

Tidal Lung Recruitment and Exhaled Nitric Oxide During Coronary Artery Bypass Grafting in Patients With and Without Chronic Obstructive Pulmonary Disease

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Abstract

Background We studied the occurrence of intraoperative tidal alveolar recruitment/derecruitment, exhaled nitric oxide (eNO), and lung dysfunction in patients with and without chronic obstructive pulmonary disease (COPD) undergoing coronary artery bypass grafting (CABG).

Methods We performed a prospective observational physiological study at a university hospital. Respiratory mechanics, shunt, and eNO were assessed in moderate COPD patients undergoing on-pump ($n = 12$) and off-pump ($n = 8$) CABG and on-pump controls ($n = 8$) before sternotomy (baseline), after sternotomy and before cardiopulmonary bypass (CPB), and following CPB before and after chest closure. Respiratory system resistance (R_{rs}), elastance (E_{rs}), and stress index (to quantify tidal recruitment) were estimated using regression analysis. eNO was measured with chemiluminescence.

Results Mechanical evidence of tidal recruitment/derecruitment (stress index <1.0) was observed in all patients,

with stress index <0.8 in 29% of measurements. R_{rs} in on-pump COPD was larger than in controls ($p < 0.05$). E_{rs} increased in controls from baseline to end of surgery (19.4 ± 5.5 to 27.0 ± 8.5 ml cm H_2O^{-1} , $p < 0.01$), associated with increased shunt ($p < 0.05$). Neither E_{rs} nor shunt increased significantly in the COPD on-pump group. eNO was comparable in the control (11.7 ± 7.0 ppb) and COPD on-pump (9.9 ± 6.8 ppb) groups at baseline, and decreased similarly by 29% at end of surgery ($p < 0.05$). Changes in eNO were not correlated to changes in lung function.

Conclusions Tidal recruitment/derecruitment occurs frequently during CABG and represents a risk for ventilator-associated lung injury. eNO changes are consistent with small airway injury, including that from tidal recruitment injury. However, those changes are not correlated with respiratory dysfunction. Controls have higher susceptibility to develop complete lung derecruitment.

Keywords Acute lung injury · Pulmonary disease · Chronic obstructive · Coronary artery bypass surgery · Nitric oxide · Perioperative period

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Introduction

Chronic obstructive pulmonary disease (COPD) is present in 4–27% of patients undergoing coronary artery bypass grafting (CABG) surgery [1]. The National Center for Health Statistics estimates that a total of 408,000 CABG procedures were performed in the United States in 2007 [2]. COPD is associated with risk for major perioperative complications after CABG such as prolonged mechanical ventilation [3], extubation failure [4], and increased hospital and 30-day mortality [5–7]. Chronic inflammation in

COPD patients could compound the acute inflammatory response to surgery and cardiopulmonary bypass (CPB) [8] to produce intraoperative lung collapse and longer post-operative recovery times. Conversely, the increased respiratory resistance and reduced elastic recoil found in COPD could provide a mechanism to retard or even prevent the development of intraoperative atelectasis [9]. Despite these pathophysiological particularities of COPD patients and the significant number of COPD patients undergoing CABG, there is minimal information on perioperative lung dysfunction specifically addressing these patients.

Mechanical ventilation settings influence the magnitude of lung inflammation during cardiac surgery. Protective ventilatory strategies with low tidal volume (V_T) and higher positive end-expiratory pressure (PEEP) have been shown to result in less inflammatory markers in both the bronchoalveolar lavage fluid and plasma [10, 11], and less time to extubation and the need for reintubation of cardiac surgical patients [12]. Such findings suggest that limiting maximal lung stretch and low-volume lung injury would reduce lung inflammation and morbidity in patients undergoing cardiac surgery. Minimization of pulmonary morbidity is an important goal because although the incidence of acute respiratory distress syndrome and acute lung injury after CPB is low (<2%), the associated mortality is high (>50%) [13, 14]. Moreover, after CABG surgery, hypoxemia has been reported as the most common cause for prolonged mechanical ventilation [15]. COPD patients present an exacerbated inflammatory response [16, 17] and could be at increased risk for respiratory complications.

