Effects of aortic nerve on hemodynamic response to obstructive apnea in sedated pigs

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Chen, Ling, and Steven M. Scharf. Effects of aortic nerve on hemodynamic response to obstructive apnea in sedated pigs. J Appl Physiol 89: 1455–1461, 2000.—In this study we test the hypothesis that aortic nerve traffic is responsible for the pressor response to periodic apneas. In nine intubated, sedated chronically instrumented pigs, periodic obstructive apneas were caused by occlusion of the endotracheal tube for 30 s, followed by spontaneous breathing for 30 s. This was done under control (C) conditions, after section of the aortic nerve (ANS), and after bilateral cervical vagotomy (Vagot). Blood-gas tensions and airway pressure changed similarly under all conditions: PO2 decreased to 50–60 Torr, Pco2 increased to ~55 Torr, and airway pressure decreased by 40–50 mmHg during apnea. With C, mean arterial pressure (MAP) increased from 111 ± 4 mmHg at baseline to 120 ± 5 mmHg at late apnea (P < 0.01). After ANS and Vagot, there was no change in MAP with apneas compared with baseline. Relative to baseline, cardiac output and stroke volume decreased with C but not with ANS or Vagot during apneas. Increased MAP was due to increased systemic vascular resistance. Heart rate behaved similarly with C and ANS, being greater at early interapnea than late apnea. With Vagot, heart rate increased throughout the apnea-interapnea cycle relative to baseline. We conclude that, in sedated pigs, aortic nerve traffic mediates the increase in MAP and systemic vascular resistance observed during periodic apneas. Increase in MAP is responsible for decreased cardiac output and stroke volume. Additional vagal reflexes, most likely parasympathetic afferents, are responsible for interacting with sympathetic excitatory influences in modulating heart rate.

vagus; arterial pressure; cardiac output; heart rate; aortic nerve; obstructive apnea

OBSTRUCTIVE SLEEP APNEA (OSA) is a common clinical condition associated with major acute hemodynamic changes, including elevations in blood pressure as well as changes in heart rate and ventricular function at night. Evidence is accumulating that OSA is a risk factor for arterial hypertension and cardiovascular morbidity (2, 10, 17, 26, 27). The autonomic nervous system is considered as one major factor mediating cardiovascular morbidity in OSA (2, 10). High levels of sympathetic discharge and fluctuating parasympathetic activity appear to be provoked by a combination of stimuli triggered by changes in blood gases, postapneic arousals, and changes in thoracic mechanics from obstructed respiratory efforts (2, 10).

As an important part of the autonomic system, the vagus nerve could play a prominent role in mediating the cardiovascular apneic response through both efferent and afferent mechanisms. Enhanced vagal (parasympathetic) efferent discharge was reported to be responsible for decreased heart rate during the late part of obstructive apneas (12). Vagal afferent fibers carry the sensory signals from a large array of peripheral receptors that influence the activity of the cardiovascular autonomic nerves. These include 1) aortic receptors (chemoreceptor and baroreceptor), located in the aortic arch and carried by the aortic nerve; 2) cardiac baroreceptors, located in the walls of the atria and ventricles, and 3) respiratory mechanoreceptors, located in chest wall and lung (24). Collectively, they provide moment-to-moment information about the pressure in cardiovascular system, the volume in the lungs, as well as the chemical composition of the arterial blood.

A recent study from this laboratory demonstrated that bilateral cervical vagotomy blunted the pressor response to periodic apnea in a sedated porcine model of periodic nonobstructive apneas (23). In that study, it was noted that blunting of the pressor response to apneas could have been due to sympathetic stimulation by vagal afferents. Alternatively, the aortic nerve, which travels with the vagus, was sectioned. This could have led to less chemoreceptive stimulatory afferent traffic.

In the present study, we have evaluated the role of the aortic nerve traffic by selective section of the aortic nerve, leaving the vagus intact. Bilateral cervical vagotomy was also performed to evaluate the effects of vagal traffic apart from the aortic nerve. We tested the hypothesis that aortic nerve traffic is responsible for the previously reported depressor effect of vagotomy during apnea (23); that is, that the previously reported effects of cervical vagotomy were primarily due to concomitant section of the aortic nerve.

