Ventilation according to the Open Lung Concept in Cardiac Surgery

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Cover: 3-D Thoracic CT-scan of a patient after coronary bypass sugery. Edited by Bob Meijboom

Backpage: Andre F Cournand, Nobel prize winner 1956. Was the first scientist to explore the role of PEEP on cardiac output. Picture edited by D. dos Reis Miranda (sr)

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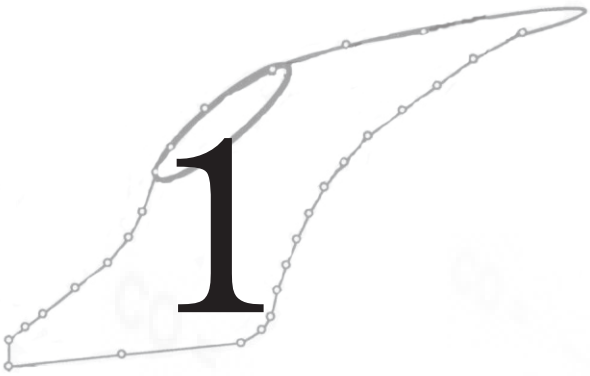
Table of Contents



Ventilation-induced lung injury and its prevention: The open lung concept

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Mechanical ventilation has become a life-saving therapy in the treatment of patients with impaired pulmonary function. Experience, however, has learned that certain modes of mechanical ventilation may be associated with related adverse effects, such as: decrease in lung compliance and gas exchange, atelectasis, pulmonary edema, pneumonitis and fibrosis. Much of these pathophysiological changes seen in ventilated patients are logically attributed to the ventilation strategies and are, therefore, called ventilator-induced lung injury (VILI). Components of VILI are biotrauma, volutrauma, barotrauma and atelectotrauma[1]. Volu-, baro- and atelectotraumas can be seen as mechanical injury to the lung; biotrauma reflects pulmonary and systemic inflammation caused by mediators originating from the ventilated lung.

Biotrauma

Biotrauma describes the process by which mechanical stress due to mechanical ventilation creates an inflammatory process[2]. Depending on the extent of the physical forces applied, stress leads to activation of pulmonary cells through mechanotransduction[3] or to rupture of membranes and, finally, tissue destruction[4]. Although it is not clear how mechanical forces are converted to biochemical signals, several pathways have been suggested such as: stretch-sensitive channels; mechanoreceptors; stress-activated signalling cascade of the mitogen-activated protein kinase (MAPK)[2;3] and activation of the transcription of the nuclear factor (NF)-κB[5]. MAPK, and probably NF-κB, leads subsequently to mRNA IL-8 production and release of IL-8[3;6-9]. MAPK is activated by various forms of extra-cellular stress and might serve an important role in the cellular responses

to ventilation-induced mediator release. It was recently demonstrated that ventilation with high inspiratory pressures stretches alveolar epithelial cells, triggering both MAPK and NF-κB cascade[3]. The subsequent cellular response is boosted by pro-inflammatory cytokines activation, explaining leukocyte recruitment into the lungs when large tidal volume and zero PEEP are applied. The latter is also called injurious ventilation[10].

The cytokines production and the cellular inflammation response due to mechanical ventilation do not only cause local injury; the local reaction spills over into the systemic circulation, causing end-organ apoptosis[1]. Especially renal and small intestine epithelial apoptosis was seen in experimental lung injury during injurious ventilation[11]. Besides end-organ damage, injurious ventilation is a predisposing factor to bacterial translocation from the lung into the systemic circulation[12;13].

In summary, evidence is growing that mechanical forces on the lung, commonly observed during mechanical ventilation, are the source of cytokine production in the lung and have the potential of systemic generalisation.

Mechanotrauma

Baro- and volutrauma

In the past VILI was automatically associated with clinical barotraumas, defined as the appearance of air leaks. That is why, for example, in 1994 the American-European consensus conference[14] recommended that plateau pressure should not exceed the arbitrary pressure limit of 35 cm H_2O, limiting the risk of barotraumas. Recently, Boussarsar and colleagues again emphasized the risk of barotraumas[15] when pressures above 35 cm H_2O are applied. The adverse consequences of these macroscopic events are usu-

ally immediately obvious; only recently, rather more subtle physiologic and morphologic alterations due to barotraumas have been recognized (as mentioned in the previous section).

Recognizing these physiologic and morphologic alterations during mechanical ventilation, clinicians tended to limit tidal volume instead of pressure, in combination with a higher PEEP level; this strategy reduced mortality in ARDS patients[16;17]. To further explore the role of tidal volume and peak inspiratory pressure on lung injury, Dreyfuss and colleagues[18] applied high inspiratory pressures in combination with high volumes in an experimental model, and found that: 1) high pressures together with high tidal volume resulted in increased alveolar permeability; 2) combining low pressure with high volume (iron lung ventilation) resulted again in increased alveolar permeability; 3) if high pressure was associated with low tidal volume (chest wall strapping) the alveolar permeability of the study group did not differ from the control group. There is nowadays sufficient evidence to show that alveolar overdistention causes lung injury[10], especially when combined with zero PEEP ventilation[1;19]. Avoiding alveolar overdistention by limiting tidal volume is optimal in a homogenized lung. In an atelectatic lung, however, alveolar overdistention is not prevented by small tidal volume ventilation due to the baby lung effect (as explained below).

Atelectotrauma

Atelectasis is a common occurrence in spontaneously breathing humans and is also present after endotracheal intubation, even in healthy lungs in volume controlled ventilation[20-25]. Depending on the amount of collapsed lung tissue, even small tidal volumes (e.g. 6 ml/kg)

will increase several-fold the actual tidal volume delivered to the open lung areas, leading to the so-called baby lung: when e.g. 75% of the lung is collapsed, the applied volume to the open part of the lung will be 24 ml/kg.

