Lung mechanical and vascular changes during positive- and negative-pressure lung inflations: importance of reference pressures in the pulmonary vasculature

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The continuous changes in lung mechanics were related to those in pulmonary vascular resistance (Rv) during lung inflations to clarify the mechanical changes in the bronchoalveolar system and the pulmonary vasculature. Rv and low-frequency lung impedance data (ZL) were measured continuously in isolated, perfused rat lungs during 2-man inflation-deflation maneuvers between transpulmonary pressures of 2.5 and 22 cmH2O, both by applying positive pressure at the trachea and by generating negative pressure around the lungs in a closed box. ZL was averaged and evaluated for 2-s time windows; airway resistance (Raw), parenchymal damping and elastance (H) were determined in each window. Lung inflation with positive and negative pressures led to very similar changes in lung mechanics, with maximum decreases in Raw [−68 ± 4 (SE) vs. −64 ± 18%] and maximum increases in H (379 ± 36 vs. 348 ± 37%). Rv, however, increased with positive inflation pressure (15 ± 1%), whereas it exhibited mild decreases during negative-pressure expansions (−3 ± 0.3%). These results demonstrate that pulmonary mechanical changes are not affected by the opposing modes of lung inflations and confirm the importance of relating the pulmonary vascular pressures in interpreting changes in Rv.

Changes in lung volume result in alterations in both the complex structure of the conducting airways embedded in the lung parenchyma and the pulmonary vasculature. Because these entities are linked via direct mechanical interactions, characterization of the interdependence between the pulmonary hemodynamics and the lung mechanics is critical for an understanding of the effects of lung expansions during breathing or under mechanical ventilation.

Positive-pressure lung inflation (PPLI), commonly applied to maintain gas exchange during mechanical ventilation, is far from being physiological and results in a number of side effects, originating from the high positive intrathoracic pressures that may subsequently worsen preexisting pulmonary lesions. PPLI may jeopardize the pulmonary hemodynamic conditions, mainly via compression of the pulmonary vessels (6, 9, 13, 19, 23, 26). These adverse pulmonary hemodynamic effects do not exist during normal breathing, because negative-pressure lung inflation (NPLI) generated by a negative pressure around the lungs exerts a different pressure gradient across the pulmonary vascular wall that generates a radial traction on the vessels as the lung parenchyma expands (3). Thus developments in mechanical ventilation based on NPLI have recently gained increasing interest as an attempt to improve ventilation-perfusion distribution by improving lung recruitment and preventing hemodynamic impairment (4, 21).

There is a consensus in the literature that PPLI decreases the airway resistance (Raw), alters the viscoelastic properties of the lungs (8, 10, 12) and increases the pulmonary vascular resistance (Rv) (3, 5, 6, 9, 19, 23, 26). However, these previous studies addressed either the pulmonary vascular or the lung mechanical changes, and their simultaneous alterations have not been characterized. In contrast with the consistent data obtained for PPLI, the findings on pulmonary hemodynamic changes during NPLI are still controversial (3, 9, 19, 24), mainly due to the inconsistency in the measurement of pulmonary vascular pressures. Whereas one study demonstrated a monotonic decrease in Rv during NPLI (3), others have documented a mild drop in Rv, followed by gradual increases at high lung volumes (9, 19, 24). Additionally, although the effects of NPLI on Rv were addressed in these previous reports, the changes in the airway and tissue mechanics during NPLI maneuvers have not been investigated. Finally, because all these previous studies characterized the pulmonary vascular and lung mechanical changes under steady-state conditions, the mechanical changes in these compartments during dynamic inflation-deflation maneuvers remain unknown.

Accordingly, the present study was designed to relate the continuous changes in lung mechanical properties to those observed in Rv during PPLI and NPLI maneuvers. This aim was achieved by continuous monitoring of the changes in the mechanical properties of the bronchoalveolar system and the pulmonary vasculature simultaneously in perfused excised rat lungs. Because the perfusion reservoirs were placed outside the box containing the lungs, the pulmonary vascular pressures were related to the pleural pressure (Ppl) during PPLI, while they were constant with reference to the alveolar pressure (Palv) during NPLI.

