Influence of arterial hypoxia on cardiac and coronary dynamics in the conscious sinoaortic-denervated dog

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Krasney, John A., and Raymond C. Koehler. Influence of arterial hypoxia on cardiac and coronary dynamics in the conscious sinoaortic-denervated dog. J. Appl. Physiol.: Respir. Environ. Exercise Physiol. 43(6): 1012-1018, 1977. —Arterial hypoxia was produced in 10 conscious, chronically instrumented, tracheostomized dogs by allowing them to breathe 7.5% O2 in N2 for 10 min. Hypoxia (Pao2 = 28 ± 0.7 (SE) Torr) caused significant increases in coronary blood flow (+196%), left ventricular dP/dt max (+60%), aortic blood flow (+48%), heart rate (+50%), and left ventricular systolic (+12%) and aortic (+10%) pressures. Left ventricular end-diastolic pressure and stroke volume were unchanged, while systemic (−30%) and coronary diastolic (−66%) vascular resistances declined significantly. When equivalent levels of arterial hypoxia were produced in four of these dogs after chronic sinoaortic denervation, the coronary, cardiac, and systemic hemodynamic responses were not significantly different, with the exception that the small arterial pressure response was abolished. Thus the peripheral chemoreflexes are not essential for the normal coronary vasodilator and cardiac adjustments to occur during hypoxia in the conscious dog. The data support the hypothesis that a large part of the cardiac adjustments to hypoxia is initiated outside the sinoaortic reflexogenic zones, probably within the central nervous system.

THE CARDIOVASCULAR RESPONSE PATTERN OF THE CONSCIOUS DOG TO ARTERIAL HYPOXIA IS RELATIVELY WELL DEFINED. In general there is an increase in heart rate and cardiac output accompanied by a slight increase of arterial pressure while systemic vascular resistance declines (19, 23). This pattern of cardiovascular adjustments is considered to represent the composite interaction of several neurogenic mechanisms that have been shown to contribute to circulatory support during hypoxia. These mechanisms include the peripheral chemoreceptors, a lung inflation reflex, and a direct influence of hypoxia on the central nervous system (CNS) (6, 7, 10). Experiments performed on anesthetized animals have led to the conclusion that the peripheral chemoreceptors provide an important reflex contribution to the peripheral vasomotor adjustments that occur during hypoxia. For example, the usual hypoxic pressor response observed in the anesthetized dog is converted to a striking depressor response when hypoxia is produced following denervation of the peripheral chemoreflexes (21). In contrast to the latter observations obtained from anesthetized animals, studies in conscious dogs have led to a somewhat different conclusion as to the role of the peripheral chemoreceptors in circulatory regulation during hypoxia. Previous studies from our laboratory have indicated that the general hemodynamic response to hypoxia is largely unaltered in the conscious dog after chronic peripheral chemoreceptor denervation. Arterial blood pressure was well maintained during either arterial hypoxia or cyanide hypoxia in the conscious chronically chemodenervated dog (22, 23). It has been shown that there is a large neurogenic contribution to the elevation in cardiac output observed during hypoxia since it can be prevented by cardiac denervation or adrenergic blockade (20). Our observations indicate that a major site of initiation of this cardiac response is located outside of the sinoaortic reflexogenic zones, probably within the CNS (23).

Although the peripheral chemoreflexes thus appear to be less important in providing for general hemodynamic support during hypoxia in the conscious dog, the possibility remains that these reflexes might contribute in several specific ways to the cardiac adjustments. In anesthetized animals it has been shown that activation of the aortic body chemoreflex causes an improvement of ventricular contractile performance, as evidenced by an increase in dP/dt max (26). It has also been demonstrated in both anesthetized and conscious dogs that a reflex coronary vasodilation can be evoked by pharmacologic stimulation of the carotid body (29). Finally, it is known that engagement of the peripheral chemoreceptor reflex can lead to neurally mediated venous constriction (1, 4). The latter event, when coupled with a decline in systemic vascular resistance, would tend to promote an increase in ventricular preload (16).