Pioneering work of Mead and colleagues[26] demonstrated that forces acting on the lung tissue in non-uniformly expanded lungs are not only the applied transpulmonary pressures. Shear forces acting on the fragile alveolar membrane in atelectatic regions predominate due to the pulmonary interdependence of the alveoli. Transpulmonary pressures of 30 cm H_2O will result in shear forces between atelectatic and normal lung areas of 140 cm H_2O. These shear forces, rather than end-inspiratory overstretching, may be the reason for epithelial disruption and the loss of barrier function of the alveolar epithelium. Epithelial disruption leads to high-permeability edema with wash-out or dilution of the surfactant and/or inactivation of the surfactant by plasma components[27]. This surfactant impairment causes an increase of atelectasis, increased formation of edema and impairment of local host defence[1]. Indeed it is shown that abnormalities of surfactant already occur in patients at risk of developing ARDS, suggesting that these abnormalities, occurring in VILI, precede ARDS[28].

We contended above that shear stress plays a key role in biotrauma, volutrauma and atelectotrauma. It was therefore speculated that avoiding shear stress would reduce VILI, which we would like to replace by the term PILI (physician-induced lung injury).

Why should we open up the lung?

In 1992, Lachmann proposed in an editorial entitled: "Open up the lung and keep the lung open"[29], a ventilation strategy aiming to protect the lung by reducing, or even

avoiding PILI. The mainstay of the open lung concept (OLC) is to avoid atelectasis, tackling the primary cause of PILI. Secondly the pressure amplitude is minimized, resulting in low tidal volume ventilation (ideally between 4-6 ml/kg) to minimize shear stress. When a lung is "open" it is characterized by an optimal gas exchange[29] and a low rate of intrapulmonary shunting (ideally less than 10%) corresponding with a PaO_2 of more than 450 mmHg on pure oxygen[30;31]. This was recently confirmed by in vivo microscopy, where alveolar instability was seen with a PaO_2/FiO_2 ratio of 170 mmHg and being reversed if the PaO_2/FiO_2 ratio was increased to nearly 450 mmHg[32].

The physiology behind this is as follows: When the lung is injured (characterized by an impaired surfactant system) the surface tension is increased requiring higher airway pressures to stabilize the alveoli. The law describing this relationship was discovered by Pierre-Simon, marquis de Laplace (1749-1827), a French astronomer and mathematician. He formulated the law (nowadays referred to as the law of Laplace): $P=2\gamma/r$, in which P is the pressure inside a bubble; γ is the surface tension at the air liquid interface of the bubble; and r the radius of a bubble. This law transferred to an alveolus means that P is the pressure inside an alveolus which keeps the alveolus open, γ is the surface tension at the air liquid interface, and r the radius of the alveolus. In a 'healthy' alveolus surfactant allows a reduction in alveolar radius by a reduction of the surface tension at the air liquid interface. This prevents collapse of the alveolus during end-expiration by keeping the quotient constant.

"The open lung management" describes the steps and methods used to safely open the lung and how to keep it open. The goal is to recruit collapsed alveoli by applying high inspiratory pressures for a very short time (5-15 s). After opening

the lung and finding the lowest end-expiratory pressure to keep it open, the resulting pressure amplitude is minimized and at the same time pulmonary gas exchange is maximized. A reduction of the mean airway pressure is generally possible after a successful alveolar recruitment [29].

With this concept care is taken to avoid atelectasis, responsible for shear stress, which is commonly the cornerstone of mechano- and biotrauma. Indeed, evidence is growing that mechano- and biotrauma is reduced by application of the OLC.

Effect of OLC on biotrauma

Although the exact pathways to biotrauma are unclear, it is widely appreciated that the origin of biotrauma is due the mechanical stress at the alveolo-capillary wall[1;2;6;10;33]. Limiting stress to the alveolo-capillary wall by avoiding end-expiratory collapse resulted in reduced levels of biochemical markers (purines) from damaged cells after high pressure ventilation. From these results one can conclude that shear stress is more damaging to the lung than is overdistention[34]. These findings were supported by studies by van Kaam et al., who demonstrated that application of the OLC in surfactant-depleted piglets resulted in a reduction of inflammatory cells and IL-8 in a broncho-alveolar lavage, in comparison to animals ventilated with low PEEP[35]. Preventing end-expiratory collapse by sufficient PEEP levels also minimizes alveolar and systemic decompartmentalization of inflammatory mediators[36] and reduced bacterial translocation[13]. Ranieri and colleagues confirmed this experimental data in ARDS patients; cytokine levels were attenuated by a ventilation strategy

avoiding atelectasis and minimizing overdistention[37]. Further on, Amato et al. could demonstrate a reduction in mortality when the OLC was applied to patients suffering from severe ARDS[16].

At present, there seems to be a bulk of evidence that ventilationstrategies aiming at avoiding atelectotrauma, as in the OLC, indeed reduces biotrauma to the lung and probably also reduces systemic inflammatory response and even mortality.

Effect of OLC on mechanotrauma

Preventing atelectasis, applying the open lung concept, preserves lung mechanics, attenuating mechanotrauma and thereby reducing mortality during ventilation[38;38-40]. In a recent experimental study, in vivo microscopic images were made and alveolar instability was seen when recruitment was followed by inadequate PEEP, while with adequate PEEP after recruitment (the open lung philosophy) alveoli were very stable[32]. Indeed, no atelectasis was demonstrated by CT-scan in anaesthetized healthy children using the OLC[25]. In patients with severe chest trauma, OLC resulted in a highly effective improvement of ventilation-perfusion mismatch, caused by massive atelectasis[41]. In addition, the OLC reduces protein leakage into the alveolus, which inactivates the surfactant system[39]. Impaired surfactant system, in turn, results in increased shear forces, which increases mechanotrauma, inducing a vicious cycle. By ventilating according to the OLC, thus reducing atelectasis, VILI can be reduced[42] or may even be prevented. It seems therefore

reasonable to conclude that "Open up the lung and keep it open" should be the philosophy for preventing PILI.