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METHODS

The experiments consisted of two phases: a sterile instrumentation phase and a data-collection phase. The local Institutional Animal Care and Use Committee approved all methods, protocols, anesthesia, and sedation involved in this study in accordance with National Institute of Health guidelines.

Instrumentation Phase

Nine female Yorkshire farm pigs (weight 18–22 kg) were preinstrumented with an electromagnetic flow probe that was used for later measurement of cardiac output and stroke volume during the data-collection phase (see Data-Collection Phase). The preparation has been reported in detail in previous studies from our laboratory (3–6, 23). In brief, the animals were anesthetized by using ketamine (20 mg/kg im) and xylazine (2 mg/kg im). Anesthesia was maintained by using 1% halothane. Animals were intubated and mechanically ventilated through an endotracheal tube. Under sterile conditions, the chest was opened and a sterile square-wave electromagnetic flow probe (Biotronix) was placed around the ascending aorta (size 14–18 mm, depending on the size of the aorta). The lead from the flow probe was led out to a subcutaneous pocket. A heparin-filled catheter was placed into the left atrial appendage and also led out into the subcutaneous pocket. The incisions were closed in two layers. Penicillin, dihydrostreptomycin, and morphine sulfate were administered intramuscularly for antibiotic prophylaxis and pain control. The animals were allowed 6–10 days for recovery from the surgery before data collection.

Data-Collection Phase

Surgical preparation. The animals were anesthetized by using ketamine and xylazine as described in Instrumentation Phase. This produced 45–60 min of surgical plane anesthesia. All the incisions were made during this anesthetic period and with local infiltration of 2% lidocaine for skin cutdown. The animals were intubated and mechanically ventilated during the surgery. Tidal volume was set to 10 ml/kg, and respiratory frequency was adjusted to yield an arterial PCO₂ ~40 Torr.

A large-bore catheter was placed in the left femoral vein via cutdown for administration of fluids and medications. A 7F thermistor-tipped catheter was inserted into the femoral artery. It was advanced into the ascending aorta for monitoring core temperature, measurement of blood pressure, and collection of blood samples for measurement arterial PO₂, PCO₂, and pH, and it allowed for calibration of the aortic flow probe. A catheter was inserted into the right femoral vein and advanced into the right atrium. The subcutaneous pocket that contained the aortic flow probe lead and the left atrial catheter tip was opened. The signals from the aortic flow probe were calibrated by the thermodilution technique, in which a 5-ml bolus of iced saline was injected into the left atrium via the left atrial catheter and blood temperature was sampled via the thermistor-tipped aortic catheter. Airway pressure was measured via a lateral tap placed in the endotracheal tube. Respiratory rate during apneas was counted from the airway pressure tracing.

The cervical trunks of vagus nerves were isolated bilaterally via cutdowns and separated when necessary from the cervical sympathetic trunk. Ligatures were placed around the nerves for later identification. In swine, there is only a single aortic nerve that travels with the left vagus nerve. The aortic nerve is either easily dissected from the vagus or constitutes a separate bundle (18, 21, 22). The aortic nerve separates from the left vagus just below the left nodose ganglion, forms a loop, and reenters the vagus above or within the ganglion (18, 21, 22). The aortic nerve was identified and isolated according to the modified methods of Schmidt (21). Bipolar silver-silver chloride electrodes were placed around the aortic nerve, and the signals were filtered, amplified, and displayed on an oscilloscope and passed through a loudspeaker. The cervical region was flooded with 38°C mineral oil to keep tissue from drying. Identification of the nerve was easily confirmed by the discharge pattern at the start of the experiments and the response to electrical stimulation at the end of the experiment. The maximum discharge rate of the aortic nerve occurred during systole, and the only audible discharge pattern perceived was synchronized with the cardiac cycle (21). Moreover, electrical stimulation of the cut central end of the sectioned aortic nerve (6 V, 0.1 ms, 135 Hz) was associated with a marked decrease in blood pressure (21).

