REVIEW

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Did studies on HFOV fail to improve ARDS survival because they did not decrease VILI? On the potential validity of a physiological concept enounced several decades ago

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Abstract High frequency oscillatory ventilation (HFOV) has been the subject of extensive physiological research for 30 years and even more so of an intense debate on its potential usefulness in the treatment of acute respiratory distress syndrome (ARDS). This technique has been enthusiastically promoted by some teams until two high-quality randomized clinical trials in adults with ARDS showed that HFOV did not decrease and might have even increased mortality. As a consequence of these results, physiological concepts such as atelectrauma and biotrauma on which ARDS management with HFOV were based should be reexamined. In contrast, the concept of volutrauma, i.e., end-inspiratory overdistension, as the cause for ventilator-induced lung injury might help explain excess mortality during mechanical ventilation of ARDS when inspiratory volumes are too high. This is what might have happened during one of the recent studies on HFOV. Failure of this complex technique must be put in perspective with the dramatic improvement of ARDS prognosis with very simple interventions such as tidal volume reduction, early pharmacological paralysis, and prone positioning which all limited end-inspiratory volume.

High frequency oscillatory ventilation (HFOV) allows adequate gas exchange despite the use of very low tidal volumes (equal to or less than the anatomical dead space) at a very high rate (12–15 Hz in neonates and 3–6 Hz in adults) [1–3]. To obtain this, quasi-sinusoidal flow oscillations are applied to the endotracheal tube. This allows gas mixing in the lungs with CO_2 and O_2 moving along their partial pressure gradient [3]. A main setting in HFOV is that of mean airway pressure around which oscillations are generated. Its purported theoretical advantages are the limitations of both volutrauma and atelectrauma [2] (these concepts will be further discussed). Thirty years ago, in a comprehensive review on gas exchange during HFOV, H.K. Chang acknowledged that mechanisms of gas exchange were not fully understood [4]. The same author warned against the risk of lung overinflation during HFOV [5]. More recently, internationally renowned specialists of HFOV explained the putative merits and also the actual risks of this technique, namely lack of effective alarms making the diagnosis of life-threatening conditions such as tension pneumothorax or tracheal tube obstruction difficult, or the impossibility of patient transport with an HFOV ventilator [3].

In these conditions, only the demonstration that HFOV actually saves lives could convince clinicians that this technique can compete with conventional mechanical

ventilation (CMV). Indeed, the amazing progresses in the prognosis of ARDS were obtained with the wise use of CMV and stemmed from extraordinary simple measures such as tidal volume reduction [6], early pharmacological paralysis [7], and prone positioning [8].

A brief physiological overview is useful to understand why HFOV modalities used in recent studies might have proven deleterious. The majority of this article will, however, be devoted to the analysis of data from evidence-based medicine whose strengths overwhelmed potential weaknesses [9–11] in this debate.

Only data from studies on adults will be extensively discussed, although data from pediatric literature should urge caution with the use of HFOV in newborns [12–14].

Some of the ideas expressed in this paper were evoked in part in a previous publication [15].

HFOV has been described as "a means of delivering 'continuous positive airway pressure' with a built-in 'shaker' to facilitate CO_2 elimination" [3]. Some investigators see ARDS as the result of widespread atelectasis that recruitment maneuvers could alleviate [3, 16]. Then, HFOV should stabilize these newly opened alveoli and avoid derecruitment [3]. This concept does not take into account the fact that ARDS was once denominated "permeability pulmonary edema". This term reminds us that alveoli are not necessarily atelectatic but may be filled with edema fluid, and/or pus during lung infection. Inflammatory infiltrates, hyaline membranes, and fibroproliferation may be combined to various extents [17]. This does not fit well with the concept of atelectasis which would be more suitable for neonatal respiratory distress due to lack of surfactant. Unfortunately the prognosis of this latter disease was not fundamentally improved by HFOV.

Despite this important difference between ARDS and surfactant deficiency, the vast majority of experimental studies on HFOV used a model of surfactant deficiency induced by repeated bronchoalveolar lavage [18, 19]. It results in a very unstable lung with many collapsed zones that are very easily recruitable by any recruitment maneuver. In these conditions, HFOV easily maintains alveoli open after recruitment and is quite efficacious for improving oxygenation and even lung lesions. But the relevance of this model for ARDS may be moderate.

The knowledge (or at least the hypothesis) that mechanical ventilation may exacerbate pulmonary lesions of ARDS was probably the most important conceptual breakthrough in this disease [20]. It is important to realize that ventilator-induced lung injury (VILI) in humans is a concept (or a paradigm) and not a demonstrated entity although this seems likely [21]. Many investigators contributed to the knowledge of VILI which is still growing [22–25]. Indeed, it formed the rationale for the first large randomized controlled trial (RCT) that showed marked improvement of ARDS prognosis with tidal volume reduction, a maneuver that may have reduced VILI [6]. Then, explaining results of clinical trials through

the prism of VILI may be disputable but proved highly operative. Experimental studies clearly showed that lungs are very susceptible (and even more so if already damaged) to overdistension. This may result in lesions that are indistinguishable from those due to ARDS (permeability pulmonary edema and hyaline membrane formation) [22, 25–27]. Figure 1 shows the macroscopic aspect of VILI in lungs subjected to high tidal volume ventilation of different duration.