Potential contra-indications

Recruitment maneuvres implicating high inspiratory pressures during a brief moment have the potential risk for barotraumas. Recently, high inspiratory pressures[15] and elevated PEEP levels[43] were correlated with an increased rate of pneumothorax, although Boussarsar et al.[15] studied high inspiratory pressures applied for a prolonged period. Weg et al., however, in a large prospective study of 725 patients suffering from ARDS found no significant correlation between high ventilatory pressures and the development of pneumothorax or other air leaks[44]. Schreiter et al. also found no increased rate of pneumothorax in patients with severe chest trauma ventilated according the to OLC[41]. This, despite mean peak inspiratory pressures of 65 cm H_2O being used during recruitment[41]. Also in our experience, the high inspiratory pressure applied for only seconds is not associated with an increased rate of pneumothorax, especially when recruitment pressure is tailored to each individual patient, according to their needs and response. Therefore, in our opinion, early application of "the open lung management" should be used in each patient that requires mechanical ventilation and thus minimizing VILI.

Another reason for not applying OLC might be an impairment of the circulatory system. OLC is accompanied by elevated intrathoracic pressures and, since the work of Cournand in 1948, elevated intrathoracic pressures are associated with

a decrease in cardiac output[45]. However, it seems that in normovolemic patients the application of a sigh (or manual bagging leading to high inspiratory pressures) does not interfere significantly, for a longer period, with the hemodynamics. Recently, Dyhr and colleagues[46] have shown that a lung recruitment maneuvre (two 20-s inflations to 45 cm H_2O) in combination with PEEP (14±3 cm H_2O) can be performed safely in ventilated patients even after coronary artery bypass surgery. In these volume-loaded patients, cardiac index did not decrease after recruitment and application of PEEP. Others also report no circulatory impairment of elevated PEEP after a recruitment maneuvre[47;48]. However, no change of cardiac output does not automatically mean that right ventricular afterload remained unaffected. Increase of right ventricular afterload can be compensated by an increase of contractility without affecting cardiac output. Indeed, an increase of airway pressure was associated with increment of right ventricular afterload in other studies[49;50]. Increase of the right ventricular afterload means that the applied airway pressures must be transmitted to the lung capillaries. However, as long as the ventilation pressures are balanced by the retractive forces of the lung, no pressure will be transmitted to the capillaries. But, during inspiration, airway pressure may overcome retractive forces of the lung and thus resulting for a short period in an increased right ventricular afterload. This suggests that tidal volume (or driving pressure) is the main determinant of right ventricular afterload. To minimize this increase in the right ventricular afterload, small tidal volume resulting in small pressure changes should be applied during mechanical ventilation. Indeed, it was demonstrated that not PEEP but large tidal volume was the main factor in increasing right ventricular afterload[51;52]. And albeit in atelectatic

lung regions, airway pressure is not transmitted into the thorax, it will increase tidal volume to open lung regions, resulting in overdistention of the already injured part of the lung.

Although many questions are still open, it seems that early application of the OLC safely attenuates VILI.

Conclusion

VILI, which we replaced by PILI (physician-induced lung injury), is caused by mechano- and biotrauma. Especially biotrauma of the lung has the potential of systemic generalisation. Shear stress is the cornerstone of both mechanotrauma and biotrauma. The OLC safely reduces or prevents PILI by reducing shear stress and thereby mechanotrauma and biotrauma.

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2

Effect of mechanical ventilation on right ventricular afterload

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Mechanical ventilation has become a life-saving therapy in the treatment of patients wih impaired pulmonary function. However, the dark side of mechanical ventilation has also emerged with the development of ventilator induced lung injury[1], pneumonia, sepsis[2] and elevation of right ventricular (RV) afterload ultimately leading to a cor pulmonale[3;4].

The RV is very sensitive to changes in afterload[5]. It is anatomically adapted for generation of sustained low-pressure perfusion. RV contraction occurs in three phases as described by Mebazaa et al.[5]: contraction of the papillary muscles, the movement of the right ventricular wall towards the inter-ventricular septum followed by "wringing" of the RV by contraction of the left ventricle. Because of the compliant upper region of the RV, peak pressure is reduced and ejection is prolonged. Therefore, the normal RV is able to increase peak systolic pressure to approximately 60 mmHg before RV contractile failure and systemic hypotension occurs[6].

This review will discuss the influence of mechanical ventilation on RV afterload. First, how to measure RV afterload is discussed, thereafter the influence of mechanical ventilation on RV afterload and last the effect of ventilation according to the open lung concept (OLC) on RV afterload.

