AJRCCM Articles in Press. Published on 11-August-2017 as 10.1164/rccm.201708-1563ED

Ventilator-induced lung injury: follow the right direction!

Another piece of the puzzle in the VILI epic

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The authors declare that they have no conflict of interest.

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Recognition of ventilator-induced lung injury (VILI) has been a major advance in ARDS treatment (1). VILI was predicted on theoretical grounds (2) in the aftermath of the first publication on ARDS (3) and demonstrated by Webb and Tierney who showed that mechanical ventilation with high inspiratory airway pressure (45 cmH2O) and zero PEEP (45/0) induced severe pulmonary edema and ultimately death in rats with previously normal lungs (4). A 10 cmH_2O PEEP (45/10) reduced the amount of edema (4). However, authors and the intensive care community, did not realize the importance of this finding (5). Edema was attributed to hydrostatic mechanisms: transmural pressure increased in extraalveolar vessels because of the phenomenon of "lung interdependence" (surrounding parenchyma exerts an outward stretch on extraalveolar vessels during inflation) and in alveolar vessels because of surfactant inactivation or depletion due to its repetitive compression and stretching (promoting alveolar collapse and a negative pressure around alveolar microvessels). Considerable increases in both endothelial and epithelial permeability and diffuse alveolar damage were later shown to be major contributors (6,7,8).

VILI concept allowed a breakthrough in ARDS management: simply reducing tidal volume dramatically improved mortality (9). The potential importance of hemodynamics and in particular the role of pulmonary vascular blood flow and right ventricular (RV) function was however overlooked. This is especially important since pulmonary edema was more abundant in rats with the less altered cardiac output (45/0 conditions) compared to those in which higher mean airway pressure (45/10) was likely to further worsen hemodynamics (4). This reduction of edema was partly abolished by administration of dopamine in order to increase blood flow (10).

Physiology of heart-lung interactions predicts a severe impairment of RV function by the major increase in RV afterload due to lung overdistension, whereas left ventricular (LV) function might be both improved because of lowered afterload, especially when applying

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PEEP (11), and impeded because of leftward septal shift. Katira et al. assessed hemodynamics, heart lung interactions and RV function during the same ventilator conditions (45/0 and 45/10) as in the original experiments (4), using RV and LV microcatheters and echocardiography. Briefly, they report large swings in RV stroke volume (SV), due to a cyclic under-filling of right ventricle during inspiration (preload effect), in 45/0 conditions (12). The decrease in RVSV during tidal ventilation of ARDS is mainly attributable to an afterload effect: for the same airway pressure, this decrease is much more pronounced in patients ventilated with a high transpulmonary pressure (tidal volume ~8 mL/kg) and no chest strapping, compared to patients ventilated with a low transpulmonary pressure (tidal volume~3.5 mL/kg) and a higher intrathoracic pressure owing to chest strapping (13). Cyclic decrease in RV outflow occurred 1 or 2 cardiac beats before the decrease in RV inflow (13). The study by Katira et al. was performed in rats with normal lungs in which no initial RV afterload effect was expected. But, authors also report that RV failed after 20 minutes of ventilation at 45/0 when pulmonary edema developed. A pattern of *cor pulmonale* with RV dilatation and septal flattening in relation now to a progressive increase in RV afterload was observed (12). A vicious circle might occur: large swings in RVSV, mainly driven by intrathoracic pressure swings (preload alterations) may participate to the development of VILI (see below) and its associated pulmonary hypertension which in turn overloads RV during systole and ultimately results in *cor pulmonale* (afterload alterations). One of the main precipitating factors of *cor pulmonale* in ARDS is the driving pressure (14), which was higher in 45/0 than in 45/10 conditions. It is however very questionable that Katira et al. do not report any increase in RV systolic pressure whereas describing *cor pulmonale* after 20 minutes of ventilation at 45/0 (12), since *cor pulmonale* is a systolic overload of the right ventricle.

Authors may misinterpret some data. First, they suggest that the increase in transmural LV end-diastolic pressure ($LVEDP_{TM}$) plays a role in the genesis of the pulmonary edema. Such an increase has been described for long when RV is overloaded and is explained by a shift in the LV pressure-volume curve and a change in LV shape (15, 16) with an increase in LV end-systolic eccentricity index and in RV/LV ratio, as reported by Katira et al. (12). $LVEDP_{TM}$ increase was modest (from 9 to 14 mmHg after 20 minutes at 45/0) and cannot cause pulmonary edema (12). Also, ventilation with 45/0 compresses alveolar vessels (17) causing a pre- and not post-capillary pulmonary hypertension. This causes RV failure which in turn limits the increase in $LVEDP_{TM}$. Indeed, Katira et al. report that $LVEDP_{TM}$ reached a plateau after 10 minutes of ventilation at 45/0, whereas the RV/LV ratio at end-expiration continued to increase (see Figures 4, 5) (12). An increase in microvascular pressure even modest, may participate to the generation of edema in face of severely increased microvascular permeability. However, lessening of edema with 45/10 is more likely ascribable to the preservation of lung surfactant (4) than to the "non-elevation" of $LVEDP_{TM}$. In other words, the hydrostatic contribution to this severe permeability edema is essentially related to the "lung interdependence" and surfactant changes described above (4, 17, 18). A potentially new and interesting hypothesis (not evoked by authors) is that a putative cardiac contribution to VILI could not be ascribed to LV but actually to RV. Large swings in RVSV (45/0 conditions) with a flow becoming nil during inspiration and restored during expiration (12) could induce cyclic overperfusion in an already stressed pulmonary circulation. This condition termed "capillary stress failure" (19) occurs when the increase in flow/pressure is "massive". Although such "massive" increase in pressure was not observed during ventilation at 45/0, cyclic overperfusion at each expiration could participate to pulmonary edema and VILI genesis.

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This study involved a huge work which deserves praise, but must not be mis- or over-interpretated: pulmonary edema during high volume ventilation is of severe permeability-type and essentially due to the stress to lungs (2,8). VILI may impair RV function through pulmonary hypertension and induce *cor pulmonale*. Potential cardiac contribution to pulmonary edema not related to LV function alteration but to the cyclic effect of tidal ventilation on RV function is a new and most interesting hypothesis.

This study is another argument for gentle ventilation of injured lungs and should contribute to clinician inclination in the "right" direction.

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