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ORIGINAL ARTICLE

# New insight: particle flow rate from the airways as an indicator of cardiac failure in the intensive care unit

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## Abstract

**Aims** Exhaled breath particles have been explored for diagnosing different lung diseases. We recently showed in an experimental model that different cardiac output results in different particle flow rate (PFR) from the airways. Given the well-known close relationship between impaired cardiac function and respiratory failure, we hypothesized that PFR in exhaled air can be used to detect cardiac failure.

**Methods** PFR was analysed using a customized PExA device. Particles in the range of 0.41–4.55 μm were measured. The included patients ($n$ = 20) underwent cardiac surgery and received mechanical ventilation as a part of routine post-operative care. Ten patients with clinical signs of pronounced post-operative haemodynamic instability and need for inotrope or mechanical support had been selected to the cardiac failure group. The control group consisted of 10 patients without signs of cardiac failure.

**Results** The patients in cardiac failure group required inotropic support in the form of dobutamine (9/10), epinephrine (2/10), or levosimendan (4/10) or use of an intra-aortic balloon pump (4/10). There was no use of inotropes or mechanical support devices among the controls. All patients in the cardiac failure group had pre-operative left ventricular ejection fraction ≤40% compared with the control group, whose pre-operative ejection fraction was ≥50%, $P < 0.001$. Patients with cardiac failure had significantly longer median total time in mechanical ventilation compared with the patients in the control group: 53.5 h (IQR 6.8–116101.0 h) and 4.5 h (IQR 4.0–5.5 h), respectively, $P < 0.001$, and the median length of stay in the ICU, 165 h (IQR 28–192 h) and 22 h (IQR 20–23.5 h), respectively, $P = 0.007$. Median PFR in patients with cardiac failure was higher than PFR in those with normal cardiac function: 80.9 particles/min (interquartile range (IQR) 25.8–336.6 particles/min), vs. 15.3 particles/min (IQR 8.1–17.7 particles/min), respectively, $P < 0.001$. Median particle mass was 8.95 ng (IQR 1.68–41.73 ng) in the cardiac failure group and 0.75 ng (IQR 0.18–1.45 ng) in the control group, $P = 0.002$.

**Conclusions** Patients with post-operative cardiac failure following cardiac surgery exhibited an increase in exhaled particle mass and PFR compared with the control group, indicating a significant difference between those two groups. The increase in particle mass and PFR in the absence of respiratory pathologies may indicate cardiac failure. In comparison with controls, impaired cardiac function was also associated with different composition of the particles regarding their size distribution.

**Keywords** Cardiac failure; Particle flow rate; Cardiac surgery; Mechanical ventilation; Particle mass

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## Introduction

The population of patients receiving mechanical ventilation (MV) in the intensive care unit (ICU) is growing worldwide.[1] There are numerous indications for endotracheal intubation and MV. In general, MV should be considered when there is pronounced impaired consciousness, oxygenation, or ventilation. A frequently encountered indication for MV is ventilatory support during the initial post-operative period. This is particularly true for patients undergoing cardiac or thoracic surgery. In the general ICU, the most common indication for initiation of MV is acute respiratory failure, which accounts

for nearly 70% of the cases.[2] Congestive cardiac failure is one of the common reasons for acute respiratory failure treated with MV in both general and cardiothoracic ICUs.[3] Post-operative respiratory failure and pneumonia are two other main causes of respiratory failure. Invasive MV is an area of intense research, and it has gained even more interest during the current COVID-19 pandemic.[4]

The introduction of positive pressure ventilation in the 1950s changed the survival of critically ill patients dramatically. Despite extensive research to improve the clinical outcome and minimize complications following invasive MV, the optimal monitoring and settings of the respirator are still under debate. In the literature, the majority of the studies examine the airways' pressure conditions, modes of ventilation, and the role of positive end-expiratory pressure.[5,6]

We have recently shown that the measurement of particle flow rate (PFR) in exhaled air has the potential as a non-invasive monitoring technique during MV.[7,8] PFR has been measured using a PExA 2.0 device customized for MV. The PExA 2.0 device incorporates an optical counter to examine particles and their mass in exhaled air; particle size distribution within a sample can also be determined. Exhaled particles are believed to originate from the respiratory tract lining fluid (RTLF) that covers the epithelial surface of the distal lung.[9,10] Transmission of particles occurs during the opening and closing of small airways and may also be carried by shear stress. Valuable diagnostic data as, for example, information on injuries within the respiratory system, may be provided with this method.[11] We have shown previously that PFR increases in the early stages of acute respiratory disorder syndrome (ARDS) in a porcine ARDS model[12] as well as in extra-corporeal membrane oxygenation models.[13]

