Effects of Hypoxia on the Closing Pressure of the Canine Systemic Arterial Circulation

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SUMMARY We studied the relationships among closing pressure (Pc) and indices of systemic arterial resistance (Ra) and compliance (Ca) during hypoxic hypoxia (HH) and carbon monoxide hypoxia (COH) in anesthetized dogs with cardiac bypass and constant ventilation. Closing pressure was measured as the lowest level to which arterial pressure (Pa) fell after inflow to the arterial bed was reduced suddenly to zero. Since the fall of Pa to Pc could be well-described as a single exponential function of time and since Pc was always greater than outflow (venous) pressure, Ra and Ca were determined by applying a "vascular waterfall" model to the arterial bed. During HH, Pc increased while Ra and Ca decreased. During COH, Pc and Ra decreased, but Ca did not change. The Pc results indicate that during HH, but not COH, a large portion of the systemic arterial bed experienced a marked increase in vasomotor tone, a qualitative difference that would have been missed if Pc had not been measured. The relationships among Pc, Ra, and Ca during hypoxia suggest these indices may have been determined largely by different portions of the arterial bed in which tone changed independently.


WHEN blood flow through a circulatory bed is stopped, inflow pressure frequently falls to a level substantially higher than outflow pressure (Nichol et al., 1951; Girling, 1952; Doyle, 1953; Alexander, 1954; Downey and Kirk, 1975; Bellamy, 1978; Lanari et al., 1956; Burton and Yamada, 1951; Yamada, 1954; Ehrlich et al., 1980). Burton (1951) proposed that this phenomenon could be explained by vascular closure and thus called the level to which inflow pressure fell the "critical closing pressure (Pc)." Since Pc increased after interventions designed to increase vasomotor tone (Burton and Yamada, 1951; Nichol et al., 1951; Bellamy, 1978; Sherman et al., 1980; Girling, 1980; Doyle, 1953; Burton and Stinson, 1960), Burton (1951) recommended that Pc be used as an index of vasomotor tone.

More often, however, vascular resistance, the ratio of driving pressure to flow, is used as an index of vasomotor tone; for example, an increase in resistance commonly is thought to reflect an increase in tone. This conclusion assumes, however, that an increase in tone causes a decrease in vascular caliber. This assumption may not always be valid (Permutt and Riley, 1963).

In a previous study in anesthetized dogs with constant ventilation (Sylvestor et al., 1979), we found that both hypoxic hypoxia (HH) and carbon monoxide hypoxia (COH) decreased total peripheral resistance (TPR), calculated as the difference between mean arterial and right atrial pressure divided by cardiac output. The purpose of the present study was to determine the effects of HH and COH on the critical closing pressure of the systemic arterial bed and to relate these effects to changes in indices of arterial resistance and compliance.

Methods

We studied 18 adult mongrel dogs weighing 18.2-23.6 kg. After premedication with ketamine (10 mg/kg, im), each animal was anesthetized with chloralose (60 mg/kg, iv), intubated and ventilated at a rate and tidal volume sufficient to maintain arterial CO2 tension between 30 and 40 mm Hg. Once this level of ventilation was established, it was not altered during the experiments. After anticoagulation with heparin (10,000 U, iv), both femoral arteries were cannulated. A midternal thoracotomy then was performed, and both atria and the pulmonary artery were cannulated. These canulas were attached to an extracorporeal perfusion system primed with blood from a donor animal (Fig. 1). Blood entering the right atrium was pumped with a roller pump (Sarns model 3500) through a heat exchanger (Sarns model 6030) and filter to the pulmonary artery. Blood entering the left atrium was pumped with a second roller pump through a heat exchanger to the femoral arteries. Starling resistors, constructed of thin-walled latex ("Penrose") tubing stretched longitudininally between stainless steel tubing mounts, were positioned between the atria and the pumps. When pump speed was increased sufficiently, the latex tubing collapsed, permitting atrial pressures to be controlled by raising or lowering the Starling resisters relative to the level of the atria. By this means, atrial pressures were maintained slightly less than zero except during certain experimental maneuvers noted below. Thus, all blood returning to the atria

