Effect of Blood Pressure Changes on Air Flow Dynamics in the Upper Airway of the Decerebrate Cat

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Background: Previous studies suggest that upper airway neuromuscular activity can be affected by changes in blood pressure via a baroreceptor-mediated mechanism. It was hypothesized that increases in blood pressure would increase upper airway collapsibility predisposing to airway obstruction at a flow-limiting site in the hypopharynx.

Methods: To examine the effect of blood pressure on upper airway function, maximal inspiratory air flow was determined through the isolated feline upper airway before, during, and after intravenous infusion of phenylephrine (10–20 \( \mu \)g·kg\(^{-1}\)·min\(^{-1}\)) in six decerebrate, tracheotomized cats. Inspiratory flow, hypopharyngeal pressure, and pressure at the site of pharyngeal collapse were recorded as hypopharyngeal pressure was rapidly decreased to achieve inspiratory flow limitation in the isolated upper airway. Pressure-flow relationships were used to determine maximal inspiratory air flow and its mechanical determinants, the upper airway critical pressure (a measure of pharyngeal collapsibility), and the nasal resistance upstream to the site of flow limitation.

Results: An increased mean arterial blood pressure of 71 ± 16 mmHg (mean ± SD) was associated with significant decrease in maximal inspiratory air flow from 147 ± 38 ml/s to 115 ± 27 ml·sec\(^{-1}\) (P < 0.01). The decrease in maximal inspiratory air flow was associated with an increase in upper airway critical pressure from -8.1 ± 3.8 to -5.7 ± 3.7 cm H\(_2\)O (p < 0.02), with no significant change in nasal resistance. When blood pressure was decreased to baseline by discontinuing the phenylephrine infusion, maximal inspiratory air flow and upper airway critical pressure returned to their baseline values.

Conclusions: Increased blood pressure increased the severity of upper airway airflow obstruction by increasing pharyngeal collapsibility. Previous studies relating baroreceptor activity to neuromuscular regulation of upper airway tone, are consistent with this effect being mediated by afferent activity from baroreceptors. These findings warrant further study because they suggest the possibility that upper airway obstruction in postoperative patients could either be caused or exacerbated by an increase in blood pressure. (Key words: Anesthesia: arterial blood pressure; baroreflex; complications. Cardiovascular: hypertension; obstructive sleep apnea; upper airway obstruction.)

IN the immediate postoperative period, two of the most common complications are upper airway obstruction and hypertension. These two complications are usually considered to occur independently of one another, i.e., hypertension may be due to inadequate analgesia whereas airway obstruction may be attributed to a reduction in upper airway muscular tone from residual inhalational or intravenous anesthetic agents. Alternatively, pharmacologic treatment of pain and anxiety can lead to airway obstruction. When the airway obstructs, ensuing hypoxia, hypercapnia, and arousal may then increase sympathetic output and arterial blood pressure. Thus, several mechanisms may account for the association between upper airway obstruction and increased arterial pressure in the postoperative period.
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Recent studies, however, suggest another mechanism relating airway obstruction and hypertension in the postoperative period. It is now recognized that as blood pressure increases, feedback from baroreceptors could affect upper airway stability by reflexively depressing activity in hypoglossal nerve traffic in cats and, as would be expected, the downstream genioglossus electromyographic activity in humans. Such a reduction in genioglossus activity may then allow pharyngeal collapse and airway obstruction to occur during inspiration. The mechanistic relationship between genioglossus activation and airway stability is the basis for new treatment strategies for obstructive sleep apnea involving direct stimulation of the genioglossus during inspiration. Thus, it is possible that pharyngeal air flow obstruction could be the consequence rather than the cause of increased arterial pressure in the postoperative period.

Because upper airway obstruction is a common problem during postoperative emergence from anesthesia, we initially set out to examine the effect of commonly used inhalational and intravenous anesthetic agents on upper airway collapsibility. The experimental preparation uses the isolated upper airway of the decerebrate cat, which has been found to model mechanical, neural, and chemical stimulus response events in humans in the absence of anesthetic agents. However, in preliminary studies when an anesthetic agent was administered, arterial blood pressure was profoundly decreased by even 0.5% end-tidal concentration halothane, or by a 0.5 mg/kg dose of intravenous propofol. To maintain hemodynamic stability and the viability of the animal preparation for the period required for completion of the experimental protocol, a phenylephrine infusion was required to increase arterial blood pressure to baseline. However, when blood pressure increased during the phenylephrine infusion, an immediate worsening of pharyngeal air flow obstruction was observed. Because any further studies of anesthetic effects would require an understanding of the relationship between changes in blood pressure and airway collapsibility independent of other effects of an anesthetic agent, the following study was carried out with blood pressure controlled with a phenylephrine infusion as the independent variable, and airway collapsibility was measured as the dependent variable. The results provide the mechanical components linking previously reported effects of acute changes in blood pressure on the neural and electromyographic activation of the upper airway musculature, which determine upper airway stability.