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METHODS

Preparation of isolated lungs. Following approval from the Animal Ethics Care Committee of the Canton of Geneva, Switzerland, eight adult male Sprague-Dawley rats (weighing 397–487 g) were anesthetized with isoflurane (3–4% induction dose). The preparation of the animals and the harvesting and perfusion of the isolated rat lungs were similar to those described in detail previously (16). Briefly, the rats were tracheotomized with a polyethylene cannula (14 gauge, Braun, Melsungen, Germany), and they were mechanically ventilated with a tidal volume of 7 ml/kg body weight and a respiratory rate of 70–80 breaths/min with a constant volume-cycled rodent ventilator (model 683, Harvard Apparatus, South Natick, MA). A positive end-expiratory pressure (PEEP) of 2.5 cmH2O was applied while anesthesia was maintained with isoflurane (1.4%). The femoral vessels were prepared surgically and then cannulated for blood sampling and continuous arterial blood pressure monitoring. Blood gases from arterial blood samples were analyzed regularly (UltimaTM, Datex/Instrumentarium, Helsinki, Finland). Airway pressure was monitored continuously (model DP 45 and model 2D15 carrier demodulator, Validyne, Northridge, CA).

The rats were fully anticoagulated with heparin (1.5 IU/g iv). Twenty milliliters of blood was then gently withdrawn over 5 min via the arterial cannula, with the collected blood being continuously replaced by intravenous infusion of colloid solution (6% hydroxy-ethyl-starch) to maintain a constant intravascular volume and a systemic blood pressure >50 mmHg so as to minimize lung ischemic lesions during this normovolemic hemodilution procedure. This resulted in the collection of 20 ml of diluted blood with a hematocrit of ~25%, which served as priming volume for the isolated perfusion circuit.

Through a median sternotomy, the main vessels of the heart-lung block were cannulated with short and light polyethylene catheters (14 gauge, Braun, Melsungen, Germany), one placed into the main pulmonary artery via the right ventricular outflow track, advanced to a point immediately below its bifurcation, and connected to medical-grade silicone tubing (catalog no. 602255, ID 1.47 mm; OD 1.96 mm, Ulrich, St. Gallen, Switzerland). Another catheter was placed in the left ventricle through the left ventriculotomy, in which a CombiFLEX-Adapter (Braun) was tightly fixed and connected to medical-grade silicone tubing. A third catheter was placed directly in the left atrium (polyethylene tubing, ID 0.88 mm; Portex, Hythe, UK). The left ventricle and the left atrium were widely opened, allowing free outflow of the remaining blood, which resulted in complete exsanguination and the death of the animal. The lungs were then immediately flushed through the pulmonary artery cannula with 30 ml of cold (10°C) 6% hydroxy-ethyl-starch solution from a height of 30 cm to minimize the warm ischemic time period necessary for the remainder of the heart-lung preparation until the start of the ventilation and reperfusion in the isolated lung chamber. The lungs and the heart were excised and extracted in a single block, dissected free of adjacent tissue, and weighed.

Establishment of the perfusion of the isolated rat lungs. The heart-lung block was placed in a humidified box (590 ml) and ventilated by applying positive pressure in the trachea or by using the rodent ventilator with room air mixed with 5% CO2 at a respiratory rate of 50/min, a tidal volume (VT) of 7 ml/kg, and a PEEP of 2.5 cmH2O by airway pressure (Paw) was measured with pressure transducer (model Z46169, Gould). VT and airflow (V) were measured with a screen pneumotachograph (type 17212, Gould Godart, Bilthoven, The Netherlands). Lung perfusion was then performed from a perfusion reservoir set initially at a pulmonary artery perfusion pressure (Ppa) of 20.4 cmH2O (15 mmHg). The distal extremity of the left ventricular outflow cannula was positioned at a height sufficient to obtain a left atrial pressure (Pia) of 6.8 cmH2O (5 mmHg) at start of reperfusion, which produced a pulmonary capillary pressure (Pc) of 13.6 cmH2O (10 mmHg) and West zone 3 conditions (Ppa > Pia > mean Paw). The blood dripping from this cannula was collected in a 5-ml collection cylinder, and it was aspirated from this reservoir with polyethylene tubing passing through a roller pump (Ismatec Pump, Glattburg, Zürich, Switzerland). The priming volume of the tubing and reservoirs was 18 ml. A transit-time flowmeter (T-201 CDS, Transonic Systems, Ithaca, NY) operated by calculating the difference in the travel of an acoustic signal between upstream and downstream directions was placed between the perfusion reservoir and the catheter cannulating the main pulmonary artery for continuous monitoring of the pulmonary blood flow (Qp). Ppa and Pia were measured continuously with calibrated pressure transducers (model 156-PC 06-GW2, Honeywell, Zürich, Switzerland) zeroed at the level of the lung hilum. Rv was calculated continuously from the vascular pressure and flow signals as Rv = (Ppa-Pia)/Qp. Pc was estimated by using the Gaar equation [Pc = Pia + 0.44 × (Ppa - Pia)] (7) and was used to assess the capillary filling pressure before the maneuvers. V, VT, pressures, circuit flow, and the calculated Rv were recorded and stored at a sampling rate of 50 Hz via an analog-to-digital interface converter (Biopac, Santa Barbara, CA) on a microcomputer (AST, Limerick, Ireland). A 100-point moving average was used for the time courses of the RV as a smoothing procedure.