It is currently unknown whether perioperative functional changes occur to justify each of the protective ventilatory interventions, i.e., PEEP and low V_T , during the intraoperative period of cardiac surgery. If hyperinflation would be the predominant dysfunction, limitation of lung stretch (low V_T) would be the relevant intervention. Instead, if tidal alveolar recruitment would be frequent, use of PEEP would be warranted since tidal opening and closing of alveoli and small airways in atelectatic regions during mechanical ventilation could increase the risk of ventilator-induced lung injury. Given that atelectasis is frequently present and the main cause of shunting and hypoxemia during cardiac surgery [18, 19], cyclic lung recruitment and concentration of mechanical forces [20] are likely during mechanical ventilation. The associated low-volume stress has been shown to be injurious in several models of acute lung injury [21, 22]. However, it is unknown to what degree low- and high-lung-volume stresses are present in patients with and without COPD undergoing cardiac surgery.

The “stress index” is a parameter derived from the airway pressure–time curve obtained at bedside during constant flow inflation to detect tidal recruitment and

hyperinflation [23]. It was associated with computed tomography findings of tidal recruitment in experimental models of healthy [24] and surfactant-depleted lungs [23, 24]. Exhaled NO (eNO) reduction has been proposed as a marker of lung injury in the setting of CPB [25, 26]. In experimental ventilator-induced lung injury, a decline in eNO has been associated with cyclic opening and closing of peripheral airways during ventilation at low volume [21, 27]. In contrast to those eNO declines as indicators of injury, in COPD patients high eNO has been suggested as a surrogate marker of disease exacerbation [28].

In this study we measured respiratory mechanics, including the stress index, eNO, and gas exchange, in the intraoperative period of CABG surgery with cardiopulmonary bypass to (1) investigate whether tidal recruitment and hyperinflation occur at different surgical phases in patients with and without COPD; (2) evaluate whether eNO changes differ in those patient groups and whether those changes correspond to deterioration in respiratory mechanics and gas exchange; and (3) characterize lung function patterns in patients with moderate COPD in comparison with patients with no previous history of pulmonary disease. Finally, we also studied those variables in a group of COPD patients undergoing off-pump CABG surgery.

Methods

Patients

The study was approved by the Institutional Review Board of the Massachusetts General Hospital and written informed consent was obtained from all subjects. We sequentially studied 28 patients: 20 with moderate COPD as defined by GOLD criteria [29] and 8 nonsmokers without a history of pulmonary disease (controls). Exclusion criteria were presence of acute respiratory failure and emergency surgery. From the 20 COPD patients, 12 underwent on-pump CABG (COPD on-pump group) and 8 off-pump CABG (COPD off-pump group). Controls underwent on-pump CABG. Off-pump CABG was performed mainly because of severe ascending aortic atheromatosis.

Regular medication was maintained until surgery. Patients were premedicated with midazolam, induced with fentanyl and propofol, maintained with isoflurane, midazolam, and fentanyl, and had muscle paralysis with cisatracurium or pancuronium. Methylprednisolone 1 g was administered after intubation. Monitoring included a radial artery and a pulmonary artery catheter. Patients were mechanically ventilated with tidal volume (V_T) = 8 ml/kg, inspired oxygen fraction ($F_{I}O_2$) = 100%, PEEP = 2.5 cm H_2O , with respiratory rate adjusted to normocarbia.

Ventilator parameters were kept constant before and after revascularization. A nitroglycerin infusion was used after revascularization at 50 mcg/min.

Procedures

All surgeries were done through a median sternotomy. We maintained the activated clotting time above 480 s. CPB was performed with systemic cooling to 30–33°C, double-stage venous cannula, and ascending aorta cannulation. Cardiac arrest was achieved by cold or warm blood antegrade and retrograde cardioplegia. The flow was maintained at 2.4 L/min/m², with a mean arterial pressure >50 mmHg. During CPB, the expiratory limb of the breathing circuit was opened to atmosphere with lungs passively deflated. Before weaning from CPB, at least one recruitment maneuver to a peak inspiratory pressure of 20–25 cm H₂O with direct visualization of lung expansion was performed. Off-pump CABG surgery was performed using a Genzyme stabilizing system (Genzyme Corporation; Cambridge, MA), Silastic rubber sutures were placed proximal and distal to the anastomotic site as coronary artery occluders, an intraluminal shunt was placed in case of hemodynamic instability, and a blower was used for insufflating humidified CO₂ to ensure a bloodless operative field. No conversion to CPB occurred.

Physiological Measurements

Physiological measurements were performed at four time points chosen to represent major interventional phases encompassing the period of initial lung insult: (1) following intubation, before sternotomy; (2) after sternotomy, before revascularization; (3) before chest closure, following revascularization (i.e., after CPB for on-pump CABG); and (4) after chest closure, at the end of surgery. Hemodynamic measurements consisted of heart rate, systemic and pulmonary artery pressure, central venous pressure, and cardiac output. Gas exchange measurements included arterial and mixed venous blood gases and shunt [30]. A respiratory analyzer (NICO, Respironics) was used for intraoperative monitoring of capnography and lung mechanics.

