Particle Flow Profiles From the Airways Measured by PExA Differ in Lung Transplant Recipients Who Develop Primary Graft Dysfunction

Ellen Broberg,[1] Snejana Hyllén,[1] Lars Algotsson,[1] Darcy E. Wagner,[2] Sandra Lindstedt[3]

Abstract

Objectives: **Primary graft dysfunction is a severe form of acute lung injury and a major cause of early morbidity and mortality encountered after lung transplant. We used a customized PExA 2.0 instrument (PExA, Gothenburg, Sweden) to measure particle flow in exhaled air during mechanical ventilation in the intensive care unit. Our objective was to discover whether patients who developed primary graft dysfunction had different particle flow patterns from the airways. We used volume-controlled ventilation and pressure-controlled ventilation to see whether changes in particle patterns could be observed in both mechanical ventilation settings.**

Materials and Methods: **First, we investigated whether it was safe to use a customized PExA 2.0 in conjunction with mechanical ventilation. Next, 12 lung transplant patients were randomized to either daily volume-controlled ventilation or pressure-controlled ventilation as the first mode of treatment until extubation.**

Results: **In our study group, 6 patients did not develop primary graft dysfunction and 6 developed primary graft dysfunction. Patients with primary graft dysfunction underwent mechanical ventilation significantly longer; they also showed a stepwise increase in particle count from day 0 until extubation. We observed no adverse events related to the PExA 2.0 device.**

Conclusions: **This study suggests that the PExA 2.0 device is safe to use in conjunction with mechanical ventilation in the intensive care unit. Lung transplant patients who developed primary graft dysfunction showed a different particle profile from the airways before clinical signs of primary graft dysfunction developed. Online assessment of ventilation impact before presentation of tissue changes may allow real-time detection of primary graft dysfunction, thus preventing or reducing its effects.**

Key words: *Artificial respiration, Intensive care, Lung transplantation*

Introduction

Lung transplant is the final treatment for end-stage lung disease. However, primary graft dysfunction (PGD) and chronic lung allograft dysfunction have high rates of occurrence, resulting in median survival of only around 5 years after lung transplant.[1-4] Primary graft dysfunction develops within the first 72 hours after the transplant procedure and is a syndrome of acute lung injury similar to acute respiratory distress syndrome (ARDS). The initial clinical diagnosis of PGD is characterized by decreasing the ratio of arterial oxygen pressure to inspired oxygen concentration (PaO_2/FiO_2) and pulmonary infiltration on chest radiography. It has an incidence of around 30% in its severest form and is associated with an increase in both short- and long-term mortality.[5-8]

Mechanical ventilation is used in the vast majority of patients during the first days posttransplant and may play a role in the onset of PGD.[9-11] The length of time in the intensive care unit (ICU) and time spent on mechanical ventilation may depend on whether the patient develops PGD.[12,13] How to optimize or individualize the mechanical ventilation strategy during the ICU stay and whether lung recruitment should be used routinely is an area of intense debate. Lung-protective ventilation is a commonly used

From the [1]Department of Cardiothoracic Anaesthesia and Intensive Care, Skane University Hospital, Lund University; the [2]Department of Experimental Medical Sciences, Lung Bioengineering and Regeneration, Lund University; and the [3]Department of Cardiothoracic Surgery and Transplantation, Skane University Hospital, Lund University, Lund, Sweden

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Corresponding author: *Sandra Lindstedt, Department of Cardiothoracic Surgery and Transplantation, Skane University Hospital, SE-221 85 Lund, Sweden*
E-mail: *sandra.lindstedt_ingemansson@med.lu.se*

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strategy. An international survey showed that pressure-controlled ventilation (PCV) is used in 37% of patients, volume-controlled ventilation (VCV) is used in 35% of patients, and a mix of both is used in the remaining percent of patients.[14]

We have recently shown that particles can be measured and monitored online using the particles in exhaled air 2.0 instrument (PExA, Gothenburg, Sweden) during mechanical ventilation in a proof-of-principal study in porcine lungs,[15] thus indicating that this might be a useful method for real-time analysis during clinical mechanical ventilation. In another porcine study, we showed that lung injury, such as ARDS, induced a trend in increased particle flow from the airways.[16]

The primary outcome in the present study was to investigate whether it was safe to use a customized PExA 2.0 instrument in conjunction with mechanical ventilation in ICU settings. Our secondary outcome was to investigate whether patients who developed PGD had different particle flow patterns from airways versus patients who did not develop PGD. We used VCV and PCV to see whether these changes in particle pattern profiles could be observed in both settings and also whether particle profiles were different in the 2 settings. Measurements were also done during daily recruitment maneuvers (RM) according to a set protocol.

Materials and Methods

Patients

From 2017 to 2018, 13 patients who underwent lung transplant were included and randomized in our study. One patient, who developed severe PGD stage 3, was excluded from further analysis due to an intervention with the administration of an inhaled drug. The study was approved by the local Ethics Committee for Research (Dnr 2017/396). All patients signed a written informed consent.

Mechanical ventilation and recruitment maneuvers

All patients arrived in the ICU posttransplant with a 7.5-mm tracheal tube. The ventilator settings were made according to local guidelines (tidal volume of 6 mL/kg, positive end-expiratory pressure [PEEP] of 5 cm H_2O, end-inspiratory pressure of < 25 cm H_2O, and target CO_2 levels of 4.6-6 kPa). Inspiratory-to-expiratory ratios of 1:2 were used in all patients. The type of ventilator used for all patients was the Maquet SERVO-I (Getinge Group, Solna, Sweden). These settings remained unchanged during the study period.

