Review Articles

Pulmonary oedema associated with airway obstruction

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The purpose of this review is to describe the pathogenesis of pulmonary oedema associated with upper airway obstruction, summarize what is known of its clinical presentation, and reflect upon its implications for the clinical management of airway obstruction. The pathogenesis of pulmonary oedema associated with upper airway obstruction is multifactorial. However, as the phrase "negative pressure pulmonary oedema" suggests, markedly negative intrapleural pressure is the dominant pathophysiological mechanism involved in the genesis of pulmonary oedema associated with upper airway obstruction. The frequency of the event is impossible to ascertain from the literature but paediatric cases requiring airway intervention for croup or epiglottitis and adults requiring airway intervention for emergence laryngospasm or upper airway tumours account for over 50 per cent of the documented cases in each age group, respectively. Individuals at risk should be observed closely while they remain at risk. The majority of cases present within minutes either of the development of acute severe upper airway obstruction or of relief of the obstruction. Resolution is typically rapid, over a period of a few hours. Rarely is anything more required for management than the maintenance of a patent airway, supplemental oxygen, and, in approximately 50 per cent of cases, mechanical ventilation and positive end-expiratory pressure.

Dans cet article, nous décrivons la pathogénése de l'oedème pulmonaire associé à l'obstruction de la partie supérieure des voies respiratoires. Nous en revoyons les aspects cliniques et, en analysons l'importance sur l'attitude à prendre devant une obstruction des voies aériennes. Les mécanismes sous-jacentes à ce type d'oedème pulmonaire sont multiples, le principal demeurant toutefois la présence de pressions intrapleurales « très » négatives. L'incidence du phénomène demeure difficile à évaluer mais il semble bien que chez les enfants, près de 50 pour cent des épisodes se produisent dans des cas de laryngite ou d'épiglottite nécessitant une intubation tandis que chez les adultes, on en retrouve une proportion semblable associée aux laryngospasmes survenant à l'émergence de l'anesthésie ou dans les cas de tumeurs situées haut dans les voies aériennes. Une fois identifiées, les victimes potentielles devraient être observées de près tant que le risque persiste même si ce sont les premières minutes qui suivent le développement ou la résolution d'une obstruction aiguë qui sont les plus critiques. Ce type d'œdème pulmonaire est transitoire, s'estompant en quelques heures. S'il survient, on doit s'assurer de la perméabilité des voies aériennes et faire respirer de l'oxygène quoique dans près de la moitié des cas, la ventilation mécanique avec pression positive en fin d'expiration s'avérera nécessaire.

Key words
AIRWAY: obstruction;
COMPLICATIONS: oedema, pulmonary;
LARYNX: spasm;
LUNG: oedema.

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Fatalities from upper airway obstruction are usually due to asphyxia from markedly diminished or absent airflow. However, rapid re-establishment of the airway does not guarantee improvement in gas exchange. It has recently been recognized that morbidity may result from the delayed effects of the obstruction.

As early as 1927 an association between upper airway obstruction and the development of pulmonary oedema was suggested in spontaneously breathing dogs exposed to inspiratory resistive loads.[1] These dogs' lungs were found at autopsy to be "boggy." However, the pathophysiological correlation between these events was not recognized until 1942,[2] and the first description of pulmonary oedema associated with upper airway obstruction did not appear until 1973.[3] The first report of the clinical significance of this phenomenon was published in 1977.[4] Since then there have been 77 case reports of pulmonary oedema associated with upper airway obstruction (Tables I and II).

TABLE I Adult cases (n = 32)

Age (yr)	*M:F*	*Common obstructive events*	*Time to onset of pulmonary oedema following airway obstruction (mins) n = 25**	*Resolution of pulmonary oedema (hrs) n = 26*	*Intubation*	*PEEP or CPAP*	*Mechanical ventilation*
Mean 37.6 ± SD 16.6	1.2:1	Laryngeal spasm 18/32	Mean 25.6 ± SD 38.8	Mean 29.7 ± SD 19.1	27/32	12/32	19/32
Range 12–79		Aiway tumour 7/32	Range 3–150 Mode 5	Range 6–72 Mode 24			

*Time to recognized resolution. Excludes cases complicated by pneumothorax, pneumonia, aspiration or heart failure.
SD = standard deviation.
PEEP = positive end-expiratory pressure.
CPAP = continuous positive airway pressure.
n = 32 unless otherwise stated.
References: 4, 6, 10, 11, 42, 43, 45–47, 50, 52, 64–78.