Respiratory Mechanics

The elastance and resistance of the respiratory system (E_{rs} and R_{rs}), and lungs (E_L and R_L) were estimated from measurements of airway (P_{aw}) and esophageal (P_{es}) pressures and respiratory flow (\dot{V}) (Venttrak, Novamatrix). The equation $P = R \cdot \dot{V} + E \cdot V + EEP$ was fit to measured data using multiple linear regression, where EEP was the

pressure at the end of expiration; the respiratory volume (V) was computed from the integral of \dot{V} ; and $P = P_{aw}$ for estimates of E_{rs} and R_{rs} or $P = (P_{aw} - P_{es})$ for estimates of E_L and R_L [31].

Tidal recruitment and hyperinflation were assessed through estimation of the stress index [23]. This index was computed by fitting the patient's P_{aw} versus time (t) curve with the power equation $P_{aw}(t) = at_i^b + c$, where t_i was the time from the beginning of the constant flow inspiration, and a , b , and c were constants. The coefficient b (stress index) describes the shape of the P_{aw} - t curve: $b = 1$, straight curve (constant compliance during lung inflation, minimal stress); $b < 1$, progressive decrease in slope (increasing compliance during lung inflation, tidal recruitment with low-volume stress); and $b > 1$, progressive increase in slope (decreasing compliance during lung inflation, tidal hyperinflation with high-volume stress). Quality of fitting was assessed with the coefficient of determination (R^2). One-minute epochs were analyzed using the Levenberg–Marquardt method (Mecanica, built in Matlab[®], The MathWorks, Inc., Natick, MA). A respiratory cycle was discarded if (1) a constant inspiratory flow portion was not present, (2) the constant flow period was less than one third of the inspiratory time, and (3) $R^2 < 0.95$.

Exhaled Nitric Oxide

eNO was measured continuously by chemiluminescence (Sievers model NOA 280; Sievers Instruments, Boulder, CO) with response time of 170 ms [32]. The analyzer was calibrated before each case with 0 and 45 ppm NO. The eNO signal was either digitized at 100 Hz or registered on paper. Gas was sampled at a rate of 250 ml/min through a Teflon tube connected to the Y-piece of the breathing circuit. Measurements of inspired NO were always less than 2 ppb. eNO was measured as the mean end-expiratory value of at least five breathing cycles. The mean values were taken from the point corresponding to the plateau of the end exhaled CO₂ reading, representing the lower respiratory tract sample.

Statistics

All results are expressed as the mean \pm standard deviation (SD) or as median [interquartile range]. We based the sample size calculation on expected shunt and eNO differences between groups, and in the same group from baseline to end of surgery. For shunt, a difference of 8% between at least two of the three groups with SD = 5.5% and a change from baseline to end of surgery of 6% were

used. For eNO, values as observed in normals [33] and COPD exacerbation [34] were applied, as well as a within-group (pairwise) expected change in eNO of 4 ppb with a SD = 6 ppb. An ANOVA-based power analysis for a power of 0.80 ($p < 0.05$) and equal variance led to a minimum sample size of 8 patients per group. Repeated-measures ANOVA with between-subjects factors were used to compare time points and groups. Post-hoc comparisons were performed with the Sidak correction for multiple comparisons. A linear correlation coefficient was used for computation of correlations. χ^2 analysis was used to compare proportions. Analysis was performed using SAS statistical software ver. 9 (SAS Institute Inc., Cary, NC). Two-tailed values of $p < 0.05$ were used to establish statistical significance.

Results

Demographic characteristics were similar in all groups (Table 1). Hemodynamics showed higher central venous pressures in both COPD groups and higher pulmonary artery pressures in COPD on-pump than controls at baseline (Table 2). The increased heart rate after chest closure was due to pacing.

Respiratory Mechanics

R_{rs} in the on-pump COPD group was larger than in controls at all time points (Fig. 1a). Following sternotomy, R_{rs} was significantly decreased in both COPD groups. In all groups, R_{rs} significantly increased after chest closure, returning to values similar to baseline.

Patients in the control and COPD off-pump groups showed a significant increase in E_{rs} at the end of surgery (Fig. 1b). The increase in E_{rs} relative to baseline was larger in controls than in the COPD groups.

The partitioning of the respiratory system mechanics into lung and chest wall components showed that most of the changes in respiratory system mechanics were due to changes in lung properties. E_{rs} had a high correlation ($r = 0.80$, $p < 0.0001$) with E_L , and R_{rs} with R_L ($r = 0.97$, $p < 0.0001$).

