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General Anesthesia in Patients with Viral Respiratory Infections: An Unsound Sleep?

Because viral upper respiratory infections are common in all populations, and particularly common in children, such infections frequently coincide with the scheduled date for elective surgery under general anesthesia. Until recently, it has been widely believed that general anesthesia should be avoided in patients with viral upper respiratory infections, although clinical studies have been mixed and experimental evidence lacking.

In 1979, McGill *et al.*¹ reported a series of 11 children who developed pulmonary dysfunction during induction of anesthesia. All but 1 of these patients had recently had a viral upper respiratory infection. The pulmonary problems developed immediately after intubation and consisted of wheezing, coarse breath sounds, hypoxia, and atelectasis that in two cases required bronchoscopy. In 1988, DeSoto *et al.*² carried out a prospective study comparing to 25 normal controls the intra- and postoperative course of 25 children suffering symptoms of upper respiratory infection during the week before surgery. They found a significantly increased risk of postoperative arterial oxygen desaturation in the infected group. The authors of both studies recommended seeking a history of recent upper respiratory infection in prospective patients and considering the urgency of surgery in deciding whether to proceed with anesthesia in such patients.

In apparent contradiction to these papers, Tait and Knight reported two series of children undergoing sur-

gical procedures at the University of Michigan.^{3,4} In the first of these studies,³ 3,585 cases were reviewed retrospectively and divided into an asymptomatic group, a group with current symptoms of upper respiratory infection, and a group with a recent history of upper respiratory infection symptoms who were asymptomatic at the time of surgery. Interestingly, there was no increase in complications of anesthesia in patients with current symptoms, but there was a greater than three-fold increase in intraoperative bronchospasm and laryngospasm in the currently asymptomatic patients with a recent history of upper respiratory infection symptoms. While the authors speculated that this may have reflected the time course of the development of airway hyperresponsiveness, it seems more probable that the apparent contradiction is a result of patient selection criteria. Patients were categorized as symptomatic on the basis of a recorded history of sore or scratchy throat, sneezing, rhinorrhea, congestion, malaise, cough, fever, and laryngitis. The most common of these complaints were rhinorrhea, cough, and congestion, all of which clearly may be chronic symptoms related to other disorders (such as allergy) rather than viral infections. If this were the case, one would expect patients with chronic symptoms of nonviral origin to be overrepresented in the currently symptomatic group, while those with symptoms resulting from acute viral infection to be overrepresented in the previously symptomatic, currently asymptomatic group. Thus, this study,³ despite the inherent limitations of a retrospective study, may actually support the association of viral infection with complications of anesthesia.

Recognizing the problems of the above study, the same authors undertook a prospective study of myringotomy and tympanostomy under general anesthesia in children with and without symptoms of viral upper respiratory in-

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fection.⁴ No difference in complications was found. However, none of these patients had their tracheas intubated, and intubation appeared to be a major risk factor precipitating bronchospasm in both the studies by McGill *et al.*¹ and DeSoto *et al.*²

In contrast, a recent prospective study* of 93 infants and 295 children (most of whom were intubated) found an alarming increase in complications in those with symptoms of upper respiratory infections. A "critical incident" was defined as an incident that caused or could have resulted in mortality or morbidity. Critical incidents occurred in 71% of infants with upper respiratory infections (as compared to 26% of asymptomatic infants) and in 30% of children with upper respiratory infections (as compared to 12% of controls).*

Thus, the evidence that exists at the current time supports the widely held clinical impression that a recent viral infection is indeed a risk factor for pulmonary complications during anesthesia, particularly when intubation of the trachea is involved. The physiologic changes underlying this increased risk were the subject of a recent study by Dueck *et al.*, the results of which are published in this issue of ANESTHESIOLOGY.⁵ The authors examined the effects of anesthesia on distribution of ventilation and perfusion, shunt, and functional residual capacity in sheep before and after infection with parainfluenza virus. The arterial oxygen tension in virus-infected animals was less than that predicted using distribution of ventilation-perfusion (V_A/Q), mixed venous oxygen tension ($P\bar{v}O_2$), mixed venous carbon dioxide tension ($P\bar{v}CO_2$), pH, hemoglobin, and P_{50} . The authors suggest that this effect is due to increased oxygen consumption by the inflamed lung, as has previously been shown with bacterial pneumonia.⁶

The mechanisms of these changes are not known. They may relate to changes in the volume of secretions or in their clearance in the infected airways, to changes in hypoxic vasoconstriction in the infected lungs, or to changes in the airway response to intubation and anesthesia. Whatever the mechanism, this finding is consistent with the clinical observation that there is an increased risk of intraoperative arterial hemoglobin oxygen desaturation in patients with recent viral upper respiratory infections.

