Pulmonary edema is a generalized descriptive term for the accumulation of fluid within the interstitium and/or the alveolar spaces of the lungs. This accumulation of fluid has a cause that may be termed cardiogenic or noncardiogenic. Pulmonary edema of cardiogenic origin is usually due to failure of the left side of the heart, but it also can be attributed to the right side of the heart. Noncardiogenic pulmonary edema (NCPE) usually is attributable to certain lung injuries or disease states, but it also can be neurogenic in origin. Some occurrences of NCPE can be traced directly to the administration of anesthesia. For example, NCPE can result from upper airway obstruction or the administration of naloxone.

Key words: Laryngospasm, Müller maneuver, nalmefene, naloxone, negative inspiratory pressure.

Objectives
1. Describe the pathophysiological processes that can result in pulmonary edema.
2. Discuss pathophysiologic factors of negative pressure pulmonary edema.
3. Describe the cardiac effects of negative pressure pulmonary edema.
4. Relate the pharmacologic etiology of noncardiogenic pulmonary edema.
5. Discuss treatment for noncardiogenic pulmonary edema.
Introduction

Pulmonary edema typically is associated with some manner of cardiac dysfunction, whether it stems from failure of the left or the right side of the heart, in conjunction with an apparent volume excess. Usually, the patient with pulmonary edema has suffered repeated cardiac insults resulting in degradation of cardiac performance, such as might be seen with myocardial infarction or the result of some form of cardiomyopathy. In any event, the heart is no longer capable of achieving adequate forward flow, which results in a buildup of fluid within the pulmonary circulation.

During the past 20 years, the phenomenon of noncardiogenic pulmonary edema (NCPE) has been described and reported numerous times in the literature. Most often, the NCPE occurs as the result of acute upper airway obstruction, of which laryngospasm is one form, but it also has been reported in association with the administration of naloxone and nalmeprine. This form of pulmonary edema often can be attributed to the administration of anesthesia and will be the focus of this Journal course.

Literature review and discussion

There are basically 4 pathophysiological processes that can result in the development of pulmonary edema:

1. Increased pulmonary capillary pressure.
2. Decreased plasma colloid osmotic pressure.
3. Increased pulmonary capillary permeability.
4. Decreased or more negative intrathoracic pressure resulting in reduced interstitial hydrostatic pressure.

A forced exhalation against a closed glottis is termed the Valsalva maneuver. The mechanical and physiologic opposite of the Valsalva is the Müller maneuver: a forceful inspiratory effort exerted against a closed glottis. Common causes of upper airway obstruction associated with anesthesia are laryngospasm and laryngeal closure at 3 levels: the supraglottic folds, the false vocal cords, and the true vocal cords. A closed glottis can be simulated by the patient emerging from anesthesia and biting down forcefully on the endotracheal tube while attempting inspiration.

The incidence of laryngospasm in a computerized retrospective study was estimated to be 8.7 per 1,000 patients undergoing general anesthesia; these investigators also estimate the incidence for the pediatric population to be about 17.4 per 1,000. Factors that increase the possibility of laryngospasm include blood and secretions, emesis, attempting intubation without adequate depth of anesthesia, exubiating the patient during the excitement phase of emergence, suctioning, and surgical stimulation. Increasing the risk of laryngospasm necessarily increases the risk of the Müller maneuver.

Although the true incidence of NCPE after upper airway obstruction has not been documented, it has been estimated at about 12% in the pediatric population and at about 11% in the adult population. If one combines these 2 estimates, the estimated incidence of NCPE after upper airway obstruction for the pediatric population would be approximately 2 per 1,000 and for the adult population, about 0.95 per 1,000. The pediatric population has a slightly higher incidence due, at least in part, to an overall greater incidence of laryngospasm, as well as a larger portion of the inspiratory effort being transmitted to the lungs because of greater chest wall compliance.

The Table lists diseases states that also are

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**Figure 1. Starling forces in the lung**

<table>
<thead>
<tr>
<th>Alveolus</th>
<th>Interstitium</th>
<th>Capillary</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P_A = 0$</td>
<td>$P_i = -4$, $\pi_i = 9$</td>
<td>Arterial end $P_c = 17$, $\pi_c = 24$, $P_i = 12$ Venous end</td>
</tr>
</tbody>
</table>

\[
\dot{Q} = KA[(P_c - P_i) - \sigma(\pi_c - \pi_i)]
\]

$\dot{Q}$ = The rate of fluid transfer to the interstitium
$K$ = Hydraulic conductance (ie, the rate of flow per unit pressure gradient across the endothelium)
$P_c$ = Hydrostatic pressure in the pulmonary microvasculature
$P_i$ = Hydrostatic pressure in the interstitium
$\sigma$ = Reflection coefficient for albumin
$\pi_c$ = Osmotic pressure within pulmonary microvasculature
$\pi_i$ = Osmotic pressure within interstitium
$A$ = Capillary surface area
$P_A$ = Alveolar pressure

*All pressures expressed in mm Hg.
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associated with NCPE.\textsuperscript{5} In addition to those predisposing factors, one should add young, healthy, athletic patients.\textsuperscript{9} Presumably because of their increased physical conditioning and muscle strength, such patients are able to generate profoundly negative intrathoracic pressures.

