Conclusions. Our results highlight the need for the development of innovative solutions for sustainably eliminating disparities in LCS and encourage further research examining the complexities underlying racial disparities in lung cancer care. ■

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Morphological Differences between Patient Self-inflicted and Ventilator-induced Lung Injury: An Experimental Study

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To the Editor:

The role of supraphysiological airway pressure and V_T in lung damage during mechanical ventilation (MV) has been studied in-depth, the phenomenon called ventilator-induced lung injury (VILI). Following the same principles, strenuous spontaneous breathing can also be harmful, and the concept of patient self-inflicted lung injury (P-SILI) is proposed (1). However, establishing P-SILI as a pathological entity in acute patients is challenging. There are few P-SILI models focusing on the respiratory effort during MV, showing histological damage in animals with intense respiratory effort (2–4). On the contrary, data regarding strong unassisted spontaneous breathing without MV is lacking. Therefore, we aimed to compare the histopathological findings in animals with acute lung injury (ALI) treated without ventilatory support, injurious MV, and protective MV.

Methods

Twenty-four Sprague-Dawley rats of 291 ± 6 g were anesthetized, intubated, and mechanically ventilated. Animals were randomized to four groups of six subjects: *1*) VILI group, ALI followed by high V_T MV; *2*) P-SILI group, ALI followed by unsupported spontaneous breathing; *3*) Protective-MV group, ALI followed by low V_T MV; and *4*) Sham group, no lung injury followed by low V_T MV.

Lavage-induced surfactant depletion ALI was performed as previously reported (5). Animals were then stabilized on

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Author Contributions: P.C., B.E., and F.D. conceived the research idea and secured funding, designed and performed the animal experiments, and acquired data. C.G. analyzed and wrote the preliminary results of histology. All authors analyzed and interpreted the experimental and histological results, drafted the manuscript, approved the submitted version of the manuscript, and have agreed to be personally accountable for their contributions and the integrity of this work.

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Table 1. Physiological Data of the Experimental Groups at the Beginning and End of the Ventilation Stage, Either for Ventilator-induced Lung Injury, Patient Self-inflicted Lung Injury, Protective Mechanical Ventilation, or Sham Groups

Group (*n*)	Time	Sp_{O_2} (%)	RR (1/min)	V_T (ml/kg)	V_E (ml/min · kg)	Driving Pressure (cmH_2O)
VILI (6)	T1	88 (85–91)†	45†‡	12†‡	540	10 (9–12)†
	T3	92 (87–94)†	45†‡	12†‡	540	12 (11–14)†‡
P-SILI (6)	T1	87 (86–88)†	109 (94–133)*†‡	4.9 (4.1–6.7)*	496 (488–626)	N/A
	T3	94 (91–94)†	125 (97–138)*†‡	6.3 (4.5–8.9)*	593 (553–1,084)§	N/A
Protective-MV (6)	T1	92 (86–92)†	90	6	540	9 (8.3–9.2)†
	T3	89 (88–100)†	90	6	540	7.7 (6.8–8.8)
Sham (6)	T1	100 (98–100)	90	6	540	4.6 (4.2–4.9)
	T3	100 (99–100)	90	6	540	6.0 (5–7)§

Definition of abbreviations: MV = mechanical ventilation; P-SILI = patient self-inflicted lung injury; RR = respiratory rate; Sp_{O_2} = oxygen saturation as measured by pulse oximetry; VILI = ventilator-induced lung injury; V_E = minute ventilation.
Data are expressed as median (interquartile range). Data without interquartile range are parameters set for mechanical ventilation.
Intergroup analysis:
*Significant difference compared with VILI.
†Significant difference compared with Sham.
‡Significant difference compared with Protective-MV.
Time-dependent analysis:
§Significant changes were detected between T1 and T3 in any of the groups.