Materials and Methods

This study was approved by the Institutional Animal Use and Care Committee. Studies were performed in six supine decerebrate, tracheotomized male cats weighing approximately 2 kg. Anesthesia was induced with 80 mg intramuscular ketamine. A stable anesthetic plane based on heart rate, blood pressure, and a lack of spontaneous movement, was maintained with 20-mg doses of intramuscular ketamine repeated as required, until surgical decerebration was completed. Atropine (0.3 mg intramuscular) was administered to dry secretions in the upper airway. Rectal temperature was maintained between 37°C and 39°C. Arterial blood pressure was monitored with a catheter in the femoral artery.

The isolated upper airway preparation is illustrated in figure 1. The cervical trachea was exposed, stripped of fascia, and transected approximately 1 cm below the cricoid cartilage. The lower trachea was cannulated with an endotracheal tube (4.5 mm ID). End-tidal carbon dioxide was monitored with infrared capnometry during spontaneous ventilation with room air. To determine the onset of inspiration, an esophageal balloon was inserted in the middle third of the esophagus, which was ligated and tied off in the mid-cervical region. A rigid cannula was inserted through the upper tracheal stump, its tip passed through the vocal cords, and positioned at the aryepiglottic folds. Inspiratory flow (Vi) was measured with a pneumotachometer.

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(Fleisch 01, Hans Rudolph, Kansas City, MO, and Valdyne, Northridge, CA; differential transducer, ±2 cm H2O) connected in series to the rigid cannula. The mouth was occluded. A 50-cm long mobile catheter (polyethylene tubing 1.4 mm ID) was then passed through one nostril into the pharynx and out of the tracheal cannula. A side-hole allowed measurement of the lateral pharyngeal pressure (Pph) along the length of the pharynx by moving the side hole from a caudal toward a cephalad position. The hypopharyngeal pressure (Phe) was monitored in the caudal stump of the upper airway.

Air flow dynamics in the isolated upper airway were examined as described previously.17,18,23,24 Briefly, Phe was rapidly decreased by applying a subatmospheric pressure to the tracheal cannula, which produces air flow in the inspiratory direction, until V1 attained a maximal level (V1 max; inspiratory air flow limitation was achieved). The location of the site of pharyngeal collapse was then determined by monitoring the lateral pharyngeal pressure with the movable side-hole catheter as it was pulled from caudal to cephalad in the upper airway and analyzing pressure-flow relationships as described previously.17,18,23,24 The collapsible site was defined by the most downstream (i.e., caudal because the air flow moves from cephalad into the trachea) Pph position at which Pph and Phe diverged at the point of V1 max. Thus, at the site at which airway collapse occurs, as the hypopharyngeal pressure continues to decrease as a result of the applied negative pressure source, the pharyngeal pressure plateaus and may even begin to rise indicating that airway collapse is present and that a more negative airway pressure cannot increase air flow, and indeed may well decrease air flow as the area of collapse increases.16 (fig. 2). The pressure measured in the mobile catheter in the pharynx at the flow-limiting site defines the critical closing pressure (Pcrit) of the airway because it must be equal and opposite to the surrounding tissue pressures tending to hold the airway open. Under normal conditions, this Pcrit is a moderately negative value reflecting the mechanical tissue forces tending to hold the pharyngeal airway open. However, in the abnormal airway, Pcrit becomes less negative and may even become positive indicating that there is sufficient surrounding tissue pressure to collapse the airway even at atmospheric pressure.22,23 In patients with obstructive sleep apnea, a positive Pcrit can occur during sleep requiring positive airway pressure to maintain a patent airway analogous to the application of continuous positive pressure to maintain patency of the airway of a patient during induction or emergence from anesthesia. Because the airway segments upstream and downstream from the site of collapse remain open, the resistance in the functionally separated upstream segment can be independently assessed when flow limitation has occurred.

