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EDITORIAL

Postpneumonectomy pulmonary oedema revisited

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Postoperative pulmonary oedema occurs early postoperatively (>6 h) and is associated with a net fluid overload. A recent survey of 8,195 major operations showed an incidence of 7.6%, with a mortality of 11.9% [1]. Postpneumonectomy pulmonary oedema (PPO) occurs after pneumonectomy [2] or lung resection [3], in the absence of left ventricular dysfunction or infection. The overall incidence is 5.1% with a mortality of 3.6% [4].

Although PPO has not yet been well defined, there is a growing body of evidence suggesting that increased pulmonary perfusion flow and the subsequent rise in net filtration pressure [5], a restricted capillary volume [2], endothelial damage, amputation of the lymphatic system [6] and hyperinflation [7] are the main causes of this poorly understood clinical entity [8].

PPO occurs more often after pneumonectomy than after partial lung resection and right pneumonectomy seems to be more frequently involved [9, 10]. Prior radiotherapy and intraoperative fluid overload are independent risk factors in cancer patients [3]. Transfusion of fresh frozen plasma and higher mechanical ventilation pressures during surgery are also independent factors [11].

Prognosis varies according to the presentation. Although some studies report a high mortality (~100%) [12], others found different degrees of lung impairment, from acute lung injury (mild-to-moderate) to adult respiratory distress syndrome (ARDS) (severe), the latter being associated with a poor prognosis [3, 4, 11].

Experimental and clinical studies suggest that factors other than fluid overload contribute to disease severity [10]. In dogs, pneumonectomy does not acutely increase susceptibility to extravascular lung water formation (EVLW) caused by haemodynamic challenge [13]. PPO occurs after contralateral pneumonectomy and mediastinal lymphatic interruption [6]. The simple procedure of thoracotomy results in an increase in EVLW, and the addition of manual compression of the lung facilitates this increase in EVLW even further [14]. Postoperative pulmonary function, assessed by means of the forced expiratory volume in one second, is reduced for ≥2 weeks, irrespective of the extent of pulmonary resection [15]. Pulmonary endothelial permeability is increased after pneumonectomy [16, 17]. All these data suggest that the pulmonary blood/gas barrier is somewhat altered in PPO because of endothelial or epithelial injury, or both.

In this issue of the *European Respiratory Journal*, JORDAN *et al.* [18] present a review of PPO with emphasis on some hypotheses regarding its pathogenesis. Among different pathogenic factors, the authors focus on the role played by ischaemia, or more precisely hypoxaemia, and reperfusion injury of the remaining lung. In the experimental model of ischaemia/reperfusion of the lungs, an imbalance between intracellular generation of toxic oxidants [19] and reduced nitric oxide production [20, 21] triggers an inflammatory response. Neutrophils begin rolling along and sticking to the vascular endothelium of the postcapillary venules, and migrate to the interstitium where they release a variety of mediators [22]. A bimodal pattern of injury is observed, consisting of both neutrophil-independent and neutrophil-mediated lung injury, as assessed by increased permeability and neutrophil sequestration [23]. Oxidant stress is also implicated in ARDS, *via* at least two different mechanisms [24]; at an early stage, the endothelial cells generate intracellular toxic oxidants; at a later stage, neutrophils and other inflammatory cells are activated and release extracellular oxidants. There may also be some degree of epithelial injury [25]. Although these mechanisms have been well established in animal models, there are few data available regarding the role of hypoxaemia/reperfusion and oxidative damage in PPO. Indirect evidence suggests that oxidative damage occurs after lung resection [26], but there is no direct evidence demonstrating that ischaemia/reperfusion is the key factor in this instance. One hypothesis proposed by the authors is that, at some stage, free radical production (of both reactive oxygen and nitrogen species) converges to "alter cellular fate" and ultimately PPO. However, if oxidative damage is a rate-limiting factor in PPO, it does not explain when and why PPO does or will not occur. Other factors may also play a role, including the level of pulmonary impairment prior to surgery, the amount of lung resected, the duration of relative hypoxaemia and reperfusion, the residual capillary bed, the nervous and lymphatic involvement, the various therapeutic interventions such as the level of oxygenation, the volu- and barotraumatism induced by mechanical ventilation, and the amount of fluid administered. Some other postoperative factors, including airway obstruction, inhalation, and early sepsis, may also be involved.