TABLE II Paediatric cases (≤10 yr) (n = 45)

Age (yr)	*M:F n = 30*	*Common obstructive events*	*Time to onset of pulmonary oedema following airway obstruction (mins) n = 30*	*Resolution of pulmonary oedema (hrs) n = 30**	*Intubation*	*PEEP or CPAP*	*Mechanical ventilation*
Mean 3.0 ± SD 2.4	2.4:1	Epiglottitis 15/45	Mean 33.3 ± SD 66.1	Mean 42.4 ± SD 30.8	41/45	16/30	14/30
Range 1/12–10		Group 18/45 Foreign body 4/45	Range 5–240 Mode 5	Range 2–96 Mode 12			

*Time to recognized resolution. Excludes cases complicated by pneumothorax, pneumonia, aspiration or heart failure.
SD = standard deviation.
PEEP = positive end-expiratory pressure.
CPAP = continuous positive airway pressure.
n = 45 unless otherwise stated.
(Galvis[61] does not give full information on 15 patients.)
References: 3, 5, 44, 49, 54–63.

The true incidence of pulmonary oedema associated with airway obstruction is not known. However, the incidence of pulmonary oedema associated with airway obstruction has been estimated at 12 and 11 per cent in paediatric and adult populations requiring active airway intervention (intubation or tracheostomy) for acute upper airway obstruction of varying aetiology.[5,6] Therefore, considering the relative infrequency with which it has been reported, in contrast to the frequency of presentation of perianaesthetic airway obstruction, pulmonary oedema associated with upper airway obstruction may go unrecognized. The purpose of this review is to describe the pathogenesis of the syndrome, summarize what is known of its clinical presentation, and reflect upon its implications for the clinical management of airway obstruction.

Pathogenesis

Figure 1 is a brief review of the Starling forces that influence the movement of fluid across the pulmonary capillaries.[7–9] The major factors favouring formation of pulmonary oedema fluid are:

1 The hydrostatic pressure in the pulmonary microvasculature (Pc).
2 The negative hydrostatic pressure in the pulmonary interstitium (Pi).
3 The colloid osmotic pressure of the pulmonary interstitium (πi).

The major factors retarding the formation of pulmonary oedema fluid are pulmonary capillary colloid osmotic pressure (πc) and pulmonary capillary integrity. When capillary integrity is impaired fluid movement into the interstitium is favoured. Capillary endothelial permeability is represented by the hydraulic conductance K (the flow rate of fluid per unit pressure gradient across the endothelium), and the reflection coefficient σ (a measure of the ability of the endothelial membrane to prevent the

movement of solute, principally albumin, across the membrane). A value of unity for the reflection coefficient indicates total reflection of solute and corresponds to zero colloid osmotic pressure in the pulmonary interstitium. A value of zero for the reflection coefficient indicates free premeability of the capillary membrane to proteins and therefore excludes colloid osmotic pressure from having any influence on the movement of water in the lungs.

The pathogenesis of pulmonary oedema associated with upper airway obstruction is multifactorial.[10,11] Recent advances in methodology have facilitated our understanding of the pathogenesis of this seemingly infrequent event.[12–16] The principal factors in the pathogenesis of pulmonary oedema associated with upper airway obstruction are shown in Table III.

Haemodynamic changes secondary to negative intrathoracic pressure

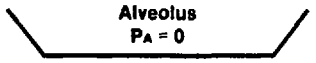
Pulmonary oedema associated with airway obstruction has been called negative pressure pulmonary oedema (NPPE) because most of the proposed pathogenetic mechanisms relate directly to the development of markedly negative intrapleural pressure (i.e., sustained peak inspiratory intratracheal pressures as low as −50 cm of water).[17,18] Furthermore, markedly negative intrapleural pressure alone can explain the association of upper airway obstruction and pulmonary oedema.[19,20]

It has recently been demonstrated by Smith-Erickson and Bo[19] and Lloyd *et al.*[20] that negative intrapleural pressures can promote lung lymph formation. Smith-Ericksen and Bo[19] demonstrated in an isolated, perfused rabbit lung preparation that negative "pleural" pressures cause pulmonary weight gains which were attributed to interstitial oedema formation. Lloyd *et al.*[20] demonstrated that inspiratory resistance loading in sheep doubled baseline lung lymph flow. The conclusion of such animal work, if extrapolated to humans, is that negative pleural pressure can cause pulmonary oedema associated with upper airway obstruction.

