Autonomic Cardiovascular Control during Hypoxia in the Dog

STEPHEN C. HAMMILL, WILTZ W. WAGNER, JR., LEONARD P. LATHAM, WARREN W. FROST, AND JOHN V. WEIL

SUMMARY The mechanisms controlling cardiovascular responses to hypoxia are poorly understood. We studied effects of parasympathetic blockade by atropine (Px) and sympathectomy by adrenalectomy plus 6-hydroxydopamine (Sx) in five unanesthetized dogs acutely exposed to hypoxic conditions (Pao₂ = 35 mm Hg). In intact dogs during hypoxia, heart rate increased by 55 ± 10 (SEM) beats/min. After either Px or Sx, heart rate increased by only 34 ± 4 beats/min during hypoxia. Combined Sx and Px abolished the heart rate response to hypoxia. In intact dogs, hypoxia decreased stroke volume by 6 ± 1 ml. After Sx, hypoxia still decreased stroke volume (6 ± 1 ml), but stroke volume increased during Px (5 ± 2 ml). The stroke volume response was eliminated by Sx plus Px. Cardiac output increased during hypoxia alone (1.2 ± 0.2 liters/min) and in the presence of Px (2.0 ± 0.5 liters/min) and Sx (0.8 ± 0.3 liter/min); this response was abolished by Sx plus Px. Systemic arterial pressure increased during hypoxia alone (16 ± 4 mm Hg) and in the presence of Px (21 ± 7 mm Hg), but failed to change during either Sx or Sx plus Px. Total systemic vascular resistance fell during hypoxia alone (5 ± 2 mm Hg/liter per min) and in the presence of Px (5 ± 2 mm Hg/liter per min) and Sx (5 ± 2 mm Hg/liter per min), but failed to fall during Sx plus Px. We conclude that the autonomic nervous system plays a major role in mediating these cardiovascular systemic responses to hypoxia. The pattern of responses suggests that sympathetic activity increases heart rate, stroke volume, cardiac output, and blood pressure during hypoxia, whereas decreased parasympathetic activity increases heart rate and cardiac output and decreases stroke volume. If both components of the autonomic system are blocked, the systemic hypoxic response is eliminated.

HYPOXIA increases heart rate (HR), cardiac output (CO), and systemic arterial pressure (BP), and decreases total systemic resistance (TSR) and stroke volume (SV) (Saltz et al., 1976; Kontos et al., 1965; Thilenius et al., 1967). However, the mechanisms whereby these responses are mediated remain unclear. The purpose of this study is to examine the role of the autonomic nervous system in modulating the systemic cardiovascular response to acute hypoxia.

Several investigators (Thilenius et al., 1967; Richardson et al., 1967; Chidsey et al., 1961; Kontos and Lower, 1969; Nahas et al., 1954; Chiong and Hatcher, 1972) have evaluated the role of the sympathetic nervous system in the cardiovascular response to hypoxia by abolishing sympathetic function surgically or pharmacologically. Both of these approaches have disadvantages. It is difficult to remove adequately all sympathetic nerves by surgery (Cooper et al., 1959), and α- and β-receptor inhibitors have significant effects other than their principal action as blocking agents (Shanks, 1967; Levy, 1968). Consequently, the introduction of 6-hydroxydopamine (60HDA) as a selective lysing agent of sympathetic nerve terminals (Gauthier et al., 1972, 1974; Kostrzewa and Jacobowitz, 1974; Kadowitz et al., 1976; Sachs and Jonson; Trippodo and Traber, 1974) provides a useful means to evaluate the role of the adrenergic limb of the autonomic nervous system in the cardiovascular response to acute hypoxia.

Although effective blockade of parasympathetic receptors with atropine has long been available, understanding the role of the parasympathetics has been difficult because of the interactions between the parasympathetic and sympathetic nervous systems. This interaction was emphasized by Vatner et al. (1974) when they demonstrated that the canine HR response to hypotension was influenced in almost equal proportion by both increases in sympathetic and decreases in parasympathetic activity. Similar interactions may be involved in the cardiovascular response to hypoxia, although this has not been investigated. This paper reports results of parasympathetic blockade and sympathetic ablation, studied separately and in combination to determine the relative roles played by the two limbs of the autonomic nervous system in the systemic cardiovascular response to acute hypoxia.