Lung mechanics. The respective contributions of the airway and tissue mechanical properties to the total lung resistance were estimated by the modified forced oscillation technique, which allows continuous assessment of the mechanical impedance of the isolated lungs (Zl), as described in detail previously (10, 18). During impedance recordings, a loudspeaker-in-box system generated a small-amplitude pseudorandom signal with frequency components between 0.5 and 19 Hz through a 100-cm-long, 2-mm-ID polyethylene catheter serving as a wave tube. Two identical pressure transducers (model 33NA002D, IC Sensors, Milpitas, CA) were used to measure the lateral pressures at the loudspeaker (P1) and at the tracheal end (P2) of the wave tube. The signals P1 and P2 were low-pass filtered at 25 Hz and sampled with a microcomputer at a rate of 128 Hz. Zl was calculated as the load impedance of the wave-tube by using the fast Fourier transformation (17). The time window of the Zl calculation was 2 s. Successive overlapping estimates were obtained every 0.125 s, resulting in 1,280 Zl estimates from a 160-s recording. To separate the airway and tissue mechanics, a model consisting of a frequency-independent Raw and airway inertance (Iaw) in series with a constant-phase tissue model (11) including parenchymal damping (G) and elastance (H) was fitted to each segmental Zl spectrum by minimizing the differences between the measured and modeled impedance values. A smoothing procedure applying a 50-point moving average was used for the time courses of the forced oscillatory model parameters.

The airway parameters were corrected for the resistance and inertance of the endotracheal tube. Zl measurements during NPLI incorporated the input impedance of the closed box. The box impedance alone was measured following the experiments and was subtracted as a serial impedance with the isolated lungs (the box G and H values were 57 cmH2O/l and 2,254 cmH2O/l, respectively).

Because the tracheal flow was always passed through the wave tube, changes in lung volume during inflation-deflation maneuvers were assessed by integrating the pressure drop across the wave tube (P1 – P2), as detailed previously (10).

Study protocol. A 15-min period of lung perfusion was necessary to establish steady-state conditions before the first maneuver of inflation with positive pressure. After the steady-state conditions had been reached, a low (160-s) lung inflation-deflation maneuver was performed by gradually elevating the pressure in the loudspeaker chamber until a maximum transpulmonary pressure (Ptp) of 22 cmH2O was attained, and passive expiration was then achieved by opening the loudspeaker chamber to the atmosphere via an adjustable leak. Following this maneuver, a period of 10 min of positive-pressure mechanical ventilation and perfusion (see above) was allowed for the lungs, and the box containing the heart-lung preparation was closed. A closed-circuit ventilator was then connected to the box, creating the same ventilation pattern (Ptp, VT, and ventilation frequency) as

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maintained during positive-pressure ventilations by inducing negative pressures in the box. Another 10-min period was necessary for steady-state hemodynamic and mechanical conditions of the lungs following the initiating negative-pressure ventilation. Ppa and Pia were adjusted during this adaptation period by elevating or lowering the blood containers supporting the arterial inflow or the venous outflow of blood so as to maintain the same levels as during positive-pressure ventilations. A slow (160-s) inflation-deflation maneuver was next achieved by gradually raising the vacuum in the box from −2.5 to −22 cmH2O while the trachea was open to the atmosphere (inflations), and the box pressure was allowed to reach the initial level by opening the box via an adjustable leak (deflations). During negative-pressure maneuvers, the same inflation-deflation times were adjusted as those maintained with positive pressures. Zt and the hemodynamic parameters (Pla, Ppa, Pe, Qe, and Rv) were recorded continuously during these inflation-deflation maneuvers on two separate computers. The changes in the mechanical and hemodynamic parameters were subsequently time matched and synchronized for further analyses.