VILI is mostly the result of end-inspiratory overdistension (volutrauma) [22, 28]. This phenomenon may occur when a very heterogeneous lung is subjected to inappropriate settings during mechanical ventilation. The most diseased zones are also the less aerated ones (because of flooding and/or atelectasis). Their reduced compliance "protects" them from overinflation since the bulk of ventilation is directed to more compliant and healthier zones. The latter are therefore exposed to overinflation during mechanical ventilation. It follows that any increase in global end-inspiratory volume may result in local overinflation. End-inspiratory volume is determined both by tidal volume but also by end-expiratory volume which can be manipulated by the level of positive end-expiratory pressure (PEEP). Any disproportionate increase of either parameter is likely to result in regional overdistension.

High tidal volume results in VILI in experimental conditions [22, 26, 27]. The clinical counterpart of this experimental finding received a resounding confirmation by a study conducted by the ARDSNet investigators [6]. Another intriguing experimental observation is that depending on its level, PEEP may be protective or deleterious. Indeed, Webb and Tierney had shown that at the same end-inspiratory distension, lungs were less edematous with
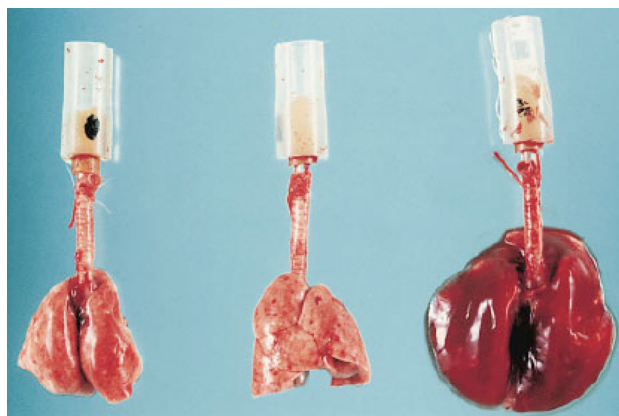
Fig. 1 Macroscopic aspect of ventilator-induced lung injury. Intact rats were mechanically ventilated with either a normal tidal volume (*left*) or with a high tidal volume for 5 min (*middle*) or 20 min (*right*). After 5 min, there were only focal congestive zones. After 20 min, lung lesions are severe as shown by marked enlargement and congestion. Tracheal edema fluid fills the cannula. Reproduced from Dreyfuss and co-workers [22] with permission