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was immediately removed by the extracorporeal perfusion system and the heart was completely "bypassed." In this system, neither arterial pressure nor flow is controlled. Rather, these variables vary in a manner determined entirely by the peripheral circulation. To prevent shifts of blood into or out of the heart from spuriously affecting our results, obstructing ligatures were placed around the aortic root and around the heart at the level of the atrioventricular valves. Blood temperature was maintained at 38°C by the heat exchangers. Since the animals were open-chested, an end-expiratory pressure of 5 cm H₂O was applied to the lungs with an underwater tube attached to the respirator.

 Appropriately positioned catheters connected to strain gauges (Statham P23) enabled measurement of pressures in the right atrium (Pra) and abdominal aorta (Pa). The zero reference level for these pressures was determined at the end of each experiment by placing the tip of each fluid-filled catheter, while still connected to its transducer, at the level of the right atrioventricular valve within the chest. Blood flow (Q) was measured with an electromagnetic flow probe (Biotronex model 610) in the right atrial outflow tubing. These variables were recorded continuously with an oscillograph (Electronics for Medicine, Inc.).

 Blood samples from the aorta were analyzed for pH and for partial pressures of oxygen (PaO₂) and carbon dioxide (PaCO₂) using standard electrode techniques. Hemoglobin concentration and saturation with oxygen and carbon monoxide were measured spectrophotometrically (Instrumentation Laboratories CO-oximeter), permitting calculation of arterial oxygen content.

 Immediately after bypass had been established, blood (0.5-1.0 liter) and NaHCO₃ (50-150 mEq) usually were administered until mean Pa was greater than 75 mm Hg; Q, greater than 1.2 liters/min, and arterial pH, greater than 7.30. Experiments were not begun until these variables were stable without support for at least 30 minutes. Nine dogs were in the HH group. HH was arbitrarily classified as moderate (inspired O₂ concentration = 12%) and severe (inspired O₂ concentration = 8%). After a 20-minute normoxic control period, each dog was exposed to moderate HH for 20-30 minutes and then to severe HH for 20-30 minutes. At the end of each period, blood samples were drawn, mean Pa and Q were determined, and a "stop-flow" maneuver was performed. In this maneuver, Q was reduced immediately to zero by simultaneously stopping the pumps and clamping the perfusion tubing as shown in Figure 1. Pa and Pra then were recorded for approximately 20 seconds before the clamps were removed and the pumps started again. This procedure enabled measurement of Pc as the lowest pressure to which Pa fell during the time that Q = 0. The response time of the recording equipment always was sufficient to prevent artifactual damping of the pressure signals.

 The other nine dogs were subjected to COH and studied in a similar manner. During hypoxic exposures, the inspired CO concentration was maintained at approximately 10,000 ppm until arterial O₂ content reached the desired value (10 vol % for moderate COH and 6 vol % for severe COH), after which it was reduced to approximately 300 ppm in order to maintain the O₂ content decrement for the remainder of the exposure period.

 To calculate indices of arterial resistance and compliance, we used the "vascular waterfall" model of Permutt and Riley (1963). This model describes the hemodynamics of a collapsible vessel with tone when closing pressure is less than inflow pressure, but greater than outflow pressure. Under these conditions, the driving pressure for flow is expressed by the difference between inflow and closing pressures rather than by the difference between inflow and outflow pressures. The rationale and evidence for this have been presented in detail by Permutt and Riley (1963) and will not be discussed here. It should be emphasized that in developing our version of this model, our intent was not to represent the systemic arterial bed literally, but rather to produce a simple analog of the bed which would allow assessment of some of its mechanical properties at the level of first-approximation. The limitations of this approach are discussed in detail below (See Discussion).
Our model is shown in Figure 2A. The arterial bed was assumed to be composed of a central compliant region (e.g., the aorta and large arteries) which discharged the blood it received from the heart through a parallel array of peripheral resistance vessels (e.g., the small arteries and arterioles). The pressure within the compliant region was \( \text{Pa} \). The pressure outside the vascular wall was assumed to be zero. Each resistance vessel had a closing pressure (\( \text{Pc} \)), which was greater than outflow pressure (\( \text{Pv} \)). If all closing pressures were the same, the parallel vessels can be represented by a single resistance vessel, as shown in Figure 2B. Since \( \text{Pc} \) exceeded \( \text{Pv} \), the driving pressure for outflow is \( \text{Pa} - \text{Pc} \), rather than \( \text{Pa} - \text{Pv} \), and resistance (\( \text{Ra} \)) can be defined by:

\[
\text{Ra} = \frac{\text{dPa}}{\text{dQ}}. \tag{1}
\]

Arterial compliance (\( \text{Ca} \)) can be defined by:

\[
\text{Ca} = \frac{\text{dVa}}{\text{dPa}} \tag{2}
\]

where \( \text{Va} \) is the volume of blood distending the compliant region. If inflow to the compliant region were immediately reduced to zero, outflow would continue until \( \text{Pa} = \text{Pc} \). Under conditions in which the relationships between \( \text{Pa} - \text{Pc} \) and \( \text{Q} \) and between \( \text{Pa} \) and \( \text{Va} \) are linear, the time course of \( \text{Pa} \) during outflow can be expressed by:

\[
(\text{Pa} - \text{Pc})t = (\text{Pa} - \text{Pc})0 e^{-t/\text{RaCa}} \tag{3}
\]

where \( (\text{Pa} - \text{Pc})0 \) is the gradient for outflow at time zero, \( t \) is the time after cessation of inflow, and \( \text{RaCa} \) is the time constant \( (\tau) \) of a single exponential process. In this case,

\[
\text{Ra} = \frac{(\text{Pa} - \text{Pc})}{\text{Q}}. \tag{4}
\]

\[ \text{Ca} = \frac{\tau}{\text{Ra}}. \tag{5} \]

As will be seen, in our experiments an arterial closing pressure was always present and the time course of \( (\text{Pa} - \text{Pc}) \) after an abrupt cessation of blood flow closely approximated a single exponential function. Thus, equations (4) and (5) were used to estimate systemic arterial resistance and compliance.

To accomplish this, the data from each stop-flow maneuver were transferred from the original paper record to magnetic tape with a coordinate digitizer (Gerber Scientific Instrument Co.). This allowed evaluation of \( \text{Pa} \) at 0.1- to 0.2-second intervals. The first 0.5 second of the record usually had to be excluded from analysis because of noise in the \( \text{Pa} \) signal. Digitization was stopped when \( \text{Pa} \) was within 2 mm Hg of \( \text{Pc} \). On this basis, an average of 57 data points (range 19-98) were used to fit each exponential (Eq. 3). Fitting was accomplished by an iterative, least-squares procedure that was considered complete when the improvement in the error mean square from an additional iteration was less than 0.00001 mm Hg\(^2\) per degree of freedom. The fitted equation provided the arterial time constant \( (\tau) \).

Our index of arterial resistance \( (\text{Ra}) \) was calculated as \( (\text{Pa} - \text{Pc})/\text{Q} \) (Eq. 4) and our index of arterial compliance \( (\text{Ca}) \) was calculated by dividing \( \tau \) by \( \text{Ra} \) (Eq. 5). In addition, total peripheral resistance \( (\text{TPR}) \) was calculated as the ratio of mean \( \text{Pa} \) to \( \text{Q} \).

Analysis of variance was used for statistical comparisons. The ratios, \( \text{TPR} \), \( \text{Ra} \), and \( \text{Ca} \), were converted to their arctangents before the analysis was performed. Differences were considered significant when \( P \) was less than 0.05. Values presented in the text are mean ± 1 SE.