The stress index was similar for all groups at baseline. Values were under 1 (=tidal recruitment, low-volume stress) for most measurement points (Fig. 2). In fact, the stress index was under 0.8 (associated with computed tomography findings of tidal recruitment) for 35% of measurements in the on-pump COPD group, 19% in the control group, and 31% in the off-pump COPD group. During open chest conditions in on-pump cases, COPD patients tended to have stress indices below 0.9 (related to histological and inflammatory changes in experimental ventilator-induced lung injury) more frequently than controls ($p < 0.1$), with 6 of 12 COPD patients having stress indices under 0.9 before CPB and 5 of those 12 after CPB, whereas 1 of 8 control patients had a stress index in that range for the same time points. When all patients were pooled, chest opening led to a significant decrease in the number of stress indices under 1 ($p < 0.05$), and chest closure had the reverse effect ($p < 0.001$). In specific groups, the stress index increased after chest opening in the COPD off-pump group and decreased after chest closure in the control and COPD off-pump groups. Measurements at the end of surgery were not significantly different from those at baseline.

Table 1 Demographic, spirometric, clinical, and intraoperative data

	Controls on-pump ($n = 8$)	COPD off-pump ($n = 8$)	COPD on-pump ($n = 12$)
Age (years)	65 [56–79]	77 [67–82]	74 [64–75]
Body mass index	26.6 \pm 4.0	26.3 \pm 4.8	28.9 \pm 6.2
Women (n)	2	1	1
FEV ₁ (% predicted)	93 [71–96]	54 [40–60]	58 [48–70]
Pack-years	0	50 [50–93]	68 [58–80]
Diabetes mellitus (n)	1	3	4
Hypertension (n)	7	6	8
Myocardial infarction (n)	3	5	4
Angina class III or IV (n)	2	6	5
No. of diseased vessels	2.5 \pm 0.9	2.5 \pm 0.7	2.7 \pm 1.0
Prior CABG surgery (n)	0	1	1
Aortic cross-clamping time (min)	73 \pm 32		76 \pm 33
Bypass time (min)	92 \pm 41		102 \pm 40
Length of ICU stay (h)	21 \pm 8	22 \pm 10	36 \pm 26
Time to extubation (h)	7 \pm 4	12 \pm 7	12 \pm 7

Values are mean \pm SD or median [interquartile range]
COPD chronic obstructive pulmonary disease, FEV₁ forced expiratory volume in 1 s, CABG coronary artery bypass grafting, ICU intensive care unit

Table 2 Intraoperative hemodynamic and arterial blood gas data of patients at baseline, before chest opening, and at the end of surgery, after chest closure

	Controls on-pump (<i>n</i> = 8)		COPD off-pump (<i>n</i> = 8)		COPD on-pump (<i>n</i> = 12)	
	Baseline	Closed chest	Baseline	Closed chest	Baseline	Closed chest
Temperature (°C)	35.3 ± 0.7	35.9 ± 0.5	35.8 ± 0.5	36.2 ± 0.7	35.7 ± 0.7	35.7 ± 0.6
Heart rate (beats min ⁻¹)	52 ± 10	86 ± 2 ^b	51 ± 7	84 ± 24 ^b	54 ± 9	86 ± 6 ^b
Mean arterial pressure (mmHg)	76 ± 9	74 ± 11	77 ± 10	84 ± 12 ^a	82 ± 13	72 ± 7 ^{b,c}
Mean pulmonary artery pressure (mmHg)	17 ± 6	17 ± 4	21 ± 3	20 ± 5	22 ± 5 ^a	18 ± 4 ^b
Central venous pressure (mmHg)	5 ± 3	7 ± 2	10 ± 2 ^a	8 ± 4	9 ± 2 ^a	7 ± 3 ^b
Cardiac output (L min ⁻¹)	4.1 ± 0.9	5.0 ± 1.9	4.3 ± 1.8	3.9 ± 1.0	4.7 ± 1.1	4.6 ± 1.0
PaO ₂ (mmHg)	431 ± 71	213 ± 104 ^b	419 ± 51	292 ± 73 ^b	369 ± 116	272 ± 113 ^b
PaCO ₂ (mmHg)	39 ± 6	41 ± 4	40 ± 5	45 ± 6	44 ± 6	47 ± 6
pH	7.43 ± 0.04	7.32 ± 0.06	7.45 ± 0.05	7.32 ± 0.07	7.38 ± 0.04	7.30 ± 0.05

