Commentary

Airway closure: the silent killer of peripheral airways

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Published: 22 February 2007
This article is online at http://ccforum.com/content/11/1/114
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Critical Care 2007, **11:**114 (doi:10.1186/cc5692)

See related review by Jain and Sznajder, http://ccforum.com/content/11/1/206

Abstract

Tidal airway closure occurs when the closing volume exceeds the end-expiratory lung volume, and it is commonly observed in general anaesthesia, particularly in obese patients. Animal studies suggest that tidal airway closure causes injury to peripheral airways, characterized histologically by rupture of alveolar-airway attachments, denuded epithelium, disruption of airway smooth muscle and increased numbers of polymorphonuclear leucocytes in the alveolar walls. Functionally, this injury is characterized by increased airway resistance. Peripheral airway injury may be a common yet unrecognized complication and may be avoided by application of low levels of positive end-expiratory pressure. Measurement of exhaled nitric oxide is a simple method that may permit early detection of unsuspected peripheral airway injury during mechanical ventilation, both in healthy and diseased lungs.

In this issue of *Critical Care*, Jain and Sznajder [1] consider the role played by the peripheral airways during mechanical ventilation in various pathologies. During mechanical ventilation the end-inspiratory transpulmonary pressure (stress), determined by tidal volume, fluctuates and has been proposed to be the main determinant of ventilator-induced lung injury (VILI) [2]. However, stress is not the sole determinant of VILI, and strain (the ratio between tidal volume and end-expiratory lung volume [EELV]) may also play a role.

Four specific mechanisms that may lead to VILI have been identified. First, regional over-distension caused by application of local stress or pressure forces cells and tissues to assume shapes and dimensions that they would not during unassisted breathing. The second mechanism, the so-called 'low EELV injury' associated with repeated recruitment and de-recruitment of unstable lung units, causes abrasion of the epithelial airspace lining as a result of interfacial forces. Third, surfactant may be deactivated by large alveolar surface area oscillations that stress surfactant adsorption and desorption kinetics and are associated with surfactant aggregate conversion. Fourth, and finally, interdependence mechanisms elevate cell and tissue stress between neighbouring structures with differing mechanical properties. However, little attention has been given to the role played by reduced EELV and airway closure in mediating damage to peripheral airways during mechanical ventilation with 'physiological' tidal volumes in healthy lungs [3].

Peripheral airways are defined as airways that are less than 2 mm in diameter and consist of small membranous, terminal and respiratory bronchioles, as well as alveolar ducts. The small membranous and terminal bronchioles have conductive functions, whereas respiratory bronchioles and alveolar ducts can have both conducting and gas-exchanging functions. They have no cartilage and so they can easily collapse at low EELV (airway closure). Tidal airway closure occurs when the closing volume exceeds the EELV.

Recent animal studies demonstrated that mechanical ventilation at low EELV, even with 'physiological' tidal volumes, may cause permanent mechanical alterations and histological damage to peripheral airways and parenchymal injury in normal lungs [4,5]. Peripheral airway injury consists of epithelial necrosis and sloughing in the membranous and respiratory bronchioles, and rupture of alveolar-bronchiolar attachments; parenchymal inflammation is reflected by an increased number of polymorphonuclear leucocytes in the alveolar septa. It has been suggested that these morphological-functional alterations are the consequence of abnormal stresses that develop locally at the level of both the bronchiolar epithelium and the parenchyma, mainly at alveolar-bronchiolar junctions, as a result of cyclic opening and closing of peripheral airways with tidal ventilation at low lung volumes. Such stresses will be enhanced in the presence of increased

EELV = end-expiratory lung volume; PEEP = positive end-expiratory pressure; VILI = ventilator-induced lung injury.

surface tension caused by surfactant depletion or inactivation, which should take place during ventilation at low lung volumes [6]. Interestingly, because the mucosa of respiratory bronchioles is the main source of exhaled nitric oxide, reduced exhaled nitric oxide concentration has been proposed as an early marker of damage to the peripheral airway mucosa [7]. The morphological-functional alterations described above were abrogated when normal EELV was preserved by application of moderate levels of positive end-expiratory pressure (PEEP); however, this persisted only while the restored normal EELV was maintained.

The inflammatory response seems to play a minor role in peripheral airway damage induced by 'physiological' tidal volume. This is suggested by the fact that there was no relation between the number of polymorphonuclear leucocytes per unit length of alveolar septa and the increase in airway resistance. Furthermore, there was no significant cytokine release, at least for tumour necrosis factor-α, in serum and bronchoalveolar lavage fluid. However, another study [8] showed that mechanical ventilation with 'physiological' tidal volume in healthy lungs induced proinflammatory cytokine gene transcription.

Reduced EELV and increased airway closure with concomitant tidal closure is common during general anaesthesia or deep sedation in both normal [9] and obese [10] patients. Injury to peripheral airways may be avoided by reducing tidal closure, which can be achieved by reducing the tidal volume, applying a PEEP level high enough to increase the EELV to above the volume at which airway closure occurs, and periodic change in body posture.

