephalic hypoxia, hypercapnia, and ischemia upon the contractility of the normally oxygenated ventricular myocardium were studied in an innervated, isovolumetric, canine left ventricle preparation. The majority of responses to cephalic hypoxia were of two types in preparations with vagi and carotid sinus nerves still intact. (a) More frequently, peak left ventricular pressure changed in biphasic fashion, consisting of an initial depression of contractility followed by subsequent augmentation. (b) Less frequently, a monophasic enhancement of contractility appeared. After transection of either the vagi or the carotid sinus nerves, a monophasic facilitation of contractility was usually evoked by cephalic hypoxia. From these data, it was concluded that two opposing influences act simultaneously upon the ventricular myocardium during cephalic hypoxia in preparations with intact vagi and carotid sinus nerves. Central nervous system hypoxia enhances myocardial contractility; its effect is mediated principally via sympathetic pathways. Hypoxia at the level of the carotid chemoreceptors depresses contractility reflexly; the efferent limb of this reflex is mediated chiefly via the vagi. At any moment in time, the effect upon ventricular contractility is the result of these opposing influences.

Cephalic hypercapnia produced effects similar to those of hypoxia. Cephalic ischemia always evoked a marked, positive inotropic effect upon the ventricles.

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