

Lung recruitment in the prone position after cardiac surgery: a randomised controlled study

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Abstract

Background: Atelectasis after cardiac surgery is common and promotes ventilation/perfusion mismatch, infection, and delayed discharge from critical care. Recruitment manoeuvres are often performed to reduce atelectasis. In severe respiratory failure, recruitment manoeuvres in the prone position may increase oxygenation, survival, or both. We compared the effects of recruitment manoeuvres in the prone vs supine position on lung aeration and oxygenation in cardiac surgical patients.

Methods: Subjects were randomised to recruitment manoeuvres (40 cm H₂O peak inspiratory pressure and 20 cm H₂O PEEP for 30 s) in either the prone or supine position after uncomplicated cardiac surgery. The co-primary endpoints were lung aeration (end-expiratory lung volume measured by electrical impedance tomography (arbitrary units [a.u.]) and lung oxygenation (ratio of arterial oxygen partial pressure to fractional inspired oxygen [PaO₂/FiO₂ ratio]). Secondary outcomes included postoperative oxygen requirement and adverse events.

Results: Thirty subjects (27% female; age, 48–81 yr) were recruited. Dorsal lung tidal volume was higher after prone recruitment manoeuvres (363 a.u.; 95% confidence intervals [CI], 283–443; n=15) after extubation, compared with supine recruitment manoeuvres (212 a.u.; 95% CI, 170–254; n=15; P<0.001). Prone recruitment manoeuvres increased dorsal end-expiratory lung volume by 724 a.u. (95% CI, 456–992) after extubation, compared with 163 a.u. decrease (95% CI, 73–252) after supine recruitment manoeuvres (P<0.001). The PaO₂/FiO₂ ratio after extubation was higher after prone recruitment manoeuvres (46.6; 95% CI, 40.7–53.0) compared with supine recruitment manoeuvres (39.3; 95% CI, 34.8–43.8; P=0.04). Oxygen therapy after extubation was shorter after prone (33 h [13]) vs supine recruitment manoeuvres (52 h [22]; P=0.01). No adverse events occurred.

Conclusions: Recruitment manoeuvres in the prone position after cardiac surgery improve lung aeration and oxygenation.

Clinical trial registration: NCT03009331.

Keywords: atelectasis; cardiac surgery; end expiratory lung volume; electrical impedance tomography; prone position; recruitment manoeuvre

Editor's key points

- Pulmonary collapse after cardiac surgery promotes ventilation/perfusion mismatch, infection, and prolonged hospitalisation.
- The authors hypothesised that recruitment manoeuvres in the prone position would improve lung aeration, oxygenation after extubation, or both following cardiac surgery.
- Stable subjects who had undergone uncomplicated cardiac surgery were randomised to standardised recruitment manoeuvres in the prone or supine position.
- Both lung aeration and oxygenation were higher after recruitment manoeuvres in the prone position, compared with supine manoeuvres.
- These proof-of-concept data suggest that this recruitment strategy can be explored as an intervention to reduce pulmonary complications after cardiac surgery.

Atelectasis with associated ventilation/perfusion mismatch is more common after cardiac surgery with cardiopulmonary bypass (CPB),^{1–3} compared with noncardiac surgery.⁴ Lung function may be impaired up to 4 months after coronary bypass surgery.⁵ Prolonged mechanical ventilation as a result of pulmonary dysfunction, prolongs ICU stay and promotes the development of multi-organ dysfunction through nosocomial pneumonia and acute respiratory distress syndrome (ARDS).^{6,7}

After cardiac surgery, early alveolar recruitment manoeuvres (RMs) in the supine position are often performed to reduce hypoxia, atelectasis, and prolonged mechanical ventilation. RMs typically consist of decrementing PEEP, with inspiratory peak pressure of 30–45 cm H₂O.^{8–11} Prone positioning after cardiac surgery has been described in ARDS,^{12,13} improving oxygenation, and reducing shunt fraction. In a mixed group of intensive care patients with severe ARDS, prone positioning decreased 28 and 90 day mortality.¹⁴ The physiological benefits of combining prone positioning with RMs has been demonstrated in ARDS patients, but not after cardiac surgery.^{15,16}