Viral infections are also associated with exacerbations of asthma⁷ and chronic obstructive pulmonary disease.⁸ Even in patients with no preexisting lung disease, viral infections cause temporary airway hyperresponsiveness.⁹⁻¹¹ The presence of airway hyperresponsiveness has to be of concern where a patient's trachea must be intubated, since reflex bronchoconstriction can be produced by touching the inside of the airway.¹² The observation

that complications are more frequent in the setting of tracheal intubation and that this may precipitate bronchospasm¹ suggests that virus-induced airway hyperresponsiveness must be involved. Thus, just as bronchospasm can be provoked by such manipulations in patients with asthma, virus-induced hyperresponsiveness may also put patients temporarily at increased risk for bronchospasm during anesthesia.

The mechanisms of virus-induced airway hyperresponsiveness have been the subject of studies for over the past 15 yr. Airway smooth muscle taken from animals with experimental viral infections contracts normally *in vitro* in response to acetylcholine, and relaxes normally in response to isoproterenol,¹³⁻¹⁵ suggesting that an intrinsic abnormality in the smooth muscle is not responsible. A variety of immunologic and inflammatory events accompany viral infections and may cause bronchoconstriction by releasing white cell mediators such as histamine.¹⁶ On the other hand, clinical studies suggest that much of the hyperresponsiveness may be neurally mediated.^{9,10} Two broad categories of neural abnormalities have been identified in virus-infected airways: 1) increased vagal reflex bronchoconstriction^{9,10,13,17,18} and 2) increased response to tachykinins.^{14,19-21}

Much of the airway hyperresponsiveness seen with viral infections in humans can be blocked by atropine, suggesting that vagal reflexes are responsible.^{9,10} It was initially postulated⁹ that epithelial damage exposed sensory nerve endings, which then were more readily stimulated, increasing the afferent limb of the reflex. However, the efferent limb of the reflex also is potentiated, as demonstrated by the findings that electrical stimulation of vagal efferent fibers causes greater bronchoconstriction in parainfluenza-infected guinea pigs than in uninfected controls.¹³ Because the response to exogenous acetylcholine is normal in the airway smooth muscle of infected guinea pigs, increased release of acetylcholine from the vagus must occur.

One likely mechanism for this effect involves inhibitory muscarinic receptors on the vagal nerve endings.²² These receptors (of the M_2 subtype) are distinct from the muscarinic receptors on the airway smooth muscle (M_3 subtype), both structurally and functionally. Stimulation of the muscarinic receptors on the smooth muscle contracts the muscle. Stimulation of the receptors on the nerve inhibits release of acetylcholine. Thus, the muscarinic receptors on the vagus nerve provide a negative feedback whereby acetylcholine released by the nerve stimulates smooth muscle contraction but at the same time inhibits further release of acetylcholine. Blocking these receptors with low doses of gallamine (a M_2 receptor antagonist) potentiates vagally mediated bronchoconstriction as much as ten-fold, whereas stimulating the receptor with pilocarpine (a M_2 receptor agonist) inhibits vagally mediated bronchoconstriction.²² Damage to this receptor would be

* Liu LMP, Ryan JF, Cote CF, Goudsouzian NG: Influence of upper respiratory infections on critical incidents in children during anesthesia. Ninth World Congress of Anesthesiologists 2:A786, 1988.

expected to increase release of acetylcholine and to potentiate vagally mediated bronchoconstriction. In guinea pigs infected with parainfluenza virus, these M₂ muscarinic receptors no longer function to inhibit release of acetylcholine.¹⁷ In this setting, the bronchoconstrictor response to electrical stimulation of the vagus is increased and can be neither potentiated by gallamine nor inhibited by pilocarpine.