**Results**

As shown in Figure 3, HH and COH caused equivalent decrements in \( \text{CaO}_2 \). Arterial \( \text{O}_2 \) tension, as expected, fell during HH, but remained above 100 mm Hg during COH. Arterial \( \text{CO}_2 \) tension did not change. Both types of hypoxia caused small, equal decreases in pH.

The effects of hypoxia on mean \( \text{Pa} \), \( \text{Q} \), TPR, and \( \text{Pc} \) are shown in Figure 4. Mean arterial pressure tended to increase during HH, but decreased during COH. Both types of hypoxia increased total blood flow. Although the increase tended to be slightly greater during HH, the difference was not significant. TPR fell during both HH and COH; however, the decrease was significantly greater during COH. The effects of HH and COH on closing pressure were opposite: during HH, \( \text{Pc} \) increased, but during COH it decreased.

An example of the time course of \( \text{Pa} \) and \( \text{Pc} \) during the "stop-flow" maneuver is shown in Figure
Figure 3. Arterial oxygen content (CaO₂), O₂ tension (Pao₂), CO₂ tension (Paco₂), and pH during hypoxic hypoxia (HH) and CO hypoxia (COH). Open symbols indicate a significant change from control values. Asterisks indicate that the effect of HH differed significantly from the effect of COH.

5. Pa achieved its lowest level (Pc) in about 5 seconds. The rapid rise in Pra was caused by filling of the previously collapsed atrium as blood continued to flow to the heart from the most compliant regions of the peripheral circulation (the small veins) for a short period of time after the pumps were stopped. Thus, Pra rose to the level of peripheral venous pressure. In every animal, the level to which Pra rose was less than Pc. The gradual rise in Pa that occurred after the attainment of Pc and the slow rise in Pra were probably due to reflex effects.

Figure 4. Mean arterial pressure (Pa), blood flow (Q), total peripheral resistance (TPR), and systemic arterial closing pressure (Pc) during hypoxic hypoxia (HH) and CO hypoxia (COH). Open symbols indicate a significant change from control values. Asterisks indicate that the effect of HH differed significantly from the effect of COH.

Figure 5. Time course of arterial (Pa) and right atrial (Pra) pressures after blood flow was stopped at time zero.
The fall of Pa to Pc during the "stop-flow" maneuver was well-described by Equation 3. During normoxia, the standard deviation of the actual data from the line obtained by fitting Equation 3 to the data averaged 1.53 ± 0.24 and 1.26 ± .35 mm Hg for the HH and COH groups, respectively. During moderate hypoxia, these values were 0.99 ± 0.14 and 0.88 ± 0.21 mm Hg, whereas during severe hypoxia they were 0.96 ± 0.14 and 0.73 ± 0.16 mm Hg. Figure 6 shows an example of a fit with an average standard deviation.

The effects of hypoxia on \( \tau_a \), Ra, and Ca are shown in Figure 7. HH and COH caused equivalent decreases in \( \tau_a \). Ra, however, decreased more during COH than during HH. Ca did not change during COH, but fell during HH.

**Discussion**

The changes in mean Pa, Q, and TPR observed during HH and COH (Fig. 4) were similar to those observed previously by us (Sylvester et al., 1979) and by other investigators (Murray and Young, 1963; Daly and Scott, 1964; Krasney, 1971) in open-chest dogs with constant ventilation, but without cardiac bypass. The difference between the effects of HH and COH on these variables probably was caused by carotid chemoreceptor stimulation, which occurred during HH, but not COH (Sylvester et al., 1979; Korner et al., 1967). The purpose of the present study was to determine whether the effects of HH and COH on arterial closing pressure also were different and, if so, to relate these differences to changes in the mechanical properties of the arterial circulation.