volume-controlled MV (VentElite, Harvard Apparatus), with V_T, 6 ml/kg; positive end-expiratory pressure, 5 cm H_2O; inspiratory to expiratory ratio, 1:2; respiratory rate (RR), 90/min; and FI_{O_2}, 1. The adequate degree of sedation was maintained with isoflurane 2%, plus intraperitoneal ketamine (30 mg/kg) and xylazine (5 mg/kg). For Protective-MV and Sham groups, the previous MV settings were maintained. In the VILI group, V_T was changed to 12 ml/kg and RR to 45/min. Animals in the P-SILI group were extubated as the respiratory effort was recuperated, maintaining a FI_{O_2} of 1. In the P-SILI group, V_T was tomographically measured (SkyScan 1278 micro-CT, Bruker), as previously reported (5). Minute ventilation was calculated as $V_T \times RR$. Vital signs were recorded at the following stages: baseline (before ALI), T1 (15 minutes of stability after ALI), and T3 (after 3 hours of ALI). Animals were killed by lethal intraperitoneal thiopental (200 mg/kg) at the end of the study.

The left lungs were fixed with 10% buffered formalin, cross-sectioned every 1 mm from apex to base (22–24 slices per lung), and stained with hematoxylin and eosin and Masson's trichrome for histological analysis of apical (fourth), intermedium (twelfth), and basal (twentieth) lung slices.

Global histological lung injury score (LIS) and topographical distribution were evaluated using a validated scale ranging from 0 to 15 (6). We used a multiparametric and semiquantitative LIS to characterize the predominant structural damage. It includes 13 parameters, scored as 0 (absent), 1 (mild), 2 (moderate), and 3 (severe) grouped into five subcategories: airway (desquamation of epithelial cells) and alveolar epithelial injury (pneumocyte desquamation, alveolar wall thickness, atelectasis, and emphysema), vascular injury (hyperemia, perivascular edema, alveolar hemorrhage, thrombosis, and hyaline membranes), inflammatory response (intensity of perivascular and bronchiolar inflammation, and bronchus-associated lymphoid tissue), and fibroproliferative response (intensity of fibrosis) (7). A board-certified pathologist (C.G.), blind to experimental groups, analyzed the samples.

Data were presented as median (interquartile range). Ordinary two-way ANOVA, followed by Dunnett's test for multiple comparisons with the P-SILI group, was used. Significance was set at $P < 0.05$. All analyses were performed with GraphPad Prism 9.3.1.

Results

Lung lavage resulted in severe hypoxemia for all injured rats (Sp_{O_2}/FI_{O_2}, 88 ± 1), without differences between injured groups in Sp_{O_2} and minute ventilation at baseline, T1, and T3 (Table 1).

Regarding global histological injury, we found a stepped damage, highest in VILI, followed by P-SILI, and lowest in Protective-MV (10.5 [7.0–13.5] vs. 5.0 [3.5–8.0], $P < 0.01$; vs. 1.5 [0–6.3], $P = 0.035$). Regarding topographic distribution, the VILI group had more damage than all other groups in apical and intermedium regions. P-SILI had more damage than the Protective-MV in basal regions. Global and regional LIS are shown in Figure 1A.

In the analysis of the specific parameters, there were no differences in vascular injury between VILI and P-SILI, and P-SILI was higher than the Protective-MV group (1.1 [0.6–1.8] vs. 1 [0.7–1.2], $P = 0.99$; vs. 0.5 [0.3–0.6], $P = 0.002$). All other subcategories of lung injury were higher in VILI than P-SILI, without differences between P-SILI and Protective-MV: Airway epithelial injury (3 [2–3] vs. 0 [0–1], $P < 0.001$, vs. 0 [0–1], $P = 0.99$), alveolar epithelial injury (1.4 [1–1.8] vs. 0.3 [0.1–0.4], $P = 0.001$, vs. 0.3 [0–0.3], $P = 0.99$), inflammatory response (1.5 [1–1.5] vs. 0.5 [0.5–0.9], $P < 0.001$, vs. 0 [0–1], $P = 0.63$), and fibroproliferative response (0.5 [0–1] vs. 0 [0–0], $P < 0.01$, vs. 0 [0–0], $P = 0.99$). The individual analysis of the 13 parameters of semiquantitative LIS is shown in Figures 1B and 1C. Representative images of lung histology for each study group are shown in Figure 1D.