We hypothesised that RMs in the prone position is advantageous by improving dorsal lung aeration (measured using electrical impedance tomography [EIT])^{17,18} and oxygenation after extubation, compared with supine position. The aim of the present study was therefore to study the combined effect of RMs in the prone position, compared with RMs in the supine position.

Methods**Study design**

The study was approved by the Gothenburg Ethics Committee (number: 371–17, 26 July 2017) and registered on December 14, 2016, in [ClinicalTrials.gov](https://clinicaltrials.gov) (ID: NCT03009331). Written informed consent was obtained from all subjects preoperatively. Enrolment was between August 2017 and March 2019. We followed the Consolidated Standards of Reporting Trials (CONSORT) recommendations on reporting randomised trials.

Inclusion criteria

Adults (age >18 yr) undergoing on-pump cardiac surgery were considered eligible for the study.

Exclusion criteria

We did not enrol patients after surgery if the following exclusion criteria were met:

- (1) Pulmonary disease, smoking, or former smoker within 5 yr
- (2) Haemodynamic instability (norepinephrine [NE] infusion >0.20 µg kg min⁻¹), milrinone infusion, or pacemaker dependency
- (3) Postoperative bleeding >100 ml h⁻¹, or reoperation
- (4) Haemothorax or large pleural effusion using ultrasonography
- (5) Pneumothorax or air leak
- (6) Postoperative PEEP >12 cm H₂O or FiO₂ >0.6

Anaesthesia and intraoperative management

Institutional routines were implemented. FiO₂ was 0.8 during induction of anaesthesia and before commencing CPB. Sevoflurane was used during surgical preparation and after weaning from CPB. Apnoea without PEEP was induced during CPB. Before weaning from CPB, a manual RM was performed, with the adjustable pressure-limiting (APL) valve set to 30–40 cm H₂O, to visually confirm the expansion of the lungs. After chest closure, FiO₂ was 0.5 with a tidal volume (V_T) of 6–8 mL kg⁻¹ of predicted body weight, a ventilatory frequency of 12–14 bpm, and PEEP of 5 cm H₂O (Flow-i; Maquet Critical Care, Solna, Sweden).

Recruitment manoeuvres

The RM consisted of an increase in PEEP from 5 to 20 cm H₂O in three steps over 30 s.¹⁹ The ventilator mode was temporarily switched to pressure control for the remaining part of the RM with inspiratory pressure of 20 cm H₂O above PEEP. The PEEP level was maintained at 20 cm H₂O for 30 s, followed by decrements to 10 cm H₂O in five steps over 2 min. Identical RMs were performed in the Supine (n=15) and Prone groups (n=15), with the timeline described in detail below ([Supplementary Fig. S1](#) details the experimental procedure including the S1–S4 time points).

Electrical impedance tomography

A 16-electrode silicon belt (Ref 84 20 0–57, -58, -59; Dräger Medical, Lübeck, Germany) was placed around the thoracic cage between the sixth and seventh intercostal spaces. This position avoided interference with the diaphragm and chest drains ([Fig. 1](#)), and was re-verified after each turn. The belt was connected to the EIT device during the entire procedure. EIT data were sampled at a rate of 40 Hz (Pulmovista 500; Dräger Medical), and a filter of 50 beats min⁻¹ was applied to minimise cardiac-induced signals. EIT data correspond to signals from a 5–10-cm-thick transverse slice of the lung. Data were continuously sampled (EIT Diag; Dräger Medical).²⁰ For each registration point, a stable phase of 30 consecutive breaths (2–3 min) was selected, with the baseline registration (S1) as reference. EIT images are reconstructed based on relative voltage deviations caused by tissue impedance variation (ΔZ), that is alterations in aeration, with multiple display options. Based on the tidal image of the reference section, ventilated area (def. $\Delta Z > 15\%$ compared with baseline) was divided into two equally large surfaces, named regions of interest (ROIs), a ventral region (the non-dependent zone) and a dorsal region (the dependent zone). In the baseline registration (S1), tidal ΔZ



