Simulation of ARDS severity

The degree of ARDS severity was simulated, on a linear scale from 0 (healthy lungs) to 100 (severe ARDS). Ps increased linearly with ARDS severity, ranging from 0.23 cm H$_2$O per cm height in healthy lungs to 0.69 cm H$_2$O/cm in the most severe ARDS \textsuperscript{[1]}. In the simulation of healthy lungs, this led to a superimposed pressure ranging from 0 cm H$_2$O in the non dependent lung zones to a maximum of 3.3 cm H$_2$O in the most dependent lung zones. In the most severe ARDS, superimposed pressure ranged from 0 cm H$_2$O to a maximum of 10 cm H$_2$O in the most dependent regions of the lung. The TOP and TCP had a Gaussian distribution, with their mean and standard deviation depending on ARDS severity (Table 1). Values for TOP and TCP were adopted from Crotti et al. \textsuperscript{[2]}. Negative values for TOP and TCP were eliminated, and TCP could not exceed TOP in all lung units. In addition, the degree of lung volume recruitability ranged from 100\% in healthy lungs to 60\% in ARDS grade 100. A non-recruitable lung unit remained closed at all time. A linear vertical gradient was chosen for the distribution of non-recruitable lung units, with the largest number in the lowermost part of the lungs.
Results.

Static P-V curve

Figure 2 displays the pressure-volume relationship of the chest wall and lungs in the case of healthy and severely injured lungs. In severe ARDS, FRC is markedly reduced; the pulmonary P-V curve (Plungs-V) is shifted to the right, due to increased TOP and Ps. The chest wall curve (Pcw-V) had a biphasic shape: exponential at low lung volumes and linear at higher lung volumes. In the healthy lungs, Pcw-V is linear above FRC, and the non-linear shape of the total P-V curve (Paw–V) is mainly determined by the lungs component. In severe ARDS, the Paw-V curve shape has changed, firstly, by the non-linear Pcw-V relation at low airway pressures on account of the lower FRC, and secondly, by the right-shifted Plungs-V curve. Interestingly, the total P-V curve shows a lower corner point around 20 cm H2O, whereas there is no clear inflection nor a lower corner point in the transpulmonary curve above FRC.

For all 20 simulations, a static P-V curve with an inflation and deflation limb was obtained, and the P-V characteristics calculated (examples in Fig. 3). FRC decreased from 2688 ± 8 ml in the healthy lungs to 1977 ± 71 ml in ARDS grade 100 (p<0.01, r=-0.98). Average values for Pcl, Pinf and Pcu for both inflation and deflation limbs are presented in Table 2. These characteristics were found at significantly (p<0.05) lower values on the deflation limb than on the inflation limb, showing the hysteresis of the modelled lungs. There was a positive correlation with ARDS grade for most variables: Pcl,I increased from 0 in grade 0 to 17 in grade 100 (r=0.97); Pinf,I from 15 to 30 (r=0.93); Pcu,I from 29 to 43 (r=0.79); Pcl,D from 1 to 6 (r=0.84). Degree of recruitability changed some of the characteristic pressures: with decreasing recruitability, Pcu,D and Pinf,D decreased (r=0.52 and 0.84 respectively), while Pcl,I increased (r= -0.46). Airway closure did not significantly influence the P-V characteristics included in our analysis, although it influenced P-V slope. In small airway closure, FRC was significantly higher compared to alveolar closure alone (2407 ± 254 ml vs 2363 ± 273 ml, p< 0.01).
With increasing Paw from ZEEP, atelectasis decreased (Table 2). Recruitment of alveolar volume coincided with increased %overstretching at Pcu,I. Overstretching was reduced but significant atelectasis appeared as Paw decreased from Pcu,D to Pinf,D with further increased %atelectasis and decreased %overstretching from Pinf,D to Pcl,D (Table 2).

Pressure-volume characteristics were also assessed for the transpulmonary pressure (Plungs) – volume curve, where Plungs = Ptm+Ps = Paw-Pcw. Pinf,I for the Plungs-V curve was not different from the Paw-V curve while Pcl,I was slightly higher (1 ± 1 cm H2O). All other Plungs-V characteristics were at slightly lower Paw (2 ± 2 cm H2O) (and volume) than their Paw-V counterparts (p<0.05, Table 2).