There is little information available concerning the nature of the adjustments in coronary blood flow and ventricular performance which occur during hypoxia in the conscious dog, particularly in the absence of peripheral chemoreflex influences. It might be anticipated that if the aforementioned cardiac, coronary, and systemic chemoreflex effects were playing an important...
role in the response to hypoxia, then the coronary and cardiac adjustments to hypoxia should be significantly altered following denervation of the peripheral chemoreflexes. Hence, the present study was performed to analyze the influence of arterial hypoxia on left ventricular performance and coronary blood flow in awake, trained, chronically instrumented dogs before and after chronic abrogation of the peripheral sinoaortic reflexes.

METHODS

Ten mongrel dogs weighing between 22 and 26 kg were used in this study. Following induction of anesthesia with methoxyflurane a left lateral thoracotomy was performed as previously described (23). Blood flow transducers were placed about the base of the aorta to record aortic flow, and about the left circumflex coronary artery to record circumflex coronary flow. A hydraulic occluder was placed distal to the flow probe on the circumflex artery to obtain mechanical flow zeros (8). A miniature solid-state pressure transducer was implanted in the left ventricle (Konigsberg Instruments, model P-17) via an apical stab wound for high-fidelity recordings of left ventricular pressure. Heparinized saline was administered for 7 days postoperatively. The aortic and left atrial catheters were flushed daily with heparinized saline.

The animals were allowed to recover from the surgery for a period of 14 days. At this time they were reanesthetized with thiopental sodium and a chronic tracheostomy was performed (28). Another 7- to 10-day period was allowed for the tracheostomy to heal. At the time of the initial experiments the dogs were afebrile, had good appetites, and were able to exercise normally.

Prior to experimentation the animals were trained to breathe low oxygen mixtures via auffed endotracheal tube inserted in the tracheostomy and held in position by a soft leather collar. The dogs stood upright in a modified Pavlov sling. All experiments were performed in a sound attenuated environmental room maintained at 18°C to prevent panting.

Arterial hypoxia was produced by allowing the dogs to breathe a 7.5% O2-92.5% N2 gas mixture from a Douglas bag for a period of 10 min (19, 23). Continuous recordings were obtained during control room air breathing, during the period of hypoxia, and during a 5-min recovery period after switching back to room air breathing. Each experiment was performed 3–7 times in the individual dogs with at least a 1-day interval allowed between each hypoxic exposure. A second series of experiments was performed on four of the dogs after they had been allowed to recover for at least 1 wk from sinoaortic denervation. In these experiments arterial oxygen tension (PO2) levels equivalent to those achieved in the intact situation were produced by having the dogs breathe a gas mixture of 12% O2-88% N2 for 10 min. This higher fractional concentration of oxygen in inspired gas (FI02) produced equivalent hypoxia because ventilation did not change appreciably during hypoxia after chemoreceptor denervation (23).

Sinoaortic denervation was performed under thiopentone sodium anesthesia. This procedure consists of stripping both carotid reflexogenic areas of nerves. The aortic depressor nerves are sectioned bilaterally by identifying the vagus nerve as the largest single component of the vago sympathetic trunk and then cutting the remainder of the trunk at the midcervical level (12, 14, 22, 23). Intravenous sodium cyanide (0.2 mg/kg) was used as a test to determine completeness of the peripheral chemoreceptor denervation. The dogs failed to show a ventilatory response and the usual pressor response to cyanide was converted to a depressor response. The pressor response to bilateral carotid occlusion was abolished. Both arterial baroreceptors and chemoreceptors are denervated by this procedure. The dogs which did not meet the above criteria for chemodenervation were excluded from further study. In addition, to determine the adequacy of the aortic arch denervation technic, two additional tracheostomized dogs were studied in the conscious state with their sinoaortic nerves intact, after sinoaortic denervation, and after total midecervical vagotomy. The vagotomy was accomplished by cutting the remainder of the previously partially sectioned vago sympathetic trunk bilaterally under thiopental sodium anesthesia. The dogs were studied 24 h later. It was observed that at equivalent levels of arterial hypoxia neither ventilation (pneumotachograph) nor arterial pH (PHa) and arterial carbon dioxide tension (PACO2) changed after sinoaortic denervation alone or after sinoaortic denervation plus vagotomy. This indicates that when the above criteria for chemodenervation are met, the technic of subtotal vagotomy effectively eliminates aortic body chemoreceptor afferents.

