Circulatory Adjustments to Hypoxia

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SUMMARY  Circulatory adjustments during hypoxia act to redistribute blood flow and maintain arterial pressure. Redistribution of blood flow is accomplished by a local effect of hypoxia, which produces dilatation in coronary and cerebral vessels, and the chemoreceptor reflex, which produces vasoconstriction in skeletal muscle and the splanchnic bed and dilatation in coronary vessels. Arterial pressure is maintained primarily by the chemoreceptor reflex. If the chemoreceptor reflex fails to maintain arterial pressure, hypoxia and hypotension together activate the central pressor response. Compensatory mechanisms usually are sufficient to maintain homeostasis during hypoxia. However, when a hypotensive stress is superimposed during hypoxia, compensatory mechanisms may fail to maintain arterial pressure. Thus, systemic hypoxia interferes with autonomic cardiovascular adjustments.

DR. DICKINSON RICHARDS received the Nobel Prize in 1956 for introducing cardiac catheterization for the study of pulmonary and cardiovascular physiology in man in health and disease. His discovery paved the way for modern cardiac catheterization, cardiology and cardiovascular surgery as practiced today. The Nobel Prize was but the crowning of a dynamic, 40-year scientific career. In his first paper, Richards demonstrated (probably for the first time) that disease states can alter oxygen-hemoglobin dissociation. He showed that anemia reduces the affinity of hemoglobin for oxygen. The topic of this report, circulatory adjustments to hypoxia, seems appropriate to honor a man who spent most of his career pursuing the link between respiration and circulation.

Critically ill patients are often hypoxic, but hypoxia also occurs in normal subjects at high altitudes. At an altitude of approximately 14,000 feet, arterial Po2 of normal subjects is 40 mm Hg. This low arterial Po2 is well tolerated by most persons because of respiratory and circulatory adjustments. In the clinical setting, hypoxia is common in patients with heart failure, pulmonary embolism, shock, and myocardial infarction. In these patients hypoxia is an added stress that may limit circulatory adjustments.

We will discuss four circulatory adjustments to hypoxia: 1) local vascular effects; 2) effects of chemoreceptor stimulation; 3) central pressor effects; and 4) modification of reflexes by hypoxia. The first three adjustments represent selective effects of hypoxia, and we analyze these responses as isolated effects. In the fourth part, we examine the integrated effects of hypoxia in normal subjects and in patients subjected to the added stress of hypotension.

The local vascular effect of hypoxia is inhibitory in that it tends to reduce arterial pressure. In contrast, the effects of hypoxia on chemoreceptors and on the central nervous system are both excitatory as they increase arterial pressure. Modification of reflexes by hypoxia is inhibitory in the sense that it prevents the appropriate circulatory response to hypotension. Thus, because some effects of hypoxia are inhibitory and some are excitatory, the net response to hypoxia in a subject depends on the magnitude of each of these components and on the integration of the components.

Local Vascular Effects

Vasodilatation

When a vascular bed is perfused with hypoxic blood and normal oxygenation is maintained in the rest of the body, blood vessels in the hypoxic bed tend to dilate. The work of Daugherty et al. and our studies...
indicate two important findings (fig. 1): First, hypoxia must be very severe, with arterial P O 2 less than 40 mm Hg, before significant vasodilatation can be detected. Second, vasodilatation is not uniform in all vascular beds; it is selective. Dilatation during hypoxia occurs predominantly in coronary and cerebral vessels; responses in limb vessels are small, and renal vessels do not dilate even at a P O 2 of 20 mm Hg. The differential effect of localized hypoxia in various organs is beneficial in that it tends to redistribute blood flow toward coronary and cerebral vessels.

Inhibition of Vasoconstriction

We have examined the effects of localized hypoxia on vasoconstrictor responses to norepinephrine and angiotensin in perfused coronary vessels and gracilis muscle. 2 When these vascular beds are perfused at constant blood flow, changes in perfusion pressure reflect changes in vascular resistance (fig. 2). Increasing doses of angiotensin raised perfusion pressure in both the coronary and the gracilis arteries when arterial P O 2 was 99 mm Hg. When P O 2 was reduced to 40 mm Hg, the vasoconstrictor response to angiotensin was abolished in the coronary bed but the constrictor response in the gracilis artery was maintained. Thus, selective retention of constriction in the gracilis muscle and its inhibition in the coronary bed would favor redistribution of flow away from skeletal muscle to the myocardium during hypoxia.