The M"uller maneuver produces markedly negative pressures, as much as \(-100\) to \(-140\) cm H\(_2\)O in adult males.\textsuperscript{9} Although this manifestation of NCPE is probably the culmination of a number of factors, it seems to be most closely associated with the decreased or more negative intrathoracic pressure, which, in turn, greatly reduces the interstitial hydrostatic pressure.\textsuperscript{1} Figure 1 reviews the forces in effect within the lungs from Starling’s equation.\textsuperscript{10}

Besides the 4 factors noted above, at least 2 more factors contribute to the development of NCPE. First, pulmonary capillary permeability is increased by the physical damage to the capillary as a result of the markedly negative intrathoracic pressure produced during the M"uller maneuver (Figure 2).\textsuperscript{10} Similar damage to the pulmonary capillaries has been demonstrated in reexpansion pulmonary edema.\textsuperscript{11} Reexpansion pulmonary edema refers to a manifestation of high permeability pulmonary edema.\textsuperscript{12} This high permeability results from widespread trauma to the capillaries that is encountered when a collapsed lung is rapidly reinflated.\textsuperscript{12} Hypoxia also is known to increase pulmonary capillary permeability.\textsuperscript{13} The hypoxia produces a central nervous system-mediated hyperadrenergic state, which also results in an increase in pulmonary capillary permeability.\textsuperscript{14,15} The induced hyperadrenergic state produces a generalized hypertension. However, the pressure within the pulmonary circuit, despite being elevated itself, is significantly less than the pressure in the systemic circulation; therefore, blood is diverted from the systemic to the pulmonary circuit.\textsuperscript{16} This increase in pulmonary circuit volume results in increased pulmonary capillary pressure as well.\textsuperscript{16}

Second, the negative pressure produced by the M"uller maneuver has direct effects on venous return, as well as the heart. Buda et al observed a decline in ventricular performance during sustained negative intrathoracic pressure.\textsuperscript{17} During the sustained negative intrathoracic pressure (M"uller maneuver), these investigators observed: 9\% to 11\% increases in end-diastolic volume, a 6\% decrease in blood pressure, no change in heart rate, an 18\% to 25\% elevation of end-systolic volume, significant decreases in ejection fraction, increased left ventricular transmural pressure, as well as significant

\begin{table}[h]
\centering
\begin{tabular}{|l|l|l|}
\hline
\textbf{Right heart} & \textbf{Lungs} & \textbf{Left heart} \\
\hline
I. Negative & I. Factors promoting pulmonary edema & I. Left ventricle dysfunction leading to decreased left ventricle stroke volume \\
Intrapleural pressure - increased venous return & 1. Negative interstitial pressure & 1. Increased afterload \\
II. Hyperadrenergic response leads to central redistribution of blood volume due to: & 2. Increased pulmonary blood volume & 2. Acidosis \\
\hspace{1cm} anxiety & 3. HPV and hyperadrenergic-environment & 3. Hypoxemia \\
\hspace{1cm} hypoxia & 4. Increased pulmonary venous pressure (left ventricle dysfunction) & II. Elevated left sided pressures secondary to decreased compliance \\
\hspace{1cm} hypercarbia & 5. Increased pulmonary capillary permeability & 1. Ventricular interdependence \\
\hspace{1cm} cerebral ischemia & II. Factors opposing pulmonary edema & 2. Hypoxia \\
B \rightarrow \textbf{Blood flow in} & 1. Auto-positive end-expiratory pressure & 3. Acidosis \\
& 2. Lymphatics & II. Elevated left sided pressures secondary to decreased compliance \\
& 3. Valsalva maneuver & \hspace{1cm} 1. Ventricular interdependence \\
& 4. Fixed vs variable extrathoracic airway obstruction & 2. Hypoxia \\
\hline
\end{tabular}
\caption{Multifactorial pulmonary edema and upper airway obstruction pathogenesis\textsuperscript{10}}
\end{table}

(Reprinted with permission from Lang SA, Duncan PG, Shephard DAE, Ha HC.\textsuperscript{10})
decreases in velocity of fiber shortening,\textsuperscript{17} all of which produce increased afterload on the ventricles. Venous return to the right side of the heart increases slightly in response to the slightly subatmospheric pressure of a normal inspiratory effort; the dramatic negative pressure generated by the Müe ller maneuver tremendously increases the venous return.\textsuperscript{10} The afterload and venous return factors, along with ventricular interdependence result in a loss of left ventricular compliance and increased left ventricular end-diastolic pressure. Ventricular interdependence refers to the direct influence mechanical events occurring within one ventricle exert upon the other ventricle\textsuperscript{18-20} Pulmonary microvascular pressures also are altered, thus facilitating pulmonary edema formation.\textsuperscript{17}