Blood flow was recorded by electromagnetic flowmeter (Biotronex). The flow transducers were calibrated by gravity feed as previously described (23). In recording aortic flow, the flow zero was taken to be that portion of the record immediately preceding the sharp systolic upstroke. Zero circumflex coronary flow was established by mechanical occlusion. Statham pressure transducers were used to record arterial and left atrial pressures with the reference zero taken to be at the level of the tricuspid valve (16). The solid state left ventricular pressure transducer was calibrated using a pressure bottle in vitro and checked by a Statham pressure transducer in vivo. Daily zero drift in the transducer was corrected for by equating the left ventricular end-diastolic pressure to the Z point recorded from the left atrial pressure pulse (3).

Recordings were made using a direct writing oscillograph and the data were additionally stored on FM magnetic tape using a Hewlett-Packard 3960 tape recorder. Mean coronary flow was obtained by electronic low-pass filtering of the pulsatile signal. Stroke volume was obtained by beat-to-beat electronic integration of the aortic flow signal. Heart rate was calculated from a cardiotachometer. Left ventricular end-diastolic pressure was obtained from high-gain recordings of the left ventricular pressure pulse. The first derivative of the left ventricular pressure (dP/dt) was recorded by an electronic differentiator. The frequency response of the
differentiator was 60 Hz and the output was demonstrated to be linear up to 6,000 Torr·s⁻¹. A triangular wave signal with a known slope (rate of change) was substituted for the pressure signal to directly calibrate the left ventricular dP/dt channel.

Systemic and diastolic coronary vascular resistances were calculated according to the formula

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\text{resistance (PRU)} = \frac{\text{mean arterial blood pressure in Torr}}{\text{blood flow in ml/min}}
\]

These PRU values were multiplied by 100 to obtain a convenient unit (Torr·100 ml⁻¹·min⁻¹). To obtain diastolic coronary resistance, a straight line was drawn through the diastolic portion of the pulsatile coronary flow record after systole and before the atrial cove to obtain average flow for that time interval (15). The arterial blood pressure was averaged over the same time interval. Diastolic coronary resistance was calculated assuming atmospheric pressure for the venous pressure.

End-tidal CO₂ levels were continuously monitored by a Beckman LB-2 CO₂ analyzer. Analyses of arterial pH and blood gases were carried out on blood samples drawn from the aortic catheter during room air breathing and during the 8th min of the hypoxia period. Determinations were made using a Radiometer BMS-2 blood microsystem.

The data were tested statistically for significance by means of the Student paired t-test. Probability values less than 0.05 were considered significant. Since several hypoxia runs were obtained in each dog, the data were analyzed by averaging the results of the several runs so that a mean value was obtained for each dog. Hence, in these experiments the n corresponds to the number of dogs. The data presented herein were sampled between 8 and 10 min of hypoxia at a time when the response appeared to be relatively stable.

RESULTS

The effects of arterial hypoxia on arterial pH and blood gases are depicted in Fig. 1. Inhalation of the low oxygen gas mixture led to a decline in arterial oxygen tension (Pao₂) to levels below 30 Torr. This was accompanied by a decline in end-tidal CO₂ of 57.7 ± 2.8 (SE)% and arterial carbon dioxide tension (Paco₂) occurring as a consequence of the hypoxic increase in ventilation. The ventilatory response patterns were similar to those described previously (23). A respiratory alkalosis developed as evidenced by the elevation in pH₄.

Sinoaortic denervation led to an elevation in Paco₂ and a decline in Pao₂ when the animals were breathing room air as reported previously (23) (Fig. 1). During ventilation with 12% O₂, Pao₂ fell to levels similar to those achieved using a lower Fb₂ in the intact animals. As ventilation was essentially unchanged, end-tidal PCO₂, Paco₂, and pH₄ did not change significantly.

The cardiac and systemic circulatory effects of arterial hypoxia produced when the dogs were intact or chemodenervated are summarized in Figs. 2-4. These data were obtained from 28 experimental runs in the 10 intact dogs and from 16 experimental runs in the 4 chemodenervated dogs.