TABLE III Factors contributing to the pathogenesis of pulmonary oedema associated with airway obstruction

Haemodynamic changes secondary to markedly negative intrathoracic pressures
Enhanced venous return to the right heart
Pooling of blood in the lungs with inspiration
Ventricular interdependence
Afterload effects on both the right and left ventricles
Loss of capillary integrity
Hypoxia and hyperadrenergic state
Nonuniform elevation of both pre- and post-capillary pulmonary vascular resistances
Loss of capillary integrity
Redistribution of blood volume to the lungs
Myocardial depression

Starling Forces in the Lung *



Interstitium
$P_I = -4$ $\pi = 9$

Capillary

Arterial End — $P_c = 17$ — $\pi_c = 24$ — $P_c = 12$ — Venous End

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

- $\dot{Q}$ = 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 interstitium
- σ = reflection coefficient for albumin
- π_c = osmotic pressure within pulmonary microvasculature
- π = osmotic pressure within interstitium
- A = capillary surface area
- P_A = alveolar pressure

* All pressures expressed in mmHg

FIGURE 1

Peters *et al.*[14,15] studied the independent effects of applying negative pleural pressure during isolated systolic and diastolic events in dogs. The application of negative pleural pressure during systole exposed the left ventricle to an afterload stress, when afterload was expressed as the transmural aortic root pressure (i.e., mean aortic pressure minus pleural pressure[9]). This caused a decrease in left ventricular stroke volume and resulted in increases in both ventricular end–systolic and end–diastolic volumes.

Browers *et al.*[13] demonstrated that lung inflation in zone 2 (West[21]) conditions will decrease pulmonary venous return because blood pools in the lungs during lung inflation. However, lung inflation in zone 3 (West[21]) conditions will increase pulmonary venous return. Thus, left ventricular end–diastolic volume changes, preload changes, during inspiration are dependent upon the net result of many factors. Negative intrapleural pressure during systole increases left ventricular end–diastolic volume via an afterload stress on the left ventricle. Depending upon the zoning conditions of the lung, the application of negative intrapleural pressure can either increase (zone 3 West[21]) or decrease (zone 2 West[21]) pulmonary venous return and left ventricular end–diastolic volume.

Starling's equation (Figure 1) states that it is the balance of hydrostatic and colloid osmotic pressures across a variably permeable membrane that determines fluid flux and is responsible for pulmonary oedema. Therefore, volume changes are only important in that they result in pressure changes.

