$P = 0.2$) for score 3+. The aHRs for cancer mortality were 1.26 (95% CI, 0.85–1.88; $P = 0.3$) for score 1/2 and 1.80 (95% CI, 1.23–2.63; $P = 0.002$) for score 3+. The results were similar when FEV_1% predicted was used instead of FEV_1 in liters (data not shown).

Our results provide new insight into the causes of death in patients with COPD by showing that airway mucus plugs are associated with respiratory and, unexpectedly, cancer deaths. The association between mucus plugs and respiratory mortality was stronger with a higher degree of mucus plug burden. Although our observational study cannot prove their causal relation, prior studies in animals and humans suggest a biological plausibility. For instance, mucus plugs might potentiate pathogenic microbial growth (7) and may contribute to worse ventilation/perfusion mismatch, potentially increasing the risks of pneumonia and respiratory failure, which are prominent respiratory causes of COPD-associated mortality (8). Further clinical studies are warranted to test whether reducing the burden of mucus plugs leads to a mortality benefit.

The association between mucus plugs and cancer death might be explained by shared inflammatory mechanisms and genetic mutations between mucus pathology and smoking-related cancer. For instance, the oncogenic P53 mutant protein is implicated in increased mucus production and the sustained lifespan of metaplastic bronchial mucus cells (9). It is also possible that the overall frailty of patients with COPD with cancer impairs their ability to expectorate. More dedicated studies are needed to further explore genetic, transcriptomic, and proteomic associations between airway mucus plugging and cancer.

This study has several limitations. First, missing adjudicated causes of death were excluded from the analysis, which may introduce bias if these were not missing at random. Second, our study included only participants who self-identified as non-Hispanic Black or non-Hispanic White. Also, our study was limited to those with a smoking history of ⩾10 pack-years. Therefore, interpretation and application of the results require caution. Despite these limitations, our study explores cause-specific mortality in participants with COPD and airway-occluding mucus plugs and highlights that airway mucus plugs may be associated with respiratory and cancer deaths in this population. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Electrical Impedance Tomography: A Monitoring Tool for Ventilation-induced Lung Injury

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To the Editor:

Mechanical ventilation may promote lung injury (ventilator-induced lung injury [VILI]), characterized by cellular rupture, edema, and a decrease in lung volume, all of which lead to a decrease in lung electrical impedance. We investigated whether electrical impedance

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Author Contributions: Study concept and design: I.F., G.H., O.M., and L.G. Acquisition, analysis, or interpretation of data: I.F., T.P., A.F., R.V.N., M.B., and F.C. First drafting of manuscript (writing committee): I.F., L.C., and L.G. Critical revision for important intellectual content and final approval of manuscript: G.H., T.P., A.F., R.V.N., M.B., F.C., O.M., and L.C. Statistical analysis: I.F., T.P., and L.C. Administrative, technical, or material support: I.F., G.H., and O.M. Study supervision: L.G.

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Table 1. Complete Set of the Main Physiological Variables Changes from the Beginning to the End of the Experiment Divided According to the Two Groups of Mechanical Power