Methods

Five mongrel dogs (20-25 kg) were studied awake, with no premedication, in an environmental
chamber. Oxygen concentration was regulated by nitrogen inflow under feedback control by a paramagnetic oxygen analyzer (Beckman model P3). Oxygen concentration was controlled within an absolute range of ± 0.2%. Carbon dioxide was monitored by an infrared analyzer (Beckman model B1) and remained below 0.5%. Each dog stood in a supportive sling in which it appeared to be relaxed and comfortable throughout the study.

The dogs first were studied 2 weeks after a carotid loop had been created surgically under pentobarbital anesthesia (30 mg/kg, iv) by exteriorization of the right carotid artery in a protective covering of cervical skin. The loop was used for percutaneous access to the arterial system. For each study the following catheters were placed: a carotid loop cannula for BP and arterial blood samples, a percutaneous jugular catheter placed 20 cm into the venous system for dye injection, and a foreleg cannula for drug infusion. HR from the electrocardiogram and systemic BP via a Statham P23DG pressure transducer positioned 5 cm dorsal to the sternum were calculated every 30 seconds on-line by a Nova 1200 computer (Data General). CO was measured from indocyanine green dye curves calculated by computer according to the Stewart Hamilton technique (Huber et al., 1976). Heparin solution, 3000-4000 units, iv, was given at the beginning of each study to prevent thrombus formation.

**Experimental Protocol**

When a stable HR was reached during control conditions, CO, TSR (mean systemic blood pressure/CO), and SV (CO/HR) were determined three times, at approximately 3-minute intervals over a 10-minute period. Then the chamber oxygen concentration was reduced to a PaO₂ of approximately 35 mm Hg. When the dog had stabilized for a 10-minute period after becoming hypoxic, CO, SV, and TSR (from three to six measurements of each), and BP and HR (10 measurements of each) again were recorded over a 10-minute period.

Normal PaO₂ then was restored, and the dog was given atropine sulfate, 0.15-0.5 mg/kg, over a 30-minute period. Then a continuous infusion of atropine sulfate, 0.05-0.1 mg/kg per hour, was given, which maintained complete parasympathetic blockade. When HR had stabilized, measurements were repeated during normoxia and hypoxia. If at the end of the study the HR during normoxia decreased from the baseline HR in the atropine-treated dog by more than 10 beats/min, indicating return of parasympathetic function, data for the part of that study relating to blockade of parasympathetic effects were discarded. We followed this protocol in three studies on each dog with intervals of at least 1 week between studies.

After the three baseline studies, the dogs were again placed under pentobarbital anesthesia, and we performed a bilateral adrenalectomy using an abdominal approach. The dogs were maintained on a replacement regimen of deoxycorticosterone acetate, 2.5 mg/day, im, and dexamethasone, 0.8 mg/day, im. In anticipation of stress related to the study, the dose of each replacement drug was doubled on the day prior to and on the day of each study. At least 2 weeks after the adrenalectomy, the dog received 60HDA hydrobromide (Regis), iv, by the following schedule: days 1 and 2: 0.5 mg/kg; day 3: 1 mg/kg; day 4: 2 mg/kg; day 5: 5 mg/kg; day 6: 10 mg/kg; day 7, AM: 25 mg/kg; and day 7, PM: 31 mg/kg, for a total dose of 60HDA hydrobromide of 75 mg/kg (50 mg/kg of 60HDA). Each dog was studied twice within 10 days of the final 60HDA injection. The progressive dosage schedule of 60HDA prevented the earlier-reported (Gauthier et al., 1972) complications of severe hypertension. The drug resulted in relaxed nictitating membranes and miosis. Mild diarrhea also occurred but was not associated with weight loss or altered food intake.