Values are mean ± SD

COPD chronic obstructive pulmonary disease

^a *p* < 0.05 compared to control group

^b *p* < 0.05 compared to baseline

^c *p* < 0.05 compared to COPD off-pump

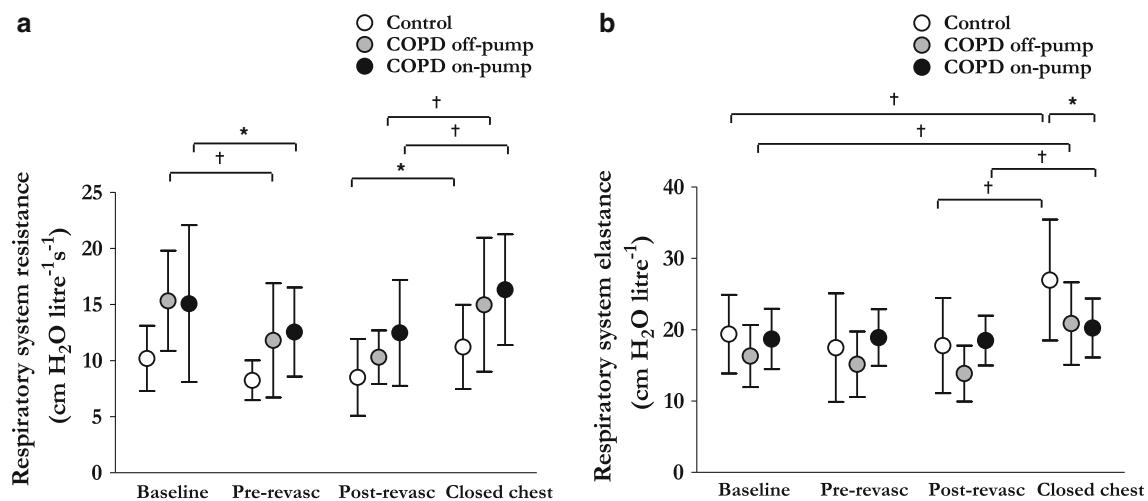


Fig. 1 Respiratory system resistance and elastance for the three studied groups at four surgical time points. Data are presented (1) following intubation, before sternotomy (Baseline); (2) after sternotomy, before revascularization (Pre-revasc); (3) before chest closure, following revascularization (Post-revasc, i.e., following cardiopulmonary bypass for control and COPD on-pump groups); and (4) after chest closure, at the end of the procedure (Closed chest). **a** Patients

with chronic obstructive pulmonary disease (COPD) had higher resistance than controls throughout the whole intraoperative period (*p* < 0.05). The resistance decreased in the COPD groups after opening the chest and increased in all groups following chest closure. **b** There was an increase in elastance after chest closure, more marked for the control group. Values are mean ± standard deviation. **p* < 0.05; †*p* < 0.01

Exhaled NO

eNO was lower at the end of surgery than at baseline for patients undergoing CPB in the control and COPD on-pump groups (Fig. 3). In fact, eNO was already reduced during open chest conditions from before to after CPB in controls (29%, *p* = 0.04) and on-pump COPD patients

(26%, *p* = 0.01). There was a high correlation between mean eNO before and after sternotomy (*r* = 0.92, *p* < 0.001) and before and after chest closure (*r* = 0.93, *p* < 0.001), and no change in mean eNO within groups was observed following opening or closure of the chest. Absolute and percent changes in eNO were not correlated to corresponding changes in *E*_{rs}, *R*_{rs}, PaO₂, or PaCO₂

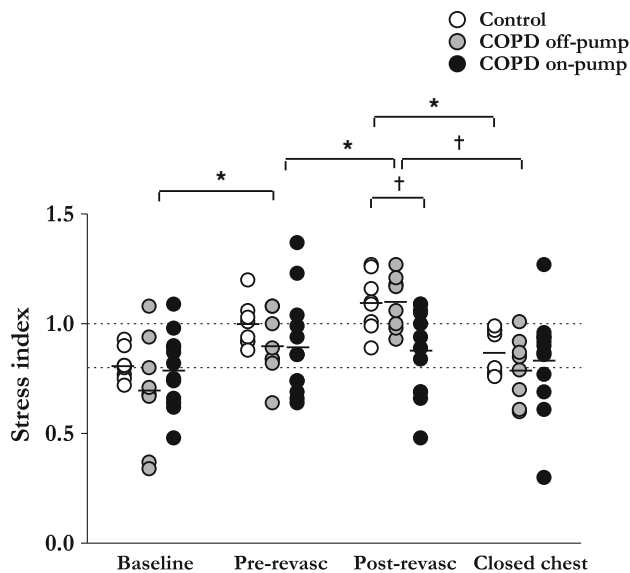


Fig. 2 Individual measurements of stress indices in the three studied groups at the four surgical time points. The majority of measurements for all groups were below 1, a range compatible with tidal recruitment of alveoli and small airways. A significant percentage of the measurements were under 0.8 and few were above 1.2. There was a significant reduction in the stress index after chest closure in the control and off-pump chronic obstructive pulmonary disease (COPD) groups. Dashes indicate mean values for each group and time point. Time points are described in Fig. 1. * $p < 0.05$; † $p < 0.01$