PEEP and reduced tidal volume than with zero PEEP (ZEEP) and very high tidal volume [25]. We confirmed and expanded these findings by showing firstly a reduction of edema with PEEP, secondly that reduction of edema was associated with preservation of alveolar epithelial lining [26], thirdly that in fact the severity of permeability alterations was identical in both conditions and that the difference was explained mainly by the hemodynamic alterations induced by PEEP (probable drop in cardiac output and hence in driving pressure for filtration through lung microvasculature) [27], and fourthly that restoration of hemodynamics by administration of dopamine resulted in a marked increase in edema in animals ventilated with PEEP [27]. What could be concluded from all these experiments? Certainly, a moderate amount of PEEP was beneficial, but part of this benefit was ascribable to hemodynamic alterations (probable decrease of cardiac output and pulmonary microvascular transmural pressure). In striking contrast, an *excessive* increase in end-inspiratory volume because of high PEEP is responsible for VILI even when a normal tidal volume is used [29] (Fig. 2a). Moreover, even a static overdistension (as can result from HFOV) may severely affect alveolar epithelial permeability (at an extreme, it becomes freely permeable to albumin) [30] (Fig. 2b). These deleterious effects of excessive PEEP (or of static overdistension) are far too often neglected. Indeed, a controversy on the main determinants of VILI opposes advocates of the major role of end-inspiratory overdistension ("volutrauma") [22, 26, 27] and those who incriminate low volume injury because of "atelectrauma" and "biotrauma" [24, 31]. Whereas the former theory insists on the overdistension of aerated zones, the latter gives precedence to lesions generated by opening and closure of collapsed alveoli with resulting shear stress and possibly initiation of inflammatory cascades. This debate is not trivial since it forms the basis of controversies on ventilator management of ARDS: is limiting overdistension and applying a moderate level of PEEP enough to reduce VILI as demonstrated by the ARDSNet trial on tidal volume reduction [6] or should a high PEEP (or high mean airway pressure during static lung inflation with HFOV) be applied to stabilize alveoli, avoid opening and collapse, and therefore minimize VILI? The choice is all the more difficult since higher PEEP may theoretically also increase the volume of ventilatable lung and therefore reduce the risk of volutrauma (although three negative studies that will be further discussed did not support this beneficial effect of PEEP). Whatever the exact mechanism, a common pathway is the generation of high shear stress during ventilation of mechanically heterogeneous lungs [32]. Discussing these two options in detail would require a full comprehensive paper of its own. Nonetheless, it must be underlined that the opening and closure theory was demonstrated in a particular setting of surfactant-depleted lungs caused by repeated bronchoalveolar lavage [33–35] or in isolated nonperfused lungs which are also prone to total collapse [31]. These
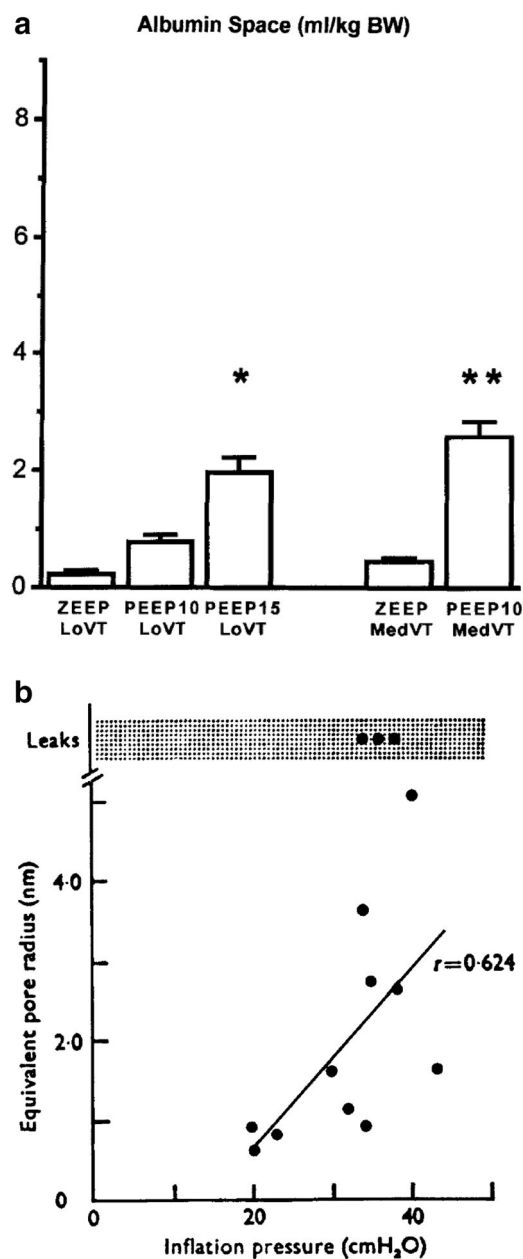

Fig. 2 Effects of increasing lung volume either by PEEP or during static inflation on alveolar-capillary permeability. **a** High-level PEEP leads to increased microvascular permeability as attested by an increase in the distribution space of albumin into the blood-free lung in intact mechanically ventilated rats. With a PEEP of 15 cmH$_2$O, permeability is altered even when tidal volume is low (LoVT 7 ml/kg BW). Application of a 10-cmH$_2$O PEEP results in the same phenomenon in the face of a moderate increase in tidal volume (MedVT 12 ml/kg BW). Reproduced from Dreyfuss and co-workers [29] with permission. **b** Effect of static inflation on alveolar epithelial permeability (expressed as equivalent pore radius) of fluid-filled sheep lung in situ. A correlation is observed between the magnitude of distension (reflected by static inflation pressure) and permeability. Large leaks (free albumin diffusion) occur when the highest distension is reached. Reproduced from Egan and co-workers [30] with permission

specific settings lead to severe lung collapse and high potential for homogeneous recruitment whichever the ventilator modality (high PEEP or HFOV). This recruitability translates into a marked lower inflection point on inspiratory lung pressure–volume curve. Setting the level of PEEP with respect to this inflection point (or statically distending lungs during HFOV) allows for a marked reduction of lesions in these particular models [31, 33–35]. Such benefit is not observed in models that resemble more adult ARDS [36]. In a particularly meaningful paper, Rolf Hubmayr challenged the significance of the lower inflection point and the concept of opening and closure of alveoli during ventilation of ARDS [37]. Reminding that distal airways and alveoli are filled with fluid and not atelectatic, he underlined the major difference between these two concepts for VILI generation. If alveoli are closed, VILI indeed occurs as a result of stress applied during every opening. If they are filled with liquid (as elegantly demonstrated in his paper), then "VILI may occur through overdistension of aerated alveoli rather than by shear stresses in airways as they open" [37].

To summarize, whereas "high volume" VILI ("volutrauma") exists in all settings and all species [22, 38] and has a clinical counterpart that was unequivocally demonstrated [6], the concept of low lung volume VILI (atelectrauma) is more debated, as long as a certain (not necessarily high) amount of PEEP is applied. In other words (and as explained above), a moderate amount of PEEP likely lessens low volume VILI (atelectrauma). No one would ventilate ARDS patients with ZEEP for obvious reasons (severe hypoxemia), except for the short time needed to stabilize a very hemodynamically unstable patient. Then, the amount of PEEP needed to improve oxygenation is very likely sufficient to prevent atelectrauma. Further raising PEEP (or static inflation) (in order to further reduce putative atelectrauma and biotrauma) did not always prove beneficial in experimental conditions and can even be responsible for further injury due to high volume VILI [29]. Interestingly, clinical studies based on the rationale of avoiding atelectrauma by increasing PEEP or lung distention more than needed for oxygenation purposes were negative at best [39–42] and deleterious at worse [1].