After surgical preparation, all surgical incisions were closed and the ventilator disconnected to allow spontaneous ventilation. For continuous sedation after surgical anesthesia, a continuous intravenous infusion with a mixture of 0.9% alaphalone and 0.3% alphadalone (Saffan, Pittman-Moore, Middlesex, UK) was begun at 3–4 mg·kg⁻¹·h⁻¹ ~20 min before the end of surgical plane anesthesia. This level of sedation is sufficient to produce heavy sedation but not surgical plane anesthesia. Previous studies have demonstrated that alaphalone-alphadalone is associated with preservation of sympathetic reflexes and minimal ventilatory suppression compared with other anesthetic and analgesic agents (1).

Protocols. Periodic obstructive apnea was accomplished by periodic occlusion of the endotracheal tube at end expiration for 30 s (apnea phase) followed by unclamping and spontaneous ventilation for 30 s (interapnea interval). Thus an apnea-interapnea cycle was defined as 1 min. We tested the effects of periodic obstructive apneas under following conditions in a sequential order: 1) control (C); 2) after selective vagotomy (Vagot); and 3) vagotomy (Vagot): bilateral section of the cervical vagus nerves. Because of the irreversible nature of the nerve sections, we could not vary the order of the experimental conditions.

Measurements were done at baseline, during the fifth to sixth apnea-interapnea cycle, and at recovery. The word “baseline” indicates measurements taken while the animals were spontaneously ventilating after at least 20 min of spontaneous ventilation before any apnea intervention. “Recovery” means the same state as baseline after a 20-min stabilization after the end of the apnea intervention. Arterial blood for measurement of gas tensions was taken at baseline and recovery. In addition, one blood-gas sample from the fourth to fifth apnea-interapnea cycle was taken over a 10-s period beginning at 5 s before apnea termination extending over the first 5 s of ventilation resumption. Hemodynamic parameters and airway pressure were digitized at a frequency of 100 Hz, and data were streamed through to a hard disk of a microcomputer by using commercially available software (model ACQ4600, Gould, Cleveland, OH). Animals were euthanized at the end of the experiments by intravenous bolus injection of 0.3 ml/kg of a solution containing 5 g/ml pentobarbital sodium.

Data Analysis

Data were analyzed off-line by using commercially available software (View II, Gould). Data during the fifth to sixth apnea-interapnea cycle were taken at specified times as follows: early apnea (EAP; first 5 s of apnea phase), late apnea (LAP; last 5 s of apnea phase), early interapnea

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(EIA; first 5 s of interapnic interval), and late interapnea (LIA; last 5 s of interapnic interval). Thus each datum point represented a 5-s period. Heart rate and mean arterial pressure (MAP) were measured from the blood pressure tracing. Cardiac output was defined as mean aortic flow. The error introduced by discounting coronary flow was considered small and ignored. Stroke volume was measured on a beat-to-beat basis by electronically integrating the stroke aortic flow. Systemic vascular resistance (SVR) was calculated as (MAP/cardiac output)·79.9 (dyn·s·cm⁻²).

Data were compiled and expressed as means ± SE. We used the statistical package SigmaStat 2.03 (Jandel, San Rafael, CA). Data were analyzed by using two-way ANOVA for repeated measures (factors: C/ANS/Vagot; time in apnea cycle). When significance was found, a Neuman-Keuls procedure was used to determine the source of significance. Previous experience with this model (4–6, 23) has demonstrated that, relative to baseline, a given variable may change in different directions with different treatments and that there is a great deal of biological variability between responses in different animals. Thus we also explored differences relative to baseline for any given treatment by hypothesizing no changes in a given variable with time (within treatment). This was done by using repeated-measures one-way ANOVA. Dunnett’s test was used to determine the significance of differences between means at different points in the apnea-interapnea cycle (EAP, LAP, EIA, LIA, recovery) and baseline. The null hypothesis was rejected at the 5% level.

RESULTS

Airway Pressure and Blood-Gas Tensions

Figure 1 demonstrates airway pressure and arterial blood-gas tensions. Obstructive apneas led to large inspiratory swing in airway pressure, which reflects changes in intrathoracic pressure when the upper airway is closed. Moreover, all the conditions were associated with hypercapnia and hypoxia indicated by changes in arterial blood-gas tensions. There were no significant differences among baseline gas tensions for the three conditions. There were also no significant differences in apnea-related changes in respiratory parameters among the three conditions (2-way ANOVA). Blood-gas tensions were all significantly different (P < 0.01) at apnea compared with baseline and recovery, but there were no differences between baseline and recovery.