In preclinical settings using *ex vivo* lung perfusion, we have shown that cardiac output is correlated to PFR.[7] However, there are no data regarding PFR in patients with cardiac failure nor on which size distribution of particles can be detected in this patient population. Therefore, a study to look at the potential of exhaled breath particles in exploring the impact of cardiac function on PFR during MV has been designed. Does PFR and particles size differ between patients with and without cardiac failure? Could PFR be used to confirm cardiac failure during MV? To try this hypothesis, the patients with and without known cardiac failure were selected to this study.

# Methods

## Study population

The study was performed in accordance with the Declaration of Helsinki, and the study protocol was approved by the ethics committee for clinical research at Lund University, Sweden (Dnr 2017/519). An individual written informed consent was obtained from all study participants. The study was conducted according to the STROBE statement. There was no bias applicable in the study.

A total of 20 patients were included in this prospective cohort study, which was conducted at Skåne University Hospital, Sweden, between April 2018 and June 2018. All patients were evaluated at the cardiothoracic ICU when they were ventilated mechanically following cardiac surgery. Ten patients with clinical signs of pronounced post-operative haemodynamic instability and need for inotrope or mechanical support had been selected to cardiac failure group. The control group consisted of 10 patients with no clinical signs of pre-operative or post-operative cardiac failure. The results of chest X-ray examinations that were performed 1 day before or 1 day after the PExA measurement were reviewed. The following data were collected from the medical records: diagnosis, indication and type of surgery, pre-operative, peri-operative and post-operative clinical characteristics including respiratory parameters, and demographic and biochemical data.

## Ventilation and anaesthesia at ICU

All patients arrived at the ICU following cardiac surgery and were intubated with an endotracheal tube size 7.5 prior to operation. Mechanical ventilation was managed using respirator Servo-I® (Getinge Group, Sweden, Solna) in accordance with local routines: tidal volume of 6 mL/kg, positive end-expiratory pressure of 5 $cmH_2O$ and end-inspiratory pressures $<25$ $cmH_2O$ and goal $CO_2$ levels of 4.6–6 kPa. Sedation was maintained with propofol infusion, and post-operative pain was treated with intravenous oxycodone and paracetamol.

## PFR measurements

The PExA 2.0 device (PExA, Gothenburg, Sweden) is designed to collect and analyse exhaled particles. The technique is based on optical counting of the particles arriving from the small airways, and it allows the collection of the exhaled particles on a filter for further chemical analysis. The main advantages of this new method are its non-invasiveness and possibility for bedside use. The number of particles in the diameter range of 0.41–4.55 μm (count) and their accumulated mass (ng) can be measured continuously.

In the present study, PExA 2.0 was customized to be used in conjunction with mechanical ventilation as described previously by our group in preclinical *in vivo* settings[7] and in clinical settings.[14] PFR, expressed as particles per minute, was calculated from the total number of particles divided by 120 min, which was the time of measurement in each patient. Particle mass was the total amount of particles during

measurement. *Figure 1* shows the respiratory circuit with incorporated optical particle counter PExA device.

### Statistical analysis

Equally distributed continuous variables are presented as the mean ± 1 standard deviation. Skewed distributed variables are expressed as the median with interquartile range (IQR) in parentheses. Categorical variables are expressed as proportions and percentages. Student's *t*-test was used for equally distributed continuous variables, and categorical data were compared using the chi-squared test or Fisher's exact test when the expected frequency was less than 5. For skewed distributed variables, the Mann–Whitney *U* test was used. Statistical significance was defined as $P < 0.05$. Statistical analysis was performed using the SPSS software package (SPSS 23.0 Chicago, IL, USA).