Despite variable changes in left ventricular end–

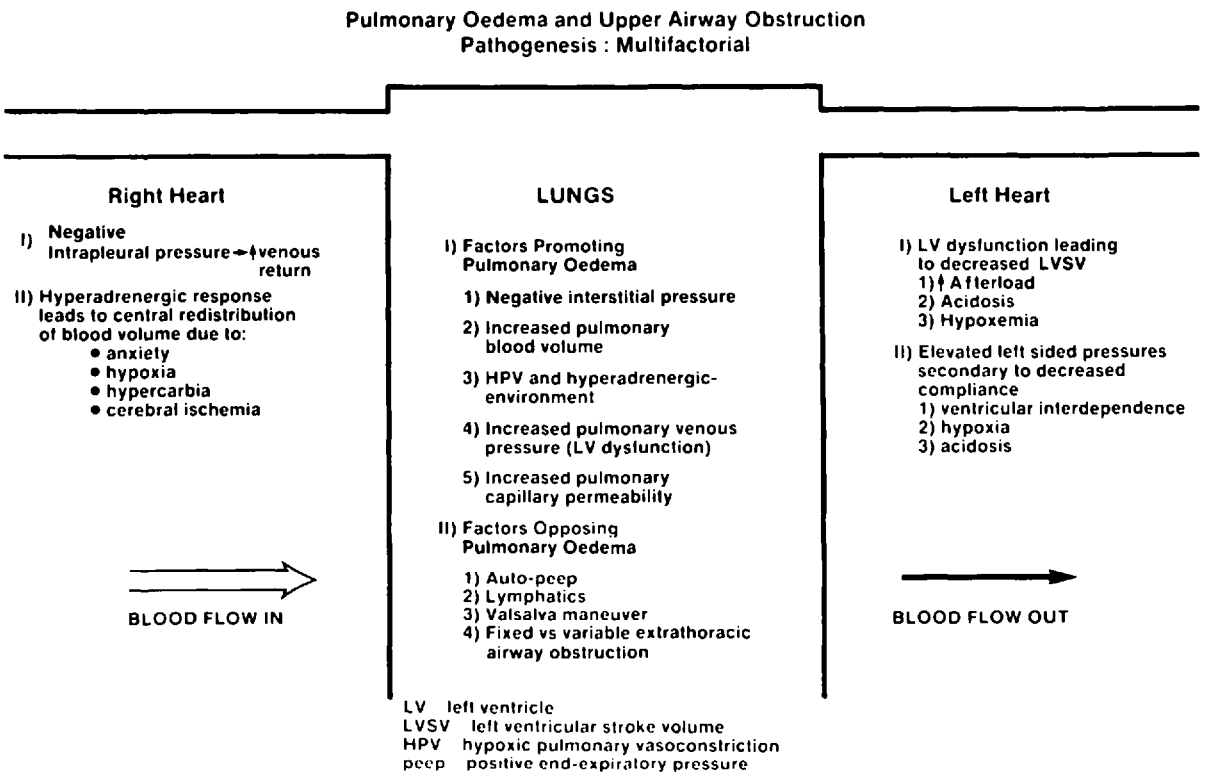


FIGURE 2 Multifactorial pathogenesis of pulmonary oedema associated with upper airway obstruction. Negative intrapleural pressure secondary to upper airway obstruction induces pulmonary oedema formation by increasing venous return to the right heart and by decreasing the output of the left ventricle thereby increasing pulmonary blood volume and microvascular pressures. These effects of negative intrapleural pressure are augmented by the hypoxia and hyperadrenergic state that develop secondary to the airway obstruction. Hypoxia and hyperadrenergia promote translocation of blood from the systemic to the pulmonary circulation, further increasing pulmonary microvascular pressures. Pulmonary capillary permeability is increased by several mechanisms and facilitates pulmonary oedema formation. See the text for a more thorough discussion of the pathogenesis of pulmonary oedema associated with upper airway obstruction and for a discussion of the factors opposing pulmonary oedema formation.

diastolic volume with inspiration, the left ventricular end-diastolic pressure has been found to increase consistently.[14,16] This is due to ventricular interdependence and because venous return to the right side of the heart consistently increases with inspiration. Ventricular interdependence refers to the fact that because of the anatomical continuity between the left and right ventricles (separated only by the interventricular septum), and their restriction within the confines of the pericardium, right ventricular distention is associated with a decrease in left ventricular compliance secondary to a leftward shift of the interventricular septum.[14,15]

Engelberg and Dubois[22] have demonstrated that pulmonary vascular compliance in animals is one-tenth to one-fifth that of the peripheral circulation. On the basis of this work Wise[9] has suggested that pulmonary microvascular pressures can increase secondary to translocation of blood from the peripheral to the pulmonary circuit. This could be due to inflation of the lung in predominantly zone 2 conditions (West[21]) or to a hyperadrenergic state (as discussed in the next section). At the moment this concept remains speculative but is supported by studies by Sarnoff *et al.*[23] Using a simple gravimetric technique they demonstrated that the translocation of 100 ml of blood to the pulmonary circuit of a dog (approximately 5 ml · kg^{-1}) in a "vasoconstricted" state increased the left auricular pressure from 10 to 40 mmHg.[23]

In humans, rapid re-expansion of a pneumothorax by the application of markedly negative pressures can result in pulmonary oedema that is thought to be due, at least partially, to the loss of capillary integrity. The pulmonary capillary permeability defect in re-expansion pulmonary oedema has been demonstrated by aspirating exudates from the lungs of animals exposed to a re-expansion stress.[24] Pulmonary oedema not associated with a permeability defect will have an associated alveolar transudate – not an exudate.[9,25] The negative pressures associated with partial or complete upper airway obstruction may similarly jeopardize pulmonary capillary integrity, although experimental evidence is lacking.

Figure 2 summarizes the theoretical factors responsible for precipitating pulmonary oedema secondary to mark-

edly negative intrathoracic pressure. Negative pleural pressure increases venous return to the right heart while simultaneously placing an afterload stress on both the right and left ventricles. Increased venous return to the right heart, by means of ventricular interdependence, causes a decrease in left ventricular compliance and elevated left ventricular end-diastolic and pulmonary microvascular pressures, which favour formation of pulmonary oedema. This is aggravated by a sustained decrease in left ventricular stroke volume, resulting in a further rise in pulmonary blood volume and microvascular pressures and, possibly, by a low pulmonary vascular compliance and a mechanically induced increase in pulmonary capillary permeability.