Respiratory Rate

Respiratory rate during apneas was 24.9 ± 2.6 breaths/min for C, 23.4 ± 3.3 breaths/min for ANS, and 22 ± 2.9 breaths/min for Vagot. The differences among the three conditions were not significant.

Hemodynamics

Relative to baseline, MAP (Fig. 2) increased significantly at all points over the apnea-interapnea cycle under C (P < 0.01). However, after ANS, there was no significant change in MAP during the apnea-interapnea cycle relative to baseline. The difference in overall means between C and ANS was significant (P < 0.02, 2-way ANOVA). There was no significant difference between ANS and Vagot, but the difference in overall means between Vagot and C reached borderline significance (2-way ANOVA, P < 0.051). There was also no
A significant change in MAP relative to baseline over the apnea-interapnea cycle for both ANS and Vagot.

Mean aortic flow was different among the three conditions (*Fig. 3; P < 0.02, 2-way ANOVA*). Mean aortic flow decreased significantly from baseline (*P* < 0.01) with C during the apnea-interapnea cycle, except at LIA. In contrast, after ANS and Vagot, mean aortic flow increased significantly at LIA relative to baseline (*P* < 0.01 for ANS and *P* < 0.05 for Vagot).

With C and ANS, heart rate (*Fig. 4*) increased compared with baseline (*P* < 0.05 for both) at LA and LIA. With Vagot, heart rate was significantly higher (*P* < 0.01) than with C and ANS (2-way ANOVA), the difference being significant at all points, including baseline. With C and ANS, heart rate was significantly greater than baseline at LIA. The difference between LIA and LAP were also significant for C and ANS (*P* < 0.05). With Vagot, heart rate was significantly higher at all points during the apnea-interapnea cycle than at baseline (*P* < 0.05). However, unlike the situation with C and ANS, there were no significant differences between LIA and LA with Vagot.

Similar to mean aortic flow, with C, stroke volume (*Fig. 5*) decreased significantly (*P* < 0.01) at LAP and EIA relative to baseline. However, compared with baseline, the changes in stroke volume during the apnea-interapnea cycle were not significant with ANS and Vagot. The difference between C and the other conditions was significant (2-way ANOVA, *P* < 0.05), with the difference coming from EIA.

SVR (*Fig. 6*) was significantly greater with C than with the other two conditions, the difference coming from LAP and EIA (2-way ANOVA, *P* < 0.02). Relative to baseline, SVR increased significantly (*P* < 0.01) at LAP and EIA with C. However, with ANS and Vagot, there was no significant change during the apnea-interapnea cycle in SVR.
given condition from BASE, P studies (C, ANS, Vagot) because of the irreversible confounded by the additional effects of arousal. Hypercapnia) and other neuroendocrine factors not idiety to evaluate the role of metabolic (hypoxia and/or tical arousals. Thus this model provided an opportu- nary demonstrated no evidence of apnea-related cor- dences baseline and recovery. Previously (5), our lab- good stability over time because there were no dif- anesthetized dogs (20, 25) and were comparable to vidual blood-gas tensions were maintained showing normal baseline arterial blood-gas tensions were maintained showing minimal respiratory depression due to sedation (Fig. 1). Inspiratory decreases in intrathoracic pressure as indicated by airway pressure swings during obstructive apneas (Fig. 1) were greater than those seen in anesthetized dogs (20, 25) and were comparable to those observed clinically (14). The model demonstrated good stability over time because there were no differences baseline and recovery. Previously (5), our lab- oratory demonstrated no evidence of apnea-related cortical arousals. Thus this model provided an opportu- nity to evaluate the role of metabolic (hypoxia and/or hypercapnia) and other neuroendocrine factors not confounded by the additional effects of arousal.

We were unable to alter the order of performing the studies (C, ANS, Vagot) because of the irreversible nature of nerve section. It might be thought that the lack of pressor response to apneas with ANS and Vagot could be time related rather than due to the effects of nerve section. We think this unlikely because multiple previous studies have been performed in which the pressor response repeats itself with every exposure to apnea, provided hypoxia occurs (3–6). Thus we are confident that the effects seen with ANS and Vagot are due to nerve section rather than loss of response with time or preparation deterioration.