Fig 1. Supine and prone positioning. Typical study subject in the supine and prone positions (note: two chest drains are positioned to not interfere with the EIT belt). EIT, electrical impedance tomography.

was calibrated to the V_T , enabling calculation of volume changes in the following registrations (S2–S4). Taking into account that changes in lung volume and V_T distribution occurs in the ventro-dorsal and baso-apical direction,^{21,22} and that only a single basal slice of the lung is examined, the calibrated volume unit is depicted as arbitrary.

Several EIT-derived variables have been described. Tidal impedance variation (TIV) is highly correlated with V_T , as measured with syringe technique, ventilator spirometry, and CT.^{23,24} A good correlation between end-expiratory lung impedance ($\Delta EELI$) changes and end-expiratory lung volume ($\Delta EELV$) changes, when calibrated against $\Delta Z/V_T$, has been demonstrated.^{25–27} Distribution of TIV and $\Delta EELI$ is demonstrated by applying one ventral and one dorsal ROI. The centre of ventilation (COV) divides the lung into one ventral and one dorsal region, to obtain two equal halves of global TIV. From dorsal (0%) to ventral (100%), a vertical percentage scale is applied to the thorax diameter, and the horizontal intersection between the regions is depicted on the scale. Values above 50% mean predominance of ventral, and values below, of dorsal ventilation.^{20,28–30}

Oxygenation

Arterial blood gases were obtained (Siemens RAPIDPoint 500; Siemens Healthcare GmbH, Erlangen, Germany) to calculate

the ratio of arterial partial pressure of oxygen to the fraction of inspired oxygen (P_{aO_2}/FiO_2).

Radiological Atelectasis Score

Chest X-ray on the second postoperative day, after chest drain removal, was performed bedside and assessed by a single blinded radiologist in accordance with the Radiological Atelectasis Score (RAS).³¹ RAS quantifies atelectasis by a 5-point score (0, clear lung fields; 1, plate-like atelectasis or slight infiltration; 2, partial atelectasis; 3, lobar atelectasis; 4, bilateral atelectasis).

Postoperative protocol

The patients were prospectively randomised (closed envelopes) for RM in the supine or PP (150–180°, left side up), after arrival in the cardiothoracic intensive care unit (CTICU) (Supplementary Fig. S1). At CTICU arrival, the patients were placed in a 20–30° head-up position with previous ventilation (pressure-regulated volume-controlled mode; Servo-U; Maquet Critical Care), and ventilatory frequency to normocapnia ($P_{CO_2}=4.7–6.0$ kPa). Patients were sedated with propofol infusion (Richmond Agitation–Sedation Scale score, –4) to avoid spontaneous breathing. The time from ICU admission to time point zero was 25–30 min, during which randomisation, positioning of EIT belt, EIT signal verification, and assessment of patient arrival status took place. After time zero, there was a 25-min equilibration period before the first EIT data sampling period of 5 min, S1. In the Prone group, the proning procedure plus RM (15 min) and de-proning (5 min) together lasted 20 min. In the Supine group, the RM was performed at the identical time point, preceded by a 10 min equilibration period. After a further equilibration period of 5 and 10 min for the Prone and Supine groups, respectively, there was a measurement period of 5 min (S2). A further equilibration period started after S2 for 25 min, followed by a measurement period of 5 min (S3). After S3 the patients emerged from sedation to facilitate extubation. After extubation, there was a 25 min equilibration period followed by S4. For all patients, data are from the supine position (S1–S4). FiO_2 was 0.5 at S1 through S3. At S4, a nomogram was used to define FiO_2 .³² Arterial blood gases were obtained at the end of S1, S2, S4.