($p = \text{NS}$ for all correlations). The COPD off-pump group had significantly lower eNO than controls at baseline and these did not change at the end of surgery.

Gas Exchange

Mean PaO₂ decreased in all groups at the end of surgery: 51% in controls, 26% in COPD on-pump, and 30% in COPD off-pump patients (Table 2). Right-to-left shunt was similar at baseline for all groups in the patients mechanically ventilated with 100% O₂ (Fig. 4). Shunt in controls increased from 19 to 26% from baseline to end of surgery and was larger than that in the COPD on-pump group after chest closure. In contrast, shunt was not significantly changed in COPD patients (Fig. 4). An increase in shunt in controls was already observed in open chest conditions following revascularization.

Despite the high alveolar-arterial gradient of O₂ (AaDO₂) in controls at arrival in the intensive care unit (ICU) (328 mmHg), consistent with the higher shunts in controls at the end of surgery, the improvement in AaDO₂ per hour until extubation tended to be faster in controls than in on-pump COPD patients ($p = 0.08$, Fig. 5), a trend confirmed when all COPD patients were included

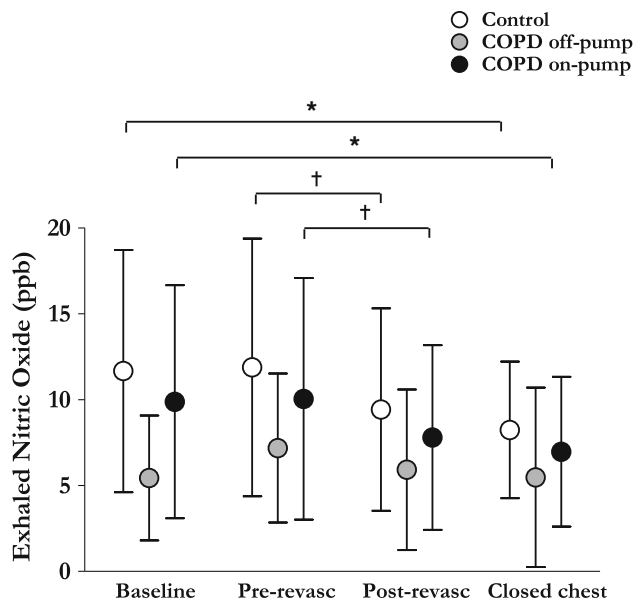


Fig. 3 Exhaled nitric oxide for the three studied groups at four surgical time points. Exhaled nitric oxide decreased from Baseline to Closed Chest and from before to after revascularization, i.e., cardiopulmonary bypass, in the control and the chronic obstructive pulmonary disease (COPD) on-pump groups. Time points are described in Fig. 1. Values are mean \pm standard deviation. * $p < 0.05$; † $p < 0.01$

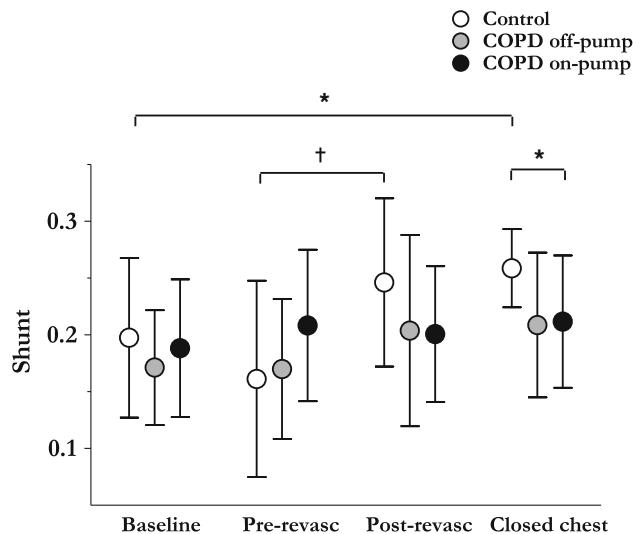


Fig. 4 Right-to-left shunt for the three studied groups at four surgical time points. There was significant increase in shunt in the control group after cardiopulmonary bypass and chest closure, but no significant changes in patients with chronic obstructive pulmonary disease (COPD). Time points are described in Fig. 1. Values are mean \pm standard deviation. * $p < 0.05$; † $p < 0.01$

($p < 0.05$, Fig. 5). This paralleled the trend for shorter time to extubation in the control group and the longer ICU stay in COPD on-pump patients (Table 1).