## Results

Patient characteristics and demographics are presented in *Table 1*. The patients in cardiac failure group required moderate or high dose of inotropic support in the form of dobutamine (9/10), epinephrine (2/10), or levosimendan (4/10) or use of an intra-aortic balloon pump (4/10). The following cardiac surgery was performed in these patients: coronary artery bypass grafting (3/10), repair of post-infarction ventricular septal defect (3/10), heart transplantation (2/10), and repair of mitral valve repair (2/10). All operations were done on-pump (20/20). There was no use of inotropes or mechanical cardiac support devices among the controls who underwent coronary artery bypass grafting (10/10). The chest X-ray was done in all patients and accessed by blinded radiologist. Post-operative pulmonary atelectasis in the basal segments were seen in all patients (20/20). In addition, mildly increased diameter of the pulmonary vessels was observed in one patient in the cardiac failure group (1/10).

All patients were ventilated with an inspiratory–expiratory ratio of 1:2. Volume-targeted pressure-controlled ventilation was used in 19 patients; one patient in the cardiac failure group had pressure-controlled mode. One patient in the cardiac failure group could breathe spontaneously; all other patients had mandatory mode of ventilation.

All patients had data on pre-operative left ventricular ejection fraction assessed by echocardiography. All patients in the cardiac failure group had pre-operative ejection fraction 40% or lower compared with the control group, whose pre-operative ejection fraction was 50% or higher, $P < 0.001$. Patients with cardiac failure had significantly longer total time, expressed as median, in MV compared with the patients in the control group: 53.5 h (IQR 6.8–116101.0 h) and 4.5 h (IQR 4.0–5.5 h), respectively, $P < 0.001$, the median length of stay in the ICU, 165 h (IQR 28–192 h) and 22 h (IQR 20–23.5 h), respectively, $P = 0.007$,

**Figure 1** Schematic overview of the respiratory circuit with incorporated optical particle counter PExA device. The non-rebreathing one-way valve separates the inspiratory and expiratory flow; arrows show the direction of the air flow. Created with BioRender.com.

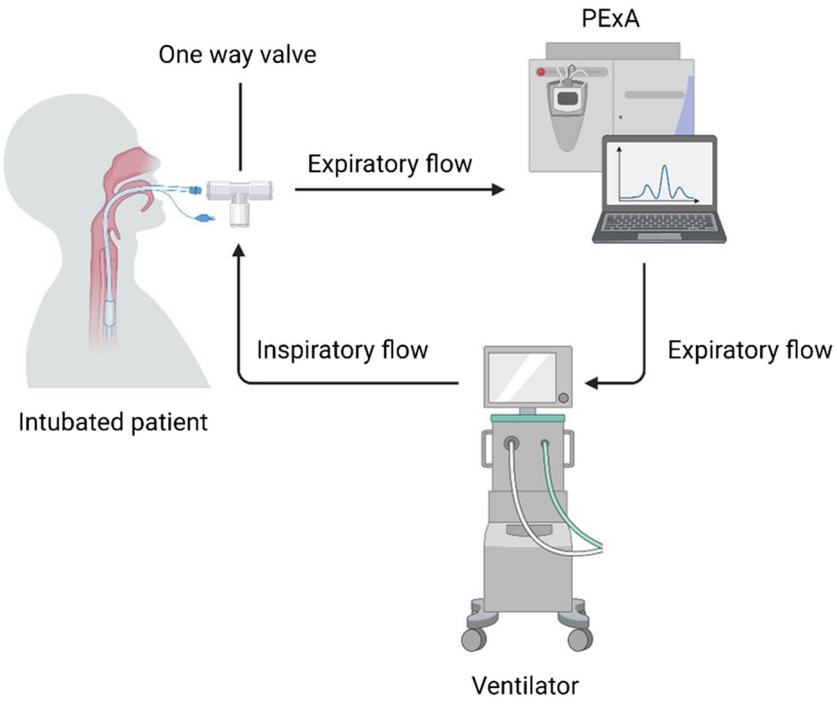



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**Table 1** Patients' characteristics at baseline