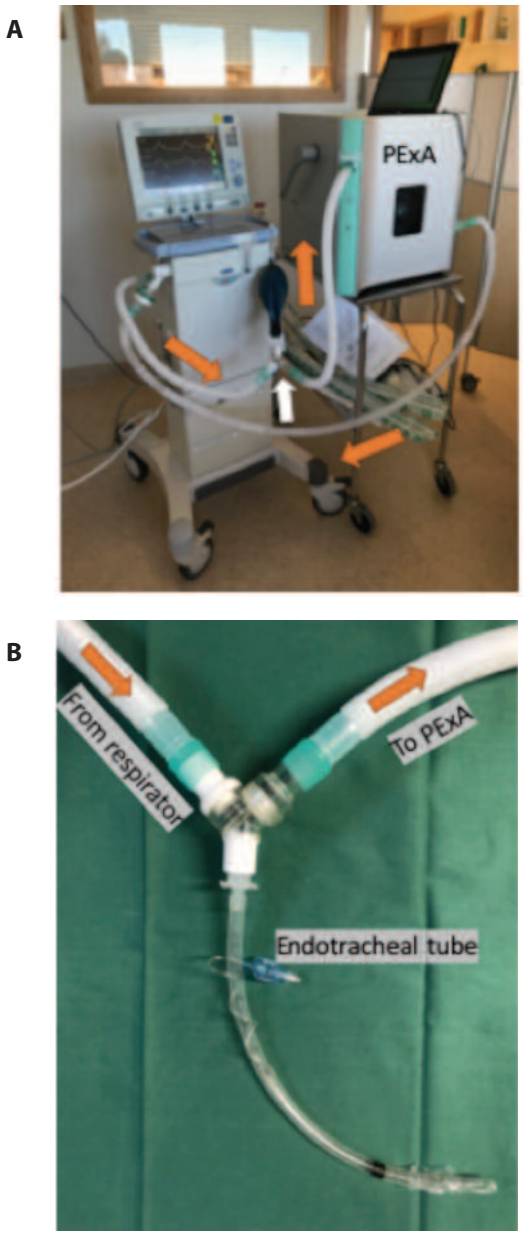
Particle outflow was measured using a modified PExA 2.0 instrument each day during 2 different ventilation modes (VCV and PCV). Patients were randomized into those who received VCV before PVC (n = 6) and those who received PCV before VCV (n = 6). Each patient was monitored daily for 1 hour during VCV and 1 hour during PCV. Before the collection period began for the second ventilation mode, there was an equilibration period of 30 minutes with the second ventilation mode.

Patients received RM twice daily during both ventilation modes (VCV and PCV), which was a 60-second period with PEEP of 10 cm H_2O, 4 breaths/min, and inspiratory-to-expiratory ratio of 2:1. Measurements were done for 3 minutes before the RM and for 3 minutes after the RM. Six patients were extubated on posttransplant day 3, 2 patients were extubated on posttransplant day 2, and 4 patients were extubated on posttransplant day 1.

PExA measurements

The PExA 2.0 instrument conducts measurements by optical particle counter and has been described previously in patients breathing room air.[17] In the present study, the instrument was customized to be used in conjunction with mechanical ventilation. The instrument was connected to the outflow tract of the respiratory circuit (Figure 1A). A non-rebreathing valve was used to connect the tracheal tube to the inflow and the outflow tract of the respiratory circuit as shown in Figure 1. The total accumulated number of particles (count) from the airways was continuously measured by the PExA 2.0 instrument during different ventilation modes for the 2 hours of collection per day (1 h during VCV and 1 h during PCV). The PExA 2.0 measurements were made starting on day 0 (< 12 h after arrival to the ICU) and were performed daily thereafter until termination of mechanical ventilation. Measurements were made during each ventilation mode (VCV or PCV), with each mode lasting for 1 hour per day, and total particle flow was measured for 3 minutes before and after RMs. Particles ranging from 0.41 to 4.55 μm in diameter were measured.

Figure 1. Respiratory Circuit and Non-Rebreathing Valve Connection



(A) Respiratory circuit. Black balloon represents the patient with the optical particle counter PExA connected to the outflow tract of the circuit. Orange arrows show the direction of air flow, and white arrow shows the nonrebreathing valve. **(B)** Non-rebreathing valve connection, with orange arrows showing the direction of air flow.

Blood samples, blood gas levels, and hemodynamic parameters

In accordance with our clinic's standard program posttransplant, all patients were followed with daily blood samples to analyze hematology biomarkers, inflammatory biomarkers, and biomarkers for kidney and liver function.

All patients had a central venous catheter and an arterial line. The blood gases were drawn from the arterial line and analyzed in a standard way, and hemodynamic parameters were continuously recorded in a standard way.

Primary graft dysfunction

Primary graft dysfunction was graded according to the International Society of Heart and Lung Transplantation and was based on results of blood gas measurements, ventilator settings, and chest radiography. The severity of PGD was graded based on PaO_2/FiO_2 and the presence or absence of infiltrate on chest radiography during the first 72 hours posttransplant[18] (Table 1).

Table 1. Primary Graft Dysfunction

PGD Grade	Pulmonary Edema on Chest Radiography	PaO_2/FiO_2 Ratio, mm Hg
Grade 0	Absent	> 300
Grade 1	Present	> 300
Grade 2	Present	200-300
Grade 3	Present	< 200

Abbreviations: PaO_2/FiO_2 ratio, ratio of arterial oxygen pressure to inspired oxygen concentration; PGD, primary graft dysfunction

Statistical analyses

Descriptive statistics, including number of patients and mean and the standard error of the mean, for the different parameters were analyzed, with results presented for the 2 different groups. A paired *t* test was used to compare the 2 groups. All statistical analyses were performed using GraphPad Prism Software (La Jolla, CA, USA). Significance was defined as $P < .05$.

Results

Demographic characteristics of the patients

The mean age of the recipients was 56 ± 3 years. Five of the recipients were women and 7 were men.