Following completion of the experimental protocol, the inferior lobe of each lung was weighed (wet weight), dried in an oven (Memmert, Schwabach, Germany) at 60°C for 2 days, and weighed again to determine the wet-to-dry lung weight ratio.

Statistical evaluation. The repeats in the parameters were expressed by the SE values. The Kolmogorov-Smirnov test was used to test data for normality. The mechanical and hemodynamic parameters were distributed normally. Accordingly, two-way repeated-measures ANOVA, with variables of inflation mode (PPLI and NPLI) and Ptp level, was used to evaluate the effects of the different lung inflation maneuvers on the lung parameters. Paired t-tests were applied to assess statistical significance when the hemodynamic or mechanical parameters obtained from the positive- and negative-pressure maneuvers were compared between inspirations and expirations. Statistical tests were carried out with the significance level set at $P < 0.05$.

RESULTS

No edema development was observed during the experiments, as substantiated by the normal wet-to-dry lung weight ratios ($5.6 \pm 0.14$) determined following the experiments.

Temporal changes in Rv and in the mechanical parameters obtained during PPLI and NPLI maneuvers in a representative lung are demonstrated in Fig. 1. Similar changes were observed in the mechanical parameters, while Rv exhibited increases during PPLI and decreased slightly with NPLI.

Changes in the airway and parenchymal mechanical parameters during PPLI and NPLI maneuvers are depicted in Fig. 2. The two different means of lung inflations had no influence on the course of the mechanical parameters: the decreases in Raw were associated with marked increases in G and H. Furthermore, the lung tissue parameters were significantly lower during deflations than during inflations ($P = 0.008$ and $P < 0.001$ for G, and $P < 0.05$ and $P < 0.001$ for H at a Ptp of 10 cmH2O).

In contrast with the mechanical parameters, Rv exhibited opposite changes in response to PPLI and NPLI (Fig. 3), with marked increases during PPLI and minor decreases when NPLI maneuvers were performed. During PPLI, the Rv-Ptp curve exhibited hysteresis opposite to that observed for the tissue mechanical parameters; i.e., Rv was statistically significantly greater during deflation than during inflation ($P < 0.001$ at a Ptp of 10 cmH2O), whereas such hysteresis was not observed for NPLI ($P = 0.16$ at a Ptp of 10 cmH2O). Differences in Rv between the inflation and deflation limbs were not apparent when the changes in Rv were expressed as a function of lung volume.

Figure 4 depicts the mechanical parameters and Rv obtained in the inflation limb of the PPLI and NPLI maneuvers at particular Ptp levels. The mechanical parameters were independent of the mode of inflation ($P = 0.40$, $P = 0.34$, and $P = 0.13$ for Raw, G, and H, respectively), whereas Rv was statistically significantly smaller during NPLI at each Ptp level ($P < 0.001$). Two-way ANOVA revealed no significant interactions between the factors, i.e., Ptp and the mode of inflation ($P = 0.613$, $P = 0.37$, and $P = 0.141$ for Raw, G, and H, respectively), suggesting the lack of differences in the pressure-dependent changes in the mechanical parameters between the NPLI and PPLI maneuvers. In contrast, these factors exhibited a highly significant interaction ($P < 0.001$), demonstrating that the mode of inflation had a significant impact on the changes in Rv.

DISCUSSION

Simultaneous changes in lung mechanical and pulmonary vascular parameters during PPLI and NPLI were related in the present study. PPLI and NPLI generated similar courses in the airway and parenchymal mechanical parameters, with decreases in Raw and marked increases in the viscous and elastic parameters of the lung parenchyma. In contrast with this similarity, the changes in Rv were influenced considerably by the mode of lung inflation: continuous increases in Rv were observed during PPLI, whereas NPLI caused mild decreases in Rv. The parenchymal parameters displayed hysteresis with the lung inflation pressure, independently of the mode of inflation, resulting in slightly lower G and H values in the expiratory phase. Conversely, hysteresis for Rv was observed only during PPLI maneuvers, where this parameter was significantly greater during the same pressures at expirations.