| | Cardiac failure ($n$ = 10) | Control ($n$ = 10) | $P$-value |
|---|---|---|---|
| Age (y) | 67.5 ± 15 | 70 ± 8 | 0.651 |
| Male | 8 (80) | 8 (80) | 1.000 |
| BMI (kg/m$^2$) | 26 ± 4 | 28 ± 5 | 0.214 |
| e-GFR (mL/min/1.73 m$^2$) | 42 ± 17 | 65 ± 10 | 0.002 |
| Saturation (%) | 96 ± 2 | 99 ± 1 | 0.001 |
| Time on respirator (h) | 21.9 ± 28.3 | 1.1 ± 0.3 | 0.009 |
| Daily fluid balance (mL) | 1507 ± 2381 | 2071 ± 860 | 0.496 |
| Cumulative fluid balance (mL) | 1744 ± 2182 | 2071 ± 860 | 0.667 |
| CRP (mg/L) | 86 ± 115 | 2.5 ± 2.6 | 0.047 |
| Haemodynamics | | | |
| HF (bpm) | 97 ± 13 | 73 ± 9 | <0.001 |
| ABPs (mmHg) | 106 ± 14 | 114 ± 8 | 0.129 |
| ABPd (mmHg) | 51 ± 10 | 62 ± 5 | 0.007 |
| ABPm (mmHg) | 70 ± 7 | 79 ± 5 | 0.007 |
| CVP (mmHg) | 12 ± 4 | 7 ± 2 | 0.003 |
| Respirator settings | | | |
| $FiO_2$ (%) | 43 ± 12 | 41 ± 10 | 0.618 |
| PEEP ($cmH_2O$) | 6.1 ± 1.9 | 5.4 ± 0.9 | 0.308 |
| Peak pressure ($cmH_2O$) | 19 ± 3 | 16 ± 2 | 0.028 |
| Tidal volume (mL) | 550 ± 123 | 499 ± 50 | 0.240 |
| Respiratory rate (breaths per minute) | 17 ± 3 | 15 ± 1 | 0.043 |
| Minute volume (L) | 8.8 ± 2.1 | 7.3 ± 0.9 | 0.071 |
| Arterial blood gases | | | |
| $PaO_2$ (kPa) | 14.6 ± 6.6 | 15.9 ± 2.7 | 0.598 |
| $PaCO_2$ (kPa) | 5.2 ± 0.4 | 5.2 ± 0.4 | 1.000 |
| pH | 7.39 ± 0.04 | 7.38 ± 0.03 | 0.674 |
| Base excess (mmol/L) | −1.3 ± 2.7 | −1.8 ± 1.0 | 0.565 |
| $HCO_3$ (mmol/L) | 23.5 ± 2.4 | 22.9 ± 0.9 | 0.462 |
| Lactate (mmol/L) | 2,6 ± 2.0 | 1.1 ± 0.4 | 0.038 |

ABPd, arterial blood pressure diastolic; ABPm, arterial blood pressure mean; ABPs, arterial blood pressure systolic; BMI, body mass index; CVP, central venous pressure; e-GFR, estimated glomerular filtration rate; HF, heart frequency; bpm, beat per minute; PEEP, positive end-expiratory pressure.
The numbers are expressed as the mean ± standard deviation or numerical values (%).

and median total length of stay in hospital, 11.5 days (IQR 6–18.5 days) and 5 days (IQR 4–6 days), respectively, $P$ = 0.003.

### PFR and total accumulated particle mass

The median PFR in patients with cardiac failure was higher than the PFR in those with normal cardiac function in the control group: 80.9 particles/min (IQR 25.8–336.6 particles/min) vs. 15.3 particles/minute (IQR 8.1–17.7 particles/min), respectively, $P < 0.001$. *Figure 2* shows the distribution of the PFR in logarithmic scale. The median particle mass was 8.95 ng (IQR 1.68–41.73 ng) in the cardiac failure group, and the median particle mass was 0.75 ng (IQR 0.18–1.45 ng) in the control group, $P$ = 0.002.

### Particle distribution depending on their size

Particles were divided up into eight groups by size, and their flow rate was measured. Patients with cardiac failure had higher PFR in all particle size groups compared with the control group, as shown in *Table 2*. The proportional distribution of the PFR is presented in *Figure 3*.

## Discussion

Cardiac failure, also known as congestive heart failure, is characterized by the heart's inability to provide an adequate supply of blood to the body. Cardiac failure is the leading cause of both hospitalization and readmission among older adults. The incidence of cardiac failure in patients older than 60 years is as high as approximately 10%.[15] Patients presenting with an acute deterioration of cardiac function are often admitted to ICUs, as well as patients after conducted cardiac surgery. The present study explores the role of exhaled particles and PFR as a diagnostic tool for cardiac failure in ICU settings. Exhaled particles and PFR in patients with and without cardiac failure in the post-cardiac surgery period were investigated; main findings are presented in Figure S1. A significant increase in PFR and in particle mass was observed in patients with cardiac failure compared with those without. The patients with cardiac failure also showed a different particle composition regarding the size of the measured particles. This is the first study showing that analysis of particles in exhaled air during MV may be helpful in monitoring cardiac function in the ICU.

