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 $\mu g \cdot kg^{-1} \cdot min$) 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_2O (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 air flow 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.)

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IN the immediate postoperative period, two of the most common complications are upper airway obstruction and hypertension.[1] 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[2-4] or intravenous[4] 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.[5-10] Thus, several mechanisms may account for the association between upper airway obstruction and increased arterial pressure in the postoperative period.
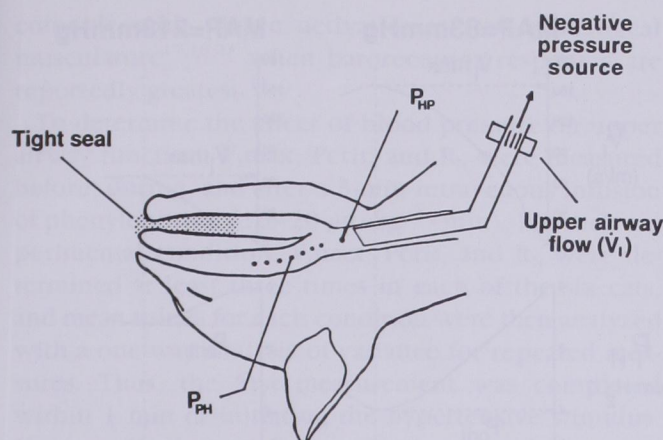
Fig. 1. Isolated feline upper airway. P_{PH} = pharyngeal pressure; P_{HP} = hypopharyngeal pressure. See text for details. (Reprinted with permission.[18]

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[11] in cats and, as would be expected, the downstream genioglossus electromyographic activity in humans.[12,13] Such a reduction in genioglossal activity may then allow pharyngeal collapse and air flow obstruction to occur during inspiration.[14] 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.[15] 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.[16-23] 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.[11-13]

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° 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 ($\dot{V}_I$) was measured with a pneumotachometer

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(Fleisch 01, Hans Rudolph, Kansas City, MO, and Validyne, Northridge, CA, differential transducer, ±2 cm H_2O) 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 (P_{PH}) along the length of the pharynx by moving the side hole from a caudad toward a cephalad position. The hypopharyngeal pressure (P_{HP}) 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, P_{HP} was rapidly decreased by applying a subatmospheric pressure to the tracheal cannula, which produces air flow in the inspiratory direction, until $\dot{V}_I$ attained a maximal level ($\dot{V}_I$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 caudad 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.*, caudad because the air flow moves from cephalad into the trachea) P_{PH} position at which P_{PH} and P_{HP} diverged at the point of $\dot{V}_I$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.[22,25] In patients with obstructive sleep apnea, a positive Pcrit can occur during sleep requiring positive airway pressure to maintain a patent air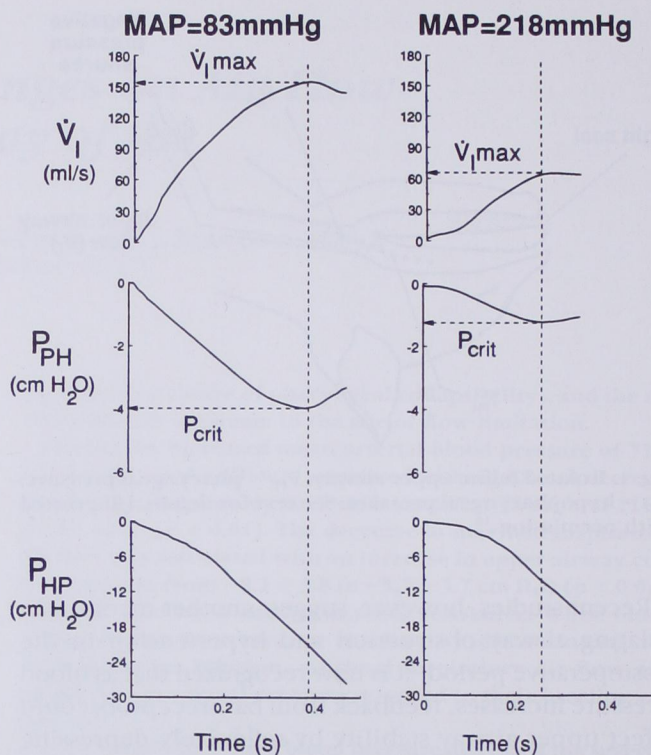way analogous to the application of continuous positive pressure to maintain patency of the airway of a patient during induction or emergence from anesthesia. Because the airway segments upstream and downstream from the site of collapse remain open, the resistance in the functionally separated upstream segment can be independently assessed when flow limitation has occurred.

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 ($\dot{V}_I$max (vertical dashed lines). At the point of $\dot{V}_I$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*).

Thus, pressure-flow relationships can be analyzed to determine $\dot{V}_I$max and its mechanical determinants, the Pcrit and the nasal resistance (R_N) upstream to the collapsible (flow-limiting) site (fig. 2). Pcrit was defined as the nadir in the P_{PH} immediately upstream to the flow-limiting site at the onset of $\dot{V}_I$max, and R_N was calculated as $(P_N - Pcrit)/\dot{V}_I$max, where P_N is the pressure at the nares, which in this study remained constant at atmospheric pressure. All measurements of $\dot{V}_I$max, Pcrit, and R_N were performed at the onset of inspiration (as esophageal pressure began to decrease) so as to

coincide with phasic activation of the pharyngeal musculature[17,18,23] when baroreceptor responses are reportedly greatest.[11]

To determine the effect of blood pressure on upper airway function, $\dot{V}_I$max, Pcrit, and R_N were measured before, during, and after a 3-min intravenous infusion of phenylephrine ($10-20 \, \mu g \cdot kg^{-1} \cdot min$). For each experimental condition, $\dot{V}_I$max, Pcrit, 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 $\dot{V}_I$ (upper panels). $\dot{V}_I$ 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 Pcrit and plateaued thereafter (middle panel). In this example, a decrease in $\dot{V}_I$max from 154 to 65 ml/s and an increase in Pcrit from -4.0 to -1.2 cm H_2O accompanied an increase in mean arterial pressure (MAP) during the phenylephrine infusion from 83 to 218 mmHg.