Of the 12 patients, 3 patients underwent single lung transplant. All 3 of these patients were retransplant patients who underwent a single lung transplant due to bronchiolitis obliterans syndrome. Primary transplant in 2 of these patients was due to cystic fibrosis, with the other patient having primary transplant due to idiopathic pulmonary fibrosis.

The remaining 9 of 12 patients had double lung transplants: 1 had chronic obstructive pulmonary disease, 4 had idiopathic pulmonary fibrosis, 2 had cystic fibrosis, and 2 had chronic obstructive pulmonary disease due to alpha-1 antitrypsin deficiency.

Feasibility of PExA 2.0 used in conjunction with mechanical ventilation

The purpose of this study was to test the feasibility of PExA 2.0 used in conjunction with mechanical ventilation. No mild, moderate, or severe adverse events, such as airway leakage, signs of rebreathing, altered pressure levels, and hemodynamic interferences, were observed in our patients. Ventilator peak pressures and mean pressures along with fraction of inspired oxygen levels, blood gases, blood pressure, saturation, and pulse are shown in in Tables 2, 3, and 4. Interestingly, we did not detect any statistically significant or clinically significant changes during all days and measurements.

Effects of volume-controlled versus pressure-controlled ventilation on total particle count

The total particle count during the 2 ventilation modes (VCV and PCV) was analyzed at every time point, with VCV compared with PCV from day 0 until extubation. At day 0, the average total particle count was 10 299 ± 3420 during VCV and 11 678 ± 3593 during PCV (P = .6288); at day 1, the total particle count was 27 117 ± 13 508 during VCV and 15 238 ± 3918 during PCV (P = .3106); at day 2, the total particle count was 61 461 ± 42 060 during VCV and 80 373 ± 61 017 during PCV (P = .3604); and, at day 3, the total particle count was 143 585 ± 60 920 during VCV and 190 497 ± 74 156 during PCV (P = .0328) (Figure 2A). Thus, we only observed significant differences between VCV and PCV on day 3.

To exclude the effects of single versus double lung transplant, we analyzed the same data (see Figure 2B) but excluded patients who had received only single lung transplants. At day 0, the total particle count was 13 023 ± 4855 during VCV and 14 442 ± 5102 during PCV (P = .7506); at day 1, the total particle count was 20 698 ± 13 933 during VCV and 15 877 ± 4991 during PCV (P = .6702); at day 2, the total particle count was 61 461 ± 42 060 during VCV and 80 373 ± 61 017 during PCV (P = .3604); and, at day 3, the total particle count was 143 585 ± 60 920 during VCV and 190 497 ± 74 156 during PCV (P = .0328) (Figure 2B). Thus, the same pattern with only a significant difference between PCV and VCV at day 3 was observed.

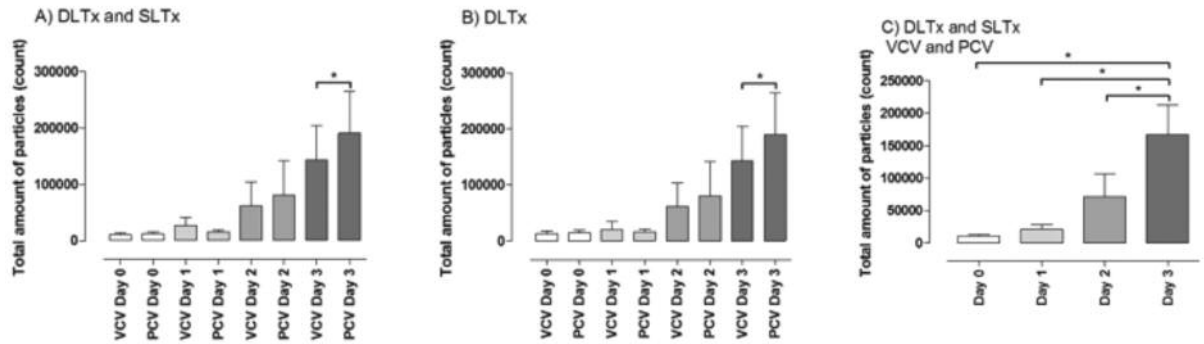
Total particle count over time until extubation

Total particle count (all VCV and PCV measurements) from day 0 until extubation was measured in all 12 transplant patients. At day 0, the total particle count was 10 988 ± 2412; at day 1, the total particle count was 21 178 ± 6989; at day 2, the total particle count was 70 917 ± 35 881; and, at day 3, the total particle count was 167 041 ± 46 296 (Figure 2C). We observed a significant increase in total particle count from the airways on day 0 versus day 3 (P = .0146), on day 1 versus day 3 (P = 0.0128), and on day 2 versus day 3 (P = .0105)

Primary graft dysfunction

During the initial 72 hours after transplant, 6 patients developed PGD and the other 6 did not. Four patients developed stage 1 PGD, 1 patient developed stage 2 PGD, and 1 patient developed stage 3 PGD. We observed no significant differences in total particle counts between VCV and PCV with regard to disease stage during the different days. When we compared the total daily particle count, patients with PGD were more prone to stay in mechanical