There is a well-known close relationship between impaired cardiac function and respiratory failure.[16] The current study was designed to explore the relationship between cardiac

**Figure 2** Particle flow rate in logarithmic scale in patients with cardiac failure and in the control group. The boundary of the boxes indicates the 25th and 75th percentiles; whiskers indicate the minimum and maximum. The line inside the box indicates the median value. The three data points shown in the diagram for controls are outliers. ***$P \leq 0.001$.

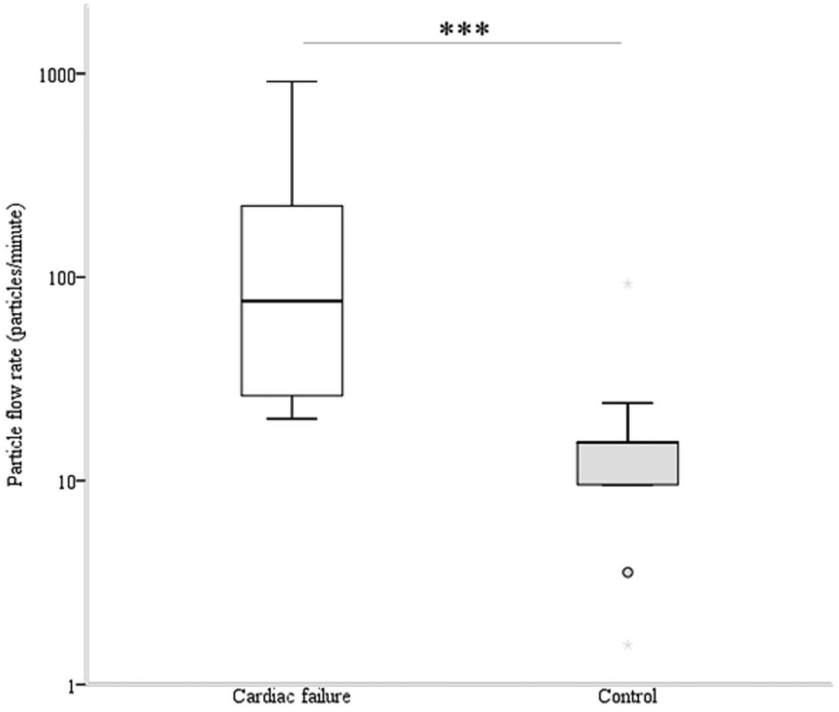


**Table 2** Particle flow rate in relation to particle size

| | Cardiac failure ($n$ = 10) | | Control ($n$ = 10) | | $P$-value | |
|---|---|---|---|---|---|---|
| Particle size | Absolute values | % | Absolute values | % | Absolute values | % |
| 1. Mean diameter 0.48 μm | 9.2 (5.1–24.7) | 12 | 3.4 (1.8–4.3) | 25 | 0.002 | 0.001 |
| 2. Mean diameter 0.59 μm | 21.1 (8.9–72.9) | 27 | 5.2 (3.1–7.2) | 37 | 0.001 | 0.001 |
| 3. Mean diameter 0.75 μm | 23.9 (7.2–102.6) | 30 | 3.7 (1.7–5.4) | 27 | <0.001 | 0.006 |
| 4. Mean diameter 0.98 μm | 15.0 (3.4–71.5) | 19 | 0.9 (0.1–2.4) | 6 | <0.001 | 0.001 |
| 5. Mean diameter 1.22 μm | 3.0 (0.8–23.8) | 4 | 0.2 (0.1–0.3) | 1 | <0.001 | 0.005 |
| 6. Mean diameter 1.67 μm | 3.3 (1.0–22.4) | 4 | 0.2 (0–0.5) | 2 | 0.002 | 0.008 |
| 7. Mean diameter 2.52 μm | 2.3 (0.7–11.1) | 3 | 0.1 (0–0.3) | 1 | 0.001 | 0.002 |
| 8. Mean diameter 3.37 μm | 1.1 (0.2–4.7) | 1 | 0.1 (0–0.3) | 1 | 0.023 | 0.401 |

The numbers are expressed as the median (IQR) or %.

failure and new respiratory parameters such as PFR. Patients who showed impaired haemodynamics without regard to causes leading to cardiac failure following cardiac surgery were compared with control patients with no clinical signs of cardiac impairment following coronary artery bypass grafting. All patients with cardiac failure needed advanced inotropic support to maintain a mean arterial pressure above 60 mmHg. Forty per cent of them requested additional treatment with a mechanical cardiac support device in the form of an intra-aortic balloon pump. None of the patients in the control group had any need of either inotropic or mechanical support therapy.