Hypoxia and a hyperadrenergic state

Although negative intrapleural pressure is the primary pathological event in the development of pulmonary oedema associated with upper airway obstruction, hypoxia and a hyperadrenergic state both contribute to its development.

There are similarities between pulmonary oedema associated with upper airway obstruction and neurogenic and high-altitude pulmonary oedema. Hypoxia increases both pre- and postcapillary pulmonary vascular resistances and this can occur in a nonuniform fashion.[26-29] This results in a generalized increase in pulmonary vascular pressures and, furthermore, can markedly increase pulmonary capillary pressures in areas with unchanged precapillary arteriolar resistances. Furthermore, in dogs, norepinephrine infusion increases postcapillary pulmonary vascular resistance to a greater extent than precapillary resistance.[30] This would also lead to increases in pulmonary capillary pressure.

Hypoxia can alter capillary integrity and precipitate a hyperadrenergic state.[10,31] In a model of neurogenic pulmonary oedema, perfusion of the brain of animals with hypoxic blood resulted in increases in pulmonary extravascular lung water.[31] Such neurogenic pulmonary oedema is associated with a massive adrenergic response.[32-34] In a model of traumatic neurogenic pulmonary oedema[35] pulmonary oedema failed to develop in animals pretreated with alpha-adrenergic blocking agents, wheras it did in untreated animals. A hyperadrenergic response is thought to redistribute blood from the systemic veins to the pulmonary circuit[23] and to increase pulmonary vascular resistance.[32,36,37] It is also speculated that the hyperadrenergic response independently alters capillary integrity.[38-40] All these phenomena may promote pulmonary oedema formation. Finally, it is recognized that hypoxia and metabolic acidosis are known myocardial depressants,[41] and may aggravate any other tendency to pulmonary oedema formation.

The effects of hypoxia and a hyperadrenergic state which are thought to contribute to the pulmonary oedema occurring with upper airway obstruction are summarized in Figure 2. Hypoxia and the resulting hyperadrenergic state promote pulmonary oedema formation by:

1 Translocation of blood from the systemic to the pulmonary circulation.
2 Generalized increase in pulmonary vascular resistance.
3 Increase of pulmonary capillary permeability.

Hypoxia and the resulting metabolic acidosis further aggravate the tendency to pulmonary oedema formation by depressing myocardial performance.

Pathophysiological puzzles

Many authors have advocated prolonged surveillance (i.e., for up to 18 hr) of patients suffering perioperative obstruction in an attempt to detect any delayed pulmonary oedema.[42,43] An adequate explanation for such delay has not been suggested and the merits of prolonged observation remain to be demonstrated. The majority of cases of pulmonary oedema associated with upper airway obstruction (80 per cent of case reports which documented the onset time of pulmonary oedema) present within minutes of the onset of severe obstruction or the relief of that obstruction.

Some authors have observed that pulmonary oedema occurs only after the airway obstruction has been corrected and not during the airway obstruction. It has been surmised that the Valsalva manoeuvres (expiration against a closed airway) that accompany the Mueller manoeuvres (inspiration against a closed airway) during respiratory efforts against a closed glottis protect the pulmonary vasculature and that only with relief of the obstruction does pulmonary oedema ensue.[44-47] However, it has been shown that, despite the Valsalva manoeuvres, the mean intratracheal pressure is still markedly negative.[17-18]

Because of the prolonged expiratory phase experienced during an asthmatic attack air trapping occurs. This results in hyperinflation of the lungs and a residual positive airway pressure at end-expiration. This phenomenon has been called "auto-peep" by Pepe *et al.*.[48] Several authors[5,10,46,49] have suggested that an "auto-peep" phenomenon (similar to that seen in asthmatics) protects the alveoli from flooding and masks the radiographic appearance of pulmonary oedema during the obstructive event.

Alternatively, the timing of pulmonary oedema, during or after the relief of upper airway obstruction, may depend on whether the nature of the obstruction is fixed or variable.[50] Fixed upper airway obstruction would result in Valsalva and Mueller manoeuvres of equal magnitude, favouring development of pulmonary oedema after relief of the obstruction. Variable extrathoracic upper airway obstruction would favour the Mueller manoeuvres (i.e.,

obstruction worsens on inspiration) and the development of pulmonary oedema during the period of obstruction and this is supported by Moore *et al.*[1] They found that pulmonary oedema occured when respiratory resistance was limited to inspiration but not when limited to expiration. Furthermore, more recent reports have described impaired gas exchange and radiographic evidence of pulmonary oedema in humans before relief of the airway obstruction.[49,51] Since the pathogenesis of pulmonary oedema associated with airway obstruction seems multifactorial, it is not unreasonable to assume that the case reports do not represent a homogeneous group, and presentations may vary with the clinical situation.