In figure 3, mean changes in MAP, Pcrit, 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 of 71 ± 18 mmHg was associated with a decrease in $\dot{V}_I$max ($P < 0.01$), an increase in Pcrit ($P < 0.02$), 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 char-
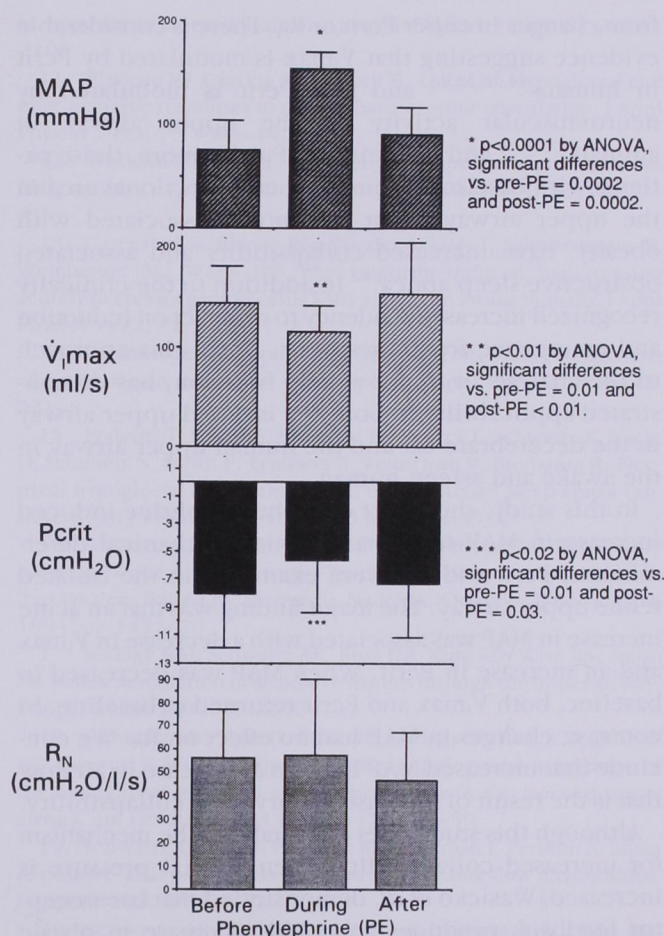

Fig. 3. Effect of phenylephrine on mean arterial pressure (*top*), maximal inspiratory flow (*second from top*), critical pressure (*second from bottom*), and nasal resistance (*bottom*), before, during, and after infusion of phenylephrine (n = 6).

acteristics of these conduits have been described.[23] First, air flow ($\dot{V}_I$) limitation has been demonstrated, characterized by a plateau in $\dot{V}_I$ at a $\dot{V}_I$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 $\dot{V}_I$ at $\dot{V}_I$max when intraluminal pressure in this segment decreases to a critical pressure (Pcrit). Thus, Pcrit is a measure of collapsibility of the flow-limiting site.

Third, $\dot{V}_I$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 $\dot{V}_I$max may result

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from changes in either Pcrit or R_N. There is considerable evidence suggesting that $\dot{V}_I$max is modulated by Pcrit in humans[19,20,22,26] and that Pcrit is modulated by neuromuscular activity in the upper airway in animals[17,23,29] and humans.[15,30] 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 $\dot{V}_I$max and its mechanical determinants, Pcrit and R_N, were examined in the isolated feline upper airway. The major finding was that an acute increase in MAP was associated with a decrease in $\dot{V}_I$max and an increase in Pcrit. When MAP was decreased to baseline, both $\dot{V}_I$max and Pcrit returned to baseline. In contrast, changes in MAP had no effect on R_N. 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 baroreceptor 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 genioglossal electromyographic activity during phenylephrine infusion in humans with increases in arterial pressure of only 15–25 mmHg.[13] Wasicko *et al.* also reported evidence consistent with a baroreceptor-mediated decrease in genioglossus 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 airway patency. It seems reasonable to suggest that the same baroreceptor-reflex–mediated mechanism accounted for the increase in mechanical pharyngeal collapsibility found in our study, and that changes in pharyngeal 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 collapsibility 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 vasoconstriction and consequent increases in airway caliber, both of which were observed in magnetic resonance 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 allowed to increase and thus would lead us to underestimate 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 relationship 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 hypertension, 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 positive feedback loop. If this speculation can be demonstrated 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 increases 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 obstructive sleep apnea, each episode of upper airway obstruction is typically relieved during cortical arousal (evidenced by EEG changes) while blood pressure increases during the apneic episode as a result of sympathetic stimulation with hypoxia and hypercapnia.[6,8] Because blood pressure increases further when the ap-

nea terminates with arousal,[32-34] 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.

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