Discussion

In this experimental ALI study, we found a stepped global morphological LIS among groups, highest in VILI, followed by

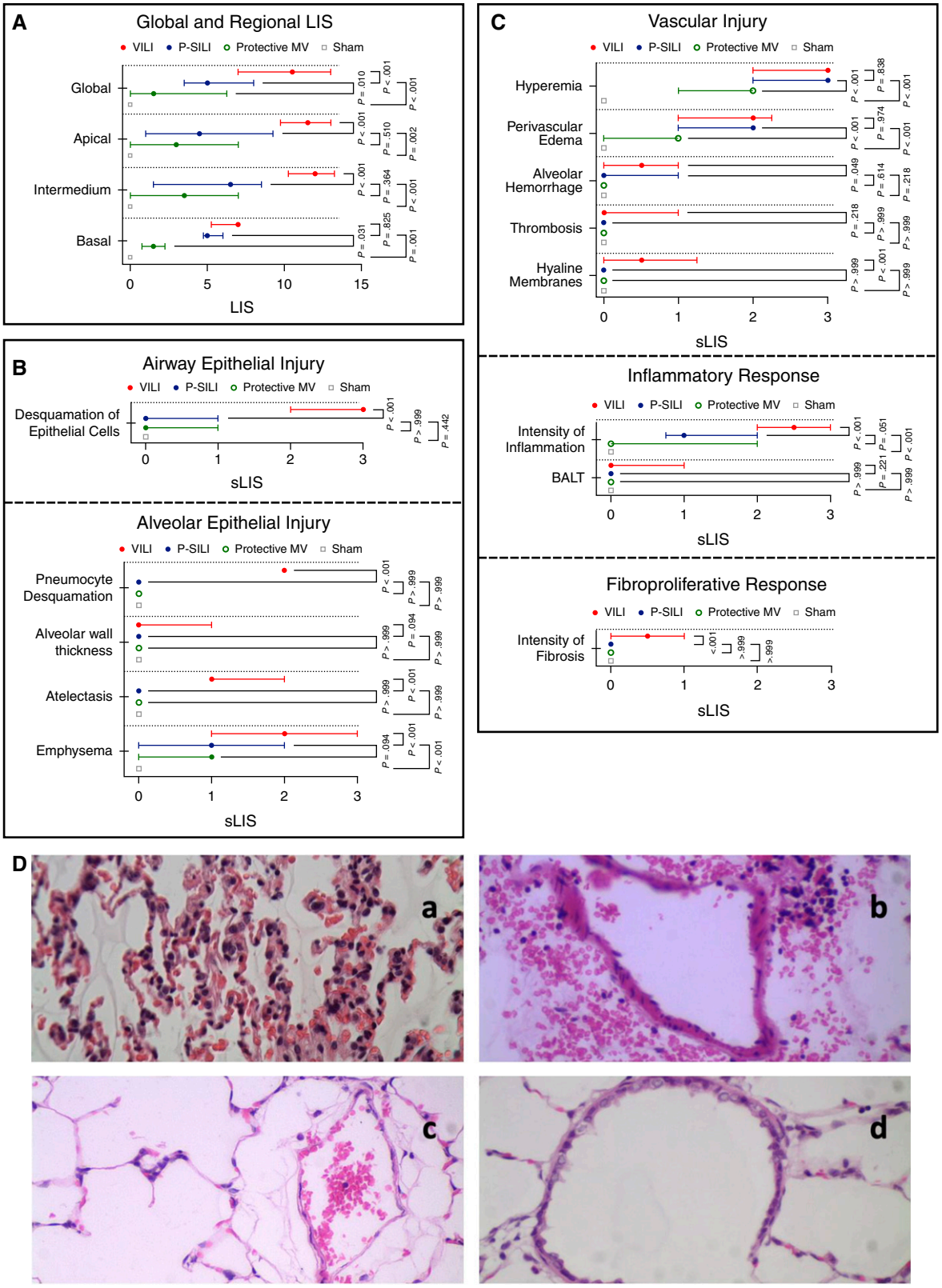

Figure 1. (*A*) Global and regional histological lung injury score. (*B* and *C*) Specific components of semiquantitative LIS. Representative images of lung histology for each study group (hematoxylin and eosin, 400×): (*D*, *a*) Image from the VILI group presented alveolar epithelial damage with atelectasis and areas of alveolar wall collapse with loss of air space. (*D*, *b*) Image from the P-SILI group presented hyperemia,

P-SILI, and lowest in Protective-MV, after 3 hours of observation. The regional distribution was predominantly in apical and intermedium regions in VILI, whereas in P-SILI, it was homogeneously distributed. Interestingly, in an exploratory analysis of the components of LIS, there was a difference in injury patterns between VILI and P-SILI. P-SILI had a similar degree of vascular damage to VILI, and both were higher than Protective-MV. However, histological damage of VILI was greater than P-SILI in terms of the airway and alveolar epithelial injury and inflammatory and fibroproliferative response. These results confirm the P-SILI phenomenon and generate hypotheses about possible mechanisms of damage, depending on whether mechanical stress on the lung is applied by MV or by the subject's respiratory activity.

Translational studies of P-SILI are lacking, being mainly an experimental description, and it is still controversial how it applies to human acute respiratory distress syndrome. Specifically, spontaneous breathing might be beneficial in mild–moderate acute respiratory distress syndrome, but in severe forms, it is detrimental.

The morphological patterns can be related to the differences in the direction of the lung strain and stress vector: negative intrathoracic pressure during P-SILI and positive pressure during VILI (5, 8). For instance, in contrast to the severe vascular injury, the preserved airway and alveolar epithelium in P-SILI might be related to large blood flow oscillations because of cyclic inspiratory negative pressures (1, 2, 4). On the other hand, airway and alveolar epithelium disruption may be distinctive of VILI (9) because it is the first structure capable of dissipating this mechanical force.