**Demonstration of Sympathectomy**

To test the adequacy of adrenalectomy, histamine was administered intravenously to release medullary catecholamines (Staszewska-Barczak and Vane, 1965). Arterial plasma catecholamine levels were measured (Upjohn Diagnostic Laboratories; Passon and Feuler, 1973) before and after a 5-minute intravenous histamine phosphate infusion was given to the dog (13.75 μg/kg/per min, 5 μg/kg/per min of the base). Histamine infusion decreased the systemic BP by 51 ± 6 mm Hg in the intact dogs and, similarly, by 49 ± 7 mm Hg in the sympathectomized dogs. In the intact dogs the resting total catecholamines were 255 ± 39 pg/ml, and they increased to 1970 ± 354 pg/ml after histamine infusion (Fig. 1). In sympathectomized dogs, resting
total catecholamines were 52 ± 9 pg/ml, and there was no significant change (56 ± 12 pg/ml) after histamine.

Effectiveness of adrenergic neural destruction by 60HDA was determined from the pressor response to tyramine, which depends on the presence of normal sympathetic nerve endings. The dogs were tested with tyramine HCl, 100 µg/kg, iv, prior to receiving 60HDA and with 200 and 400 µg/kg, iv, during each study after 60HDA administration. The intact dogs responded to tyramine HCl, 200 µg/kg, was noted within the 1st week after receiving 60HDA and with 200 and 400 µg/kg, iv, but the BP increase caused by tyramine HC1, 200 µg/kg, was less than 5 mm Hg. Return of early sympathetic function (active nictitating membrane and an increase in diastolic tension) was noted within 1 week after the initial atropine dose and atropine sulfate (0.4-0.5 mg/kg) consistently was necessary to achieve adequate blockade in the sympathectomized dogs. The following variables decreased significantly (P < 0.05) after sympathectomy: hematocrit, from 42 ± 2% to 35 ± 2%; creatinine, from 1.2 ± 0.4 mg/dl to 0.9 ± 0.1 mg/dl; and chloride, from 112 ± 3 mg/dl to 108 ± 2 mg/dl. The decreases in these variables may be explained by hemodilution, because increased vascular capacitance accompanies sympathetic denervation (Weil and Chidsey, 1968).

Statistical analysis was performed by either of the following tests when appropriate: two-way analysis of variance followed by Dunnett's multiple comparison test (Dunnett, 1964), or Student's t-test (Remington, 1970). The results of the 1st study day were omitted from the data pool to minimize any training effect. The results of neither the 2 presympathectomy nor the 2 postsympathectomy study days showed any progressive trends suggesting training effect (P > 0.05). The individual dog's mean for each condition (normoxia or hypoxia when intact, parasympathetically blocked, sympathectomized, or during combined denervation) was determined by averaging the three observations for normoxia and hypoxia on each of 2 days and then averaging the two daily means for each condition. The five individual means then were averaged to determine the values recorded in Tables 1 and 2.

### Results

Arterial blood gas levels during inspiration of room air (Table 1) were stable and comparable throughout the four study conditions (intact, parasympathetic blockade, sympathectomy, and combined blockade). Similarly, hypoxic arterial blood gas levels showed little variability among the four conditions.

Parasympathetic blockade increased HR and CO during normoxia (P < 0.05) and decreased the SV and TSR (P < 0.05). BP remained unchanged. Sympathectomy did not alter HR, SV, CO, or TSR during normoxia but did decrease BP significantly (P < 0.05). Combined autonomic denervation increased the HR during normoxia (P < 0.05) and decreased SV (P < 0.05), whereas CO, BP, and TSR remained unchanged.