Similarly, the concept of biotrauma (the production of inflammatory cytokines by lungs subjected to injurious mechanical ventilation) is often put forward to justify a high level of end-inspiratory (or continuous) distension. Indeed, a seminal experimental paper [31] showed that cytokine production by lungs ventilated with identical end-inspiratory distension was considerably higher in those lungs ventilated with high tidal volume and zero PEEP (volutrauma plus atelectrauma) than with a lower tidal volume and a high PEEP (prevention of atelectrauma). As a matter of fact, lung lavage levels of TNFalpha were 56-fold increased as compared with controls in the former situation whereas they were increased by only threefold in the latter. It is beyond the scope of this paper to discuss the relationship between VILI and cytokines which is the subject of much controversy [24, 31, 43, 44]. Obviously, even if there is some link between VILI and cytokines, there is no sufficient evidence to justify the use of high PEEP just in order to try to reduce cytokine production and biotrauma. Figure 3 summarizes mechanisms of VILI and how they are affected by ventilator settings.

Hope of stabilizing lung (i.e., avoiding putative opening and closure of alveoli) underlies the use of both HFOV and high level of PEEP. Clinicians have been fascinated by high levels of PEEP for more than 40 years [45]. But three very well conducted clinical studies failed to demonstrate a beneficial effect of higher (15 cmH$_2$O) versus lower (10 cmH$_2$O) PEEP during ARDS [39–41]. A meta-analysis suggested that moderate–severe ARDS might benefit from higher PEEP [46]. This is, however, not totally convincing for three reasons: first, finding a better prognosis in a subgroup defined a posteriori from a negative study implies that the other subgroup fared worse, even if this finding does not reach significance due to lack of power. Second, meta-analyses have often been contradicted by the results of larger studies. This was just the case with HFOV, as will be discussed [1, 42, 47]. Third, studies on high PEEP (and the ensuing meta-analysis) were conducted before demonstration of the dramatic effect of prone positioning on survival. As a matter of fact, few patients benefited from this maneuver in these studies [39–41]. Guérin and co-workers [8] ventilated patients with severe ARDS (PaO$_2$/FiO$_2$ ≤150 mmHg) with a PEEP of 8–9 cmH$_2$O only and observed a 90-day mortality of 24 %, whereas it was 34 % in ARDS patients (P/F ratio ≤200 mmHg) ventilated with a PEEP of 13–15 cmH$_2$O in the abovementioned meta-analysis [46]. Table 1 summarizes salient features of these studies. Higher PEEP levels may certainly be used in order to improve oxygenation but their putative effect on "atelectrauma" remains elusive.

How can these findings be relevant for HFOV studies? Obviously, they were designed before results of this study on prone positioning [8] were available. The unfortunate consequence is that control groups of studies on HFOV [1, 42] could no longer be considered as "best practice according to scientific evidence" nowadays. In that sense prone positioning should rapidly become "standard" or "usual" care [48, 49] during severe ARDS except if the results of previous study [8] were refuted by another one. Even more importantly, the design of studies on HFOV, and in particular the last one that might spell the end of this technique [1], considered that the main risk during mechanical ventilation of ARDS was lack of recruitment with the ensuing putative risk of atelectrauma. Maybe the risk of lung overdistension was not sufficiently taken into account. As a result, high distending pressures were applied to lungs with disappointing results. Using very small tidal volumes during HFOV may have given false reassurance on the safety of this technique, whereas potential adverse effects of frequency on cells may have

Fig. 3 Putative mechanisms of VILI. Their respective contributions are critically discussed in the text. High volume ventilation always results in VILI. The ⊕ signs indicate that the effects of low volume ventilation may conjugate with those of surfactant inactivation and of pulmonary edema to favor repetitive opening and closure of distal units. The complexity of the effects of PEEP is explained with the smileys. 🙂 indicates that PEEP has a protective effect against some mechanisms of VILI (PEEP may protect against surfactant inactivation, atelectasis, and repetitive opening and closing of distal units). It may also favor recruitment and therefore lessen the magnitude of lung distensible volume reduction (a given Vt will find more ventilatable lung, which may result in less regional overdistension). The level of PEEP needed to observe these beneficial effects is not necessarily high. ☹ indicates the potential major deleterious effect of PEEP in experimental (and possibly clinical) situations. Too high a level of PEEP (or of static distension as in HFOV) may favor high volume VILI because of the occurrence of regional or global overinflation. This might contribute to explain the failure of a recent HFOV trial [1]. All these issues are detailed in the text. Adapted from Dreyfuss and coworkers [22] with permission