Thus, pressure-flow relationships can be analyzed to determine V1 max and its mechanical determinants, the Pcrit and the nasal resistance (Rn) upstream to the collapsible (flow-limiting) site (fig. 2). Pcrit was defined as the nadir in the Pph immediately upstream to the flow-limiting site at the onset of V1 max, and Rn was calculated as (Pn - Pcrit)/V1 max, where Pn is the pressure at the nares, which in this study remained constant at atmospheric pressure. All measurements of V1 max, Pcrit, and Rn were performed at the onset of inspiration (as esophageal pressure began to decrease) so as to

![Fig. 2. Pressure-flow relationships in the isolated upper airway without (left) and with (right) phenylephrine infusion. A ramplike decrease in hypopharyngeal pressure (bottom) resulted in an increase in inspiratory flow (top), which plateaued at a maximal level (V1 max (vertical dashed lines). At the point of V1 max (horizontal dashed line) in the top panels, pharyngeal pressure (middle) reached a nadir and plateaued at critical pressure (horizontal dashed line, middle). Mean arterial pressure was 83 mmHg (left) and 218 mmHg (right).]
coincide with phasic activation of the pharyngeal musculature when baroreceptor responses are reportedly greatest. \(^{11}\)

To determine the effect of blood pressure on upper airway function, \(V_i\)max, \(P_{crit}\), and \(R_N\) were measured before, during, and after a 3-min intravenous infusion of phenylephrine (10–20 \(\mu\)g · kg\(^{-1}\) · min). For each experimental condition, \(V_i\)max, \(P_{crit}\), and \(R_N\) were determined at least three times in each of the six cats, and mean values for each condition were then analyzed with a one-way analysis of variance for repeated measures. Thus, the first measurement was completed within 1 min of initiating the hypertensive stimulus. Newman-Keuls post hoc comparisons made between groups (before, during, and after phenylephrine infusion) were then made. All data are presented as mean ± SD.

**Results**

In figure 2, representative pressure and flow recordings during a control period and during phenylephrine infusion are illustrated. A ramp decrease in \(P_{HP}\) (lower panels) was associated with an initial increase in \(V_i\) (upper panels). \(V_i\) then plateaued (to right of vertical dashed lines) as \(P_{HP}\) continued to decrease, indicating the onset of inspiratory air flow limitation. When flow limitation occurred, the \(P_{PH}\) immediately upstream to the flow-limiting site (where the pharynx collapsed) reached its nadir at \(P_{crit}\) and plateaued thereafter (middle panel). In this example, a decrease in \(V_i\)max from 154 to 65 ml/s and an increase in \(P_{crit}\) from –4.0 to –1.2 cm H\(_2\)O accompanied an increase in mean arterial pressure (MAP) during the phenylephrine infusion from 83 to 218 mmHg.

In figure 3, mean changes in MAP, \(P_{crit}\), and \(R_N\) before, during, and after phenylephrine infusion are illustrated for the pooled data from six cats. For the pooled data, an increase in MAP at 71 ± 18 mmHg was associated with a decrease in \(V_i\)max \((P < 0.01)\), an increase in \(P_{crit}\) \((P < 0.02)\), and no change in \(R_N\).

**Discussion**

Previous studies indicate that when inspiratory air flow obstruction occurs in the upper airway, the upper airway functions as a simple collapsible conduit or Starling resistor with relatively rigid segments on either side of the collapsible segment. \(^{19,20,22,25,26}\) Three characteristics of these conduits have been described. \(^{25}\)

First, air flow (\(V_i\)) limitation has been demonstrated, characterized by a plateau in \(V_i\) at a \(V_i\)max that is not exceeded as pressure downstream to the upper airway decreases progressively during inspiration.

Second, previous studies have demonstrated that flow limitation is associated with airway collapse at a discrete locus or flow-limiting site. \(^{27,28}\) A characteristic of this flow-limiting site is that it collapses and limits \(V_i\) at \(V_i\)max when intraluminal pressure in this segment decreases to a critical pressure (\(P_{crit}\)). Thus, \(P_{crit}\) is a measure of collapsibility of the flow-limiting site.

Third, \(V_i\)max is determined by the characteristics of the flow-limiting site and upstream segment, as given by the algebraic expression in Methods. When \(P_N\) is atmospheric pressure, alterations in \(V_i\)max may result...
from changes in either Pcrit or Rn. There is considerable
evidence suggesting that V1,max is modulated by Pcrit
in humans19,20,22,26 and that Pcrit is modulated by
neuromuscular activity in the upper airway in
animals17,23,25 and humans.15,50 Furthermore, those
patients with baseline diminished cross-sectional area
in the upper airway, most commonly associated with
obesity, have increased collapsibility and associated
obstructive sleep apnea,22 in addition to the clinically
recognized increased tendency to obstruct on induction
and emergence from anesthesia. Thus, this approach
to the analysis of upper airway function, has
demonstrated applicability to both the isolated upper airway
in the decerebrate cat and the human upper airway
in the awake and asleep human.