HR (Table 2) increased during hypoxia in the intact dogs. The response of the intact dogs was reduced by 37% during either sympathectomy or parasympathetic blockade. During total autonomic

---

**Table 1** Arterial Blood Gas Values

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normoxia</th>
<th>Hypoxia</th>
<th>Parasympathetic blockade</th>
<th>Sympathectomy</th>
<th>Sympathectomy + parasympathetic blockade</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.41</td>
<td>7.51</td>
<td>7.39</td>
<td>7.49</td>
<td>7.39</td>
</tr>
<tr>
<td></td>
<td>±0.01</td>
<td>±0.01</td>
<td>±0.01</td>
<td>±0.02</td>
<td>±0.01</td>
</tr>
<tr>
<td>PaO₂ (mm Hg)</td>
<td>71.6</td>
<td>34.2</td>
<td>75.3</td>
<td>34.4</td>
<td>70.8</td>
</tr>
<tr>
<td></td>
<td>±1.2</td>
<td>±0.4</td>
<td>±1.6</td>
<td>±0.4</td>
<td>±1.5</td>
</tr>
<tr>
<td>PaCO₂ (mm Hg)</td>
<td>33.7</td>
<td>22.0</td>
<td>33.3</td>
<td>23.5</td>
<td>33.9</td>
</tr>
<tr>
<td></td>
<td>±0.8</td>
<td>±0.7</td>
<td>±1.2</td>
<td>±1.9</td>
<td>±1.1</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SE; n = 5.
TABLE 2 The Influence of Autonomic Denervation on the Cardiovascular Response to Hypoxia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intact Normoxia</th>
<th>Hypoxia</th>
<th>Parasympathetic blockade Normoxia</th>
<th>Hypoxia</th>
<th>Sympathectomy Normoxia</th>
<th>Hypoxia</th>
<th>Sympathectomy + parasympathetic blockade Normoxia</th>
<th>Hypoxia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>87 ± 7</td>
<td>142 ± 15</td>
<td>197 ± 6</td>
<td>231 ± 7</td>
<td>76 ± 3</td>
<td>110 ± 6</td>
<td>150 ± 6</td>
<td>155 ± 4</td>
</tr>
<tr>
<td>Δ</td>
<td>55 ± 10*</td>
<td></td>
<td>34 ± 4†</td>
<td></td>
<td>34 ± 5†</td>
<td></td>
<td>5 ± 3</td>
<td></td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>41 ± 4</td>
<td>35 ± 3</td>
<td>27 ± 2</td>
<td>32 ± 3</td>
<td>41 ± 4</td>
<td>36 ± 5</td>
<td>26 ± 3</td>
<td>26 ± 3</td>
</tr>
<tr>
<td>Δ</td>
<td>-6 ± 1*</td>
<td></td>
<td>5 ± 2</td>
<td>-5 ± 1†</td>
<td>0 ± 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac output (liters/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>3.5 ± 0.2</td>
<td>4.7 ± 0.4</td>
<td>5.3 ± 0.3</td>
<td>7.3 ± 0.6</td>
<td>3.1 ± 0.2</td>
<td>3.9 ± 0.4</td>
<td>3.8 ± 0.3</td>
<td>4.0 ± 0.4</td>
</tr>
<tr>
<td>Δ</td>
<td>1.2 ± 0.2†</td>
<td></td>
<td>2.0 ± 0.5*</td>
<td></td>
<td>0.8 ± 0.3†</td>
<td></td>
<td>0.2 ± 0.3</td>
<td></td>
</tr>
<tr>
<td>Systemic arterial blood pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>109 ± 4</td>
<td>125 ± 4</td>
<td>119 ± 7</td>
<td>140 ± 4</td>
<td>95 ± 4</td>
<td>99 ± 3</td>
<td>116 ± 3</td>
<td>121 ± 2</td>
</tr>
<tr>
<td>Δ</td>
<td>16 ± 4</td>
<td></td>
<td>21 ± 7†</td>
<td></td>
<td>4 ± 2</td>
<td></td>
<td>5 ± 3</td>
<td></td>
</tr>
<tr>
<td>Total systemic resistance (mm Hg/liters/min)</td>
<td>33 ± 2</td>
<td>28 ± 2</td>
<td>23 ± 1</td>
<td>20 ± 2</td>
<td>32 ± 1</td>
<td>27 ± 2</td>
<td>32 ± 3</td>
<td>32 ± 3</td>
</tr>
<tr>
<td>Mean</td>
<td>-5 ± 2†</td>
<td></td>
<td>-3 ± 1†</td>
<td></td>
<td>-5 ± 2</td>
<td></td>
<td>0 ± 2</td>
<td></td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SE; n = 5.