How to measure RV afterload

There is debate on measuring right ventricular afterload by means of a pulmonary artery catheter (PAC). The most used parameters obtained from a PAC which would estimate RV afterload are RV ejection fraction and pulmonary vascular resistance(PVR). Calculation of the pulmonary vascular resistance (PVR) is contro-

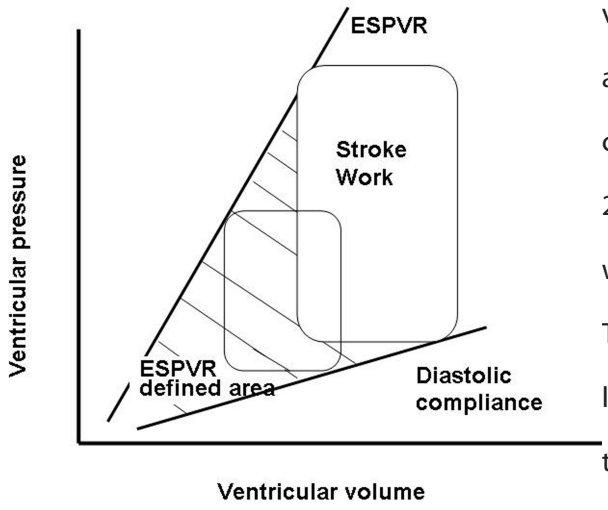

Fig 1. Ventricular pressure-volume diagram. The end-systolic pressure-volume relationship (ESPVR) is the relationship between the end-systolic pressure (upper right box) and volume during normal conditions and the end systolic pressure-volume during preload reduction (lower left box).

versial since Versprille published an editorial, explaining why calculation of PVR is meaningless, 20 years ago[7]. One year later, this was underscored by McGregor[8]. The main criticism of the calculation of PVR is the assumption that the vessels have rigid walls. Because of the recruitable nature of the pulmonary circulation, PVR has a variable relationship to the Poiseuille resistance. Therefore, since PVR cannot express oscillatory and kinetic power components, right ventricular power is underestimated by approximately 50%[9]. To assess pulmonary vascular resistance, Naeije[10] proposes to use a pressure-flow diagram. On the vertical axis the pressure drop through the pulmonary circulation (mean pulmonary artery pressure - wedge pressure) is displayed and on the horizontal axis cardiac index (CI). Changes in pressure drop through the pulmonary circulation and CI are compared with baseline values, indicating pulmonary vasoconstriction or dilatation. Whether this dynamic pressure-flow plot reflects the RV afterload adequately is yet not known.

There have been attempts to relate the end-systolic pressure-volume relationship (ESPVR) to ventricular afterload. The ESPVR is the relationship between each

end-systolic volume with the concomitant pressure while changing the preload. The ESPVR-defined area, (consisting of the ESPVR, end-systolic volume and diastolic compliance) plus the stroke work(Fig 1), is proportional to myocardial oxygen consumption[11]. It is conceivable that myocardial oxygen consumption, and thus ESPVR, is related to ventricular afterload, but also to contractility. Pinsky[12] hypothesized that contractility and afterload could be separated out by the ESPVR. Increases in contractility would increase the ESPVR slope, while changes in the afterload would covary end systolic pressure and volume, but along the line described by the ESPVR[12]. However, the relation between this co-variation of end-systolic pressure and volume along the ESPVR line and RV afterload has, to our knowledge, never been established.

Echo-Doppler measurements of the blood velocity and acceleration have been used as indices of ventricular afterload. For example, left ventricular afterload seems to be adequately reflected by acceleration of the aortic flow[13;14]. Acceleration of the aortic flow is reduced by afterloading[13] and increased by unloading[14]. Similarly, RV afterload could be assessed by measuring the acceleration of the pulmonary flow (Fig 2). Acceleration of the pulmonary flow has been successfully assessed in several papers studying heart-lung interactions during mechanical ventilation[15-17].

Right ventricular afterload during expiration

It has been shown that positive end-expiratory pressure (PEEP) affects RV afterload. Biondi et al.[18] have shown that the use of PEEP levels above 15 cm H_2O increased right ventricular (RV) volume and decreased elastance, indicating an increase in RV after-

load and a decline in RV contractility. Spackman and colleagues[19] have shown that during high frequency ventilation, mean airway pressure above 12 cm H_2O result in a decrease in the RV ejection fraction and is associated with an increase in the RV end-systolic volume. The authors attributed these findings to an increase in the RV afterload due to increased mean airway pressure. Dambrosio et al.[20] found that RV ejection fraction and the RV stroke work/RV end-diastolic volume ratio started to decrease at PEEP levels higher than 10 cm H_2O in acute respiratory failure patients. Schmitt et al.[15] used echo doppler data obtained by transoesophageal echocardiography to assess the effect of PEEP on the RV outflow impedance. In their study, use of high PEEP levels (13 ± 4 cm H_2O) caused an increased RV afterload. These studies show clearly that RV afterload is elevated during mechanical ventilation with high PEEP levels.

Two factors that may have a role in increasing the RV afterload during high PEEP ventilation are: direct compression of the pulmonary vascular bed and atelectasis. Atelectasis can increase the RV afterload by two mechanisms: 1) producing hypoxic pulmonary vasoconstriction[21-23] and 2) necessitating high tidal volume ventilation. This use of large tidal volumes increase RV outflow impedance as assessed by Doppler TEE[16]. Moreover, large tidal volume ventilation is more likely to occur in the presence of atelectasis because of the so-called baby-lung effect[24]: if one imagines a lung with 50% atelectasis, then a pre-set tidal volume of 10 ml/kg would result in a tidal volume of 20 ml/kg in aerated lung areas[24]. Therefore, atelectasis may cause an increase in the RV afterload due to: a) an increase in the tidal volume in aerated lung areas (baby-lung effect) b) hypoxic pulmonary vasoconstriction in non-aerated