![Fig. 1. Influence of arterial hypoxia on arterial pH and blood gases in conscious dogs before and after sinoaortic denervation. Asterisk indicates variable significantly different from room air breathing, or significantly different from dogs with intact sinoaortic reflexes. C = control room air breathing; H = hypoxia; brackets indicate ±1 SE.](http://jap.physiology.org/)

![Fig. 2. Effect of arterial hypoxia on systemic hemodynamics in conscious dogs. C = control room air breathing; H = hypoxia; brackets indicate ±1 SE.](http://jap.physiology.org/)
HYPOXIA AND CORONARY BLOOD FLOW

The left ventricular end-diastolic pressure (LVEDP) did not change in significant fashion in either of the two experimental circumstances (Fig. 3). The maximum rate of rise of left ventricular pressure (LV dp/dt max) rose progressively during the period of hypoxia to a plateau at about 5 min in the intact and denervated experiments (Fig. 3).

The mean left circumflex coronary blood flow (CCQ) also rose progressively in response to the step reduction in FIO2 in both the intact and chemodenervated experiments. CCQ increased by 196% in the intact dogs and by a similar increment (+266%) in the chemodenervated dogs (Figs. 4 and 5). These CCQ responses were accompanied by equivalent decreases in coronary distal vascular resistance in the intact and chemodenervated experiments (Fig. 4). In general, the time course of the heart rate and LV dp/dt max responses paralleled that of the CCQ response (Fig. 5).

Figure 6 shows an original record depicting the cardiovascular response of one intact conscious dog to breathing 7.5% O2 in N2 for 10 min.

DISCUSSION

This study represents the first analysis of the influence of arterial hypoxia on coronary blood flow and ventricular performance in the conscious sinoaortic-denervated dog. These experiments confirm and extend our previous reports (22, 23), as well as those of other investigators (19), as to the nature of the general hemodynamic adjustments occurring during hypoxia in the awake dog. When the peripheral chemoreflexes were intact, arterial hypoxia produced an increase in cardiac output, heart rate, and arterial pressure, whereas systemic vascular resistance declined. After chronic sinoaortic denervation the pattern of these general hemodynamic adjustments to hypoxia was largely similar. However, as reported previously (23), the modest arterial pressor response was eliminated, and instead arterial pressure was well maintained during hypoxia.

Left circumflex coronary blood flow increased by a factor of twofold during relative steady-state levels of acute hypoxia in the intact, conscious dogs. Similar increases in coronary flow during hypoxia in the con-
Fig. 6. Original record of cardiovascular response of an intact conscious dog to arterial hypoxia.

10% 7.5% O₂

H- Mind

15 Sec.

On 7.5% O₂

Off 7.5% O₂
Hydroxy and coronary blood flow

conscious intact dog have been reported by Wirthlin and Beck (30) and Erickson and Stone (13). The coronary flow increment in our experiments was associated with a 65% decline in diastolic coronary vascular resistance. Diastolic coronary vascular resistance represents a reliable index of the vasomotor status of the coronary arterioles. What is significant, however, is that circumflex coronary flow increased and diastolic coronary resistance fell to similar levels during hypoxia in the conscious dog following chronic chemoreceptor denervation. This observation indicates that the peripheral chemoreflexes are not essential for the normal coronary flow adjustment to hypoxia. It is of interest that these hypoxic circumflex flow increases are of comparable magnitude to those coronary vasodilator responses which have been reported to occur during maximum reactive hyperemia, or moderate muscular exercise in the conscious dog, but less than those observed during spontaneous excitement (24). In muscular exercise the coronary flow per heartbeat (stroke coronary flow) decreases so that the increase in coronary flow in exercise is largely related to the increase in heart rate (18). In contrast, although a tachycardia occurred routinely during hypoxia in the present study, the stroke coronary flow doubled. Thus, during hypoxia the increase in coronary flow is not limited by the heart rate increase, as is the case with exercise.

It seems reasonable to consider that these circumflex coronary flow responses were primarily related to arterial hypoxia and increased myocardial O2 consumption. Case et al. (5) have proposed that arterial Pco2 might play a regulatory role in the coronary circulation. However, the coronary blood flow responses to hypoxia were similar both in the intact animals, where ventilation increased and hypocapnia occurred, and after chemodenervation, where Paco2 did not change.