* P < 0.01; † P < 0.001; ‡ P < 0.05.

blockade, the HR response was eliminated.

SV (Table 2) fell in response to hypoxia in the intact dogs. This was not altered by sympathectomy. During parasympathetic blockade, SV showed a significant increase during hypoxia, which contrasted with the usual fall seen during control conditions. In the absence of autonomic activity, the SV was unchanged by hypoxia.

CO (Table 2) increased significantly during hypoxia in the intact dogs. This effect was reduced by sympathectomy but was uninfluenced by parasympathetic blockade. In the absence of both limbs of the autonomic nervous system, the CO response was abolished.

BP (Table 2) increased during hypoxia in the intact and parasympathetically blocked dogs. However, without the sympathetic nervous system, the BP did not change in response to hypoxia.

TSR (Table 2) fell significantly during hypoxia in the intact, parasympathetically denervated and sympathetically denervated dogs. However, this vasodilation during hypoxia was abolished in the autonomically denervated dog.

Discussion

Hypoxia in the awake dog results in increased HR, CO, and BP, and a fall in SV and TSR. When both limbs of the autonomic nervous system are removed, all of the responses are eliminated. Thus the autonomic nervous system plays a major role in mediating the systemic cardiovascular responses to acute hypoxia.

Questions concerning the completeness of sympathectomy may be raised: first, in relation to the efficacy of 60HDA for neural sympathectomy; and second, whether there is chromaffin tissue outside the adrenal medulla which would be unaffected by adrenalectomy. 6-Hydroxydopamine was chosen to ablate the influence of the neural components of the adrenergic nervous system because it selectively causes degeneration of adrenergic neurons while not affecting mast cells, cholinergic neurons, or other vasoactive mediators (Kostrzewa and Jacobowitz, 1974; Kadowitz et al., 1976; Sachs and Jonson, 1975). As stated previously, our dogs tolerated the drug and were unresponsive to intravenous tyramine used to test for the presence of catecholamines in nerve endings. Whether adrenalectomy removes all catecholamine-producing tissues is a matter of importance, because lysis of sympathetic nerve endings by 60HDA results in supersensitivity to residual catecholamines (Gauthier et al., 1974; Kostrzewa and Jacobowitz, 1974). Response to histamine, which releases catecholamines (Staszewska-Barczak and Vane, 1965) from catecholamine-producing tissue, was abolished, indicating the absence of active chromaffin tissue. The small residual catecholamine concentration may represent brain catecholamine production (60HDA does not cross the blood-brain barrier; Kostrzewa and Jacobowitz, 1974) and catecholamines from tissues...
such as the vas deferens and the spleen, which are less sensitive than other tissues to the effects of 60HDA (Kostrzewa and Jacobowitz, 1974).

Our data in the normoxic dog, whether intact, sympathectomized, or parasympathetically blocked, are comparable to those reported by others (Saltz et al., 1976; Thilenius et al., 1967; Kontos and Lower, 1969; Trippodo and Traber, 1974; Vatner et al., 1974; Atkins and Horwitz, 1977). However, previous investigation of the role of the adrenergic nervous system in the cardiovascular response to acute hypoxia has produced inconsistent results. Thilenius et al. (1967) and Kontos and Lower (1969), using the β-blocker propranolol, blocked the HR, SV, and CO responses to acute hypoxia in the awake dog. The direct myocardial depressant effects of propranolol make it difficult to interpret these findings, although a recent report (Harrison and Marlon, 1971) indicates that, in moderate doses, propranolol may not be a myocardial depressant. Tucker and Reeves (1975) reported that in anesthetized dogs β-blockade with practolol attenuated but failed to eliminate the CO increase during hypoxia. Their results resemble those in studies of patients in whom adrenergic blockade does not abolish the HR or CO responses to hypoxia. Richardson et al., (1967), using propranolol, lessened but did not eliminate the increase in cardiac index during hypoxia whereas the HR response was unaltered. Chidsey et al. (1961) used syrosingopine (a depleter of adrenergic nerve ending catecholamine stores), which decreased but did not abolish the HR response to hypoxia. These results are consistent with our findings that adrenergic denervation attenuates but does not eliminate HR and CO increases during hypoxia.