been overlooked. Indeed, both oscillation amplitude and frequency influence the material properties (elastic and frictional properties) of cells and tissues. Therefore the large (several orders of magnitude) increase in breathing frequency imposed by HFOV has the potential of raising cell and lung parenchyma stress to injurious levels at lower than "physiologic" tidal volumes [50]. Moreover, agitation of edema fluid by HFOV may have lead to generation and destruction of foam, which in turn is associated with cell injury during liquid bridge fracture [51]. Indeed, interfacial stress associated with the generation and destruction of liquid bridges in airspaces has been considered as a major biophysical cell injury mechanism in mechanically ventilated lungs [52]. All these phenomenon would lead to important increase in energy delivered to the lung during HFOV given the high frequency with which the parenchyma is being agitated. In addition, resonant amplification of the delivered gas volume (i.e., delivery of a gas volume higher than

expected at certain frequencies) may contribute to VILI during HFOV [53]. Table 2 summarizes these concerns. Anyway, the strategy of increased recruitment may have been favored by the often impressive effect of HFOV on oxygenation (at least in experimental conditions). But the relationship between improvement of oxygenation and mortality is complex as illustrated by the finding that patients with higher tidal volume had an increase both in oxygenation and mortality [6] whereas patients ventilated prone improved both these parameters [8].

Although recruiting lungs is usually associated with improved oxygenation, it may also cause overdistension and be responsible for increased mortality. These considerations may weaken the assertion that "High-frequency ventilation is the optimal physiological approach to ventilate ARDS patients" [2] which formed the rationale for a randomized control study that unfortunately proved the deleterious effects of HFOV [1]. Indeed, authors of this position paper contended that

Table 1 Respiratory variables and outcomes in major recent RCTs on ARDS ventilatory management

	ALVEOLI Higher PEEP 2004 (n = 276)	EXPRESS Higher PEEP 2008 (n = 385)	LOV Higher PEEP 2008 (n = 475)	ACURASYS NMBA 2010 (n = 177)	PROSEVA Prone 2013 (n = 237)	OSCILLATE, 2013 HFOV (n = 275)	OSCILLATE, 2013 Control (n = 273)	OSCAR, 2013 HFOV (n = 398)	OSCAR, 2013 Control (n = 397)
PaO_2/FiO_2 at baseline (mmHg) (SD)	151 (67)	144 (58)	145 (48)	106 (36)	100 (30)	121 (46)	114 (38)	113 (37)	113 (38)
Ventilator settings at day 1									
PEEP (cmH_2O) (SD)	14.7 (3.5)	14.6 (3.2)	15.6 (3.9)	9.6 (2.7)	10 (3)		18 (3.2)		11.4 (3.6)
Tidal volume (ml/kg PBW) (SD)	6.0 (0.9)	6.1 (0.3)	6.8 (1.4)	6.3 (0.8)	6.1 (0.6)		6.1 (1.3)		8.3 (2.9)
Plateau pressure (cmH_2O) (SD)	27 (6)	27.5 (2.4)	30.2 (6.3)	24 (5)	24 (5)		32 (5.7)		30.9 (11)
Mean airway pressure (cmH_2O) (SD)	20 (5)	18.5[b]	21.2[b]	15[b]	15[b]	31 (2.6)	24 (4)	26.9 (6.2)	21.9[b]
Adjunctive therapies									
Inhaled nitric oxide (%)	NA	14.8	NA	28	9.7	9.1	10.3	NA	NA
Prone position (%)	NA	8.8	NA	28	100	2.6	3.7	NA	NA
NMBA (%)	NA	53	43.8	100	91	83	68	52.5	41.6
Barotrauma or pneumothorax[a] (%)	11	6.8	11.2	5.1	6.3	18	13	NA	NA
Mortality									
In hospital (%)	27.5	35.4	36.4	32.2	NA	47	35	50.1	48.4
At day 28 (%)	23	27.8	28.4	23.7	16	40	29	41.7	41.1

[a] Barotrauma was defined as pneumothorax, pneumomediastinum, pneumopericardium, or subcutaneous emphysema in ALVEOLI, LOV, ACURASYS, and OSCILLATE and pneumothorax only in PROSEVA and EXPRESS

[b] Values computed from those of plateau pressure (see text for methodological details)

(during HFOV) "Because cyclic alveolar stretch is minimal, volutrauma can be avoided even when the mean airway pressure is set to higher levels than can be reasonably set with PEEP on conventional ventilation". We contend that it is precisely because the fact that volutrauma may occur during static distension [29, 30] (as discussed above) and can also associate with severe hemodynamic compromise was omitted that this trial resulted in a marked increase in incidence of barotrauma and of mortality [1]. In addition, specific deleterious effects of HFOV (linked to energy transfer to the lungs) that were detailed above may have contributed to this poor outcome.