Is the selective inhibition of vasoconstriction the result of greater sensitivity of vascular smooth muscle of coronary vessels to hypoxia? Or is the difference in responsiveness related to the fact that the myocardium is contracting and requires more oxygen than the gracilis muscle? We tested the latter hypothesis by increasing oxygen requirements of the perfused gracilis muscle with simulated exercise. 3 When the gracilis muscle was contracting and its arterial P O 2 was reduced, the vasoconstrictor effect of norepinephrine was completely abolished. The inhibition of vasoconstrictor responses to angiotensin and norepinephrine during hypoxia appears to be primarily a function of the metabolic requirement of the organ that is being perfused. Selective inhibition of vasoconstriction allows redistribution of flow to organs that are most active metabolically.

Chemoreceptor Stimulation

The local vascular effects of hypoxia are inhibitory and, if unopposed, they cause vasodilatation and hypotension. Arterial pressure is sustained during hypoxia in normal subjects, however, apparently by activation of arterial chemoreceptors. Chemoreceptor stimulation by hypoxia has two main effects: it increases arterial pressure 4 and produces redistribution of blood flow.

Increase in Arterial Pressure

Evidence for a pressor response to stimulation of chemoreceptors in man is provided by the work of Lugliani et al. 4 The investigators examined the
response to hypoxia in two groups of subjects: normal subjects and patients who had undergone carotid body resection for the treatment of asthma. In normal subjects arterial pressure was maintained or increased during hypoxia, whereas in the subjects who had undergone resection of the carotid bodies, arterial pressure decreased significantly (fig. 3).

Experiments in animals indicate that the increase in arterial pressure during chemoreceptor stimulation is related primarily to an increase in peripheral vascular resistance. In addition, there is an important inotropic response in myocardium to chemoreceptor stimulation.6

Redistribution of Blood Flow

Arterial pressure is maintained during chemoreceptor stimulation primarily by vasoconstriction in skeletal muscle6 and several other vascular beds. However, the constriction is not uniform. Certain vascular beds or vascular segments, such as venous segments, may dilate in response to chemoreceptor stimulation.7 This was demonstrated by perfusing the isolated carotid artery with hypoxic blood or by injecting nicotine or cyanide into the carotid artery. Activation of carotid chemoreceptors either with hypoxia or with nicotine and cyanide triggers similar reflexes. Stimulation of chemoreceptors produces marked reflex vasoconstriction in skeletal muscle and vasodilatation in a cutaneous bed.6,8

Similar studies were performed to examine effects of chemoreceptor stimulation on coronary vessels. In these experiments, carotid chemoreceptors were activated by injection of nicotine or cyanide and changes in myocardial contractility were minimized by administering propranolol or propranolol. This resulted in significant dilatation of coronary vessels and a small increase in coronary sinus Po2 (fig. 4). The vasodilatation is neurogenic and mediated through vagal efferent fibers.

The effect of chemoreceptor stimulation on cerebral blood flow is controversial. Ponte and Purves10 suggested that chemoreceptors play an important role in increasing cerebral blood flow during hypoxia. We have not been able to demonstrate any reflex response in cerebral vessels during chemoreceptor stimulation.11 As summarized in a recent review,12 other studies have supported both views. However, it appears that local mechanisms are sufficient to account for cerebral vasodilatation during systemic hypoxia, and one need not invoke a contribution from the chemoreceptor reflex.13

We interpret the differential reflex responses (vasoconstriction in muscle and vasodilatation in coronary vessels) as another mechanism for redistributing blood flow to organs with high metabolic requirements. This effect, in addition to the local vascular effect, facilitates effective use of oxygen. Figure 5 summarizes the reflex and local effects of hypoxia in several vascular beds.