Cardiac failure patients had neither increased oxygen demand nor more advanced respiratory conditions, such as positive end-expiratory pressure or ventilated volumes, compared with the control patients, indicating that the differences in particle mass and PFR between two groups can originate from the cardiac failure. However, peak inspiratory pressure and respiratory rate were significantly higher in the cardiac failure group. These two parameters are known to be associated with increased mechanical power of ventilation[17] and an increase in lung oedema and lung damage.[18] A theoretical explanation for the increased mechanical power of ventilation in the cardiac failure group


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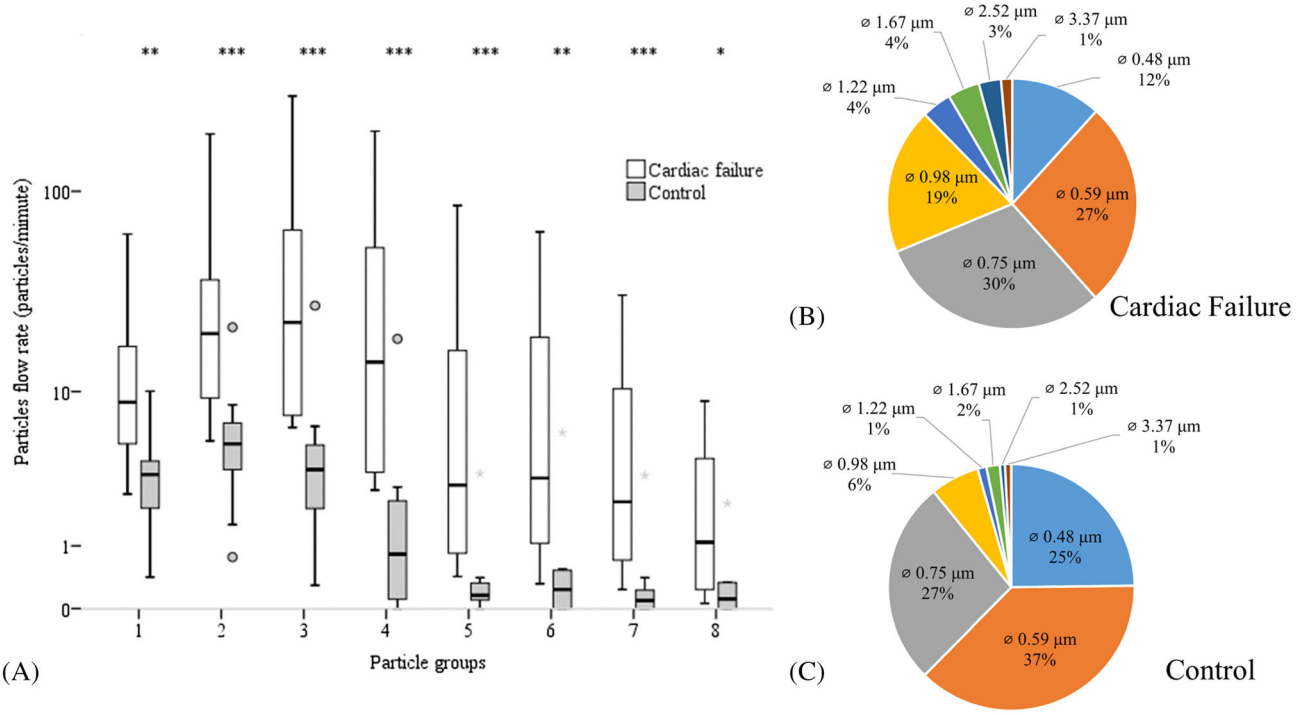
**Figure 3** Particle distribution depending on their size. Particle flow rate in logarithmic scale (A) and the percentage distribution by particle size group in patients with cardiac failure (B) and in the control group (C). The boundary of the boxes indicates the 25th and 75th percentiles; whiskers indicate the minimum and maximum. The line inside the box indicates the median value. The data points shown in the diagram are outliers. The means of the particle diameters in Groups 1–8 are 0.48, 0.59 μm, 0.75, 0.98, 1.22, 1.67, 2.52, and 3.37 μm. ***$P \leq 0.001$, **$P \leq 0.01$, *$P < 0.05$. ⌀ represents diameter.