Figure 2. Total Accumulated Particle Count Measured by PExA 2.0

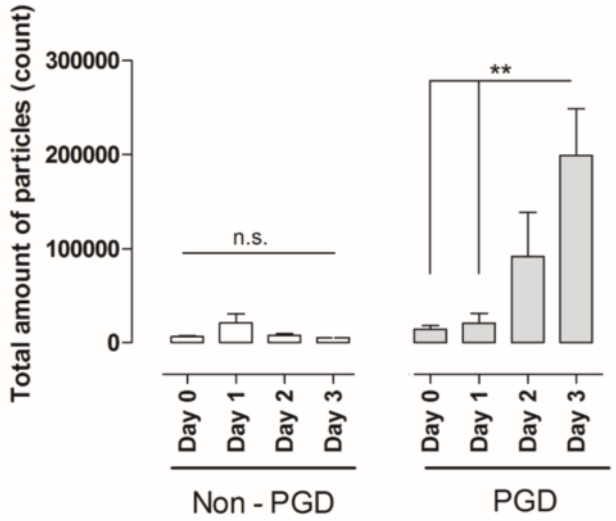


Abbreviations: DLTx, double lung transplant; PCV, pressure-controlled ventilation; SLTx, single lung transplant; VCV, volume-controlled ventilation
(A) Results for all lung transplant recipients (n = 12) showing VCV versus PCV during daily measurements from day 0 until extubation at day 3. **(B)** DLTx results (n = 9) showing VCV versus PCV during daily measurements from day 0 until extubation at day 3. **(C)** Mean VCV and PCV PExA 2.0 measurements from day 0 until extubation at day 3. Note the stepwise increase of particle flow from the airways between the days. *P < .05.

ventilation for a longer time and showed a stepwise and significant increase in particle count over time (Figure 3). These results were independent of the mode of ventilation that was used. In the PGD group, the total particle count on day 0 was 14 539 ± 3981; on day 1, it was 21 040 ± 10 601; on day 2, it was 91 782 ± 46 751; and, on day 3, it was 199 349 ± 49 473. There was a significant difference in total particle count between day 0 and day 1 compared with day 3 (P = .0065 and P = .0082, respectively). In the non-PGD group, the total particle count was 6650 ± 1125 on day 0, 21 315 ± 9585 on day 1, 8323 ± 1432 on day 2, and 5500 +/- 1900 on day 3.

Patients who developed PGD had a significantly longer treatment time in mechanical ventilation (2.3 ± 0.2 days) compared with patients who did not develop PGD (1.5 ± 0.3 days) (P = .0041).

Figure 3. Particle Counts in Patients Who Did and Did Not Develop Primary Graft Dysfunction



Abbreviations: ns, not significant; PGD, primary graft dysfunction
Patients who developed PGD showed a stepwise increase in total particle flow from the airways, as measured by PExA 2.0. However, the same pattern could not be observed among the patients who did not develop PGD. **P < .01.

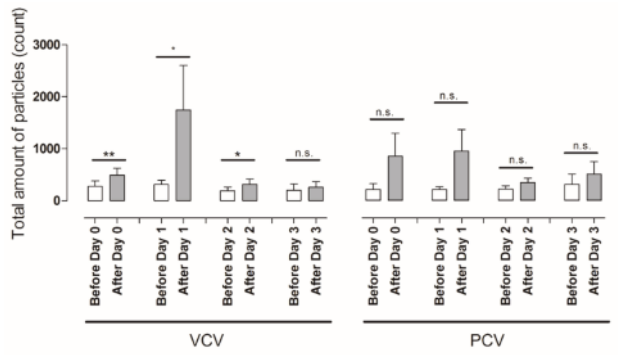
Recruitment maneuvers

To determine whether RM affected particle flow from the airways, RMs were performed twice daily until day 3 posttransplant. The total particle count was measured for 3 minutes before the RM and for 3 minutes after the RM. Each RM was performed in the same manner during both VCV and PCV.

During VCV, total particle count was 277 ± 107 before and 492 ± 134 after RMs on day 0, with a significant difference observed in particle flow before and after RM (P = .0063). The total particle count differed significantly before and after RMs on day 1 versus day 2, showing 313 ± 83 before RM and 1749 ± 852 after RM on day 1 (P = .0495) and 192 ± 70 before RM and 319 ± 100 after RM on day 2 (P = .0303). The total particle count was not significantly different (P = .1724) on day 3 before and after RMs, which showed 205 ± 121 before and 259 ± 108 after RM (Figure 4).

During PCV, no significant differences were observed before or after the RMs. The total particle count was 215 ± 112 before RM and 854 ± 443 after RM on day 0 (P = .1118). On day 1, the total particle count was 215 ± 50 before RM and 954 ± 413 after RM (P = .0818), whereas the total particle count was 220 ± 69 before RM and 350 ± 81 after RM on day 2 (P = .0645). On day 3, the total particle count was 312 ± 203 before RM and 511 ± 236 after RM (P = .2406) (Figure 4).

Figure 4. Total Particle Counts Before and After Recruitment Maneuvers



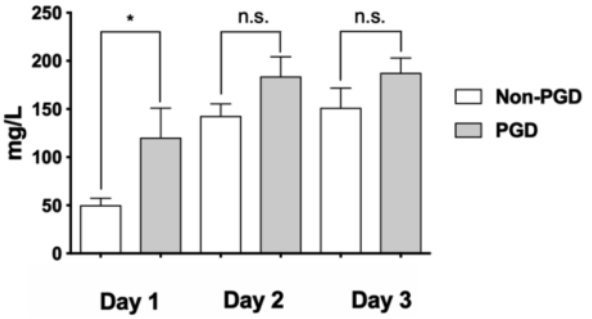
Abbreviations: ns, not significant; PCV, pressure-controlled ventilation; RM, recruitment maneuver; VCV, volume-controlled ventilation
All patients underwent RMs twice daily, starting at day 0 posttransplant until extubation (day 3 posttransplant). Total particle count was measured before and after RM on day 0, day 1, day 2, and day 3 after transplant during VCV and PCV. Note that particle flow significantly increased after RM during the first 48 hours with VCV but not with PCV (*P < .05; **P < .01).