Co-primary outcomes

The primary outcome measures were dorsal V_T , dorsal EELV, and P_{aO_2}/FiO_2 ratio after extubation (S4).

Secondary outcomes

Secondary outcome measures were COV, RAS, postoperative oxygen requirement, and safety of the RM and PP (including oedema of lips; oedema of eyelids; pressure sores, facial bruising, or both).

Statistical analysis

The Shapiro–Wilk test confirmed normal distribution. Analyses were performed using SPSS ver. 24 (IBM, Chicago, IL, USA). Two-way analysis of variance (ANOVA) for repeated measurements (time vs group) evaluated differences between the groups, and t-test was used for post-hoc analyses (Supplementary Tables S2 and S3). For other analyses we performed unpaired t-test as a primary comparison. A P value

<0.05 was considered statistically significant. Results are presented as mean with standard deviation (SD). Effect size was calculated using Cohen's *d*.

Sample size estimation

To detect a 20% difference in dorsal V_T at S4 between prone vs supine RM, 14 patients in each group were required (alpha 0.05, power 0.8), by the use of IBM SPSS SamplePower .

Results

Subject characteristics

Informed consent was obtained from 30 patients (Table 1; Supplementary Fig. S2), who were randomised to either RM in the prone ($n=15$) or supine position ($n=15$). More patients in the Supine group had an isolated valve procedure, but the duration of CPB ($P=0.182$), cross-clamp time ($P=0.506$), ventilatory settings (Supplementary Table S2), and ICU stay (prone: 23 h [7], vs supine: 25 h [8]); $P=0.40$) were similar between groups.

Table 1 Subject characteristics. Data are presented as mean (standard deviation) or (range), except as noted. Vasopressor treatment refers to low-dose norepinephrine ($0.05\text{--}0.20\ \mu\text{g kg min}^{-1}$). CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass.

	Supine ($n=15$)	Prone ($n=15$)
Female sex, n (%)	4 (27)	4 (27)
BMI, kg m^{-2}	28.3 (4.5)	29 (3.1)
CABG, n	9	11
Valve, n	5	0
CABG+valve, n	1	4
CPB time, min	68.3 (34.7)	83.3 (24.4)
Aortic cross-clamp time, min	50.0 (27.1)	56.3 (21.2)
Vasopressor treatment, n (%)	8 (53)	8 (53)

Co-primary outcomes

Lung aeration

The dorsal regional V_T increased in both groups (Fig. 2), but to a greater extent in the Prone group ($P<0.001$). The dorsal regional V_T was higher in the Prone group at S2 ($P=0.043$) and S4 ($P=0.001$) compared with the Supine group, but no difference was seen at S3 ($P=0.065$). There were no differences between groups in ventral regional V_T ($P=0.169$).

Both dorsal and global ΔEELV were higher in the Prone group (Fig. 3) compared with the Supine group at all time points (S2–S4, $P=0.001$). After extubation, the dorsal and global ΔEELV was sustained above baseline only in the Prone group ($P<0.001$). Ventral ΔEELV was higher in the Prone group at S2 ($P=0.039$).

Oxygenation

In both groups, lung oxygenation improved after RM (Fig. 4); however, it was more pronounced in the Prone group at S2 ($P=0.007$) and S4 ($P=0.041$).

Secondary outcomes

Centre of ventilation

COV shifted from ventral to dorsal regions after RM in both groups (Fig. 5), but was more pronounced in the Prone group ($P=0.011$). Dorsal ventilation was significantly more pronounced in the Prone group at S4 ($P=0.045$).

Radiological Atelectasis Score

RASs were similar for the Prone and Supine groups (1.6 [0.7] and 1.8 [0.5], respectively; $P=0.41$).