Methodological considerations. The experimental setting applied in the present study has been shown to be an ideal model for investigation of the interactions between the pulmonary hemodynamics and the mechanical conditions of the lungs (16). Besides the possibility of continuous monitoring of Rv and the lung mechanical parameters, this model allows the control of other pulmonary hemodynamic variables (pressures and blood flow) and also the performance of lung inflation and deflation maneuvers with positive and negative pressures in the same lung. Furthermore, this experimental model permits detailed investigations of the mechanical interdependence between lung mechanics and pulmonary hemodynamics without the confounding influence of systemic hormonal and/or neurogenic variables. An important feature of the ventilation-perfusion circuit applied in the present study is that the reservoirs were placed outside the box containing the lung. Thus vascular pressures were kept constant relative to the Ppl during PPLI, whereas they were kept constant relative to Palv during NPLI. The minor difference in rate of inflation-deflation, occasionally observed between PPLI and NPLI maneuvers (e.g., Fig. 1) is unlikely to bias the findings, because inflation-deflation rate changes of had no major effects on the traces of either the mechanical or the vascular mechanical parameters (data not shown).

The opposite changes in Rv between PPLI and NPLI evidence that the transmural pressure differences in the pulmonary vasculature were indeed different in the two modes of infla-
lations, because the blood reservoirs supporting the pulmonary artery and collecting blood from the pulmonary vein have been kept on a common pressure level during the different inflation maneuvers. In the experimental model, the standardization of the perfusion pressures avoids the confounding influences due to the altered cardiac output induced by the different inflation maneuvers in an intact chest. Therefore, the present findings highlight the primary importance of the pressure differences both across the airway tree and the pulmonary vasculature, while the absolute pressure level in these compartments per se does not matter: the NPLI and PPLI maneuvers lead to similar pressure gradient through the tracheobronchial tree, whereas they exert opposing transmural pressure gradients.

It has been established that the interpretation of the changes in the pulmonary vascular mechanics with altered lung volume is fundamentally dependent on the manner by which the vascular pressure is related to different reference pressures (i.e., Ppl or Palv) (14). In the present study, we standardized our pressure regimen by maintaining constant Ppa and Ppv with reference to atmosphere during the PPLI and NPLI maneuvers, by keeping both the arterial and venous perfusion reservoirs outside the box used to perform inflation-deflations. This approach ignores the possible changes in the perfusion pressure that may occur in a closed chest during lung expansions with negative pressure around the chest, and thus extrapolation of the present results to an in vivo condition is not straightforward.

**Effects of lung inflations on lung mechanics.** The $Z_l$ parameters obtained from the forced oscillatory measurements before inflations are in excellent agreement with those obtained at

Fig. 1. Changes in pulmonary vascular resistance ($R_v$) and in the mechanical parameters during lung inflation-deflation maneuvers with positive airway pressure and with the generation of negative pressure around the pleura in a representative lung. Raw, airway resistance; $G$, tissue damping; $H$, tissue elastance; Ptp, transpulmonary pressure.
around functional residual capacity in closed- (12) and open-chest rats (20) and in isolated rat lungs (16). The patterns of changes in the airway and lung parenchymal mechanical parameters with Ptp also exhibit good qualitative agreement with those obtained in response to PPLI in open-chest rats (20), and they are similar to those observed for the lungs in the intact-chest condition (12). Moreover, the quality and the pattern of change during tracking of the impedance parameters in the present study are in qualitative concordance with those obtained in closed-chest mice (10). As described previously (10, 12, 20), the decreases in Raw reflect pressure-dependent increases in the airway caliber, while the increases in the parenchymal mechanical parameters are related to the increased damping and stiffness of the lung tissue at high inflation pressures.