Inflammatory biomarkers

We next investigated whether we could correlate early biomarkers with the onset of PGD. Interestingly, patients who developed PGD had significantly higher C-reactive protein (CRP) levels directly after transplant on day 0 (120 ± 31 mg/L) compared with patients who did not develop PGD (50 ± 7 mg/L) (P = .0420) (Figure 5). During the remaining postoperative measurement days, no significant differences were observed between the 2 groups. In the PGD, group, CRP was 184 ± 20 mg/L on day 2, 188 ± 16 mg/L on day 3, 147 ± 17 mg/L on day 4, and 124 ± 18 mg/L on day 5. Among patients who did not develop PGD, the CRP levels were

143 ± 12 mg/L on day 2, 151 ± 21 mg/L on day 3, 144 ± 22 mg/L on day 4, and 151 ± 28 mg/L on day 5.

Figure 5. C-Reactive Protein Levels in Study Patients



Abbreviations: ns, not significant; PGD, primary graft dysfunction
Patients in the study group who developed PGD had significantly (*$P < .04$) higher C-reactive protein levels directly after lung transplant than patients who did not develop PGD.

Blood gases, hemodynamics, and mechanical ventilation settings

Blood gas and hemodynamic measurements and mechanical ventilation settings during the different ventilation modes and during the different days are shown in Table 2 and Table 3. Measurements were taken at the start and at end of each ventilation mode. In Table 4, the same parameters are shown, showing those taken 3 minutes before RM and 3 minutes after RM. All patients were stable during all measurements, and no significant changes in blood gases, hemodynamics, or mechanical ventilation settings could be found.

Discussion

The PExA 2.0 device has formerly only been used on patients who are breathing room air and has never previously been used on intubated patients in the ICU. In 2 preclinical porcine model studies, we demonstrated the use of the PExA 2.0 device in conjunction with mechanical ventilation.[15,16] In the present study, we established the clinical feasibility of measuring particle flow from airways during mechanical ventilation and have applied this for the first time in the ICU in lung transplant recipients. No mild, moderate, or severe adverse events, including airway leakage, signs of rebreathing, altered pressure levels, and hemodynamic interferences, were seen. As shown in Tables 2, 3, and 4, we did not detect any significant changes during all measurement days. Furthermore, we observed no harmful effects in patients, as shown by either ventilator measurements or hemodynamic measurements; therefore, we believe this technique can safely be used in conjunction with mechanical ventilation.

Mechanical ventilation can be a life-saving instrument in a variety of clinical conditions; however,

Table 2. Results With Volume-Controlled Ventilation

	Day 0		Day 1		Day 2		Day 3	
	Start VCV	End VCV	Start VCV	End VCV	Start VCV	End VCV	Start VCV	End VCV
Blood gas levels								
PCO_2, mm Hg	5.7 ± 0.6	5.5 ± 0.4	5.8 ± 0.2	5.2 ± 0.5	6.1 ± 0.2	5.9 ± 0.2	5.7 ± 0.2	5.7 ± 0.2
PO_2, mm Hg	16.2 ± 3.5	13.7 ± 1.1	13.5 ± 1.2	12.9 ± 0.6	12.6 ± 0.5	13.0 ± 0.6	11.5 ± 0.7	11.9 ± 0.6
pH	7.4 ± 0.02	7.4 ± 0.02	7.4 ± 0.01	7.4 ± 0.01	7.4 ± 0.01	7.4 ± 0.01	7.5 ± 0.02	7.5 ± 0.03
Bicarbonate, mmol/L	2.5 ± 1.0	2.4 ± 1.3	1.8 ± 0.6	2.1 ± 0.5	5.6 ± 1.1	5.3 ± 1.1	6.5 ±1.9	5.7 ± 1.8
Base excess, mmol/L	26.5 ± 0.7	26.6 ± 1.1	25.8 ±0.5	26.1 ± 0.5	28.8 ± 1.0	28.6 ± 0.9	30.3 ± 1.7	29.6 ± 1.7
Lactate, mmol/L	1.8 ± 0.3	2.1 ± 0.4	2.6 ± 0.4	2.8 ± 0.3	1.8 ± 0.1	1.8 ± 0.2	1.5 ± 0.2	1.6 ± 0.3
Mechanical ventilation results								
Volume/min, L	9.9 ± 1.1	9.4 ± 0.7	9.9 ± 0.6	9.9 ± 0.5	9.8 ± 0.5	9.2 ± 0.4	9.5 ± 0.6	10.1 ± 0.3
Breaths/min	19 ± 1	19 ± 1	19 ± 1	19 ± 1	19 ± 1	19 ± 1	19 ± 1	19 ± 1
PEEP, cm H_2O	5 ± 0	5 ± 0	5 ± 0	5 ± 0	5 ± 0	5 ± 0	5 ± 0	5 ± 0
FiO_2	37.5 ± 3.2	36.2 ± 3.7	35.8 ± 2.0	35.4 ± 2.0	32.2 ± 1.2	32.2 ± 1.2	32.5 ± 1.7	32.5 ± 1.7
Peak pressure, cm H_2O	21.2 ± 2.3	19.8 ± 1.6	22. 0 ± 1.4	20.5 ± 0.7	21.0 ± 0.6	19.9 ± 0.7	23.2 ± 1.5	22.3 ± 1.6
Mean pressure, cm H_2O	10.2 ± 0.9	11.2 ± 0.6	11.0 ± 0.7	11.1 ± 0.6	11.2 ± 0.8	10.9 ± 0.8	11.3 ± 1.4	11.3 ± 1.4
Compliance, mL/cm H_2O	46.0 ± 7.0	42.2 ± 5.3	39.8 ± 3.8	44.4 ± 4.4	40.9 ± 5.5	44.7 ± 5.1	37.2 ± 2.8	46.8 ± 10.7
WOB, J/L	1.0 ± 0.1	0.9 ± 0.1	1.2 ± 0.1	1.0 ± 0.1	1.2 ± 0.1	1.0 ± 0.1	1.4 ± 0.2	1.1 ± 0.2
Hemodynamics								
Pulse, beats/min	71 ± 5	72 ± 6	78 ± 4	78 ± 4	95 ± 5	92 ± 5	91 ± 9	92 ± 8
SBP, mm Hg	103 ± 5	108 ± 3	103 ± 3	106 ± 3	109 ± 4	110 ± 3	105 ± 8	114 ± 7
DBP, mm Hg	58 ± 2	60 ± 5	59 ± 2	60 ± 2	62 ± 3	63 ± 3	61 ± 1	63 ± 2
MAP, mm Hg	71 ± 3	73 ± 4	74 ± 2	74 ± 3	77 ± 3	78 ± 3	75 ± 2	79 ± 3
Saturation, %	98 ± 1	99 ± 1	98 ± 0.5	98 ± 0.4	97 ± 0.5	98 ± 0.4	97 ± 0.8	98 ± 0.8
End-tidal CO_2, kPa	3.9 ± 0.5	4.0 ± 0.4	4.0 ± 0.2	4.0 ± 0.2	4.5 ± 0.3	4.6 ± 0.3	4.0 ± 0.3	4.1 ± 0.3