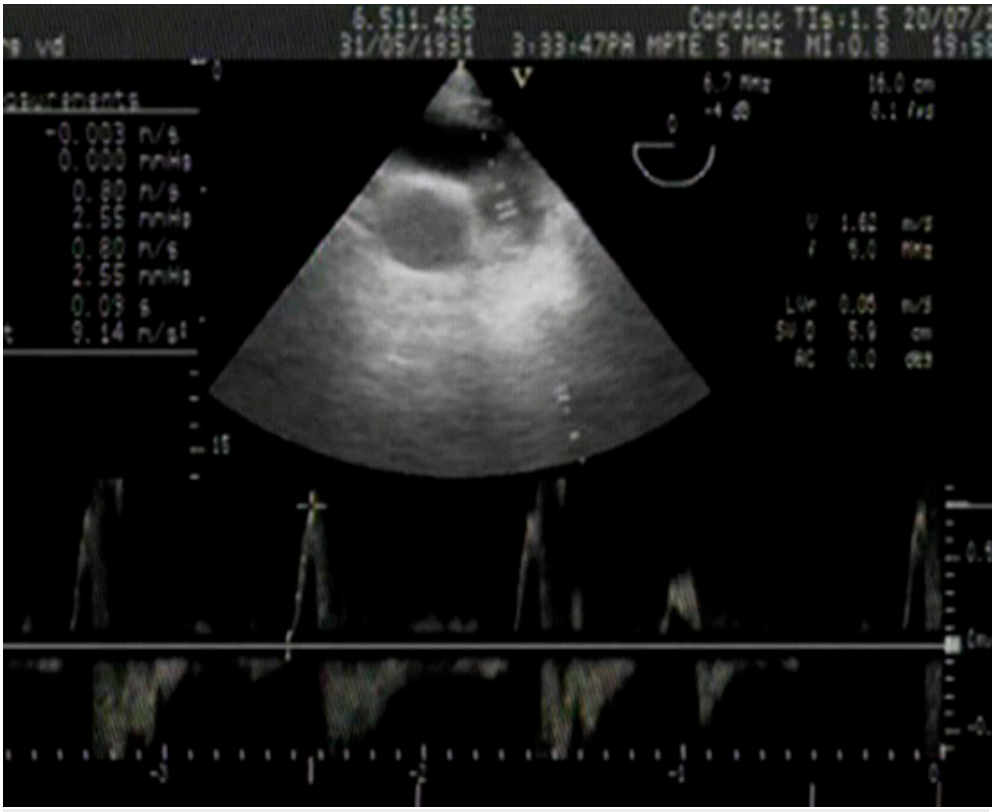

Figure 2, Echo-Doppler of the pulmonary artery. Bottom line represents airway pressure. Dotted line in the second beat indicates the acceleration of the pulmonary flow during inspiration.

lung areas. This atelectasis cannot be reversed with the use of high PEEP ventilation, only by the application of recruitment manoeuvres[25].

Right ventricular afterload during inspiration

RV afterload is not only increased by high PEEP levels; also during inspiration RV afterload increment is observed[16;26]. Poelaert et al.[26] showed that inspiration rather than expiration with high levels of PEEP caused RV afterload increment in cardiac surgery patients. Vieillard-Baron et al.[16] also showed that RV afterload is mainly increased during inspiration in patients with acute respiratory distress syndrome

(ARDS). These authors separated the effects of peak inspiratory pressure (PIP) and tidal volume by chest trapping and application of PEEP. They found that tidal volume, and not PIP or PEEP increased RV afterload. Although these results were very clear, theoretically this is hard to explain. Only intra-thoracic pressure, but not volume, generates a force which could compress pulmonary capillaries, increasing RV afterload. In addition, of course volume changes require pressure changes. The physiological explanation for the finding that tidal volume, not PIP, increases RV afterload is not known yet. However, this is more than a semantic discussion: if PIP and not tidal volume is to increase RV afterload, then elevated PEEP levels, should increase RV afterload because of the increased PIP.

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3

The effect of open lung ventilation on right and left ventricular function in lung-lavaged pigs

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Abstract:

INTRODUCTION: Ventilation according to the open lung concept (OLC) consists of recruitment maneuvers, followed by low tidal volume and high positive end-expiratory pressure (PEEP), aiming at minimizing atelectasis. Minimizing atelectasis reduces right ventricular (RV) afterload, but the increased intrathoracic pressures, used by OLC ventilation, could increase RV afterload. We hypothesized that when atelectasis is minimized by OLC ventilation, cardiac function is not affected despite the higher mean airway pressure.

METHODS: After repeated lung-lavage, each pig (n=10) was conventionally ventilated and ventilated according to OLC in a randomized cross-over setting. Conventional mechanical ventilation (CMV) consisted of volume-controlled ventilation with 5 cm H_2O of PEEP and tidal volume of 8-10 ml/kg. No recruitment maneuvers were performed. During OLC ventilation, recruitment maneuvers were applied until $PaO_2/FiO_2 > 60$ kPa. Peak inspiratory pressure was set to obtain a tidal volume of 6-8 ml/kg. Cardiac output (CO), right ventricular (RV) preload, contractility and afterload were measured with a volumetric pulmonary artery catheter. A high resolution computed tomography (CT)-scan measured whole lung density and left ventricular (LV) volumes.

RESULTS: RV end-systolic pressure-volume relationship, representing RV afterload, during steady-state OLC ventilation (OLC: 2.7$\pm$1.2 mmHg/ml) was not significantly different compared to CMV (3.6$\pm$2.5 mmHg/ml). Pulmonary vascular resistance (OLC 137$\pm$49 vs CMV 130$\pm$34 dynes.sec.cm^5) was comparable between groups. OLC led to a significantly lower amount of atelectasis

(13±2% of the lung area) compared to CMV (52±3% of the lung area). Atelectasis was not correlated to PVR or ESPVR.

LV contractility and afterload during OLC was not significantly different compared to CMV. Compared to baseline, LV end-diastolic volume (66±4 ml) decreased significantly during OLC (56±5 ml) ventilation and not during CMV (61±3 ml). Also, CO was significantly lower during OLC ventilation (OLC:4.1±0.3 l/min vs CMV 4.9±0.3 l/min).

CONCLUSION: In this experimental study, OLC resulted in significantly improved lung aeration. Despite the use of elevated airway pressures, no evidence was found for a negative effect of OLC on RV or LV afterload which might be associated with a loss of hypoxic pulmonary vasoconstriction due to alveolar recruitment. The reduction in CO and mean pulmonary artery pressure were consequences of a reduced preload.