Postoperative oxygen requirement

The mean duration of nasal oxygen delivery was shorter in participants randomised to prone RM (33 h [13]) compared with supine RM (52 h [22]; $P=0.010$).

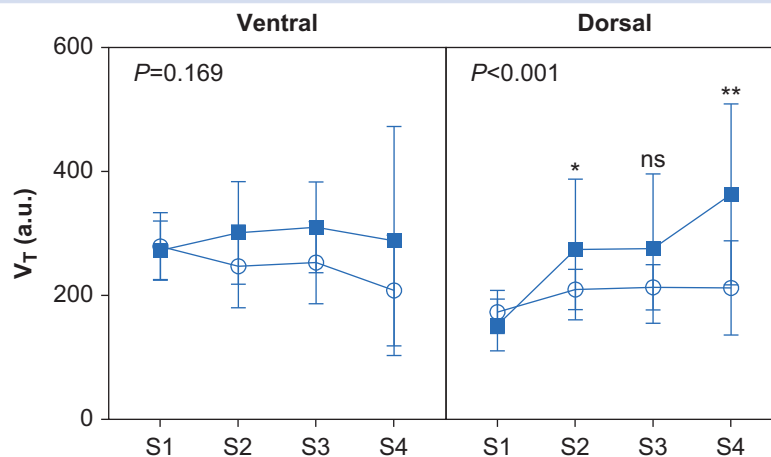


Fig. 2. Effect of recruitment manoeuvres on tidal volume. Ventral, ventral regional tidal volume; Dorsal, dorsal regional tidal volume; S1, before the recruitment manoeuvre; S2, immediately after the recruitment manoeuvre; S3, 30 min after the recruitment manoeuvre; S4, 30 min after extubation during spontaneous ventilation; a.u., arbitrary unit. Values are mean (SD). * $P<0.05$, ** $P<0.01$. Filled boxes: Prone group; open circles: Supine group.