Abbreviations: DBP, diastolic blood pressure; FiO_2, fraction of inspired oxygen; MAP, mean arterial pressure; PEEP, positive end-expiratory pressure; SBP, systolic blood pressure; VCV, volume-controlled ventilation; WOB, work of breathing

Table 3. Results With Pressure-Controlled Ventilation

	Day 0		Day 1		Day 2		Day 3	
	Start PCV	End PCV	Start PCV	End PCV	Start PCV	End PCV	Start PCV	End PCV
Blood gas levels								
PCO_2, mm Hg	5.7 ± 0.4	5.8 ± 0.4	5.6 ± 0.1	5.6 ± 0.2	6.1 ± 0.2	6.0 ± 0.2	5.7 ± 0.2	5.8 ± 0.2
PO_2, mm Hg	13.1 ± 1.1	13.1 ± 0.8	12.6 ± 0.6	13. 0 ± 0.5	12.7 ± 0.6	13.0 ± 0.3	12.2 ± 0.5	14.7 ± 1.5
pH	7.4 ±0.02	7.4 ± 0.02	7.4 ± 0.01	7.4 ± 0.01	7.4 ± 0.01	7.4 ± 0.01	7.4 ± 0.02	7.4 ± 0.03
Bicarbonate, mmol/L	2.5 ± 1.2	1.4 ± 1.2	2.2 ± 0.5	2.4 ± 0.5	5.6 ± 1.0	5.8 ± 1.1	5.8 ± 1.9	5.7 ± 1.9
Base excess, mmol/L	26.6 ± 1.0	25.5 ± 0.9	26.3 ± 0.4	26.4 ± 0.5	28.7 ± 0.9	29.1 ± 1.0	29.6 ± 1.7	29.5 ± 1.7
Lactate, mmol/L	2.1 ± 0.4	2.9 ± 0.6	2.8 ± 0.3	2.9 ± 0.2	1.8 ± 0.2	1.8 ± 0.2	1.6 ± 0.2	1.6 ± 0.2
Mechanical ventilation results								
Volume/minute, L	9.0 ± 0.4	9.3 ± 0.3	9.9 ± 0.5	10.0 ± 0.4	9.2 ± 0.3	9.4 ± 0.3	9.8 ± 0.3	9.5 ± 0.7
Breaths/min	19 ± 1	19 ± 1	19 ± 1	19 ± 1	19 ± 1	19 ± 1	19 ± 1	19 ± 1
PEEP, cm H_2O	5 ± 0	5 ± 0	5 ± 0	5 ± 0	5 ± 0	5 ± 0	5 ± 0	5 ± 0
FiO_2	36.2 ± 3.7	36.2 ± 3.7	35.4 ± 2.0	35.4 ± 2.0	32.2 ± 1.2	32.2 ± 1.2	32.5 ± 1.7	35.8 ± 3.3
Peak pressure, cm H_2O	19.2 ±1.0	20.0 ± 1.2	20.8 ± 1.2	20.8 ± 1.1	19.0 ± 1.0	19.0 ± 1.0	21.8 ± 2.2	21.2 ± 2.0
Mean pressure, cm H_2O	11.2 ± 1.0	11.5 ± 1.0	10.8 ± 0.4	11.0 ± 0.4	10.3 ± 0.6	10.6 ± 0.6	11.7 ± 0.8	10.5 ± 0.6
Compliance, mL/cm H_2O	41.2 ± 4.3	39.7 ± 5.4	42.9 ± 3.6	43.8 ± 4.5	39.1 ± 3.0	44.0 ± 6.0	36.5 ± 3.9	36.7 ± 3.3
WOB, J/L	0.9 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	0.9 ± 0.04	0.9 ± 0.05	1.1 ± 0.1	1.1 ± 0.1
Hemodynamics								
Pulse, beats/min	72 ± 7	71 ± 6	77 ± 4	79 ± 5	91 ± 5	90 ± 5	92 ± 8	88 ± 7
SBP, mm Hg	109 ± 4	115 ± 10	104 ± 3	108 ± 5	113 ± 3	114 ± 4	107 ± 7	104 ± 8
DBP, mm Hg	58 ± 3	62 ± 7	61 ± 2	62 ± 3	68 ± 3	64 ± 3	62 ± 3	59 ± 3
MAP, mm Hg	73 ± 4	78 ±9	75 ± 3	77 ± 3	81 ± 2	79 ± 3	76 ± 4	74 ± 5
Saturation, %	99 ± 0.7	99 ± 0.5	99 ± 0.4	99 ± 0.4	98 ± 0.2	98 ± 0.6	98 ± 0.9	98 ± 0.6
End-tidal CO_2, kPa	4.2 ± 0.4	4.4 ± 0.5	3.9 ± 0.2	3.9 ± 0.3	4.5 ± 0.2	4.4 ± 0.2	4.1 ± 0.4	4.1 ± 0.3