This appears to be the first reported study of the lung mechanical changes during NPLI maneuvers. Our results revealed that the mode of inflation does not affect the pressure-dependent changes in the airway and parenchymal mechanics, as an indication that the forces determining the airway caliber and changes in viscous properties and elastic recoil of the lung are independent of the manner in which Ptp is maintained. The pressure gradient between the alveoli and the airway opening is similar for the two maneuvers, merely the absolute values of the airway opening and hence the Palv being greater during PPLI, which may result in a decrease of a few percent in the alveolar gas compliance (Cg). Because the effect of Cg is negligible relative to that of the lung tissue compliance, small changes in Cg are unlikely to be detected, which explains the lack of difference between the mechanical effects on NPLI and PPLI.

Effects of PPLI on Rv. In agreement with the results of previous studies (3, 5, 6, 9, 19, 23, 26), we observed monotonic increases in Rv during PPLI maneuvers. The underlying physiological phenomena have been well established and may involve the compression of the intra-alveolar vessels by the increased positive lung inflation pressure leading to compression and distortion of the capillaries, in addition to the elongation of intra- and extra-alveolar vessels (6, 9, 13, 19, 23, 26). These mechanisms seem to predominate in the changes in Rv in the present study, whereas the enlargement of extra-alveolar vascular compartments (9, 13, 23) is not reflected in its net changes.

Although the changes in Rv with lung inflation or deflation have been extensively investigated previously, the effects of cyclic changes in PPLI (as occurs during mechanical ventilation) have been addressed in only a few investigations (5, 23, 26). In the present study, Rv was consistently higher during deflations than during inflations at isopressure points, and this hysteresis diminished when the changes in Rv were plotted against lung volume. Although this finding is fully consistent with the results of previous investigations (5, 23, 26), the mechanisms responsible for this pattern of change have not been clarified. Studies of individual pulmonary vessels by using morphological (25) or mechanical approaches (22) suggest that pulmonary vascular volumes are greater during lung deflations, which seemingly contradicts the present and previous findings obtained for the whole lung. This apparent controversy can be explained by the possibility that the intra-alveolar capillaries collapse in consequence of a PPLI that compresses the alveolar walls (6, 9, 13, 19, 23, 26). If this pulmonary capillary derecruitment occurs during PPLI, Rv at

![Fig. 2. Changes in the airway and parenchymal mechanical parameters as functions of the transpulmonary pressure (Ptp) when the lungs are inflated with positive (right) or negative pressures (left). ●, Inflations; ○, Deflations.](image)

![Fig. 3. Changes in Rv as a function of the Ptp (left plane) and as a function of the lung volume (V; back plane) when the lungs are inflated with positive (squares) or negative pressures (triangles). Solid symbols, inflations; gray symbols, deflations; solid lines, projection curves of the negative-pressure lung inflation maneuvers; dotted lines, projection curves of the negative-pressure lung inflation maneuvers.](image)
isopressure points remains higher for the inspiratory limb because, during expiration, the pulmonary capillaries regain their patency when Pc overcomes the compression pressure exerted by the positive intra-alveolar pressure. This phenomenon may be a consequence of approaching West zone 1 condition by the end of positive-pressure inflation (Pav > Ppa > Pla) where capillaries collapse. To provide experimental evidence for the presence of this mechanism, we performed additional experiments in five further lungs perfused and studied in an identical manner as those involved in the main protocol group, except that the PPLI maneuvers were repeated in these lungs at a physiological (Pc = 13.6 cmH2O) and at an elevated Pc of 20.4 cmH2O (Fig. 5). We hypothesized that an elevated Pc would counteract the compression of the capillaries generated by the compression of the alveolar walls, and accordingly, by maintaining West zone 2 and 3 conditions, it would diminish the hysteresis in the Ptp-Rv relationship. Indeed, elevation of Pc to 20.4 cmH2O led to a marked reduction in this hysteresis, suggesting that closure of the intra-alveolar capillaries plays a role in the elevated Rv values obtained in the main study population during expiration.