**DISCUSSION**

As previously demonstrated by our laboratory (23), we demonstrate that Vagot eliminates the apnea-associated pressor response. We also observed that ANS produced almost all of the effects of Vagot by effectively eliminating apnea-induced increases in MAP and SVR. There were no additional effects of Vagot on these apnea-related responses. The only effect of Vagot on the apnea response beyond that of ANS was increased baseline heart rate and increased heart rate through- out the apnea-interapnea cycle relative to baseline.

**Experimental Preparation**

The advantages and limitations of our sedated por- cine model have been extensively reviewed previously (3–6, 23). In brief, acute major surgery and anesthesia at the time of data collection are avoided by using sedated and chronically instrumented animals, thus minimizing cardiorespiratory depression. Alphaxalone-alphadolone is known to preserve sympathetic and vagal reflexes associated with chemoreceptor and baroreceptor stimulation and to produce minimal ventilatory suppression compared with other agents (1, 11). Therefore, the present model is appropriate for investigating autonomic control during apnea. Normal baseline arterial blood-gas tensions were maintained showing minimal respiratory depression due to sedation (Fig. 1). Inspiratory decreases in intrathoracic pressure as indicated by airway pressure swings during obstructive apneas (Fig. 1) were greater than those seen in anesthetized dogs (20, 25) and were comparable to those observed clinically (14). The model demonstrated good stability over time because there were no differences baseline and recovery. Previously (5), our laboratory demonstrated no evidence of apnea-related cortical arousals. Thus this model provided an opportunity to evaluate the role of metabolic (hypoxia and/or hypercapnia) and other neuroendocrine factors not confounded by the additional effects of arousal.

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**Blood Pressure Response**

Consistent with previous studies with this porcine model (3–6, 23), the hemodynamic responses to peri- odic obstructive apneas include increased MAP (Fig. 2) and SVR (Fig. 6) and decreased cardiac output (Fig. 3) and stroke volume (Fig. 5). We have previously presented evidence that the depression in cardiac output and stroke volume results from increased left ventricu- lar afterload (increased MAP) that is associated with vasoconstriction during apnea (3–6, 23), an explana- tion consistent with our present findings.

Our findings indicate that reflexes carried by the aortic nerve mediate vasoconstriction, which leads to some of the adverse hemodynamic consequences. The addition of Vagot to ANS did not further alter the apnea responses of these variables. Thus the previously observed effects of Vagot (3, 23) are due to con- comitant section of the aortic nerve that travels with the left vagus in pigs. Thus the demonstrated importance of the vagus in maintaining the pressor response to apneas (3, 23, present study) lies in its association with the aortic nerve.

The aortic nerve is distributed to the aortic bodies that are formed by glomus cell clusters situated along the aortic arch and other great intrathoracic arteries. The aortic nerve of swine contains primarily afferent fibers from aortic receptors, although there are also some sympathetic efferent fibers (21, 18). Those afferent fibers coming predominantly from the aortic baroreceptors have greater excitability to electrical stimulation, which in turn leads to bradycardia and hypotension. The afferent C fibers carrying aortic chemoreceptor traffic have lower excitability, and their activation leads typically to excitation, including cardiac acceleration and increased blood pressure (21). In our studies, ANS would have eliminated both aortic baroreceptor and chemoreceptor afferents. However, we believe that loss of afferent input from chemoreceptors is responsible for the observed blunting effects of ANS on the pressor response during apneas. This is because the predominant effect of ANS was depression of the MAP response, which would result from the loss of an excitatory influence (chemoreceptors). Had the predominant effects of ANS been due to elimination of the aortic baroreflex, which is inhibitory, then we would have expected to observe greater stimulation (greater increase in MAP and heart rate than in C during apneas), the exact opposite of what was observed. However, we cannot rule out some effects of
baroreflex elimination, and it remains possible that the degree to which the pressor response to apneas was altered with ANS was modulated to some degree by loss of aortic baroreflex activity in our studies.