The open lung concept (OLC) is a ventilation strategy intended to avoid atelectasis causing shear forces during repeated opening and closing of atelectatic lung areas[1;2]. This is achieved with a recruitment maneuver and application of sufficient positive end-expiratory pressure (PEEP) to counterbalance retractive forces. However, this strategy increases intrathoracic pressure, which could increase right ventricular (RV) afterload[3-7] and reduce safety.

Many studies (without recruiting the lung) show that elevated airway pressures increase RV afterload in patients with respiratory failure[3;6-8]. One reason for this increase in RV afterload is alveolar overdistention of aerated lung areas in the presence of atelectasis; another reason is the occurrence of hypoxic vasoconstriction in atelectatic lung areas, as shown in experimental studies by Duggan et al.[9] and Cramer et al.[10]. We have shown that avoiding atelectasis by application of OLC ventilation did not lead to an increased RV afterload in cardiac surgery patients, despite the use of increased airway pressures[11;12]. Data on RV afterload in these latter studies were obtained by means of a pulmonary artery catheter or use of echocardiography. These methods are often used for measuring RV afterload, but they have not yet been validated. In addition, in these latter studies, we were not able to assess atelectasis and therefore could not demonstrate a relationship between RV afterload and atelectasis.

Therefore we designed an experimental study, investigating RV afterload during OLC ventilation compared to a low airway pressure ventilation strategy allowing atelectasis. RV afterload is assessed by the load-independent[13] afterload marker end-systolic pressure volume relationship (ESPVR)[14-16]. The amount of atelec-

tasis was assessed with a multi-slice whole lung computed tomography (CT)-scan. As the influence of OLC during steady-state ventilation on left ventricular (LV) afterload is unknown, LV volumes were also measured during the whole cardiac cycle using this multi-slice CT-scan.

We hypothesized that when atelectasis is minimized by OLC ventilation, right and left ventricular afterload are not affected despite the use of higher mean airway pressures in an experimental lung injury model.

Methods

The study was approved by the institutional animal investigation committee and the care and handling of the animals were in accordance with the European Community guidelines. In 10 pigs, weighing 32±1.3 kg, anesthesia was induced with ketamine hydrochloride (35 mg/kg, i.m.) and midazolam (0.5 mg/kg, i.m.). The animals were tracheotomized, connected to a Servo ventilator 300 (Siemens-Elema, Solna, Sweden) and ventilated in a volume-controlled mode, with pure oxygen, at a rate of 20 breaths per minute, tidal volume 8 ml/kg, PEEP of 5 cm H_2O and an inspiratory/expiratory ratio of 1:2. Neuromuscular block was induced with pancuronium bromide (0.5 mg/kg i.v.) and anesthesia was maintained with a continuous infusion of fentanyl (20 µg/kg/h), midazolam (0.3 mg/kg/h) and pancuronium bromide (0.3 mg/kg/h).

After induction, an indwelling ParaTrend 7+ blood gas analyzer probe (Philips, Boblingen, Germany) was inserted in the carotid for continuous blood gas analyses.

An 8 Ch Foley catheter was inserted in the femoral vein. A correct position in the inferior caval vein was assured by CT-scan of the abdomen. To reduce cardiac preload, the Foley balloon was inflated with 5 ml water. One CCO 774HF75 series pulmonary artery catheter (PAC) (Edwards, Irvine, CA, USA) was inserted through the right internal jugular vein with the tip in the pulmonary artery (measuring pulmonary artery pressures) and another catheter was also inserted through the jugular vein with the tip in the right ventricle (measuring right ventricular pressures). Hemodynamic measurements consisted of right atrial pressure (RAP), right ventricular pressure, pulmonary arterial pressure, and pulmonary capillary wedge pressure (PCWP). Cardiac output (CO), RV end-diastolic volume (REDV) and REF were calculated using a Vigilence cardiac output computer (Edwards, Irvine, CA, USA), connected with the PAC catheter. From these values, PVR (mean pulmonary artery pressure minus PCWP divided by CO and multiplied by 79.9) and RV end systolic volume (RESV) were calculated. The end-systolic pressure-volume relationship (ESPVR) was considered in each animal. During each ventilation strategy, ESPVR was measured by calculating the slope of end-systolic pressure and volume obtained with and without inflation of the balloon on the Foley catheter in the inferior caval vein. RV stroke work (RVSW) was calculated by : 0.0136 x [mean pulmonary artery pressure –RAP] x stroke volume[14]. The preload recruitable stroke work (PRSW) was considered in each animal during each ventilation strategy as the slope of RVSW and REDV obtained with and without inflation of the balloon on the Foley catheter in the inferior caval vein. Systemic vascular resistance (SVR) was calculated by subtracking right atrial pressure (RAP) from mean arterial pressure (MAP) divided by CO multiplied by 79.9.

After instrumentation, respiratory failure was induced by repeated saline lavage (50 ml/kg; 37 °C) as described by Lachmann et al.[17]. Lavages were repeated at 3-minute intervals until PaO_2 was below 13 kPa.

To minimize the effect of confounding variables, conventional and OLC ventilation were applied in a cross-over design. The order of the applied ventilation strategies was randomized by sealed envelopes. Ten minutes after the last lung lavage, the first ventilation strategy was started. Before each ventilation strategy, the ventilation was disconnected for 15 seconds, which has been shown to result in an immediate lung collapse[18] and substantiated by the CT measurements. Conventional mechanical ventilation (CMV) was started with volume control ventilation at the following settings: tidal volume of 8-10 mL/kg, PEEP of 5 cm H_2O, I/E ratio of 1:2; FiO_2 was set at 1.0 and respiratory rate was adjusted to achieve a $PaCO_2$ between 4.5 and 5.5 kPa.