Recently, studies have been conducted to evaluate the effects of protective ventilation strategies ('physiological' tidal volume and PEEP) during general anaesthesia and postoperatively. Mechanical ventilation with larger intraoperative tidal volume was associated with increased risk for postpneumonectomy respiratory failure [11], but protective ventilatory strategies reduced the inflammatory response in cardiac surgery patients [12], and they decreased the proinflammatory systemic response, improved lung function and resulted in earlier extubation after oesophagectomy [13]. On the other hand, in an inhomogeneous group of patients undergoing major thoracic and abdominal surgical procedures [14], protective mechanical ventilation was not associated with increased intrapulmonary and systemic levels of inflammatory mediators. Furthermore, in cardiac surgery patients other investigators could not find any evidence that protective ventilation prevents some of the adverse effects of cardiopulmonary bypass on the lung, or that it decreased systemic cytokine levels, postoperative pulmonary function, or duration of hospitalization [15].

In conclusion, tidal airway closure occurs commonly during general anaesthesia, particularly in obese patients. Animal and human studies suggest that tidal airway closure causes peripheral airway injury, which may be avoided by application of 'physiological' tidal volume and low PEEP levels. Jain and Sznajder [1] must be congratulated for their evaluation, conducted in both healthy and diseased lungs, of the role of airway closure in determining peripheral airways injury during mechanical ventilation.

Competing interests

The authors declare that they have no competing interests.

References

1. Jain M, Sznajder JI: **Bench-to-bedside review: Distal airways in adult respiratory distress syndrome.** *Crit Care* 2007, **11:**206.
2. Tremblay L, Slutsky A: **Ventilator induced lung injury: from bench to bedside.** *Intensive Care Med* 2006, **32:**24-33.
3. Milic-Emili J, Torchio R, D'Angelo E: **Closing volume: a reappraisal (1967-2007).** *Eur J Appl Physiol* 2007 [Epub ahead of print].
4. D'Angelo E, Pecchiari M, Baraggia P, Saetta M, Balestro E, Milic-Emili J: **Low-volume ventilation causes peripheral airway injury and increased airway resistance in normal rabbits.** *J Appl Physiol* 2002, **92:**949-956.
5. D'Angelo E, Pecchiari M, Saetta M, Balestro E, Milic-Emili J: **Dependence of lung injury on inflation rate during low-volume ventilation in normal open-chest rabbits.** *J Appl Physiol* 2004, **97:**260-268.
6. D'Angelo E, Pecchiari M, Gentile G: **Dependence of lung injury on surface tension during low-volume ventilation in normal open-chest rabbits.** *J Appl Physiol* 2007, **102:**174-182.
7. D'Angelo E, Pecchiari M, Della Valle P, Koutsoukou A, Milic-Emili J: **Effects of mechanical ventilation at low lung volume on respiratory mechanics and nitric oxide exhalation in normal rabbits.** *J Appl Physiol* 2005, **99:**433-444.
8. Bregeon F, Roch A, Delpierre S, Ghigo E, Autillo-Touati A, Kajikawa O, Martin T, Pugin J, Portugal H, Auffray J, *et al.*: **Conventional mechanical ventilation of healthy lungs induced proinflammatory cytokine gene transcription.** *Respir Physiol Neurobiol* 2002, **132:**191-203.
9. Tokics L, Hedenstierna G, Strandberg A, Brismar B, Lunquist H: **Lung collapse and gas-exchange during general anesthesia: effects of spontaneous breathing, muscle paralysis, and positive end-expiratory pressure.** *Anesthesiology* 1987, **66:**157-167.
10. Pelosi P. Ravagnan I, Giurati G, Panigada M, Bottino M, Tredici S, Eccher G, Gattinoni L: **Positive end-expiratory pressure improves respiratory function in obese but not in normal subjects during anesthesia and paralysis.** *Anesthesiology* 1999, **91:**1221-1231.
11. Fernandez-Perez ER, Keegan MT, Brown DR, Hubmayr R, Gajic O: **Intraoperative tidal volume as a risk factor for respiratory failure after pneumonectomy.** *Anesthesiology* 2006, **105:**14-18.
12. Zupancich E, Paparella D, Turani F, Munch C, Rossi A, Massaccesi S, Ranieri VM: **Mechanical ventilation affects inflammatory mediators in patients undergoing cardiopulmonary bypass for cardiac surgery: a randomized clinical trial.** *J Thorac Cardiovasc Surg* 2005, **130:**378-383.
13. Michelet P, D'Journo XB, Roch A, Doddoli A, Marin V, Papazian L, Decamps I, Bregeon F, Thomas P, Auffray AP: **Protective ventilation influences systemic inflammation after esophagectomy randomized controlled study.** *Anesthesiology* 2006, **105:**911-919.
14. Wrigge H, Uhlig U, Zinserling J, Behrends-Callsen E, Ottersbach G, Fischer M, Uhlig S, Putensen C: **The effects of different ventilatory settings on pulmonary and systemic inflammatory responses during major surgery.** *Anesth Analg* 2004, **98:**775-781.
15. Koner O, Celebi S, Balci H, Cetin G, Karaoglu K, Cakar N: **Effects of protective and conventional mechanical ventilation on pulmonary function and systemic cytokine release after cardiopulmonary bypass.** *Intensive Care Med* 2004, **30:**620-626.