Abbreviations: DBP, diastolic blood pressure; FiO_2, fraction of inspired oxygen; MAP, mean arterial pressure; PCV, pressure-controlled ventilation; PEEP, positive end-expiratory pressure; SBP, systolic blood pressure; WOB, work of breathing

Table 4. Results Before and After Recruitment Maneuvers

	Day 0		Day 1		Day 2		Day 3	
	Before	After	Before	After	Before	After	Before	After
Blood gas levels								
PCO_2, mm Hg	5.7 ± 0.3	5.9 ± 0.3	5.7 ± 0.1	5.8 ± 0.1	6.0 ± 0.2	6.1 ± 0.2	5.8 ±0.1	5.9 ± 0.1
PO_2, mm Hg	13.5 ± 0.7	12.9 ± 0.7	13.2 ± 0.5	13.1 ± 0.4	12.3 ± 0.2	12.3 ± 0.3	12.1 ± 0.6	11.9 ± 0.6
pH	7.4 ± 0.01	7.4 ± 0.01	7.4 ± 0.01	7.4 ± 0.01	7.4 ± 0.01	7.4 ±0.01	7.4 ± 0.02	7.4 ± 0.02
Bicarbonate, mmol/L	2.3 ± 0.8	2.2 ± 0.8	1.9 ± 0.6	1.9 ± 0.3	5.6 ± 0.7	5.7 ± 0.7	5.7 ±1.3	5.8 ± 1.4
Base excess, mmol/L	26.4 ± 0.6	26.2 ± 0.6	26.2 ± 0.3	25.9 ± 0.3	29.0 ± 0.6	29.0 ± 0.6	29.5 ± 1.2	29.6 ± 1.3
Lactate, mmol/L	2.1 ± 0.3	2.3 ± 0.4	2.8 ± 0.2	2.8 ± 0.2	1.8 ± 0.1	1.7 ± 0.1	1.7 ± 0.2	1.6 ± 0.2
Mechanical ventilation results								
Volume/minute, L	9.3 ± 0.3	9.5 ± 0.3	10.0 ± 0.3	10.1 ± 0.6	9.7 ± 0.3	9.5 ± 0.3	9.8 ± 0.3	10.3 ± 0.3
Breaths/min	19 ± 1	19 ± 1	19 ± 1	19 ± 1	19 ± 1	19 ± 1	19 ± 1	19 ± 1
PEEP, cmH_2O	5 ± 0	5 ± 0	5 ± 0	5 ± 0	5 ± 0	5 ± 0	5 ± 0	5 ± 0
FiO_2	36.9 ± 2.3	36.9 ± 2.3	36 ± 1.4	36 ± 1.4	32.2 ± 0.8	32.2 ± 0.8	32.5 ± 1.1	34.2 ± 1.8
Peak pressure, cm H_2O	20.0 ± 1.0	20.0 ± 0.9	21.7 ± 0.9	21.0 ± 0.7	19.8 ± 0.7	19.9 ± 0.7	22.2 ± 1.4	21.9 ± 1.4
Mean pressure, cm H_2O	11.0 ± 0.6	11.2 ± 0.5	11.2 ± 0.4	11.2 ± 0.3	10.9 ± 0.5	10.7 ± 0.5	11.6 ± 0.7	10.8 ± 0.8
Compliance, mL/cm H_2O	42.4 ± 3.6	40.9 ± 3.4	42.1 ± 2.7	42.1 ± 2.7	40.3 ± 2.8	41.8 ± 3.2	37.8 ± 2.5	41.0 ± 3.6
WOB, J/L	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.04	0.9 ± 0.04	0.9 ± 0.04	1.1 ± 0.1	1.1 ± 0.1
Hemodynamics								
Pulse, beats/min	72 ± 4	73 ± 4	78 ± 3	78 ± 3	92 ± 3	92 ± 3	91 ± 6	90 ± 5
SBP, mm Hg	102 ± 3	105 ± 3	105 ± 3	106 ± 2	113 ± 3	113 ± 3	106 ± 6	109 ± 5
DBP, mm Hg	56 ± 2	60 ± 2	60 ± 2	62 ± 1	65 ± 2	64 ± 2	61 ± 2	64 ± 2
MAP, mm Hg	70 ± 3	73 ± 3	75 ± 2	75 ± 2	81 ± 2	80 ± 2	75 ± 3	80 ± 2
Saturation, %	99 ± 0.4	99 ± 0.3	98 ± 0.3	98 ± 0.3	98 ± 0.3	98 ± 0.3	98 ± 0.7	97 ± 0.9
End-tidal CO_2, kPa	4.2 ± 0.4	4.3 ± 0.3	4.0 ± 0.2	4.0 ± 0.2	4.5 ± 0.2	4.6 ± 0.2	4.1 ± 0.2	4.3 ± 0.3

Abbreviations: DBP, diastolic blood pressure; FiO_2, fraction of inspired oxygen; MAP, mean arterial pressure; PEEP, positive end-expiratory pressure; SBP, systolic blood pressure; WOB, work of breathing

it can also cause several severe complications leading to pulmonary tissue damage.[19] The mechanisms of action for complications include structural damage through extension of the lung and injury caused by repeated opening and closing of the distal airways. Mechanical ventilation increases the tendency for collapse of the distal airways and alveoli and the development of atelectasis, and it also leads to mucous stagnation and increased levels of inflammatory markers, such as cytokines. Previous studies have shown that lowering the tidal volume along with PEEP may reduce the release of cytokines; the systemic release of cytokines has been shown to play a significant part in multiorgan failure and

death.[20-25] There is a need to better understand, control, and individualize ventilator settings with an aim to minimize the severe negative effects of mechanical ventilation, such as chronic lung damage, multiorgan failure, and death.