This loss of function of the inhibitory M₂ muscarinic receptors may be due to the viral enzyme neuraminidase, which is a component of parainfluenza and influenza viruses. The M₂ muscarinic receptors contain sialic acid residues that are important for agonist binding and are susceptible to cleavage by neuraminidase. Decreased agonist affinity for the M₂ muscarinic receptor would lead to loss of inhibitory feedback, increasing release of acetylcholine in virus-infected airways. This effect of viral neuraminidase has been demonstrated using *in vitro* ligand binding studies.¹⁸

Viral infections also increase airway smooth muscle contraction in response to tachykinins.^{14,19,20} Tachykinins are a family of sensory neuropeptides found in vagal afferent C-fibers in the airways. These mediators contract airway smooth muscle, both by direct effects and by facilitating cholinergic neurotransmission. Release of tachykinins can be induced by capsaicin and by electrical stimulation. The stimuli that release tachykinins normally in the lungs are unknown, but bradykinin, histamine, and nicotine have all been demonstrated to release tachykinins from pulmonary nerve endings.²³

Virus-induced potentiation of the response to tachykinins is due to loss of the enzyme neutral endopeptidase, which is normally present in airway tissue.^{14,20} Neutral endopeptidase breaks down tachykinins into inactive metabolites. Inhibiting neutral endopeptidase activity with phosphoramidon potentiates the smooth muscle response to both exogenous tachykinins and tachykinins released from nerve endings by capsaicin or electrical stimulation. Viral infections, by causing a 50% decrease in airway neutral endopeptidase activity, potentiate the bronchoconstrictor effects of tachykinins to a similar magnitude to that seen after pretreatment with phosphoramidon.^{14,20} Both the release of tachykinins and the smooth muscle receptors for the tachykinins appear to be normal.

Viral infections also alter the quality and character of airway secretions. This may be responsible for the atelectasis reported in one series of intubated, anesthetized patients.¹ While little is known about the control of secretions in virus-infected airways, under normal circumstances both tachykinins and acetylcholine stimulate airway submucosal gland secretion. Whether the abnormalities in smooth muscle response to tachykinins and to vagal stimulation will also apply to the glandular response has not yet been studied.

Despite some controversy in the literature, it appears

wise to avoid anesthesia when possible for at least several weeks after recovery in patients with viral infections. When anesthesia must be undertaken in the face of recent viral infection, it may be prudent to address the problems that can be predicted either from clinical reports or from our knowledge of the physiology of virus-infected airways. In view of numerous reports of arterial hemoglobin oxygen desaturation (perhaps due to shunting, as suggested in the paper by Dueck *et al.*⁵), hemoglobin oxygen saturation should be monitored both during anesthesia and in the recovery room. Because increased vagally mediated reflex bronchoconstriction is an almost universal finding in both clinical and animal studies, the use of atropine-like drugs to interrupt the reflex arc before tracheal intubation (which can be reliably predicted to stimulate vagal afferents) may be warranted.

Future developments may include more effective antiviral medications, although such evidence as exists, based on experience with amantadine for influenza infections, suggests that while the course of the illness may be shorter and milder, the degree and duration of airway hyperresponsiveness may not be altered.¹¹

Development of more selective anticholinergic medications that would selectively block the M₃ receptor on the airway smooth muscle without blocking the inhibitory M₂ receptor on the nerve would also be desirable. This might be particularly important if the M₂ receptor were partially damaged by viral infection. None of the anticholinergic medications currently available for use in humans is selective. At the same time as a nonselective antagonist opposes the effect of acetylcholine on the smooth muscle, it increases release of acetylcholine from the vagus nerve.²² A selective M₃ antagonist would not have this disadvantage. The prototypes of selective M₃ antagonists are hexahydrosiladifenidol and its analogue para-fluorohexahydrosiladifenidol,²⁴ which have not yet been tested in humans.

Another intriguing possibility is the use of recombinant human neutral endopeptidase to replace the airway neutral endopeptidase lost during viral infections. When Kohrogi *et al.*²⁵ administered this to guinea pigs, coughing induced by inhaled capsaicin or substance P (a tachykinin) was markedly attenuated for at least 2 h. Even such a short-term effect might eliminate the effects of viral infection on airway function during surgery. Furthermore, Piedimonte *et al.*²¹ have shown that treatment with dexamethasone attenuates tachykinin-induced plasma extravasation in rat airways and blocks virus-induced increases in this response. This effect may be due to stimulation of the production of neutral endopeptidase by dexamethasone, as has been shown in cultured airway epithelium.²⁶ If so, glucocorticoids may also ameliorate virus-induced airway hyperresponsiveness to tachykinins.

Thus, study of the pathophysiology of viral airway infection will lead to new therapeutic strategies. An under-

standing of the changes in control of airway function that occur with viral infection may ultimately allow us to avoid the complications of general anesthesia in this setting.

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