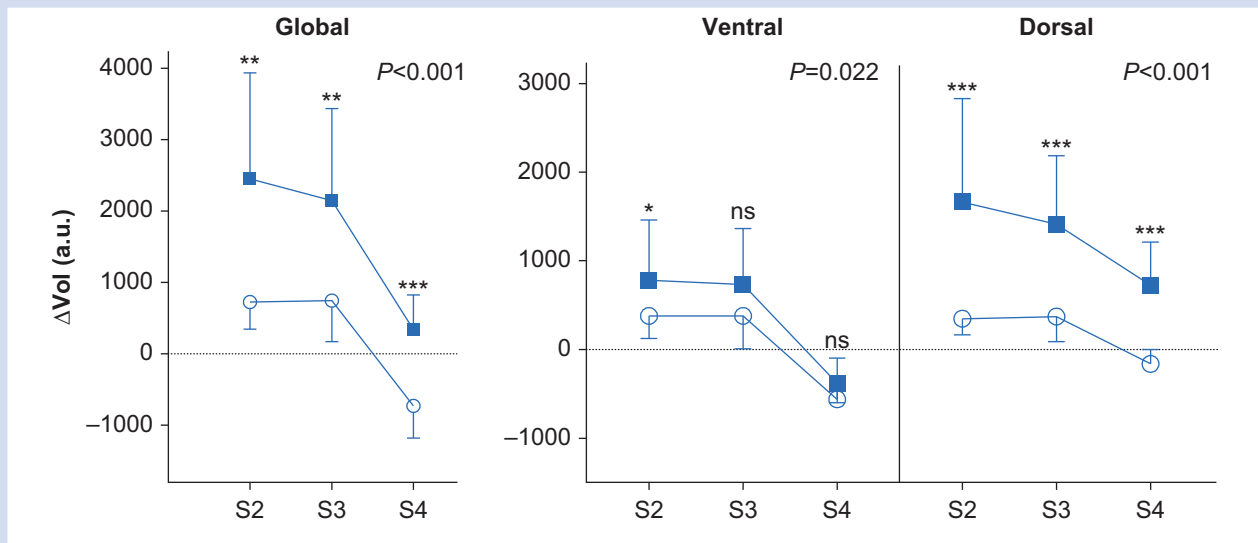


Fig 3. Effect of recruitment manoeuvres on end-expiratory lung volume. Global, changes in global end-expiratory lung volume; Ventral, changes in ventral end-expiratory lung volume; Dorsal, changes in dorsal end-expiratory lung volume. S1, before the recruitment manoeuvre; S2, immediately after the recruitment manoeuvre; S3, 30 min after the recruitment manoeuvre; S4, 30 min after extubation during spontaneous ventilation; a.u., arbitrary unit. Values are mean (SD). * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$. Filled boxes: Prone group; open circles: Supine group.

Haemodynamics

There was no difference in duration of NE infusion in the CTICU between the Prone group (171 [128] min) and the Supine group (264 [171] min; $P = 0.24$), or in MAP and HR, 5 min before, during, and 5 min after the RM ($P = 0.40$; [Supplementary Table S3](#)).

Safety of prone positioning

There were no adverse events associated with the RM or PP, with no accidental extubation or need for reintubation within 24 h.

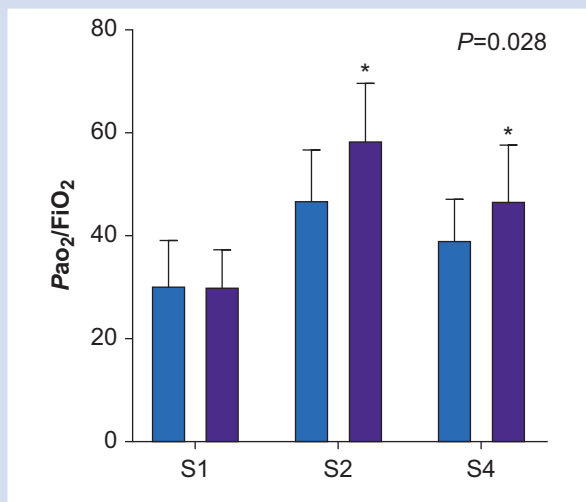


Fig 4. Effect of recruitment manoeuvres on P_{aO_2}/F_{iO_2} ratio. S1, before the recruitment manoeuvre; S2, immediately after the recruitment manoeuvre; S4, 30 min after extubation during spontaneous ventilation. Values are mean (SD). F_{iO_2} , fraction of inspired oxygen; P_{aO_2} , arterial partial pressure of oxygen (kPa), * $P < 0.05$. Blue, supine. Purple, prone.

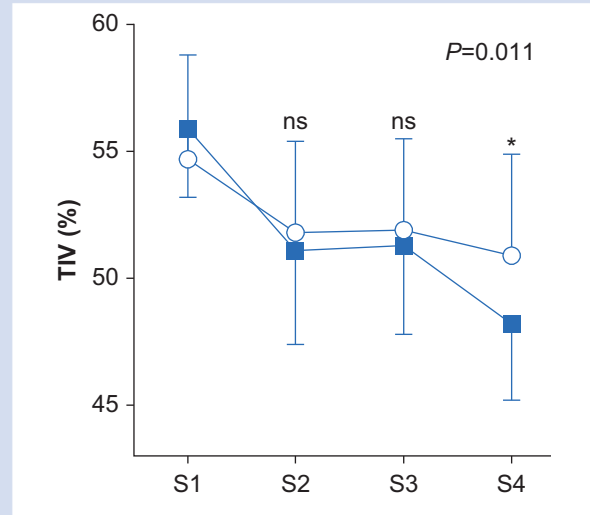


Fig 5. Effect of recruitment manoeuvres on centre of ventilation. S1, before the recruitment manoeuvre; S2, immediately after the recruitment manoeuvre; S3, 30 min after the recruitment manoeuvre; S4, 30 min after extubation during spontaneous ventilation; TIV, tidal impedance variation. Values are mean (SD). * $P < 0.05$. Filled boxes: Prone group; open circles: Supine group.