0.9–1.1 range, i.e., a range within normal values reported in previous studies [41]. Those observed differences likely characterize the mechanical response of the COPD lung to the very distinct set of intraoperative conditions occurring between those two time points: Whereas the on-pump COPD lungs were exposed to the acute inflammatory response to CPB and an average of 102 min of passive lung deflation, the off-pump COPD group was continuously ventilated and not subjected to the inflammatory response to CPB. The correlations of the changes in the stress index and the respiratory mechanics and shunt provide insight on the potential causes for the observations. In the on-pump COPD group, there was a significant correlation between the ratio of the stress index after to before revascularization and the shunt ratio ($r = 0.61$, $p < 0.05$), suggesting that changes in stress index were predominantly influenced by lung collapse. In contrast, for the off-pump group the stress index ratio was inversely correlated to the R_{rs} ratio at the same time points ($r = -0.90$, $p < 0.005$). The larger the R_{rs} reduction after revascularization, the more inflated the lung conditions. In the patients not subjected to CPB, continuous mechanical ventilation with an open chest could have facilitated progressive airway expansion, with recruitment of collapsed areas and shifting to a more inflated condition of the COPD lung. Controls had an average but nonsignificant increase in the stress index after revascularization. Interestingly, in controls, also exposed to CPB, the stress index ratio correlated with the shunt ratio ($r = 0.74$, $p < 0.05$) and tended to correlate with the R_{rs} ratio ($r = -0.66$, $p < 0.08$). This could indicate a combination of effects, including increased lung collapsibility associated with CPB and R_{rs} contribution leading to more lung inflation as R_{rs} decreased. Redistribution of regional lung aeration probably occurs in the studied cases and leads to complex effects on the stress index [24]. Studies using measurements of regional perfusion and aeration will be required to provide an accurate explanation for these respiratory mechanics and associated gas exchange findings.

Increases in E_{rs} and R_{rs} during CABG have been described [44, 45]. Less is known about perioperative lung function in specific groups, a relevant point since distinct mechanisms of respiratory dysfunction can imply different management strategies. Baseline measurements of E_{rs} and R_{rs} were consistent with those of previous studies [44, 45], with R_{rs} in COPD patients larger than that in controls. R_{rs} did not increase in COPD patients and controls after CPB, in contrast to most [45, 46] but not all [44] studies.

While COPD patients did not show significant intraoperative worsening of R_{rs} , they had significantly slower improvement in oxygenation in the ICU than controls, indicating a limited capacity to recover postoperatively, which is compatible with their higher risk for

complications [3, 6] and their observed longer time to extubation and ICU stay [3, 4, 47]. Such observations may be at least partially explained by the role of absorption atelectasis as the main determinant of AaDO₂ in controls. Such regions of derecruited lung would be progressively reduced in the ICU as PEEP and F_IO₂ < 100% were applied. In contrast, the major determinant of AaDO₂ in COPD patients is ventilation-perfusion mismatch associated with the severity of emphysema and small airway and vascular abnormalities, potentially exacerbated perioperatively [48–50]. Indeed, COPD patients have a differential inflammatory response during cardiac surgery with increased release of cysteinyl leukotrienes [16]. This could add to the potential small airway dysfunction discussed above. Additionally, inhibition of the hypoxic pulmonary vasoconstriction due to inflammatory mediators and vasoactive medications [51–53] could contribute to perfusion heterogeneity. Such factors could have combined with the chronic inflammation [54] and lung dysfunction [49, 50] during COPD to produce the trend toward slower improvement in oxygenation observed in our COPD patients.