In this study, the effect of a phenylephrine-induced
increase in MAP on V1,max and its mechanical
determinants, Pcrit and Rn, were examined in the isolated
feline upper airway. The major finding was that an acute
increase in MAP was associated with a decrease in V1,max
and an increase in Pcrit. When MAP was decreased
to baseline, both V1,max and Pcrit returned to baseline. In
contrast, changes in MAP had no effect on Rn. We
conclude that increased MAP leads to a decrease in air flow
that is the result of increased pharyngeal collapsibility.

Although this study does not establish the mechanism
for increased collapsibility when arterial pressure is
increased, Wasicko et al demonstrated that barorecep-
tor feedback produces an ~30% decrease in phasic
hypoglossal nerve activity with a comparable increase
in carotid sinus pressure to that used in our study.11
Consistent with this finding, Garpestad et al found a
~50% decrease in human genioglossus electromyographic
activity during phenylephrine infusion in humans
with increases in arterial pressure of only 15–25
mmHg.13 Wasicko et al also reported evidence con-
sistent with a baroreceptor-mediated decrease in ge-
inioglossus electromyographic activity in humans using
a tilt table to acutely increase blood pressure.12 Thus,
substantial evidence from both animal and human
studies suggests that baroreceptor modulated activation
of the pharyngeal musculature can regulate upper air-
way patency. It seems reasonable to suggest that the
same baroreceptor-reflex-mediated mechanism ac-
counted for the increase in mechanical pharyngeal col-
lapsibility found in our study, and that changes in pha-
ryngeal muscle activity mediated this response.23

It is also possible that local hemodynamic effects
cause alterations in the pharyngeal Pcrit. However,
Wasicko et al demonstrated that pharyngeal collapsi-

bility increases with nitroglycerin-induced vasodilation
and tends to decrease during phenylephrine infusion
when blood pressure was maintained constant.31 This
decrease in collapsibility was attributed to mucosal va-
soconstriction and consequent increases in airway cal-
iber, both of which were observed in magnetic reso-
nance images. Thus, it is likely that a direct effect of
phenylephrine on the pharyngeal mucosa (independent
of changes in blood pressure) decreased pharyngeal
collapsibility. This effect would attenuate the observed
increase in collapsibility when blood pressure is al-
lowed to increase and thus would lead us to underes-
timate the increase in pharyngeal collapsibility due to
the baroreflex.

Large changes in arterial blood pressure were studied
in this initial investigation to determine if the rela-
tionship between blood pressure and airway flow could be
found in a reproducible manner. These increases are
greater than those observed in most clinical situations
(e.g., obstructive sleep apnea), but changes in systolic
arterial pressure of 50–100 mmHg are not uncommon
in the postoperative period, and substantial changes in
human genioglossus electromyographic activity have
been observed with changes in mean arterial pressure
of only 15–25 mmHg.13 Thus, episodes of hyperten-
sion, either primary or secondary to pain, hypoxia, or
hypercapnia, may increase upper airway collapsibility
in the postoperative or sedated patient, particularly
in those predisposed to obstructive sleep apnea. Resulting
upper airway obstruction might then lead to further
hypoxia, hypercapnia, and hypertension as sympathetic
outflow increases, potentially setting up another posi-
tive feedback loop. If this speculation can be dem-
strated under clinical conditions, it would suggest
that inadequate control of postoperative hypertension
may precipitate or exacerbate air flow obstruction by
increasing upper airway collapsibility.

It is also possible that our findings are relevant to
the pathogenesis of obstructive sleep apnea as follows.
Specifically, the response in air flow dynamics to in-
creases in blood pressure may be important in the
pathogenesis of obstructive sleep apnea, which has
been demonstrated to be pathogenetically related to
an increased Pcrit in the upper airway.20,22,25 In ob-
structive sleep apnea, each episode of upper airway
obstruction is typically relieved during cortical arousal
(evidenced by EEG changes) while blood pressure in-
creases during the apneic episode as a result of symp-
thetic stimulation with hypoxia and hypercapnia.6,8
Because blood pressure increases further when the ap-

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nea terminates with arousal, increases in upper airway collapsibility that might ensue could contribute to the development of the next obstructive episode. This may set up a positive feedback loop, causing repetitive episodes of airway obstruction producing arterial hypertension, which in turn predispose to the next episode of airway obstruction.

In conclusion, an increase in blood pressure causes increased upper airway collapsibility in the isolated feline upper airway. Current evidence suggests this effect may be mediated via a baroreceptor mechanism. Our findings suggest the possibility that upper airway obstruction in postoperative patients could be either caused or exacerbated by an increase in blood pressure. Further studies are required to evaluate whether this mechanism is clinically relevant by examining whether elevations in blood pressure may increase pharyngeal collapsibility in postoperative patients, particularly those with blood pressure lability, obstructive sleep apnea, or a combination of the two.

References

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