Particle flow from the airways during mechanical ventilation might be a valuable noninvasive method for evaluating the different settings and modes in patients undergoing mechanical ventilation but may also help differentiate among various lung pathologies. In the present study, we measured particle flow during mechanical ventilation in lung transplant patients from the day of transplant until extubation. All patients were fully anesthetized, and no patient initiated or took their own breaths during the study period. Interestingly, we saw a stepwise increase in particle flow from the airways in patients who developed PGD.

Approximately 30% of lung transplant recipients develop PGD within 72 hours of transplant. Primary graft dysfunction is a lung injury and clinically and histologically analogous to ARDS.[6,18] The initial clinical diagnosis of PGD is characterized by decreased PaO_2/FiO_2 and pulmonary infiltration on chest radiography.[5] In lung transplant patients, lung-protective ventilation strategies (low tidal volume and low to moderate PEEP) have been shown to improve outcomes; therefore, these strategies are commonly used. In the present study, all patients were ventilated with tidal volumes of 6 mL/kg and PEEP at 5 cm H_2O. Of the 6 patients who developed PGD, 67% developed mild, stage 1 PGD. Among clinicians, stage 1 PGD is commonly not regarded as a state that leads to longer time in mechanical ventilation or increased risks for complications. Of interest in our study, patients with stage 1 PGD also stayed in mechanical ventilation for a significantly longer time than the patients who did not develop PGD. Also of interest, the patients who developed PGD showed a significant stepwise increase of particle flow from the airways over the 3 days, whereas the patients who did not develop PGD did not show a similar profile pattern. Patients with PGD also had significantly higher CRP levels the day immediately posttransplant compared with the patients who did not develop PGD. We believe there is a difference in the particle flow pattern from airways during mechanical ventilation between patients who develop PGD and those who do not develop PGD.

In a porcine model of ARDS with mechanical ventilation, we recently showed that particle flow was significantly higher from airways compared with that shown in a non-ARDS porcine model,[16] which support the findings of our present study. An increased particle flow from the airways might therefore be representative of a lung injury, such as that seen in our PGD cohort. Increased particle flow may be related to an increased inflammatory response in the respiratory tract-lining fluid, which is supported in our own data by increased CRP levels in patients with PGD. Fluid in the respiratory tract lining covers the epithelial wall of the airways and differs in composition in different parts of the airways. Exhaled breath particles are believed to be formed from the respiratory tract-lining fluid in the distal parts of the lung during the opening and closing of small airways. We also previously showed that phospholipids are a major component of the exhaled breath particles collected during mechanical ventilation in the porcine model. Surfactant A is also a known component in exhaled breath particles and is produced by type II alveolar cells, which reside in the distal region of the lung.[17,26-28] Particles in exhaled air have so far been poorly investigated; this area of study has the potential to become a new area of interest in the field of respiratory research.

Recruitment maneuvers are thought to improve oxygenation by opening more alveoli available for gas exchange. It is not yet clear whether RMs induce lung injury; therefore, the choice of this therapeutic option should be adjusted to the pulmonary condition and duration of the mechanical ventilation.[29-33] An improvement in oxygenation after RMs occurs immediately, but the effect is short-lived.[33-36] Recruitment maneuvers are widely debated. Some believe that RMs are useful during the first days during mechanical ventilation but may inflict harm after a few days of mechanical ventilation; others are more cautious toward the positive effects of RMs.[33-35,37] In our study, all patients received RM twice daily according to our clinical protocol: once during VCV and once during PCV. The 60-second RM period included having PEEP at 10 cm H_2O, 4 breaths/min, and inspiratory-to-expiratory ratio of 2:1. The total particle flow was measured for 3 minutes before the RM and for 3 minutes after the RM. Interestingly, a significant increase in particle flow was seen after compared with before RM during the first 48 hours posttransplant when using VCV;

however, a significant increase could not be observed using PCV. We believe these findings imply that different ventilation modes during RM have different effects and open up the lung differently. After 48 hours, we could not detect any differences in particle flow before and after RM using any ventilation mode. Interestingly, we showed similar results in the study of RMs in the porcine model.[16]

Whether RMs are beneficial or not cannot be definitively determined from this study. One possibility is that an increased particle flow from the airways might reflect increased pulmonary tissue damage. Alternatively, the short-lived increase in particle flow in the minutes after RM might instead reflect the results of closed lung parenchyma (ie, atelectasis that has opened up as a result of the RM). We found that particle flow eventually returned to the levels shown before the RM. Therefore, it is likely that no sustained lung injury had occurred and the short-lived increase in particle flow only represented the contact between respiratory tract-lining fluid of the former closed alveoli and the bronchus and main airways. However, further studies are needed to clarify exactly what this change in particle flow before and after RM means and how this information can be used clinically.

Limitations

Despite our small study cohort, the initial results presented here indicate the potential of the PExA 2.0 technique to generate further important knowledge with regard to both the physiology of the lung during mechanical ventilation and to changes of the lung during mechanical ventilation. We anticipate that this technique and our results will be applicable to other patient groups, for example, in patients with ARDS, sepsis, and pneumonia; however, further studies need to be performed.

Conclusions

This study suggests that the PExA 2.0 instrument is safe to use in conjunction with mechanical ventilation in ICU settings. Lung transplant recipients who developed PGD showed different particle flow profiles from the airways before showing clinical signs of PGD. The ability to assess the impact of ventilation before tissue changes are observed might allow for real-time detection of PGD to prevent or reduce the effects of PGD. We believe that the PExA 2.0 instrument could be used to individualize mechanical ventilation by repeated measurements to follow the development of physiologic and biological changes in the lung; this would allow clinicians to observe new information about the patient's condition over time, although more studies are needed.

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