Another mechanism alluded to by JORDAN *et al.* [18] refers to the mechanical stress of the pulmonary blood/gas barrier. This phenomenon, described as stress failure [27], relates to ultrastructural changes in the endothelial layer, alveolar/epithelial layer and, sometimes, the extracellular matrix of this barrier. The endothelial and/or epithelial breaks, with oedema and/or haemorrhage, have been observed in the case of increased pulmonary capillary pressure in neurogenic oedema, high-altitude pulmonary

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oedema, exercise-induced pulmonary haemorrhage, mitral stenosis and Goodpasture′s syndrome. Although this has not been thoroughly investigated yet, postpneumonectomy pulmonary oedema might represent another situation in which increased pulmonary capillary pressure, either after clamping of the pulmonary artery or because of a localized area of hypoxaemia, and/or inflammatory mediators, can induce endothelial injury. Moreover, overinflation of the remaining lung may induce an associated epithelial injury. It has been demonstrated that stress failure occurs more frequently at high than at low lung volumes for a given transmural pressure [28]. There is a spectrum from low- reversible, permeability oedema [29] to high-, probably more irreversible, permeability oedema [30], as the transmural pressure is raised. The fact that previous radiotherapy, for instance, is an independent risk factor for postpneumonectomy pulmonary oedema, suggests that some impairment of the interstitium may also play a role. Therefore postpneumonectomy pulmonary oedema could be another example of stress failure, but more studies are needed to further delineate and define a syndrome which encompasses a broad variety of situations.