We also note that the carotid chemo- and baroreceptors were intact in our preparation. Given the importance of these structures in regulating ventilatory and circulatory responses during hypoxia, it is possible that the response to ANS would be different if these structures were not intact. The modulating role of carotid reflexes on the aortic baroreflex regulation of the circulation during apneas thus remains to be elucidated.

Finally, it might have been possible that the effects of ANS on the MAP response to apneas could have been due to effects on the ventilatory response to hypoxia associated with elimination of aortic chemoreflex input. Although this study was not designed to assess ventilatory responses, we believe that there were few effects of ANS. This is because for comparable degrees of hypoxia, all three conditions produced the same changes in respiratory rate and maximum decrease in airway pressure during apneas, suggesting comparable ventilatory drive in all three conditions during apneas.

Our results are consistent with many previous clinical and animal studies indicating that hypoxia is one of major mechanisms mediating acute cardiovascular changes during apneas (2, 3–6, 23). In patients, of course, the effects of postapneic arousal are superimposed on those of hypoxemia. Effects of hypercapnia are small in this model (5), consistent with the weak aortic chemoreceptor responses to hypercapnia and acidosis (9, 19).

The mechanisms by which the aortic chemoreceptor reflex participates in the regulation of the circulation are incompletely understood. However, it is known that stimulation of the aortic chemoreceptors exerts sympathetic excitatory effects on peripheral blood vessels leading to increased systemic vascular tone (8), consistent with the present observations of increased SVR during apneas (Fig. 6). Stimulation of the aortic chemoreflex also leads to increases in cardiac contractility (7) that could lead to changes in stroke volume and cardiac output. In previous studies (3), we failed to observe an inotropic effect on left ventricular function in normal pigs. In addition, it is known that both sympathetic and parasympathetic efferent pathways are involved in the aortic chemoreflex. In fact, elevated sympathoadrenal tone is a major mechanism mediating the pressor response to apnea in this model (4, 6). Although parasympathetic efferents are important regulators of heart rate during apnea (see Heart Rate Response), these play little role in regulating SVR and MAP because there is little parasympathetic efferent nerve supply to mammalian vessels and ventricles (15). Indeed, in the present studies, eliminating of all parasympathetic efferents carried by the vagus nerve with Vagot did not demonstrably alter the response to apneas compared with simple ANS.

Heart Rate Response

As previously demonstrated (4, 6), with C we observed a significant increase in heart rate at LIA relative to the baseline and LIA (Fig. 4). It has been proposed that the autonomic reflex response to hypoxemia rather than hypoxemia per se mediates the heart rate response to apnea (6, 23). Control of heart rate during the apnea-interapnea cycle appears to involve cyclic changes in the relative balance of sympathetic (cardioacceleration) and parasympathetic (cardiac slowing) efferent tone to the heart. It is likely that during apneas, both sympathetic and parasympathetic efferent tone increase, the balance being such that there is no change in heart rate (Fig. 4, Refs. 6 and 23). Immediately after apnea termination, there is effective withdrawal of parasympathetic efferent tone. Withdrawal of vagal tone after apnea termination may be related to resumption of breathing and/or to correction of hypoxemia. Withdrawal of vagal tone in the presence of continued sympathetic tone would lead to cardioacceleration (23), as was observed. Similarly, elimination of parasympathetic efferents by Vagot allows the effects of sympathetic stimulation to be unopposed, and heart rate increases throughout the apnea-interapnea cycle relative to baseline (Fig. 4).

Thus, although aortic chemoreceptor afferent activity appears to be an important influence for MAP and SVR, vagally carried parasympathetic efferents are important regulators of heart rate. This conclusion is consistent with clinical studies demonstrating the disappearance of the bradycardic response to apnea after atropine administration (12). Further studies are needed to determine the mechanisms activating efferent cardiac vagal tone during apnea in this model. These mechanisms include carotid chemoreflexes (5, 7, 8, 23, 25) and cyclic changes in respiratory mechanoreceptor activity during apneas.

Last, we note that our findings in sedated pigs may not be directly applicable to human sleep apnea. This is because of the lack of arousal effects and the fact that the role of aortic chemoreceptors in circulatory regulation is incompletely understood in humans. It is possible that these receptors may play a greater or lesser role in sleep apnea than suggested in the present studies.

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