It would be an oversimplification to conclude that the only reason why large tidal volumes or large pressure amplitudes cause injury is because end-inspiratory volumes exceed a certain safe threshold. As for HFOV, deformation amplitude and the associated dynamic stress certainly contribute to the genesis of VILI. In that sense, driving pressure must also been taken into account. This is the conclusion of a very sophisticated and interesting paper by Amato and co-workers [54]. These authors analyzed the results of several major papers on ARDS conventional (not HFOV) ventilatory management. They found that the higher driving pressure (tidal volume divided by respiratory system compliance) was, the higher mortality was. In their analysis, driving pressure was the major factor explaining mortality. This extremely stimulating hypothesis nevertheless poses a problem. A superficial interpretation of this paper would lead to the conclusion that since driving pressure is probably very low (because of very low tidal volume), then mortality should be the lowest with HFOV. Unfortunately, clinical experience showed this is not the case. This questions the generalizability of the concept.

Neonatal use of HFOV is beyond the scope of this study. However, despite the fact that experimental models of surfactant deficiency more closely mimic neonatal distress (which formed the rationale for the use of HFOV), one must admit that the initial enthusiasm for this technique has been tempered by results of randomized trials. Indeed, the HIFI study [12] did not find any reduction in mortality with HFOV. Moreover, neurological complications occurred more often in HFOV-treated neonates. A more recent meta-analysis on patient data found no difference in any outcome measure (survival, bronchopulmonary dysplasia, neurological sequelae) with HFOV compared to conventional ventilation [13]. Very recently, two studies added more doubt on the clinical usefulness of this technique: a retrospective study on a very large sample suggested increased mortality with HFOV [14], whereas long-term follow-up of a randomized controlled study showed that older children (11–14 years old) who had been ventilated with HFOV for neonatal respiratory distress had significantly, albeit modestly, better outcomes in tests of small-airway function than those who had been supported by conventional ventilation

Table 2 Likely arguments why HFOV failed to improve mortality and to decrease VILI

Experimental arguments	Clinical arguments	Other
HFOV tested on disputable animal models of ARDS: lung injury induced by saline lavage, a highly recruitable model of surfactant deficiency (homogeneous injury). This model is very different from adult ARDS, which is heterogeneous and less recruitable	High mean airway pressure in the 2 recent RCTs on HFOV [OSCILLATE 31 ($\pm$2.6) cmH$_2$O; OSCAR 26.9 ($\pm$6.2) cmH$_2$O] may have caused lung overdistension as attested by:	Difficulties inherent to the technique: Lack of effective alarms making the diagnosis of life-threatening conditions such as tension pneumothorax and tube obstruction difficult
End-inspiratory overdistension caused by high Vt or high PEEP both induce VILI	High incidence of barotrauma with the higher mean airway pressure	No possibility of patient transport while on HFOV
Static lung overdistension also generates VILI	Right ventricular failure as suggested by hemodynamic compromise with the higher mean airway pressure	
Oscillation amplitude and frequency potentially raise cell and lung parenchyma stress		
Energy delivered to the lung may be quite high because of deformation amplitude and high frequency		
Resonant frequency may promote delivery of higher pressures/volume		

[55]. Unfortunately, this latter finding cannot be viewed as a major argument in favor of HFOV, which remains much more complicated to implement than conventional mechanical ventilation and possesses its own additional risks [3]. Concerning children, maybe caution should also be exercised given these data and those we present concerning adults below.

The question is even more complicated in adults. Indeed, given the very different pathophysiology of adult ARDS which, as explained below, cannot be simply viewed as alveolar collapse, one may wonder whether the rationale for HFOV was really strong. This uncertainty on the potential role of HFOV was reinforced by recent dramatic progresses of conventional mechanical ventilation [6–8] as will be discussed below.

A recent meta-analysis, based on small studies, concluded that HFOV "might improve survival and is unlikely to cause harm" [47]. Unfortunately, this assertion was refuted by two recent large randomized clinical trials from the UK [42] and Canada [1]. The former did not show any difference in mortality with HFOV compared to CMV, whereas the latter reported an increase in mortality with HFOV. Simple examination of these results might end the debate, but careful attention to the study protocols suggests that the deleterious effects of HFOV may be explained by overdistension. Indeed, as explained in Table 1, mortality was identical in both groups of the UK study. Unfortunately, detailed analysis of ventilatory conditions is not possible (lack of data on mean airway pressure in the control group), but it seems probable that mean airway pressure was moderately higher with HFOV than with CMV. In the Canadian study, mortality was much higher with HFOV and, interestingly, mean airway pressure was also much higher with this modality (Table 1). Moreover, mean airway pressure on HFOV was markedly higher in the Canadian than in the UK study. High mean airway pressure suggests that lung overdistension occurred in the Canadian study. This impression is reinforced by the occurrence of hemodynamic compromise in this study as acknowledged by authors and attested by more frequent and prolonged infusion of vasopressors. Of note is the fact that increased mortality might also have been due in part to right ventricular failure because of considerable increase in afterload as a result of lung overdistension [56]. The same observations were also made during CMV when plateau pressure is too high [57]. Although we already questioned the actual significance of biotrauma [43], it is interesting to note that some investigators suggested that HFOV might aggravate lung inflammation [58]. Finally, a minute number of patients (less than 4 %) were ventilated prone. The difference in mortality between HFO and CMV might even have been mirrored by the fact that patients receiving CMV might also have experienced lung overdistension. Indeed, ventilator settings were unusual since tidal volume was set at 8.3 ml/kg BW in the UK study and PEEP at 18 cmH$_2$O in the Canadian one. One must keep in mind that this PEEP level was higher than in the high PEEP groups in recent studies on PEEP during ARDS [39–41]. This higher PEEP may be explained by the fact that patients were more hypoxemic at baseline in the Canadian study. Notwithstanding, these particular settings resulted in high plateau pressure: 30.9 and 32 cmH$_2$O in the UK and Canadian study, respectively. For comparison, plateau pressure was 25 cmH$_2$O only in the low tidal volume arm of the ARDSNet study [4].