may be an increased amount of lung fluid in the lung parenchyma due to the cardiac failure. Nevertheless, peak inspiratory pressure was within the expected range in both groups and could not be seen as a diagnostic parameter for cardiac failure in those patients. Therefore, an increase in particle mass and in PFR in the absence of respiratory pathology on chest X-ray may confirm cardiac failure. The underlying pathophysiology behind the increased particle flow in exhaled air in cardiac failure in the lack of any pronounced differences in respiratory parameters between the groups is interesting and hypothesis-stimulating. The measurement of particle mass and PFR as in fact calculation of the mechanical power of ventilation[19] can be a sensitive method to reveal small changes in peripheral lung parenchyma, for example, incipient lung oedema, which cannot be detected with conventionally chest X-ray exam.

Particles are believed to originate from the RTLF during opening and closing of small airways or by shear stress. The recent review by Bake *et al*. describes the airway reopening hypothesis as an explanation of particles in exhaled air.[10] These particles have been shown to reflect the overall composition of the RTLF, which changes due to various respiratory conditions. To date, both exhaled particles and other volatile compounds have been explored as a diagnostic tool for asthma,[20] chronic obstructive pulmonary disease,[21] sarcoidosis,[22] and pulmonary fibrosis.[23] Our previous studies have also shown that an increased PRF was associated with pathological lung conditions, such as ARDS,[12] including COVID-19-induced ARDS,[13] and primary graft dysfunction after lung transplant.[14] The current study showed the impact of the cardiac failure on particles in exhaled air in the absence of respiratory pathologies during MV. This indicates that PFR and particle mass can be used during MV to identify developing cardiac failure.

The composition of the particles grouped by their mean diameter may theoretically mirror various lung and heart conditions. The current study showed that the patient with cardiac failure expressed different composition of the exhaled particles depending on their size compared with the control subjects. This is in line with a previous observation when the early stage of ARDS presented with a unique particle composition pattern compared with healthy animals in an experimental model.[21] Therefore, the finding regarding the composition of the particles is very promising. Further studies are needed to confirm the results and explore the possibility to find the pathognomonic composition of the particles in exhaled air for various diseases.

Our research group has recently modified the PExA device to investigate exhaled air during MV. Various ventilations modes during *in vivo* and *ex vivo* conditions were studied in experimental models.[7,24] PFR and particle composition remained stable in healthy animals during several days of observation. The modified PExA device has been evaluated in clinical trials during thoracic surgery and during MV after cardiothoracic surgery.[14] These studies showed the relationship between PFR and positive end-expiratory pressure, tidal and minute volumes. Because these parameters did not differ between patients with and without cardiac failure, PFR and particle mass are likely to reflect the real difference between the groups.

The current study confirms the safety and usefulness of the modified PExA device as a possible bedside monitoring technique in the ICU.

### Limitations

This is a rather small study investigating a limited number of patients with and without cardiac failure by analysing exhaled air. The results were generated in a single centre and have a descriptive character. This research was conducted mainly as a hypothesis, generating study ideas for further investigations. Neither the impact of acute or chronic cardiac failure or time as an impact factor on PFR was the subject of this study.

The accumulated particle mass was sent for biochemical analyses. However, the given total particle mass in each collection, approximately 1–5 ng, was too low to perform the analyses of the exhaled substances. Nevertheless, we believe that the biochemical evaluation of the particles from RTLF has a large potential to identify early and sensitive biomarkers for various pathological conditions. More refined biochemical techniques are needed for future investigations.

### Conclusions

This study showed that patients with post-operative cardiac failure following cardiac surgery exhibited an increase in exhaled particle mass and PFR compared with the control group, indicating a significant difference between those two groups. The increase in particle mass and PFR in the absence of respiratory pathologies may be an indicator of cardiac failure. In comparison with control subjects, impaired cardiac function was also associated with a different particle composition pattern regarding the size distribution.

## Conflict of interest

None declared.

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## Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Figure S1.** Supporting Information

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