	MP/Weight (≤0.545 J/min/kg) (*n* = 49)	MP/Weight (>0.545 J/min/kg) (*n* = 49)	P_{MP}	P_{TIME}	$P_{INTERACTION}$
Gas exchange					
Pa_{O_2}:FI_{O_2}, mm Hg					
0.5 h	555 (528 to 580)	613 (589 to 635)	<0.001	<0.001	0.057
48 h	523 (505 to 543)	565 (540 to 596)			
Vd/Vt, %					
0.5 h	0.52 (0.48 to 0.56)	0.47 (0.43 to 0.53)	0.534	<0.001	0.358
48 h	0.49 (0.41 to 0.52)	0.47 (0.39 to 0.53)			
Respiratory mechanics					
Peak airway pressure, cm H_2O					
0.5 h	22 ± 5	38 ± 12	<0.001	<0.001	0.012
48 h	23 ± 5	40 ± 9			
Driving pressure, cm H_2O					
0.5 h	13 ± 4	19 ± 7	<0.001	0.035	<0.001
48 h	13 ± 4	19 ± 5			
Respiratory system elastance, cm H_2O/L					
0.5 h	32 (27 to 35)	37 (33 to 43)	<0.001	<0.001	<0.001
48 h	31(27 to 37)	44 (38 to 51)			
MP, J/min					
0.5 h	9 (8 to 12)	27 (22 to 30)	<0.001	<0.001	<0.001
48 h	9 (8 to 13)	28 (23 to 33)			
Hemodynamics					
Mean pulmonary arterial pressure, mm Hg					
0.5 h	18 (17 to 22)	25 (22 to 30)	<0.001	<0.001	<0.001
48 h	15 (13 to 17)	30 (22 to 36)			
Pulmonary artery occlusion pressure, mm Hg					
0.5 h	7 ± 3	16 ± 7	<0.001	<0.001	<0.001
48 h	7 ± 2	17 ± 7			
Electrical lung impedance					
End-expiratory impedance total lung (relative ΔZ), $\times 10^3$					
0.5 h	−2 (−2 to 1)	−5 (−23 to −1)	<0.001	<0.001	<0.001
48 h	−70 (−96 to −25)	−155 (−211 to −103)			
Fluid balance					
Fluid balance, ml					
0.5 h	80 (−3 to 149)	807 (370 to 1,370)	<0.001	<0.001	<0.001
48 h	645 (418 to 898)	3362 (2,083 to 6,859)			
Delta body weight, kg	0.7 (0.2 to 2.2)	3.2 (2.2 to 5.8)		<0.001	
Pathology					
Lung weight, g/kg	14.1 (12.1 to 20.2)	20.4 (14.9 to 27.2)		<0.001	
Wet-to-dry ratio, lung	6.0 ± 0.7	6.5 ± 0.6		0.003	
Wet-to-dry ratio, liver	4.4 ± .5	4.0 ± 0.4		<0.001	
Histology					
Ruptures, %	13 (9 to 16)	18 (12 – 22)		0.001	
Inflammation, %	32 (21 to 52)	32 (14 to 69)		0.977	
Alveolar edema, %	8 (2 to 14)	10 (1 to 37)		0.487	
Atelectasis, %	8 (1 to 20)	17 (12 to 24)		0.001	
Total score, %	8 (1 to 20)	19 (12 to 24)		0.001	

Definition of abbreviations: MP = mechanical power; Vd/Vt = physiological dead space.
Data are expressed as median (interquartile range) or as mean ± SD.

tomography (EIT) can detect the onset and progression of VILI, compared with changes in oxygenation, respiratory mechanics, and lung pathology, in an animal model of VILI.

Methods

We performed a retrospective analysis on 98 healthy female domestic pigs (median weight, 25.2 [interquartile range, 22.8–27.2] kg) that were ventilated for 48 hours in a prone position with mechanical power (MP) ranging between 5 and 60 J/min. We selected pigs from previous experiments (1–4) (LAVES Niedersächsisches Landesamt für Verbraucherschutz und Lebensmittelsicherheit, Projekte 16/2223, 18/2795, 19/3142, 19/3141) with at least 80% of EIT measurements (67 pigs, 100%; 22 pigs, 90%; and 9 pigs, 80%). Animals were divided into two groups according to the median MP value per kilogram actual body weight (MP/kg; 0.545 J/min/kg). Ventilatory settings were kept constant throughout the experiment, and gas exchange,