Surgical sympathectomy was studied by Nahas et al. (1954). In awake dogs that previously were subjected to sympathetic denervation from C2 to T8, they found decreased but significant HR and CO responses to hypoxia. However, Chiong and Hatcher (1972), who studied the response to hypoxia before and after surgical sympathectomy (stellate ganglion to T5), found an increased CO response after sympathectomy, whereas the HR response was attenuated. Although both of these studies are complicated by problems in achieving and demonstrating complete, selective denervation (Cooper et al., 1959), their results are consistent with our findings.

Analysis of the consequences of selectively eliminating sympathetic and parasympathetic function provides insight into their relative roles in hypoxia. The increase in CO during hypoxia persists despite either sympathetic or parasympathetic blockade, but is eliminated during combined denervation. In intact and sympathectomized dogs with parasympathetics intact, the CO increase is associated with increased HR (while SV falls); but after parasympathetic blockade when sympathetics are present, the increase is associated with increases in both HR and SV. Thus both sympathetic and parasympathetic systems contribute to the CO increase, the former through HR and SV effects and the latter by HR alone. We did not investigate the possible role played by the spleen in augmenting the CO increase during hypoxia. Splenic contraction contributes to increased CO by increasing effective blood volume and cardiac filling pressures (Liang and Huckabee, 1973), but how this might have been altered by autonomic blockade was not evaluated. Histological evidence suggests that sympathetic terminals in the spleen may be more resistant to 60HDA than those in other tissues (Kostrzewa and Jacobowitz, 1974). However, the functional effects of 60HDA on the spleen have not been studied.

The increase in HR during hypoxia was reduced, but remained significant, during both sympathectomy and parasympathetic blockade. Parasympathetic blockade with sympathetics intact significantly increased the baseline HR during normoxia, which may account for the diminished HR response to hypoxia. Nonetheless, in the absence of either the sympathetic or parasympathetic nervous systems, hypoxia significantly increased HR. This may reflect increased β-adrenergic activity when the sympathetic nervous system is intact, and parasympathetic withdrawal when parasympathetics are intact. Whether these effects represent a direct autonomic action of hypoxia or a consequence of baroreceptor stimulation by systemic vasodilation is not directly resolved by this study. However, the rise in systemic BP should lead to a baroreceptor-mediated decrease in HR, making the baroreceptor an unlikely mediator of hypoxic tachycardia.

SV fell during hypoxia and remained low after sympathectomy when parasympathetics were intact. During parasympathetic blockade with sympathetics intact, SV increased in response to hypoxia. The mechanism for these changes remains unclear because several hemodynamic variables influence SV, including HR, inotropic state, peripheral resistance, and filling pressure of the left ventricle. The decreased SV during hypoxia in the intact and sympathectomized dogs may reflect the reciprocal fall in SV that accompanies an increase in HR. Pacing at a constant HR could resolve this question, but was not done in the present study. However, previous descriptions (Noble et al., 1966) of the decrease in SV associated with pacing-induced tachycardia indicate that the SV decrease produced by hypoxia in our study for intact, sympathectomized, and autonomically denervated conditions can be explained by the associated tachycardia. From the relationship between HR and SV found by Noble et al. (1966), a calculated SV for the intact dog during normoxia would be 41 ml; this figure is identical to the value we measured during normoxia. During hypoxia, the intact dogs' measured SV was 35 ± 3 ml; the SV calculated for the observed increase in HR would be 31 ml. Similarly, during sympathectomy the SV measured during
normoxia (41 ± 4 ml) agrees well with the calculated SV of 44 ml, and the measured SV during hypoxia of 36 ± 5 ml is consistent with the calculated value of 37 ml for comparable HR. The SV measured in the autonomically denervated dogs was 26 ± 3 ml during both normoxia and hypoxia, and the calculated value would be 31 ml. Although these calculations suggest that much of the observed decrease in SV during hypoxia is attributable to HR, it must be pointed out that the HR-SV relationship was defined under normoxic conditions and ignores possible effects of hypoxia on myocardial function, venous capacity, and splenic contraction. For this reason these conclusions should be interpreted with caution. The relationship of decreasing SV with increasing HR was not found during parasympathetic blockade with intact sympathetics, rather, SV increased during hypoxia despite an increase in HR. This may reflect an adrenergically mediated increase in inotropic state unopposed by negative parasympathetic effects (Higgins et al., 1973). Changes in ventricular filling pressure reflecting altered venous capacity and splenic contraction may have contributed to altered SV but were not measured.