Modulation of Cardiovascular Effects by Hyperventilation

The chemoreceptor reflex produces hyperventilation as well as direct cardiovascular effects. Pulmonary stretch receptors are stimulated by hyperventilation and these receptors modulate the direct cardiovascular responses to chemoreceptor stimulation. For example, the chemoreceptor reflex produces bradycardia when ventilation is maintained constant. When ventilation is allowed to increase during chemoreceptor stimulation, however, activation of pulmonary stretch receptors overrides the direct effect of chemoreceptors and heart rate increases.15

The effect of chemoreceptor stimulation on vessels in skeletal muscle, mesenteric, and renal beds is altered significantly by stimulation of pulmonary stretch receptors.15,16 Hyperventilation may attenuate, or sometimes reverse, the constrictor response in these vessels. Thus, in examining the integrated cardiovascular response to hypoxia, it is important to consider the interaction of arterial chemoreceptors and pulmonary stretch receptors.17

Potentiation of Chemoreceptor Responses

The chemoreceptor response is not an all-or-none response. Although chemoreceptors are activated by hypoxia, the magnitude of the response may be modified by several other factors that often work in concert to effect a strong circulatory adjustment. Three interventions can potentiate the chemoreceptor drive during hypoxia: acidosis, catecholamines and systemic hypotension.

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**Figure 3.** Effect on arterial pressure of breathing 10% oxygen in normal subjects (upper tracing) and in patients after carotid body resection (CBR) (lower tracing).4
1) Acidosis and hypercapnia. Pelletier\textsuperscript{18} demonstrated that the increase in systemic arterial pressure during carotid hypoxia, which is a reflection of the magnitude of the chemoreceptor reflex, is augmented in the presence of hypercarbia and alkalosis (fig. 6).

2) Catecholamines. Norepinephrine produces hyperventilation in normal humans. We have observed that the response to norepinephrine is significantly greater when the subjects are hypoxic than when they are normoxic.\textsuperscript{19} When subjects breathe 100\% oxygen, which suppresses the chemoreceptor drive, the response to norepinephrine is reduced. The response to norepinephrine is blocked by propranolol even in the presence of hypoxia. Thus, it appears that stimulation of 3-adrenergic receptors may augment the chemoreceptor response to hypoxia. One might postulate that norepinephrine, which is present in the glomus cells of the carotid body, may be released by hypoxia to sensitize the afferent nerve terminals of the chemoreceptors.

3) Hypotension. Recent studies indicate that a decrease in systemic arterial pressure augments the chemoreceptor reflex. This interaction between arterial baroreceptor input and chemoreceptor input is important because, in the intact animal and in patients, the two reflexes are often activated simultaneously. Patients who are hypoxic may also be hypotensive or hypovolemic or subjected to other kinds of stress. Evaluation of effects of multiple afferent impulses is important in understanding the circulatory adjustment that takes place in the intact organism.

This interaction of reflexes is shown in figure 7. The results of several experiments in our laboratory indicate that a rise in arterial pressure (with an increase in baroreceptor activity) suppresses the chemorecep-

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure4.png}
\caption{Stimulation of carotid chemoreceptors with nicotine produces reflex coronary vasodilatation.\textsuperscript{a}}
\end{figure}

\begin{figure}[h]
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\includegraphics[width=\textwidth]{figure5.png}
\caption{Vascular response to hypoxemia depends on reflex effects of chemoreceptor stimulation (top) and local dilator effect of hypoxia (below). The values for reflex effects are responses to maximal chemoreceptor stimulation during normotension in anesthetized, ventilated dogs; the values for local effects are responses at an arterial $P_{o_2}$ of 30 mm Hg. Values are estimated from studies by the authors, Daugherty et al.\textsuperscript{1} and Mancia.\textsuperscript{14}}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure6.png}
\caption{The pressor response to stimulation of carotid chemoreceptors with hypoxic blood is augmented by hypercapnic acidosis and attenuated by hypocapnic alkalosis. Adapted from Pelletier.\textsuperscript{16}}
\end{figure}
Thus, the chemoreceptor reflex response to hypoxemia appears to be significantly potentiated by three factors that often occur in association with hypoxemia in patients: acidosis, an increase in circulating catecholamines and systemic hypotension. These factors apparently act in concert to potentiate the chemoreceptor reflex response and effect a significant circulatory adjustment.