References

1. Arieff AI. Fatal postoperative pulmonary edema: pathogenesis and literature review. *Chest* 1999; 115: 1371–1377.
2. Caras WE. Post-pneumonectomy pulmonary edema: can it be predicted preoperatively? *Chest* 1998; 114: 928–931.
3. Parquin F, Marchal M, Mehiri S, Herve P, Lescot B. Postpneumonectomy pulmonary edema: analysis and risk factors. *Eur J Cardiothorac Surg* 1996; 10: 929–932.
4. Hayes JP, Williams EA, Goldstraw P, Evans TW. Lung injury in patients following thoracotomy. *Thorax* 1995; 50: 990–991.
5. Rubia M, Gandia F, Duque JL. Recording effective capillary pressure: a useful technique in postpneumonectomy edema. *Arch Bronconeumol* 1996; 32: 483–485.
6. Little AG, Langmuir VK, Singer AH, Skinner DB. Hemodynamic pulmonary edema in dog lungs after controlateral pneumonectomy and mediastinal lymphatic interruption. *Lung* 1984; 162: 139–145.
7. Deslauriers J, Aucoin A, Gregoire J. Postpneumonectomy pulmonary edema. *Chest Surg Clin N Am* 1998; 8: 611–631, ix.
8. Faisy C, Bazelly B, Saidi F, Lafon B, Tordjman R, Parrot A. Postpneumonectomy pulmonary edema. Review of the literature. Apropos of 2 new cases. *Rev Pneumol Clin* 1996; 52: 253–260.
9. Verheijen-Breemhaar L, Bogaard JM, van den Berg B, Hilvering C. Postpneumonectomy pulmonary edema. *Thorax* 1988; 43: 323–326.
10. Waller DA, Gebitekin C, Saunders NR, Walker DR. Noncardiogenic pulmonary edema complicating lung resection. *Ann Thorac Surg* 1993; 55: 140–143.
11. Van der Werff YD, van der Houwen HK, Heijmans PJ, *et al*. Postpneumonectomy pulmonary edema. A retrospective analysis of incidence and possible risk factors. *Chest* 1997; 111: 1278–1284.
12. Turnage WS, Lunn JJ. Postpneumonectomy pulmonary edema. A retrospective analysis of associated variables. *Chest* 1993; 103: 1646–1650.
13. Lee E, Little AG, Hsu WH, Skinner DB. Effect of pneumonectomy on extravascular lung water in dogs. *J Surg Res* 1985; 38: 568–573.
14. Chiyontanda S. Extravascular lung water with special reference to thoracotomy, manual lung manipulation, and rapid fluid transfusion. *Jpn J Surg* 1988; 18: 376–383.
15. Hallfeldt KK, Siebeck M, Thetter O, Schweiberer L. The effect of thoracic surgery on pulmonary function. *Am J Crit Care* 1995; 4: 352–354.
16. Mathru M, Blakeman B, Dries DJ, Kleinman B, Kumar P. Permeability pulmonary edema following lung resection. *Chest* 1990; 98: 1216–1218.
17. Waller DA, Keavey P, Woodfine L, Dark JH. Pulmonary endothelial permeability changes after major lung resection. *Ann Thorac Surg* 1996; 61: 1435–1440.
18. Jordan S, Mitchell J, Quinlan G, Goldstraw P, Evans TW. The pathogenesis of lung injury following pulmonary resection. *Eur Respir J* 2000; 15: 790–799.
19. Adkins WK, Taylor AE. Role of xanthine oxidase and neutrophils in ischemia/reperfusion injury in rabbit lung. *J Appl Physiol* 1990; 69: 2012–2018.
20. Moore TM, Khimenko PL, Wilson PS, Taylor AE. Role of nitric oxide in lung ischemia and reperfusion injury. *Am J Physiol* 1996; 271: H1970–H1977.
21. Lu YT, Liu SF, Mitchell JA, Malik AB, Hellewell PG, Evans TW. The role of endogenous nitric oxide in modulating ischemia-reperfusion injury in the isolated, blood-perfused rat lung. *Am J Respir Crit Care Med* 1998: 157: 273–279.
22. Granger DN, Kubes P. The microcirculation and inflammation: modulation of leukocyte-endothelial cell adhesion. *J Leukoc Biol* 1994; 55: 662–675.
23. Eppinger MJ, Jones ML, Deeb GM, Bolling SF, Ward PA. Pattern of injury and the role of neutrophils in reperfusion injury of rat lung. *J Surg Res* 1995; 58: 713–718.
24. Brigham KL. Oxidant stress and adult respiratory distress syndrome. *Eur Respir J Suppl* 1990; 11: 482s–484s.
25. Hasleton PS, Roberts TE. Adult respiratory distress syndrome - an update. *Histopathology* 1999; 34: 285–294.
26. Williams EA, Quinlan GJ, Goldstraw P, Gothard JW, Evans TW. Postoperative lung injury and oxidative damage in patients undergoing pulmonary resection. *Eur Respir J* 1998; 11: 1028–1034.
27. West JB, Mathieu-Costello O. Stress failure of pulmonary capillaries: role in lung and heart disease. *Lancet* 1992; 340: 762–767.
28. Fu Z, Costello ML, Tsukimoto K, *et al*. High lung volume increases stress failure in pulmonary capillaries. *J Appl Physiol* 1992; 73: 123–133.
29. Elliott AR, Fu Z, Tsukimoto K, Prediletto R, Mathieu-Costello O, West JB. Short-term reversibility of ultrastructural changes in pulmonary capillaries caused by stress failure. *J Appl Physiol* 1992; 73: 1150–1158.
30. Tsukimoto K, Mathieu-Costello O, Prediletto R, Elliott AR, West JB. Ultrastructural appearances of pulmonary capillaries at high transmural pressures. *J Appl Physiol* 1991; 71: 573–582.