In addition to a physical cause for the development of NCPE, a pharmacologic cause also must be considered. Antagonism of the depressant effects of opioids is a common practice. However, numerous adverse effects have been reported, including the acute development of pulmonary edema.\textsuperscript{21-23} Because naloxone is a pure antagonist devoid of any agonist properties, it competes with the opioid at the receptor sites.\textsuperscript{24} The competition for the receptor sites within the central nervous system effectively produces a low-dose opioid effect. This low-dose effect may produce an increased catecholamine release from the adrenal medulla, inducing a hyperadrenergic state.\textsuperscript{25} Acute pulmonary edema also has been reported after administration of the new narcotic antagonist, nalmefene; this new antagonist is equipotent with naloxone but demonstrates a longer duration of action.\textsuperscript{26} Prough et al suggested that pulmonary edema observed in healthy patients, after narcotic antagonism, might be of neurogenic origin and have a secondary stimulation of the central nervous system, in turn, resulting in pulmonary venoconstriction and hypertension.\textsuperscript{27}

In the hyperadrenergic state, the systemic circulation becomes a high-resistance pathway, whereas the pulmonary circuit becomes a lower-resistance pathway.\textsuperscript{25} Blood shifts into the pulmonary circulation resulting in a relative volume overload that may damage the pulmonary vessels and result in increased pulmonary capillary permeability.\textsuperscript{25} Although the generalized hypertension is transient, the injury to the pulmonary circuit persists in the form of increased pulmonary capillary permeability and pulmonary edema, even when the general hemodynamics and cardiac function have returned to a more normal state, similar to that found in neurogenic pulmonary edema.\textsuperscript{28}

The onset of NCPE following upper respiratory obstruction can be immediate but also may be delayed from several minutes to several hours after the insult. Both forms of NCPE discussed are distinctive because of the rapidity of resolution, usually within 12 to 24 hours.\textsuperscript{10}

### Treatment

As with any complication, prevention is preferable. In the event of laryngospasm, early recognition, acquisition and maintenance of an adequate airway, and delivery of supplemental oxygen are of paramount importance.\textsuperscript{10} Most often, supplemental oxygen is sufficient to maintain adequate arterial oxygenation. However, with more severe manifestations of NCPE, more aggressive and/or invasive measures may be required. These measures include paralysis (to relieve the glottic spasm), intubation, and ventilatory support—with or without positive-end expiratory pressure or continuous positive airway pressure.\textsuperscript{9} In addition, the patient suspected of having suffered laryngospasm should be observed for a longer period of time in the postanesthesia care unit (PACU) than otherwise would be expected.\textsuperscript{1} Suggested length of stay for such a patient in the PACU ranges from 2 to 12 hours because of the delay in onset of pulmonary edema that is possible. Continuous pulse oximetry is an integral part of the monitoring for such a patient. Diuresis, particularly using furosemide, may prove beneficial. Furosemide has demonstrated

| Table. Disease states associated with noncardiogenic pulmonary edema$^a$ |
|-------------------|---------------------|
| Sepsis            | Fat/air embolism    |
| Smoke inhalation  | Pancreatitis        |
| Oxygen toxicity   | Inhaled chemical-induced lung injury |
| Near drowning     | Transfusion reaction |
| High altitude rapid ascent | Postreexpansion of the lung |
| Uremia            | Postradiation of the pulmonary system |
| Aspiration of gastric contents | Drug ingestion |
| Disseminated intravascular coagulation | Interstitial viral pneumonia |
| Craniocerebral trauma | Traumatic pulmonary contusion |
the ability to mildly increase peripheral venous capacitance. The increase in venous capacitance, which precedes diuresis by about 15 minutes, reduces the ventricular preload and can help reduce the workload of the stressed myocardium. No clear efficacy for the use of furosemide has been demonstrated for cases of NCPE, but in view of these derived benefits, it would seem reasonable and appropriate.

As mentioned, prevention is best. There are measures that may reduce the possibility of laryngospasm and the Müller maneuver. These measures are adequate suctioning of the oropharynx and avoiding extubation during the excitation phase of emergence. Although recommending these measures may seem elementary, they are of vital importance, as is patience in preparing the patient for tracheal extubation.

**Summary**

Noncardiogenic pulmonary edema is an emergency condition that can, at times, be directly attributable to 2 anesthesia entities: laryngospasm and the administration of naloxone; although other entities, unrelated to anesthesia, exist (see Table). These anesthesia-related causes of NCPE, in particular that resulting from upper airway obstruction, have been reported with seemingly increased frequency in recent years. Both causes can be viewed as preventable and avoidable. By understanding the pathophysiology involved, avoidance of naloxone or nalmefene, vigilance, and patience in the preparation for extubation, the incidence of these manifestations of NCPE can be greatly reduced.

**REFERENCES**


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