Discussion

Our RCT found that an early postoperative RM in the prone position was superior to supine RM, as assessed by recruitment of dorsal atelectatic areas, dorsal redistribution of V_T , and improved lung oxygenation. The beneficial effect of prone RM remained after extubation and presumably until the second postoperative day, as suggested by the shorter duration of postoperative oxygen supplementation. Prone RM was not associated with any adverse events.

This is the first investigation to demonstrate the superiority of RM in the prone position in cardiac surgical patients. Beneficial effects of RM in the supine position in cardiac surgery patients were recently demonstrated by Costa Leme and colleagues.¹⁰ Among patients with hypoxaemia, the use of an intensive and extended alveolar recruitment strategy resulted in less severe pulmonary complications and shorter ICU and hospital stay.¹⁰ Similar to our study, there was an increase in compliance of the dependent lung regions in the intensive strategy group, demonstrated by EIT. Their study was the first to demonstrate a positive clinical outcome attributed to postoperative RM.¹⁰ These beneficial effects seen after cardiac surgery were absent in patients undergoing abdominal surgery.³³ One explanation is that the post-cardiac surgery lungs are more vulnerable and prone to atelectasis formation resulting from the inflammatory effect of the CPB, open chest surgery, and ischaemia–reperfusion injury,² amplified by postoperative gravitational forces of the heart and mediastinum on nearby pulmonary segments.³ In other words, different genesis of atelectasis may affect lung recruitability. The patients in the present study were not hypoxaemic before inclusion as in the study by Costa Leme and colleagues.¹⁰ However, we have shown that the improved oxygenation of an RM, in the Supine group and even more pronounced in the Prone group, persists after extubation also in uncomplicated post-cardiac surgery patients, confirming previous studies showing improved oxygenation with early RM in cardiac surgery patients up to 3–5 days after extubation.^{2,34} The shorter duration of supplemental postoperative oxygen in our Prone group supports the superiority of a prone RM.

Although improved outcome of PP in ARDS patients is not associated with increased oxygenation,³⁵ in post-cardiac surgery patients, improvement in postoperative oxygenation results in earlier extubation, and ICU and hospital discharge. Extended and prolonged RMs in ARDS in the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial (ART) had harmful acute effects on oxygenation or haemodynamics, and in 16% of the patients the RM had to be interrupted. Furthermore, there was increased mortality in the lung recruitment and titrated PEEP group.^{36,37} Regarding the Prone group in our study, a shorter and less extended RM compared with that in the ART study was a safe procedure with no difference in MAP, HR, or postoperative NE infusion time, compared with the Supine group (Supplementary Table S3). The PP *per se* in post-cardiac surgery and ARDS have negligible or favourable effects on haemodynamics.^{12,38} In patients with Acute Respiratory Failure (ARF) after cardiac surgery, PP reduced atelectasis and improved oxygenation.¹² Data on the persisting effects of PP and RMs on lung volumes and oxygenation after extubation are lacking. Poor lung oxygenation postoperatively may increase ICU stay and pulmonary complications.