During normoxia, Pc averaged 25.1 ± 1.3 mm Hg. Previous measurements of closing pressure in the vascular beds of the rabbit's ear and hindlimb (Nichol et al., 1951; Girling, 1952), the rat's hindlimb (Doyle, 1953), the dog's intestinal (Alexander, 1954), coronary (Downey and Kirk, 1975; Bellamy, 1978; Sherman et al., 1980), and femoral beds (Ehrlich et al., 1980), and the human forearm and finger (Lanari et al., 1956; Burton and Yamada, 1951; Yamada, 1954) ranged from 10 to 74 mm Hg, the higher values obtained during increased vasoconstrictor activity. The closing pressure of the entire systemic
The arterial bed has been estimated previously by linearly extrapolating systemic pressure-flow curves to zero flow (Wetterer and Pieper, 1955; Ehrlich et al., 1975; Sagawa and Eisner, 1975; Jackman and Green, 1977). Values obtained by this method ranged from 25 to 70 mm Hg. The differences among these values probably are due to physiological differences among the experimental preparations.

As shown in Figure 4, arterial closing pressure increased during HH and decreased during COH, whereas TPR fell during both types of hypoxia. Interpreted in the standard manner, the TPR results suggest that both HH and COH caused a decrease in systemic vasomotor tone. The Pc results, however, indicate that HH caused vasomotor tone to increase, whereas COH caused it to decrease. It was possible that this apparent inconsistency originated in the definition of TPR. Because it is calculated as (Pa-Pra)/Q, TPR will measure changes in the systemic arterial pressure-flow relationship with absolute accuracy only if the relationship is linear and intercepts the pressure axis at Pra. In our experiments, however, the pressure-axis intercept (Pc) always was greater than Pra. We therefore wondered if a more consistent relationship between closing pressure and resistance would be obtained if the latter were assessed according to a “vascular waterfall” model, which assumes the back pressure to flow to be Pc instead of Pra. Using this approach, Bellamy (1978), for example, found that in general coronary resistance varied directly with coronary closing pressure.

The changes in Ra, calculated as (Pa-Pc)/Q are shown in Figure 7. Like TPR, Ra decreased during both HH and COH. Therefore, the vascular waterfall model did not resolve the apparent inconsistency between the observed changes in closing pressure and resistance. Rather, the data suggested that the intercept (Pc) and slope (estimated by Ra) of the systemic arterial pressure-flow relationship changed independently.

We next evaluated the relationship between closing pressure and Ca, our index of the capacitive properties of the systemic arterial bed. That this evaluation could be performed was first suggested by the observation that the fall of Pa to Pc during the stop-flow maneuver could be surprisingly well described as a single exponential function of time. The standard deviation of the actual Pa values from the line obtained by fitting Equation 3 to the data averaged 1.064 ± 0.21 mm Hg, a value no larger than that expected on the basis of noise in the pressure signal and the accuracy with which the original record could be read by inspection. This degree of “goodness of fit” was surprising for two reasons. In the first place, a single exponential decay of Pa to Pc implied either that actual arterial resistance and compliance were constant during the decay or that they changed in an exactly reciprocal manner so as to preserve a constant Q. The latter seemed unlikely. On the other hand, the pressure-flow relationship of the arterial bed can be nearly linear (Sagawa and Eisner, 1975; Jackman and Green, 1977), particularly if the baroreflexes are eliminated (Levy et al., 1954). Although these reflexes were present in our animals, as evidenced by a marked overshoot in Pa upon reinstitution of blood flow after the “stop-flow” maneuver (Fig. 6), they probably had no chance to act in the 5 seconds or so it took Pa to fall to Pc (Ito, 1969; Kornier, 1971; Wang and Borison, 1947). In addition, although the pressure-volume relationships of the aorta and larger muscular arteries are clearly linear over a wide range of pressure, they can approach linearity over a limited range of pressure, such as that encountered during the “stop-flow” maneuver (Halllock and Benson, 1937; Alexander, 1954; Bader, 1963; Dobrin and Rovick, 1969; Berry et al., 1975; Cox, 1976; Wiggers and Wegriz, 1938). Thus, our experimental conditions may have fortuitously provided sufficient linearity of the pressure-flow and pressure-volume relationships to allow a good fit of Equation 3 to the data. In the second place, we were surprised because the model assumed that all closing pressures in the circuit were the same. Possibly, under the stress of hypoxia and cardiac bypass, the perfused bed consisted of vessels that were more homogeneous in this respect than they would have been otherwise. In any case, these considerations underscore the need to emphasize that the model shown in Figure 2 should not be viewed as a literal representation of the systemic arterial bed. Rather, it is a simple functional analog which, under the conditions of our experiments, allowed a rough estimation of the mechanical properties of the more complex system it represented.