Ventilation according to the OLC was started by switching the ventilator to a pressure-controlled mode with a respiratory frequency of 40/min. FiO_2 was set at 1.0, PEEP of 10 cm H_2O, I/E ratio of 1:1 and a driving pressure to obtain a tidal volume of 6-8 mL/kg aiming at a $PaCO_2$ of 4.5 and 5.5 kPa. A lung recruitment maneuver was performed by increasing peak inspiratory pressure (PIP) to 40 cm H_2O during 10 s in order to increase the PaO_2/FiO_2 ratio to a value greater than 60 kPa. If this value was not reached, a recruitment maneuver was repeated by adding 5 cm H_2O to the previous PIP, up to a maximum PIP of 60 cm H_2O. If the PaO_2/FiO_2 ratio decreased slowly below 60 kPa after recruitment indicating renewed lung collapse, PEEP was increased with 2 cm H_2O and the recruitment maneuver (again beginning at 40

cm H_2O) was repeated. If PaO_2/FiO_2 ratio decreased below 60 kPa during the study period, PEEP was not increased but a new recruitment maneuver was performed.

All measurements were performed once before lung lavage (= baseline), and twice after lung lavage during each ventilation strategy. Following lung lavage, one CT scan of the thorax was made to confirm lung collapse. During both ventilation strategies, measurements were done once without balloon inflation of the Foley catheter in the inferior caval vein and once with inflation (5 ml saline) of the balloon of the Foley catheter.

Fluid management during the study was based on the REDV provided by the PAC. REDV before lung lavage was considered as the optimal REDV. After lung lavage, (and a REDV below optimal) REDV was treated with starch colloids (Voluven®). During inflation of the Foley balloon, a decrease of REDV was not treated.

The CT scan protocol was performed using a State-of-the-Art 64-slice Sensation 64 CT scanner (Siemens Medical Solutions, Forchheim, Germany) with 0.4mm voxel size and 330ms gantry rotation time. Each scan was performed twice: first with a standard protocol for thoracic imaging (standard scan) and then with a dedicated software able to synchronize the reconstructed image with cardiac phase (ECG gated scan)[19]. The scan parameters were: number of slices 64/rotation, individual detector width 0.6mm, effective spatial resolution 0.4^3mm, 120 kilovolt, 120 milliAmpere/second (900mAs for the ECG gated scan), feed/rotation 58mm/pitch: 1 (11.52mm/pitch: 0.2 for the ECG gated scan), effective reconstructed slice thickness 0.6mm, reconstruction increment 0.4mm. The standard scan was reconstructed as a volumetric data set and a slice every 20 mm starting at the apex of the thorax was

selected for the analysis. For the assessment of the left ventricle a short-axis multiphasic reconstruction was performed dividing the cardiac cycle (using as reference points two R waves) in 10 phases and the left ventricle in 8 levels[20]. The standard thoracic scan was used to analyze the lung parenchyma by means of dedicated PulmoCT software (Siemens Medical Solutions, Forchheim, Germany). The ECG gated scan and the left ventricle were analyzed with a dedicated ARGUS software platform (Siemens Medical Solutions, Forchheim, Germany).

CT data analysis was performed in all cases by an experienced radiologist. For the lung parenchyma evaluation we used 3 main ranges of attenuation (measured in Hounsfield Units: HU) representing the usual location of tissues in the HU spectrum: –1000 HU to –600 HU as good aerated lung tissue (voxels with a prevalent content of air); –600 HU to –200 HU as poorly aerated lung tissue (mostly voxels with air and with some soft tissues or fluid); –200 HU to +200 HU as non-aerated lung tissue (mostly voxels with a mixture of fat, fluid and soft tissues). The operator segmented in a semi-automatic mode the lung parenchyma of the right and lung slice by slice (usually between 10 and 14 slices depending on the phase of the experiment and on the size of the animal's lung). The results were expressed as percentages of each sub-range of attenuation as compared to the total lung area.

For evaluation of the left ventricle, the endocardial contours were semi-automatically detected by the operator on the images reconstructed on the short axis. The 8 levels throughout the left ventricle allowed a volumetric interpolation of the whole left myocardium allowing calculation of the end-systolic volume and of the end-diastolic volume.

Table 1, Hemodynamic data at baseline and during conventional and open lung ventilation

	Baseline	CMV	OLC
HR (beats/min)	105±5	86±5*	94±5
MAP (mmHg)	93±4	104±4*	80±4#*
RAP (mmHg)	4.2±1	5.9±1*	8.1±2*
CO (l/min)	5.3±0.3	4.9±0.3	4.1±0.3#*
REDV (ml)	165±11	173±13	148±13
RESV	112±10	119±11	103±11
PAsys (mmHg)	30±3	31±3	28±2
PAmean (mmHg)	17±3	20±2	17±2#
PCWP (mmHg)	9.3±2	12.1±3	12.5±2*
REF (%)	33.1±1.7	33.1±1.7	31.1±1.9
PVR (dynes sec cm^5)	126±38	130±34	137±49
LEDV (ml)	66±4	61±3	56±5*
SVR (dynes sec cm^5)	1379±120	1693±139*	1508±124
LEF (ml)	49.5±1.6	53.2±2.1	43.2±5.6

CMV= Conventional mechanical ventilation, OLC= Open lung ventilation, HR= Heart rate, MAP= mean arterial pressure, RAP= right atrial pressure, CO= cardiac output, RESV= Right ventricular end-systolic volume, REDV= Right ventricular end-diastolic volume, PAsys= Systolic pulmonary pressure, PAmean= Mean pulmonary arterial pressure, PCWP= pulmonary capillary wedge pressure, REF= Right ventricular ejection fraction, PVR= pulmonary vascular resistance, LEDV= left ventricular end-diastolic volume, SVR= systemic vascular resistance, LEF= Left ventricular ejection fraction. # $p<0.05$ OLC vs CMV, * $p<0.05$ vs baseline

Statistics

Between group differences for hemodynamic parameters were tested with a paired, two-sided Student's *t*-test. Results are presented as mean ± SEM. A relationship between end-systolic pressure and volume was calculated for each pig and these regression coefficients were then averaged. The relationship between RV afterload and lung aeration was calculated by the Pearson's correlation coefficient.