E_{rs} increased significantly in controls after chest closure, which is consistent with previous studies [44–46]. Shunt increased concurrently in controls, suggesting that at least part of the derecruited lung remained perfused. In contrast, E_{rs} did not increase significantly in the COPD on-pump group. This indicates that the process of perioperative lung derecruitment in moderate COPD patients differs from that in controls. Patients with healthy lungs typically present perioperative atelectasis and shunt [40, 55]. In contrast, Gunnarson et al. [56] observed increased ventilation-perfusion mismatch but no increase in shunt (mean 1%) in COPD patients during enflurane anesthesia. These patients had minor or no atelectasis on computed tomography and minimal reduction of chest dimensions, suggesting minimally affected functional residual capacity [56]. These findings are consistent with the resistance of spontaneously breathing nonintubated COPD patients to develop oxygen absorption atelectasis [49, 56], thought to be additionally associated with increased collateral ventilation, and their more homogeneous vertical distribution of density and ventilation [50]. Our findings expand those observations by suggesting that this reduced propensity to lung derecruitment is also present in intubated, mechanically ventilated COPD patients undergoing cardiac surgery. Thus, the presence of airway obstruction and prolonged expiratory time constants found in COPD, generating a potentially protective auto-PEEP effect, combined with the reduced elastic recoil limiting the perioperative reduction of functional residual capacity likely contributed to the observed maintenance of lung elastance.

Changes in E_{TS} and R_{TS} were smaller than previously reported [44, 45]. A possible explanation is the relatively small number of patients in the studies, with differences due to distinct patient samples and the fact that previous studies did not stratify patients according to their initial pulmonary function. Since the studies were performed years ago, our findings may also represent management improvements such as biocompatibility of the CPB system and cardiac protection techniques resulting in less lung dysfunction.

Exhaled Nitric Oxide

There is limited information on eNO in intubated COPD patients. We found similar baseline eNO in on-pump COPD and control groups, consistent with measurements in nonintubated stable COPD patients and controls [34, 57], but in contrast with increased eNO observed in stable COPD by others [58]. Such discrepancies may be explained by differences in COPD classification, smoking history [58], eNO assessment methods, and use of steroids.

eNO was reduced after on-pump CABG in subjects with and without COPD. This is compatible with observations of decreased eNO induced by CPB in CABG surgery [25, 59, 60]. D'Angelo et al. [21, 27] found a significant relationship between the decrease in eNO and bronchiolar epithelial damage in an experimental model of low-volume lung injury and proposed the use of eNO reduction as a sign of peripheral airway injury. Reduced eNO has also been suggested as reflective of bronchial epithelial dysfunction after hypoxia and reoxygenation on CPB [61]. Low levels of eNO have been associated with lung damage in other conditions such as with impaired function in cystic fibrosis [62] and different forms of smoke inhalation [63–65]. Thus, our findings of reduced eNO after CPB and of a stress index under 0.8 in a significant percentage of patients could suggest decreased endogenous production and/or elimination due to injury to the airway epithelium. This could have resulted from tidal opening–closing of small airways, in addition to perioperative ischemia–reperfusion associated with cardiac surgery [21, 27]. Given that many other factors influence eNO changes [25, 27, 60, 66–68], further studies will be required to clarify the causes of reduced perioperative eNO in patients with and without COPD.

Finally, it is apparent that eNO did not reflect exclusively pulmonary injury. Although reduced after on-pump CABG, eNO was not correlated to any variable related to pulmonary dysfunction. Indeed, whereas eNO changes were similar in on-pump COPD patients and controls, respiratory mechanics and gas exchange were distinct. This is also consistent with the dissociation between lung function and inflammatory markers in COPD outpatients [69]. Consequently, our results suggest that in the

intraoperative period of CABG surgery, eNO is not an accurate predictor of acute lung injury.

This study has several limitations. Clinical COPD is significantly heterogeneous. Thus, the limited number of patients in our study does not allow for generalization of our results to all subsets of COPD patients. Computation of the stress index in COPD patients may be influenced by the volume dependence of their airway resistance, which decreases during inspiration [70]. This could result in a downward concavity in the pressure–time curve and lead to overestimation of tidal recruitment. Our analysis of eNO is a significant simplification compared to compartmental models that address airway and alveolar contributions to eNO [71]. Future studies will be necessary to establish whether the similar perioperative changes in eNO in controls and COPD patients are distinct at the compartmental level.

In conclusion, intraoperative respiratory mechanics during CABG surgery were compatible with tidal alveolar recruitment during CABG surgery in patients with and without COPD and are suggestive of risk for ventilator-associated lung injury. Strategies to limit low-volume injury during mechanical ventilation may be particularly relevant in these patients. Changes in respiratory function in the perioperative period showed greater susceptibility to lung derecruitment in controls, with worsening of elastance and development of shunt. Controls and patients with moderate COPD showed an equivalent and significant decrease in eNO after CABG surgery, which is compatible with small-airway injury and likely has a multifactorial mechanism. The decrease in eNO was not uniquely related to perioperative respiratory dysfunction.

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