The EIT technique has previously been used to optimise PEEP in respiratory failure¹⁸ and after cardiac surgery.^{8,9,11,39} It

reveals atelectasis perioperatively,⁴⁰ and may substitute, and be preferred to, thoracic CT.^{8,18,30,41} In contrast to CT, EIT provides irradiation-free, online, continuous bedside measurements. The lung ultrasound score is not recommended for quantification of bedside lung recruitment.⁴² In a study using a similar RM to ours,¹¹ regional ventilation measured by EIT compared with respiratory compliance, was considered a better variable to detect 'best PEEP'. The best PEEP according to maximum dorsal EELV was about 10 cm H₂O, the level we chose after the RM. The EIT-derived EELV has been used as a surrogate for true measurement of functional residual capacity (FRC), with good accuracy.^{26,27} The EIT technique has also been used in spontaneously breathing patients after cardiac surgery,⁴³ and during general anaesthesia,²⁹ to detect beneficial effects in EELV and ventilation distribution. In two recent studies, EIT in the PP was successfully used in ARDS patients, with⁴⁴ or without extracorporeal membrane oxygenation (ECMO),⁴⁵ to measure Δ EELV and V_T distribution and to identify patients likely to benefit from PP.

Most patients after cardiac surgery have basal and dorsal atelectasis.^{8,9,11,12,39} In the present study, PP plus RM improved dorsal V_T in the extubated patients to a larger extent compared with supine RM, most likely as a result of redistribution from ventral and apical areas. Redistribution from apical to basal regions during a PEEP trial, using one apical and one basal EIT belt,³⁹ has previously been shown. The increase in dorsal V_T is expected to improve the dorsal ventilation/perfusion ratio, reflected by better lung oxygenation and a shorter postoperative requirement of nasal oxygen delivery, seen in the Prone group.

The increase in dorsal Δ EELV and the improved lung oxygenation, persisting after extubation, was significantly more pronounced in the Prone group, indicating an improvement in alveolar recruitment, FRC, and dorsal aeration.^{26,41,46} In a previous study in post-cardiac surgery patients, an early open lung concept strategy improved FRC averaged over the first 5 postoperative days.³⁴ In the present study, all patients in the Prone group were responders in dorsal V_T , oxygenation, and dorsal Δ EELV, between S1 and S4, whereas 10, 12, and two patients, respectively, were responders in the Supine group (Supplementary Fig. S3). We speculate that the decrease in ventral Δ EELV below zero, in both groups after extubation, is not harmful, but reflects the return to EELV levels before induction of anaesthesia, and the cessation of the ventral overdistension caused by positive pressure ventilation.

A limitation of the present study is that ventilation distribution is based on a single lung slice.^{27,40} Hence, it is debatable whether EIT data represent global aeration. However, cardiac surgery predominantly causes dorso-basal atelectasis, well correlating to the selected EIT belt position.³ A second limitation is the lack of FRC measurement after extubation. However, there is a good correlation between regional and global Δ EELV and FRC.^{26,27} A third limitation is that we did not study the aeration beyond 30 min after extubation. Nevertheless, studies after cardiac surgery using the 'open lung tool concept' improved FRC for 5 days,³⁴ and decreased pulmonary complications and ICU or hospital stay,¹⁰ which is supported by less postoperative oxygen supplementation in the Prone group of the present study. A fourth limitation is that the assessor was not blinded for the intervention. However, the EIT data were collected and presented by the dedicated software²⁰ at identical time points in all patients. Future studies will clarify whether this new strategy for alveolar recruitment has long-

term beneficial effects on lung volumes and oxygenation in post-cardiac surgery patients.

In summary, early after cardiac surgery, a lung RM in the prone position improves lung oxygenation, dorsal tidal ventilation, and dorsal end-expiratory lung volumes, compared with a lung RM in the supine position. Dorsal alveolar recruitment is accompanied by an improved dorso-basal ventilation/perfusion relationship. These beneficial effects on lung volumes and function are maintained after extubation.

Authors' contributions

Conduct of experiments: AM

Data analysis: AM

Statistical analysis: AM, EH

Data interpretation: EH, AW, SL, AT

Writing the first draft of the manuscript: AM

Manuscript revision: EH, AW, SL, AT

All authors gave final approval of the submitted version.

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Declarations of interest

None of the authors report any conflict of interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bja.2020.12.039>.

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