Depression of the Chemoreceptor Response

Recent observations indicate that dopamine, another catecholamine that is present in glomus type I cells of the carotid body, may suppress chemoreceptor drive. Based on several experiments in animals which suggest that dopamine may have an inhibitory effect on chemoreceptors, we considered the possibility that dopamine may suppress the hyperventilatory response to hypoxia in man and that this suppression may be mediated by an effect on chemoreceptors. The results (fig. 9) indicate that there was significant suppression of the hyperventilatory response to hypoxia by intravenous infusion of dopamine. When the subjects breathed room air, ventilation was decreased by dopamine, but the reduction was not profound because the magnitude of chemoreceptor drive was low. Finally, when the chemoreceptor stimulus was suppressed by allowing the subject to breathe 100% oxygen, dopamine had no effect. These results are compatible with the hypothesis that when hypoxia activates afferent nerves in the carotid body and simultaneously releases dopamine from type I cells, dopamine may then suppress the magnitude of afferent chemoreceptor discharge at the nerve terminal. The response to dopamine during hypoxia has an important clinical implication: It alerts us to the possibility that dopamine may decrease ventilation when it is used in clinical shock states.

![Diagram of chemoreceptor and baroreceptor reflexes](image)
Central Pressor Effect of Hypoxia

Two points should be made concerning the central pressor effect of hypoxia. First, hypoxia by itself must be extremely severe before any central pressor effect is apparent. Second, if hypoxia is associated with decreased cerebral perfusion pressure, such as during hypotension, the pressor effect will be manifested during less severe hypoxia.

Several years ago Sagawa et al.\textsuperscript{24} perfused the brain at progressively lower arterial pressures. It was not until pressure fell below 40 mm Hg that systemic arterial pressure, which is a reflection of a centrally mediated reflex, rose (fig. 11). More recently, Hainsworth and Karim repeated these experiments and confirmed the finding.\textsuperscript{25} These investigators also demonstrated that the reflex rise in arterial pressure in response to cerebral hypotension is markedly augmented when the blood perfusing the brain is hypoxic (Po$_2$ = 46 mm Hg). Thus, during hypoxia, the pressor response to cerebral hypotension is markedly augmented: Significant increases in arterial pressure are noted at a perfusion pressure of 80 mm Hg (fig. 12).

What causes potentiation of the central pressor response during hypoxia? During normoxia, cerebral vessels dilate during hypotension to maintain relatively normal cerebral blood flow and brain ischemia is minimized. During hypoxia, however, cerebral vessels are dilated and may lose their capacity to autoregulate and dilate further during hypotension. Thus, when hypotension is superimposed on hypoxia, the fall in pressure may reduce cerebral blood flow and ischemia may be sensed by vasomotor centers in the medulla, leading to a rise in systemic pressure. Recent studies\textsuperscript{26} indicate that a lesion in the reticular formation of the medulla prevents the pressor and vasoconstrictor responses to cerebral hypotension, suggesting that this region may be responsible for the central pressor effects of ischemia.

The central pressor response during hypoxia should be contrasted with the role of central chemoreceptors. Mitchell et al.\textsuperscript{27} have described chemosensitive areas on the ventrolateral surface of the medulla. These central chemoreceptors appear to be responsive to changes in Pco$_2$ and pH, but are not stimulated by hypoxia. Central nervous system hypoxia, in fact, appears to be depressant rather than stimulatory.\textsuperscript{28, 29} Ventilatory effects of central chemoreceptors appear to be more marked than cardiovascular effects. Thus,
the central pressor response during hypoxia, with a marked cardiovascular response, should not be confused with the response to stimulation of central chemoreceptors.

Modification of Reflexes

In the preceding three sections we examined selective effects of hypoxia at the level of blood vessels, on chemoreceptors and on the central nervous system. Now we will consider the integrated effect of hypoxia in intact animals and man; specifically, the subject who is exposed to hypoxia and then to a hypotensive stress produced by acute hypovolemia. The message will be that, during hypoxia, arterial pressure can be maintained if the subject is not exposed to additional stress. But when a hypotensive stress occurs during hypoxia, compensatory mechanisms may not be sufficient to prevent a fall in arterial pressure.