The increase in BP during hypoxia was preserved in parasympathetically blocked sympathetically intact dogs. However, in the absence of the sympathetics, BP failed to change with hypoxia, indicating that the sympathetic nervous system plays a major role in the BP increase during hypoxia. These changes reflect the lesser increase in CO in the face of falling vascular resistance when sympathetic function is eliminated.

Hypoxic vasodilation (decreased TSR) in the intact dog was preserved during either sympathectomy or parasympathetic blockade, but was eliminated during autonomic denervation. Thus, vasodilation caused by hypoxia is mediated autonomically and may represent combined effects of β-adrenergic stimulation and cholinergic consequences of baroreceptor stimulation. We were impressed by the absence of vasodilation when autonomic function was blocked. Several studies (Costin and Skinner, 1970; Heistad and Wheeler, Daugherty et al., 1967) indicate that hypoxia has direct local vasodilator effects. However, these studies evaluated local vasoactivity and not total systemic vascular state. Local vasodilation insufficient to lower TSR may have occurred in our study. Thus, hypoxia may indeed have direct local vasodilator effects, although it does not appear to have an intrinsic general direct dilator effect, at least for the degree of hypoxia we studied. Regional perfusion studies would help to clarify the interaction of the autonomic nervous system and hypoxia on local vascular beds. The maintenance of normal CO, BP, and TSR during hypoxia despite total absence of autonomic function suggests that other important vasoactive mediators (possibly histamine, prostaglandin, or angiotensin) must be important in maintaining cardiovascular stability.

No previous study has examined the interaction of the parasympathetic and sympathetic nervous systems in controlling the reflex response of the cardiovascular system to hypoxia in the awake dog. However, responses to other stresses such as hypotension (Vatner et al., 1974) and exercise (Atkins and Horwitz, 1977) also involve combined interaction of the sympathetic and parasympathetic nervous systems.

Our study assumes that interaction of the sympathetic and parasympathetic nervous systems is linear. However, the interaction may be nonlinear. If this is true, total elimination of each autonomic limb as done in the current study, in contrast to graded elimination, may represent an oversimplified model. Still it would appear that the sympathetic limb contributes to the systemic response to hypoxia by increasing HR, SV, CO, and BP, and decreasing TSR, whereas the parasympathetic's role is to increase HR and CO, and decrease SV and TSR.

References


Kostrzewa RM, Jacobowitz DM: Pharmacological actions of 6-
AUTONOMIC CARDIOVASCULAR CONTROL DURING HYPOXIA

Levy JV: Myocardial and local anesthetic actions of \( \beta \)-adrenergic receptor blocking drugs: Relationship to physiochemical properties. Eur J Pharmacol 2: 280-257, 1966


Autonomic cardiovascular control during hypoxia in the dog.
S C Hammill, W W Wagner, Jr, L P Latham, W W Frost and J V Weil

_Circ Res._ 1979;44:569-575
doi: 10.1161/01.RES.44.4.569

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1979 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/44/4/569.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation Research_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation Research_ is online at:
http://circres.ahajournals.org/subscriptions/