Effects of NPLI on Rv. We observed mild, but statistically significant decreases in Rv during the NPLI maneuvers, which is in accordance with the results of the pioneering study by Burton and Patel (3) in rabbits. Other authors, however, have reported decreases in Rv at low and moderate levels of Ptp, followed by increases in Rv at high inflation pressures, when lung expansions were generated by a vacuum around excised dog lungs (9, 24) and in open-chest dogs (19). Although the reason for this discrepancy in the literature is not completely clear, the difference in the position of the perfusion reservoirs relative to the ventilation apparatus or the dynamics of lung inflation (steady state vs. dynamic) may be involved, as follows. In the present study, the reservoirs were kept at atmospheric pressure, and thus perfusion pressures were not submitted to the changes in the Ptp. The fundamental importance of the positioning of the perfusion reservoirs during NPLI has been highlighted by Permutt et al. (14), who concluded that the differences observed in the changes in Rv during PPLI and NPLI disappear when the lung perfusion pressures were kept constant relative to Ptp. Moreover, we generated in the present study slow lung inflations rather than elevating Ptp stepwise. Maintaining Ptp elevated for a longer period may have biased the influence of lung inflation on Rv in these previous studies through activation of the autonomous nervous system in the in vivo experiments (19) and through the facilitation of edema.
development by the sustained maintenance of a subatmospheric Palv.

The present experimental setting allows clarification of the mechanisms responsible for the mild decreases in Rv during NPLI with constant perfusion pressures, because only the mechanical effect of Ptp on the pulmonary vasculature is involved in the present model and all other confounding factors are excluded. Thus it seems plausible that NPLI exerts radial traction on the capillaries in the walls of the subpleural alveoli, which subsequently results in a slight increase in their cross-sectional area. It is noteworthy that the hysteresis in the Ptp-Rv curve diminishes during NPLI, confirming that the forces acting around the pulmonary vessels lead to mild expansions of the vascular diameter rather than a compression (the latter was observed at positive pressures). This mechanism excludes the development of closures in the pulmonary vasculature during NPLI.

Interdependence between lung mechanics and pulmonary vasculature. Although there have been numerous previous studies separately of the effects of different modes of inflation on the lung vasculature (3, 5, 6, 9, 19, 23, 24, 26) or on the lung mechanics (8, 10, 12), this is the first report of simultaneous changes in these compartments during PPLI and NPLI maneuvers. The experimental setting we used made it possible to reveal the potential interactions between the pulmonary mechanics and the circulation. The effects of the parenchyma on the mechanical status of the capillaries are rather trivial, because the transmission of Ptp to the vascular wall during breathing is determined by the local and overall viscoelastic properties of the parenchyma. As regards the alternative mechanism representing the other direction of the interdependence was proposed long ago by von Basch (2), there is evidence that filled pulmonary capillaries exert a mechanical tethering force to maintain the normal alveolar geometry and hence lung compliance (1, 15). Because the filling of the alveolar capillaries is more promoted during NPLI maneuvers, this phenomenon may be expected to result in lower values of lung tissue parameters during these maneuvers. The fact that we did not observe significant differences in the mechanical parameters between the PPLI and NPLI maneuvers (Fig. 4) suggests that this phenomenon did not play a role in the range of Ptp levels employed in the present study. Furthermore, during PPLI maneuvers, the pulmonary capillaries tend to empty only at high Ptp levels, where Ptp alone determines the alveolar geometry (15).

Summary and implications. The present study has characterized the simultaneous changes in the lung mechanical and pulmonary vascular parameters during PPLI and NPLI. We have demonstrated that the same lung mechanical condition is achieved with these opposing modes of inflation, which is an expected finding, although one that has never been proven experimentally previously. Our results imply that recruitment maneuvers with positive airway pressure may jeopardize the pulmonary hemodynamic conditions by derecruiting the pulmonary capillaries and subsequently affecting the afterload of the right ventricle. The adverse changes observed in Rv were fairly small; however, they may have a greater impact at the higher Ptp levels often reached during positive-pressure mechanical ventilation, especially in clinical conditions where pulmonary hypertension is already present (e.g., congenital heart disease, acute lung injury, or chronic pulmonary diseases). Extrapolation of the present findings to a physiological condition is prohibited by the fact that the perfusion pressures during NPLI remained constant. Nevertheless, the decrease in Rv observed in the present study during NPLI may be beneficial under particular clinical conditions where the lungs can be ventilated with negative pleural pressure and where the perfusion is independent of the Ptp regimen (e.g., extracorporeal membrane oxygenation or right ventricular assistance). However, the specification of the reference pressures to which pulmonary vascular pressures are related is critical in understanding basic pulmonary vascular mechanics during lung inflation.

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