Anyway, the obvious conclusion is that lung overdistension during HFOV likely occurred in the Canadian study and may have resulted in additional VILI despite there being no statistical difference in the occurrence of macroscopic barotrauma between groups. However, the

incidence of barotrauma was very high (18 %) with HFOV (much more than in all other recent studies on ARDS ventilation) (Table 1). Although the difference in the incidence of barotrauma with conventional ventilation was not significant, this may have been the result of lack of power in a (adequately) prematurely terminated study. As a matter of fact the incidence of barotrauma was also rather high (13 %) in the conventional ventilation arm of this study. This may be explained by the already mentioned higher PEEP and plateau pressure in the conventional arm of this study than in other recent studies of ARDS ventilation. Indeed, although VILI and air leaks are different phenomena [22], one can reasonably assume that since they may share risk factors in common, the more macroscopic barotrauma occurs the more VILI is likely to occur. Unfortunately, the incidence of barotrauma was not reported in the UK study. Anyway, as already explained VILI is a concept that is difficult to prove in humans [21].

In support of the deleterious effects of high airway pressure, even in static conditions, interesting observations can be made from analysis of data from Table 1. Indeed, correlations can be evidenced between mean airway pressure on the one side and barotrauma and hospital mortality on the other (Fig. 4). To draw these correlations, we had to either use the values of mean airway pressure provided in the articles (as reported in Table 1) or to estimate these values from plateau pressure (as reported in Table 1). To do this, we computed the mean difference between plateau pressure and mean airway pressure observed in several large randomized trials (that provided these values) in ARDS patients ventilated with a reduced tidal volume (8–10 ml/kg BW) [6, 39, 59, 60]. We observed that the mean difference was 9 cmH_2O. Thus, we substracted this value from that of plateau pressure in Table 1 to obtain mean airway pressure values. Caution is warranted in the interpretation of these correlations: first, they were computed despite several

missing values, second they can only be seen as hypothesis-generating and not as definite clue. Keeping in mind the potential weaknesses of our approach, our hypothesis should nevertheless foster analysis of individual data with sophisticated methods to overcome these pitfalls.

To understand why the effects of high airway pressure (volume) are not immediately obvious (for instance, why was mortality not higher with higher PEEP and plateau pressure in three recent studies [39–41]?), one must keep in mind that, although there is clinical debate on this point, there is ample experimental literature that VILI (in particular microvascular and epithelial alveolar permeability) does not vary linearly with pressure. Two studies by independent teams showed that the relationship was rather exponential, explaining that a threshold is observed before which no significant change occurs [61, 62]. Once this threshold is reached, permeabilities vary considerably in response to increased pressure (volume). Figure 5 illustrates this finding.

Independently of this analysis, results of the two recent HFOV studies challenge the underlying concept for HFOV utilization. Indeed, HFOV is supposed to prevent or reduce VILI by avoiding putative alveolar opening and closure (atelectrauma) and the also putative inflammatory cytokine release due to alveolar instability (biotrauma). As a matter of fact, it is difficult to imagine a better means to stabilize alveoli than HFOV. In contrast, the observation that the higher airway distending pressure was associated with increased mortality suggests the validity of the concept of high volume (end-inspiratory or static overdistension) VILI (or volutrauma) [29], as already shown by improved mortality by simple reduction of tidal volume [6].

These conclusions are developed by the authors of the Canadian trial in their discussion and also in the accompanying editorial [63]. The following sentences are from the papers in question: "Our results are inconsistent with the physiological rationale for HFOV and with the results
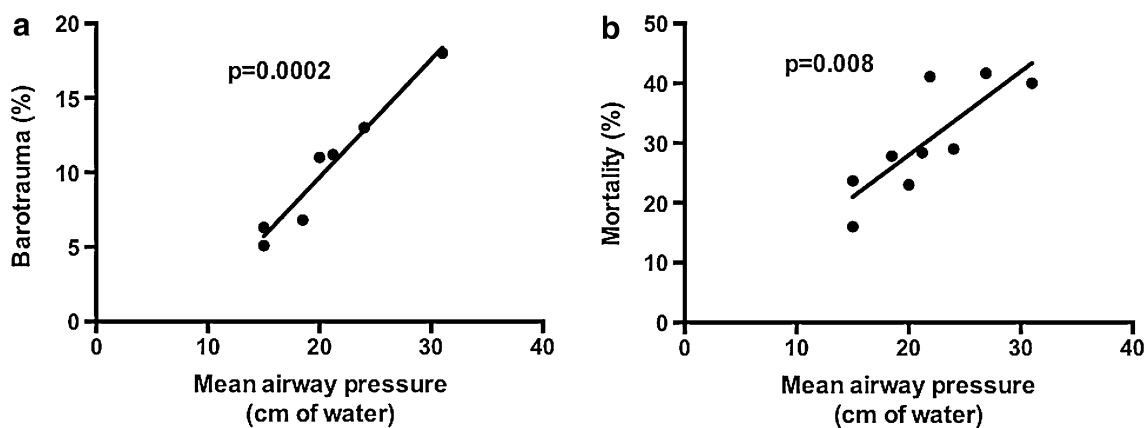