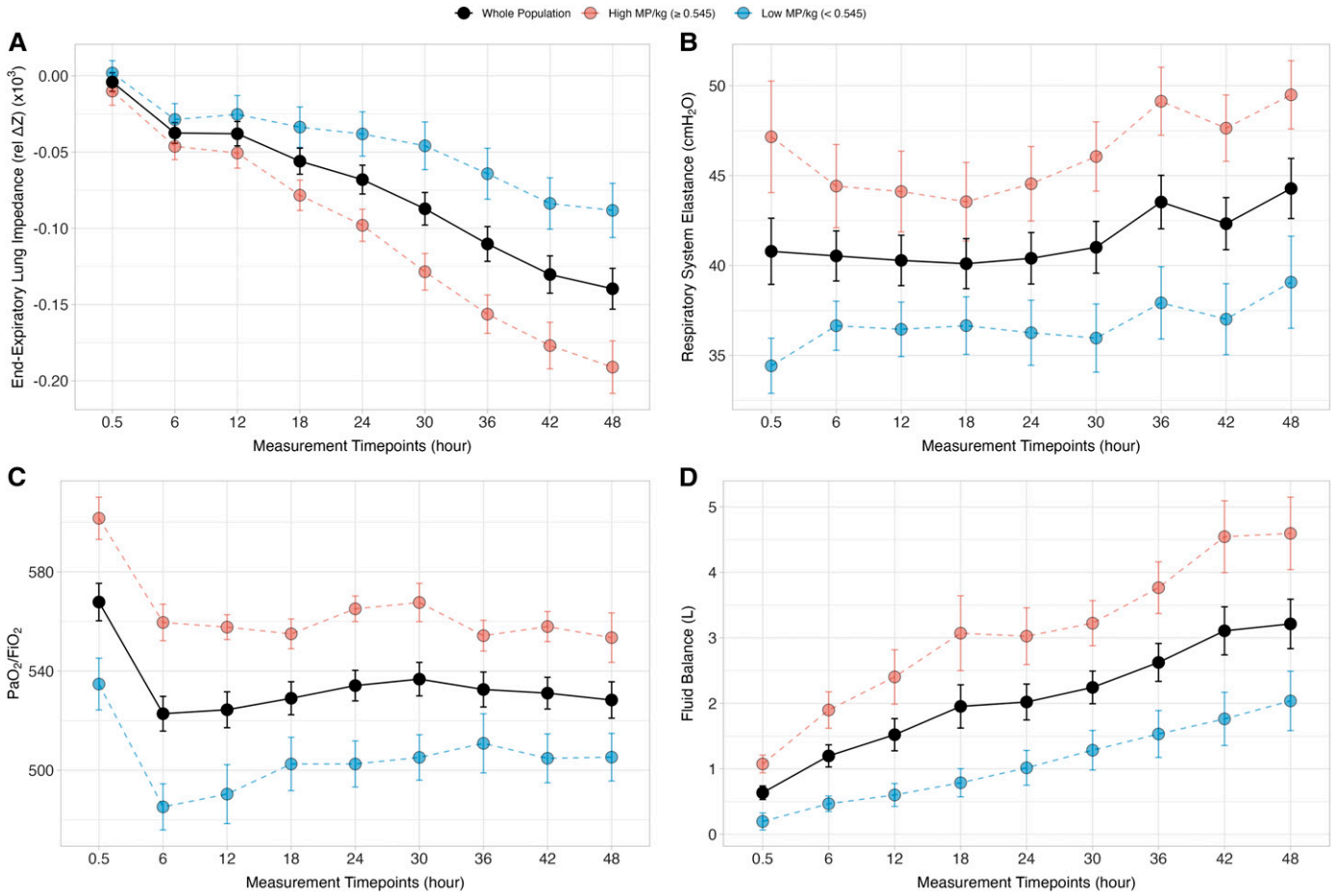

Figure 1. Time courses of end-expiratory lung impedance, respiratory system elastance, Pa_{O_2}:FI_{O_2} ratio, and fluid balance in the whole population (black dots) and in groups with low (blue dots) and high (red dots) mechanical power. For end-expiratory lung impedance, $P_{GROUP} \leq 0.001$, $P_{TIME} = 0.035$, and $P_{INTERACTION} \leq 0.001$; for respiratory system elastance, $P_{GROUP} < 0.001$, $P_{TIME} < 0.001$, and $P_{INTERACTION} < 0.001$; for Pa_{O_2}:FiO_2 ratio, $P_{GROUP} = 0.571$, $P_{TIME} < 0.001$, and $P_{INTERACTION} = 0.015$; and for fluid balance, $P_{GROUP} < 0.001$, $P_{TIME} < 0.001$, and $P_{INTERACTION} < 0.001$ (two-way ANOVA). MP/kg = median MP value per kilogram actual body weight.

hemodynamics, respiratory mechanics, and EIT were measured every 6 hours.

At 48 hours, the animals were killed, and the lung weight and wet-to-dry ratios of lungs, liver, kidney, bowel, and muscle were measured. We obtained 10 tissue samples from each lung and then calculated histological scores for alveolar rupture, inflammation, edema, and atelectasis. EIT measurements were performed using PulmoVista 500 (Dräger). The changes in end-expiratory lung impedance (EELI) were analyzed offline using custom-made software (MATLAB; The MathWorks, Inc.). MP/kg groups were compared using Student's *t* test or the Wilcoxon-Mann-Whitney *U* test. To assess the effects of MP over time, we used two-way ANOVA for repeated measures with MP/kg groups as a between fixed effect and time as a within fixed effect. *P* values <0.05 were considered to indicate statistical significance. All analyses were performed using RStudio (RStudio Team).