With decreasing recruitability, Pcl,D decreased (p < 0.05, r= 0.85).
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Discussion.

The model

The model used was previously described by Hickling [3,4]. We modified this model, in that we added variability of ARDS severity with threshold opening and closing pressures as well as vertical hydrostatic pressure gradients adapted from the literature [5,6]. In Hickling’s papers, the lungs were completely collapsed at ZEEP (in fact transmural pressure) and chest wall influences were neglected. To be able to inflate the lung from ZEEP, airway pressure—rather than transmural ZEEP—and to relate volume changes to changes in airway pressures, a simulated chest wall with fixed characteristics was added to the model. Impairment of chest wall elastic properties may vary with the underlying disease responsible for ARDS [7]. Chest wall compliance may be normal in ARDS caused by pulmonary disease, but is markedly decreased in ARDS secondary to an extrapulmonary cause [8]. A decreased chest wall compliance would lead to an increase of pleural pressure and therefore airway pressure at a given transmural pressure or lung volume. As a result, Psi, PEEPmin, lower and upper corner points and inflection point would have been found at higher values. The shape of the Plungs-V curve is not influenced by changes in chest wall properties. The exact shape of the Paw-V curve however cannot be determined without sufficient data on the low lung volume Pcw-Volume curve. Since data on low lung volume chest wall mechanics in humans is lacking, variable chest wall mechanics were not incorporated into the model.

It has been suggested that in ARDS, not only alveolar but also small airway collapse may play a role [9]. This was incorporated in our model and simulations with alveolar closure only and with 75% alveolar and 25% small airway closure were performed. These percentages could not be based on the literature and were chosen arbitrarily.

Although in early ARDS it is claimed to be possible to recruit lung volume to a point were there is little or no atelectasis and optimal gas exchange [10], this may be impossible in ARDS that has existed for a longer period with associated ventilator induced lung injury. In the fibroproliferative phase of ARDS, deposition of elastic system fibres takes place and this may contribute to alveolar mechanical dysfunction and remodelling that occur in acute lung
disease\[^{11}\]\. Also, when the prevalent pathology is lung tissue consolidation such as in pneumonia, application of pressure should induce only a moderate lung volume recruitment and possible alveolar overdistension\[^{12}\]. We modelled the altered alveolar function as non-recruitability, with a vertical distribution gradient towards the dependent lung zones.

Simulations were performed with lungs that could either be completely recruited (as a model of early ARDS) as well as with lungs with part of their alveoli not recruitable even at infinite airway pressure as a model of damaged or partly fibrotic lungs. In our model, the extent of this simulated damage was linearly related to ARDS severity.

Current knowledge of micromechanics of the injured lung is limited. In order to construct a mathematical model, some assumptions (e.g. distribution of alveolar and small airway closure, the acceptable amounts of atelectasis, reexpansion of collapsed alveoli and overstretching) had to be made.

In vivo, both recruitment and derecruitment show some time dependence\[^{13}\], and this was not incorporated in our model. Time dependence of recruitment and derecruitment could limit the amount of recruitment occurring during a tidal inflation in ARDS. A study of pulmonary injury in pigs showed that most of the recruitment during inspiration and derecruitment during expiration occurred within 1.4 second\[^{14}\], a finding supported by others\[^{15}\]. We studied the influence of pressure at static end inspiration and expiration in the static P-V manoeuvre and tidal ventilation at no flow conditions and assuming extremely long inspiration and expiration. At low frequencies, stress relaxation in the viscoelastic elements is essentially completed at end inspiration and inertive contribution to respiratory mechanics is negligible\[^{16,17}\]. Resistive contribution to respiratory mechanics is most evident at low frequencies\[^{18}\]. Since at no-flow the influence of resistance is eliminated, and assuming viscoelastic time constants of approximately 1.5 second we believe that our model is realistic for mechanical ventilation at low rates (e.g. below 10 breaths.min\(^{-1}\)) and can be used to generate hypotheses that could be tested clinically. Although methodologically superior, incorporation of frequency dependent viscoelastic properties into our model would have significantly complicated the model used. With extrapolation of our findings to higher ventilatory frequency ranges therefore, the increase of inertia and decrease of viscoelastic effects should be taken into account.
Reference List