Fig. 4 Correlations between mean airway pressure and barotrauma (**a**) or mortality (**b**) in recent studies on mechanical ventilation of ARDS patients (values are extracted from Table 1). The incidence of barotrauma was not reported in one recent study on HFOV [42]. See text for details on computation of mean airway pressure

Fig. 5 Relationship between plateau pressure and alveolar microvascular and epithelial permeability to proteins (assessed by passage of radiolabeled transferrin and albumin, respectively). The relationship is exponential and exhibits a threshold. Reproduced from de Prost and co-workers [61] with permission
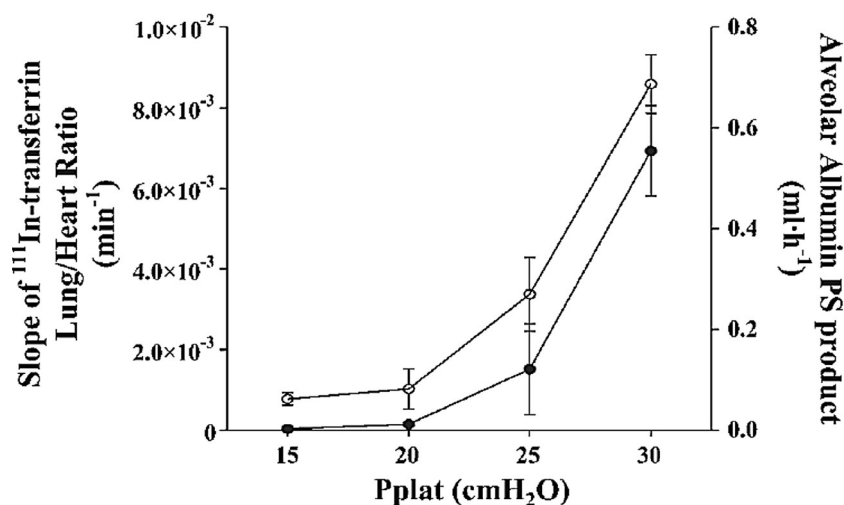
of studies in animals. In studies in animals in which benefits of HFOV were observed, lung injury was induced with the use of saline lavage—a highly recruitable model of surfactant deficiency—which our results suggest does not translate directly to human with adult ARDS in whom recruitability can be heterogeneous" [1]. Finally, the authors concede that "it is possible that an HFOV protocol that uses lower mean airway pressure…might have led to different results". This might have resulted at best in equivalence of HFOV and CMV as in the UK study [42]. The accompanying editorial [63] states that "Among patients with homogeneous, recruitable lung, increasing mean airway pressure may well be beneficial; however, among patients with heterogeneous and nonrecruitable lung, increasing mean airway pressure may lead to overdistension of some lung regions without increased aeration of collapsed or flooded alveoli". This contention fits well with a previous section of this paper.

Table 2 summarizes potential explanations for HFOV failure to improve ARDS prognosis. In face of this failure of HFOV, it is interesting to realize that the fantastic successes of severe ARDS treatment stemmed from the very simple concept of avoiding overdistension of open zones [22] which also translated into simple therapeutic measures: tidal volume reduction [6], early pharmacological paralysis [7], and prone positioning [8] (see Table 1). All these measures share in common the limitation of end-inspiratory overdistension. The tremendous improvement of mortality with prone positioning is

certainly not solely explained by its effects on oxygenation (dying from intractable hypoxemia is rare during ARDS). It may well be the result of diminished overdistension and resulting VILI as demonstrated in landmark experimental studies by John Marini's team which showed that prone positioning both redistributed (dependent zones had less severe lesions) and lessened severity of VILI [64, 65].

To conclude, one should keep in mind the words of caution written by Marini before the results of large RCTs on HFOV were available: "…this unfamiliar and seemingly exotic technique seems to offer little advantage over ventilation performed conventionally with equivalent attention to the principles of lung protection" [66]. The most important principle of such lung protection is probably the avoidance of lung overdistension [67–70]. This may have been omitted because of excessive enthusiasm with HFOV.

Ironically, the concept of VILI was most effective for designing studies and improving ARDS prognosis but it is not possible to prove or disprove that mortality improved because VILI was avoided. Simply, everything happened as if it was predicted by theory. This may just be the same with the increased mortality observed with HFOV.

Compliance with ethical standards

Conflicts of interest All authors have no conflict of interest related to this article.

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