Our study has some limitations. Esophageal pressure and arterial blood gases were not measured to quantify respiratory effort intensity and hypoxemia. Animals were in an awake prone position that can modify the respiratory pattern in the P-SILI group, limiting extrapolation to supine-positioned subjects. Finally, the short duration of observation prevents the extrapolation to other settings. Despite these limitations, we described the morphology of P-SILI in detail, comparing it to VILI and Protective-MV as known positive and negative control groups, respectively. We highlight the unique character of this exploratory, experimental design to study distinctive features related to P-SILI.

Conclusions. This murine ALI study found significant differences between groups in global LIS and morphologic injury patterns. Specifically, vascular damage was found in P-SILI, whereas other structures were preserved. Therefore, future studies must include dynamic biomarkers related to these structures (i.e., vascular integrity and apoptosis) to improve the understanding of the underlying mechanobiology and deepen knowledge linked to the microstructural characteristics of lung damage in P-SILI. ■

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Figure 1. (*Continued*). perivascular edema, and hemorrhage. (*D*, *c*) Image from the Protective-MV group presented mild perivascular edema and alveolar wall rupture. (*D*, *d*) Image from Sham group presented normal lung sections. Data are expressed as median (interquartile range). Significant within-group differences are denoted by $P < 0.05$. BALT = bronchus-associated lymphoid tissue; MV = mechanical ventilation; P-SILI = patient self-inflicted lung injury; LIS = lung injury score; sLIS = semiquantitative lung injury score; VILI = ventilator-induced lung injury.