During normoxia, estimated arterial compliance averaged 0.92 ± 0.24 ml/mm Hg, a value which compares favorably with measurements obtained in dogs by other methods (Shoukas and Sagawa, 1973). This comparability supports the use of Ca as an index of arterial compliance. As shown in Figure 7, Ca decreased during HH, but did not change during COH. Thus, neither Ra nor Ca bore a consistent relationship to Pc. Moreover, the relationship between Ra and Ca was also inconsistent.

How can these results be explained? One possibility is that Pc, Ra, and Ca were determined largely by different portions of the systemic arterial bed, whose tone changed independently. For example, Pc may have been determined mainly by the distal elements of the bed, such as the precapillary arterioles and sphincters; Ca, by the proximal elements, such as the aorta and large muscular arteries; and Ra, by the intermediate elements. During both HH and COH, vascular smooth muscle in all portions of the bed would be subjected to the relaxant effects of local hypoxia. During COH, hemodynamic changes can be viewed as resulting primarily from
these local effects (Sylvestre et al., 1979). Thus, the observed decreases in Pc and Ra may reflect vasodilation in the distal and intermediate portions of the arterial bed, respectively. During HH, the bed was subjected not only to the vasodilator influence of local hypoxia, but also to the vasoconstrictor influence of chemoreflex activation. In the microcirculation, Baez et al. (1977) has found that the smaller the vessel, the greater its vasoconstrictor response to reflexes generated by central nervous system stimulation. Thus, the increased Pc caused by HH may have resulted from a marked vasoconstrictor influence of the chemoreflex on the distal elements of the bed. In the intermediate portion of the bed, the influence of this reflex may not have been strong enough to overcome the vasodilator effects of local hypoxia. Thus, Ra fell, but less than it did during COH.

The changes in Ca are more difficult to explain. The effects of alterations in smooth muscle tone on the shape and intercept of the pressure-volume curve of the aorta have been inconsistent (Wiggers and Wegría, 1938; Alexander, 1954; Bader, 1963; Berry et al., 1975). One-half of the total arterial compliance, however, is thought to reside outside the aorta (Bader, 1963). In large muscular arteries, which undoubtedly contribute substantially to this extra-aortic compliance, increases in vasomotor tone have consistently shifted pressure-volume or pressure-diameter curves toward the pressure axis (Peterson et al., 1960; Bader, 1963; Dobrin and Rovick, 1969; Cox, 1976). Thus, the decrease in Ca observed during HH may have been caused by the vasoconstrictor effects of the chemoreflex on larger muscular arteries. During COH, Ca did not change. Perhaps tone in the larger muscular arteries during normoxia was already minimal and could not be decreased further by local hypoxia.

Whatever the explanation, our results demonstrate a major qualitative difference between the effects of HH and COH on the systemic arterial bed. During HH, but not COH, a large portion of this bed experienced a marked increase in vasomotor tone. This difference would have been missed if closing pressure had not been measured. In addition, although both types of hypoxia caused the bed to empty more rapidly, our data suggest that during COH this was achieved mainly by means of a decrease in resistance, whereas during HH a decrease in compliance also contributed. Finally, the relationships among Pc, Ra, and Ca suggest that during hypoxia these indices may have been determined largely by different portions of the systemic arterial bed, whose tone changed independently.

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