Left ventricular contractile performance increased during hypoxia in both the conscious intact, and sinoaortic-denervated dogs, as evidenced by increases in LV dp/dt max (2). This response is in accord with earlier reports by Downing et al. (11) based on studies of the cardiac influence of hypoxia using anesthetized, isolated, supported heart preparations. Downing (9) found also that the LV dp/dt max response to hypoxia was similar after acute chemodenervation in anesthetized, supported heart preparations. Erickson and Stone found similar increases in LV dp/dt during hypoxia in conscious intact dogs (13). This LV dp/dt response reflects in large part enhanced myocardial adrenergic activity since it can be attenuated by adrenergic blockade (10). In addition, the increased LV dp/dt max may in part reflect a positive inotropic effect caused by the increase in cardiac frequency. The contribution of this latter factor is probably of minor importance, however, since Higgins et al. (17) found that increasing the frequency of contraction of the normal heart of the conscious dog causes only a slight inotropic effect.

The cardiac output increase during hypoxia is primarily related to the cardiac acceleration, as stroke volume did not change. The lack of change of stroke volume is in accord with the fact that there was no significant change in LVEDP, and hence no significant change in left ventricular preload during hypoxia. Under these conditions of relatively constant ventricular preload and stroke volume, hypoxia produced small but consistent increases in LVSP in both the awake intact and awake chemodenervated situations. The LVSP elevations may be interpreted to be due largely to enhanced ventricular sympathetic activity. These changes in left ventricular function led to an 85 ± 2.5 (SE)% increase in the calculated left ventricular time-tension index (TTI). The TTI is closely correlated with myocardial oxygen consumption (2).

The peripheral chemoreceptors have been demonstrated to be potentially capable of reflexly enhancing ventricular performance and contributing to coronary vasodilation during hypoxia (26, 29). While these reflexes may contribute to the cardiac and coronary responses of the intact animal to hypoxia, it is apparent that these neural mechanisms are not essential for the normal cardiac and coronary adjustments to occur. The coronary vasodilator and enhanced ventricular contractile responses to hypoxia were similar in magnitude in the conscious dog following chronic sinoaortic denervation.

The peripheral chemoreflexes have been shown to cause venous constriction (4). In addition the mean circulatory filling pressure increases during hypoxia (25). These factors, when coupled with the hypoxic decline in systemic vascular resistance, should act to augment venous return and ventricular preload. We found no evidence that this influence is important in left heart dynamics during hypoxia as LVEDP and stroke volume were unchanged. It is possible that such an effect may have been manifest on the right side of the heart. However, if a significant increase in right ventricular preload occurred, it is reasonable to expect that such an effect would be diminished on the left side of the heart as a consequence of the well-known hypoxic pulmonary vasoconstrictor response (27).

In summary, arterial hypoxia causes significant increases in heart rate, cardiac output, circumflex coronary blood flow, left ventricular systolic pressure and dp/dt max, and mean arterial blood pressure in the conscious chronically instrumented dog. Hypoxia produces similar changes in these parameters following chronic denervation of the peripheral chemoreceptors and baroreceptors. These experiments lend further support to the hypothesis that the major site of initiation of the neurogenic cardiovascular adjustments to hypoxia is located outside the sinoaortic reflexogenic zones, probably within the central nervous system (10, 23). This hypothesis which proposes the existence of chemosensitive areas within the CNS that influence the circulation but not respiration is derived by a process of exclusion based on the denervation experiments reported in the present study and the fact that the existence and importance of peripheral chemoreceptors located outside the sinoaortic reflexogenic zones remains to be demonstrated in the dog (23). This notion is reinforced by numerous studies which have demonstrated that hypoxia confined to the CNS elicits a powerful sympathoadrenal response (9, 10). The present results do not permit an analysis of the role of the
peripheral chemoreflexes and the CNS hypoxic mechanism during hypoxia in the intact animal under closed-loop conditions. It is unclear whether this CNS hypoxic mechanism normally plays a role in the intact animal or whether it is a compensatory mechanism activated after abrogation of the peripheral chemoreflexes.

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