To examine effects of a hypotensive stress, we produced simulated hemorrhage in normal subjects and in patients by pooling blood in the lower extremities. A suction box was applied to the lower part of the body and, by creating negative pressure inside the box using a commercial vacuum cleaner, one can pool from 600–800 ml of blood in less than a minute. This sudden, reversible "hemorrhage" produces a marked fall in central venous pressure, a decrease in forearm blood flow (measured with a strain gauge plethysmograph) and tachycardia. Arterial pressure is maintained despite the sudden dramatic hemorrhage by reflex vasoconstriction and tachycardia.

Several years ago we demonstrated in normal subjects that arterial pressure fell during lower body negative pressure when the subjects breathed a gas mixture that contained 10% oxygen.30 Hypoxia attenuated reflex vasoconstrictor responses in forearm vessels and interfered with circulatory adjustments to an acute hypotensive stress.

In another series of experiments we tested the hypothesis that patients with chronic hypoxia from lung disease adapt to the hypoxic state so that they can withstand hypotensive stresses despite hypoxemia.31 Patients with chronic lung disease, however, became hypotensive during lower body negative pressure and had minimal reflex vasoconstriction of forearm vessels (fig. 13). Of great interest was the finding that, when the patients were given oxygen to restore their arterial Po2, the vasoconstrictor response was restored and the patients' capacity to maintain arterial pressure in the face of lower body negative pressure was restored. Figure 13 shows that when a patient's Po2 was 45 mm Hg, arterial pressure fell without vasoconstriction in forearm vessels during lower-body negative pressure. In contrast, within 10 minutes after starting the administration of 100% oxygen (which increased arterial Po2 to 240 mm Hg), there was restoration of the vasoconstrictor response to lower body negative pressure and arterial pressure was maintained during the episode of simulated hemorrhage.

Thus, chronic hypoxia continues to interfere with circulatory adjustments to hypotensive stresses without effective adaptation. However, there does not seem to be a permanent defect in autonomic transmission during chronic hypoxia, because restoration of arterial oxygen saturation acutely restores autonomic reflexes.

Summary

We have examined circulatory effects of hypoxia and described four components of the response: 1) Local vascular effects of hypoxia are inhibitory. Vasodilatation occurs during marked hypoxia, with a preferential effect on vessels supplying organs that are very active metabolically. This beneficial adjustment redistributes flow to the organs with a greater dependence on oxygen for their metabolism. 2) The chemoreceptor reflex tends to maintain arterial pressure and to produce a favorable
redistribution of blood flow. A vasoconstrictor response occurs in skeletal muscle and the bowel, thereby maintaining arterial pressure. There is little response in cerebral vessels and vasodilation occurs in coronary vessels so that blood flow is maintained in these organs.

The chemoreceptor response to hypoxia is potentiated significantly by factors that are often associated with hypoxia, including acidosis, circulating norepinephrine and systemic hypotension. These three factors act in concert with hypoxia to augment the chemoreceptor reflex drive and produce a more efficient adjustment. Chemoreceptor activity in response to hypoxia may also be suppressed: Dopamine, which is present in glomus type I cells of the carotid body, may be released by hypoxia to produce a negative feedback regulation of the activity of chemoreceptor afferent nerves.

3) The central pressor effect of hypoxia is more apparent in the presence of cerebral hypotension. This response contributes to restoration of arterial pressure to maintain cerebral perfusion.

4) Systemic hypoxia in the presence of hypotensive stress prevents autonomic circulatory adjustments. This autonomic failure occurs in patients with chronic hypoxia, but it can be reversed abruptly by correcting arterial oxygen desaturation.

In conclusion, we will return to Dickinson Richards and recall a conviction and a virtue that he had. The conviction was that scientific pursuit and compassion for the sick are not and should not be mutually exclusive in a physician or a clinical scientist. A great virtue of this man was his modesty. Andre Cournand wrote, "Modesty and greatness seldom harmonize in an individual. D. W. Richards was one of those in whom these qualities balanced one another." 32

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