Results

Table 1 summarizes the comparisons between the changes in oxygenation, respiratory mechanics, and pathology in the groups at lower or higher MP/kg. The higher MP/kg group had higher lung weight, higher lung and liver wet-to-dry ratios, higher fluid balance, worse respiratory mechanics, and higher pulmonary arterial and occlusion pressures. In addition, the higher MP/kg group showed a higher frequency of alveolar septal ruptures and atelectasis and overall grater histological injury scores (Table 1). The time courses of Pa_{O_2}:FI_{O_2} ratio, respiratory system elastance, fluid balance, and ΔEELI are displayed in Figure 1. As shown, the Pa_{O_2}:FI_{O_2} ratio decreased significantly after 0.5 hours but remained stable afterward, while respiratory system elastance worsened gradually only after 24 hours (Table 1). In contrast, the value of ΔEELI decreased after 0.5 hours and continued to decline progressively throughout the experiment, particularly in the high-MP group. The reduction in ΔEELI was attributed predominantly to MP rather than fluid balance. Although fluid balance affected the value of ΔEELI, the temporal rate of change in ΔEELI for MP (>20 J/min) was similar between animals with lower (1.9 ± 1.0 L) and with higher (7.7 ± 2.1 L) fluid balance.

Discussion

The main findings of this study, which serves as a hypothesis-generating endeavor, are that higher MP/kg resulted in higher fluid balance, lung weight, wet-to-dry ratio, respiratory elastance, and

pulmonary artery and occlusion pressures. These changes were associated with higher frequencies of atelectasis and alveolar septal rupture, an objective marker of VILI.

In this study, MP was applied to healthy lungs, and we speculate the following sequence of events: higher MP causes an increase in pleural pressure and hemodynamic compromise, leading to fluid administration to restore hemodynamics and water retention by the kidney. The direct effect of MP on the lung parenchyma may result in alteration of the extracellular matrix and alveolar rupture (5). The resultant inflammation (5) increases capillary permeability, inflammatory lung edema, lung weight, and therefore compression atelectasis (6–8).

Monitoring the progression of VILI using objective methods such as histology is obviously not feasible in clinical practice. However, it is possible to monitor some of the "consequences" of the anatomical injuries, such as edema, gas volume reduction, and inflammation. These alterations are commonly tracked using changes in Pa_{O_2}:FI_{O_2} or respiratory system elastance. In our study, Pa_{O_2}:FI_{O_2}, after an early decrease, remained stable throughout the rest of the experiment, despite the increase in respiratory elastance. A possible explanation for the stability in Pa_{O_2}/FI_{O_2} despite the increase in edema is the possible coexistence of two phenomena: *1*) the activation of pulmonary hypoxic vasoconstriction, with the aim of maintaining oxygenation, and *2*) intratidal recruitability, which attenuated the worsening in gas exchange (9, 10).

The other common variable used to monitor VILI is respiratory elastance. However, in our study. elastance increased significantly only after 24 hours. This is in accordance with previous findings showing that that the impairment in respiratory mechanics occurs several hours after the first appearance of computed tomography scan lung densities associated with mechanical injury (10).

In contrast, we argue that the progression of these alterations can be quantified using changes in ΔEELI. Consistent with this hypothesis, we found that ΔEELI decreases early and progressively throughout the experiment. This was consistent with the described temporal progression of focal parenchymal lesions, evident after 5 hours of harmful ventilation and increasing over 48 hours (2, 10). The decrease of ΔEELI is a composite phenomenon that depends on three distinct events: *1*) the decrease of gas content, *2*) the increase of edema (lung water), and *3*) alterations or rupture of cell membranes. In this study, we found that a decrease in FRC and an increase in fluid balance were both significantly related to the changes in ΔEELI and increased alveolar septal rupture. The rate of change of ΔEELI was affected predominantly by high MP and was similar in animals with largely different degrees of fluid balance. A limitation of this study is the absence of biological markers for inflammation and injury to support ΔEELI findings.

Conclusions. ΔEELI changes may occur early in VILI (8), potentially reflecting the severity and progression of injury. EIT monitoring could be a promising avenue for future research in detecting VILI. ■

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VENT-AVOID Trial: Avoiding Acute Hypercapnic Respiratory Failure!

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To the Editor:

We read with interest the much-anticipated VENT-AVOID (Extracorporeal CO2 Removal with the Hemolung RAS for

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