It seems unlikely that increased capillary permeability can play a major role in light of the seemingly benign nature of negative pressure pulmonary oedema.[20] Most cases resolve within six to 24 hours with little more than intubation and administration of oxygen.[52] However, there is good evidence that permeability defects can recover rapidly in high altitude pulmonary oedema.[25]

Clinical recognition and treatment

The clinical characteristics of this condition, as described in the published case reports, are summarized in Tables I and II. In adults, laryngospasm during emergence from anaesthesia and patients with upper airway tumours account for more than 50 per cent of the cases, while in children aged ten years or less epiglottitis and croup constitute more than one half of the cases. In general, the condition appears more commonly in healthy young individuals than in older ones. The onset is rapid (within minutes) but it may be delayed for up to four hours following the occurrence of the obstructive event. Although no conclusions can be made, a review of the case reports suggests that the rapidity with which pulmonary oedema develops following upper airway obstruction relates to the rate of onset and the severity of the airway obstruction. The pulmonary oedema is self-limited, usually resolving within 12 to 24 hours, and in most cases nothing more than supportive care, including oxygen administration, is required.

In both adults and children, 85 per cent required tracheal intubation for a short period, which emphasizes the importance of ensuring a patent upper airway. Analysis of the case reports indicates that approximately 50 per cent of the patients required pulmonary ventilation and about 50 per cent of the patients required continuous positive airway pressure or positive end–expiratory pressure (i.e., CPAP and PEEP, respectively). Mechanical ventilation and PEEP should be reserved for the treatment of patients in whom adequate oxygenation cannot be maintained despite the maintenance of a patent upper airway and the administration of supplemental oxygen. In most cases, neither aggressive haemodynamic monitoring nor drug therapy is needed, assuming the diagnosis is clear.

The primary alternative diagnosis is aspiration pneumonia. Aspiration pneumonia cannot be conclusively ruled out as the cause of pulmonary oedema even without a history of frank regurgitation. However, the management of aspiration pneumonia is identical to that of pulmonary oedema associated with upper airway obstruction unless an infectious complication ensues.[53] Of more importance is the exclusion of the causes of pulmonary oedema whose management differs from that of NPPE (especially iatrogenic volume overload and cardiogenic aetiologies). Differentiation should be possible in most cases from a review of the patient's history (looking for evidence of preexisting myocardial dysfunction), a physical examination of the patient (e.g., gallop rhythm, murmurs), electrocardiography (e.g., rhythm disturbances and abnormalities suggestive of ischaemia or infarction) and in rare instances echocardiographic assessment of myocardial performance or invasive haemodynamic assessment (i.e., pulmonary artery catheterization).

Pulmonary artery catheterization of individuals thought to have NPPE has revealed normal central venous pressures, pulmonary artery pressures and pulmonary capillary wedge pressures when the procedure is performed after the development of pulmonary oedema.[47,62,66,77] This is important in situations where the diagnosis is unclear. However, these observations may not be relevant to a discussion of the cause of pulmonary oedema associated with upper airway obstruction as events leading to the development of pulmonary oedema are transient and need not be sustained after relief of the airway obstruction.

In brief, the keys to management are recognition of the condition and provision of adequate arterial oxygenation (arterial saturation of at least 90 per cent) by maintenance of the airway, administration of supplemental oxygen and, if necessary, institution of positive pressure ventilatory support (i.e., CPAP or mechanical ventilation with PEEP) while the condition resolves spontaneously.

Summary

Pulmonary oedema associated with upper airway obstruction is an increasingly recognized phenomenon. Although the real incidence is unkown it appears to be a common occurrence in both the paediatric and adult age groups. The pathogenesis appears to be multifactorial and the myriad of case reports may not represent a homogeneous group. Nevertheless, it is thought that the primary pathophysiologic events are related to the markedly negative intrapleural pressures associated with upper airway obstruction.[2,16,19,20,51] In conclusion, the pres-

ence of pulmonary oedema secondary to upper airway obstruction may complicate an otherwise simple clinical course and, although both self-limited and benign, may produce an unanticipated and dangerous decrease in arterial oxygenation.

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