Results

Hemodynamic data are given in Table 1. In summary, mean pulmonary artery pressure, cardiac output, mean arterial pressure (MAP) were higher during CMV compared to OLC ventilation.

Table 2,Ventilatory measurements at baseline and during conventional and open lung ventilation

	Baseline	CMV	OLC
PEEPtot (cm H_2O)	5±0.4	6±0.3	14±0.6*#
PIP (cm H_2O)	20±0.5	28±1#	26±0.4#
Vt (ml)	271+5	270±6	240±11*#
PaO_2/FiO_2 (kPa)	60±5	13±2	72±2*
HU -1000 to -600 (%)	51±3	10±2#	29±3*#
HU -600 to -200 (%)	29±2	36±2	57±3*#
HU -200 to 200 (%)	20±2	52±3#	13±2*

PEEPtot= intrinsic + extrinsic positive end-expiratory pressure, PIP= Peak inspiratory pressure, Vt= Tidal volume, HU= Houndsfield units, expressed in % of the lung area. * p<0.05 vs CMV, # p<0.05 vs baseline.

As indicators of RV afterload, regression coefficient between systolic pulmonary pressure and RV end-systolic volume were comparable between the two ventilation strategies (Table 1). Within the applied fluid management, the dynamic pressure-flow diagram (Fig 1) showed a significantly lower cardiac output during OLC (Table 1) but the pressure drop through the pulmonary circulation (PAmean minus PCWP pressure) was not significantly higher during OLC ventilation (OLC 6.0±2.3 vs CMV: 7.4±2.5 mmHg). Also PVR was comparable between the two groups (Table 1).

In the right ventricle, contractility during OLC was not significantly different compared to CMV. The regression coefficient of the ESPVR was comparable between groups (OLC 2.7±1.2 mmHg/ml vs CMV 3.6±2.5, Fig 2). The regression coefficient of the PRSW was also not different between groups (OLC 0.07±0.07, CMV 0.24±0.16 g.m./

Table 3. Correlation between lung aeration and indicators of right ventricular afterload.

r^2	Good aerated	Poorly aerated	Non-Aerated
PVR	0.7	-0.1	-0.7
CO	-0.2	-0.2	-0.2
PAmean-PCWP	0.2	-0.1	-0.7

r^2 = correlation coefficient, PVR= pulmonary vascular resistance, CO= cardiac output, PAmean-pulmonary capillary wedge pressure (PCWP)= pressure drop through the pulmonary circulation. Good aerated lung tissue was defined as Houndsfield Units between -1000 and -600, poorly aerated between -600 and -200, non-aerated between -200 and 200. None of the correlations was significant.

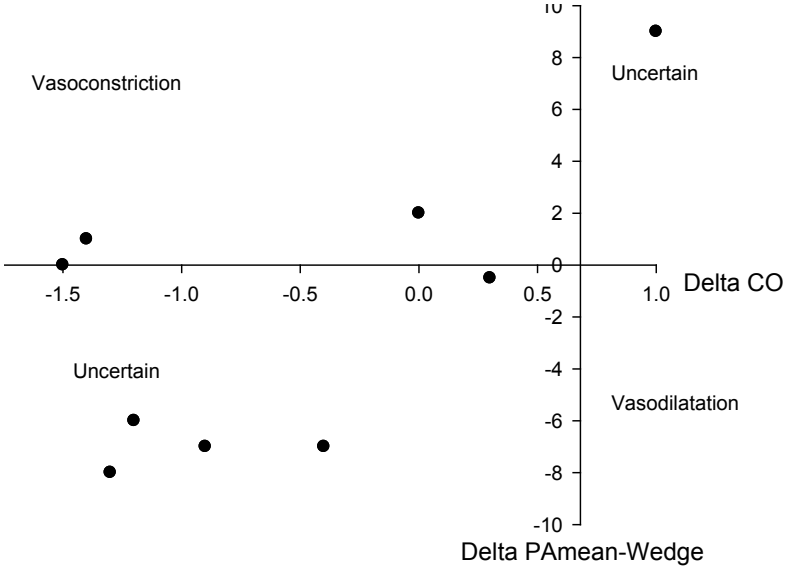

Fig 1, Dynamic pressure-flow plot. The effect of OLC on flow and pressure drop through the pulmonary circulation is displayed compared with conventional ventilation. On the vertical axis, change of pressure drop through the pulmonary circulation is displayed (PAmean-pulmonary capillary wedge pressure during OLC minus PAmean-pulmonary capillary wedge pressure during CMV). On the horizontal axis, change of cardiac output (CO) is displayed. PAmean= mean pulmonary artery pressure. OLC= Open lung Concept, CMV= Conventional mechanical ventilation.

beat.m^2.ml, p=0.36). REF was also not different between the two groups (Table 1).

In the left ventricle, contractility during OLC was not significantly different compared to CMV. The regression coefficient of the ESPVR was comparable between the groups (OLC 43±26, CMV 61±30 mmHg/ml). Left ventricular ejection fraction (LEF) was also not different between the two groups (Table 1). SVR, reflecting LV afterload, tended to be lower during OLC ventilation compared with the CMV (p=0.056) (Table 1).

Considering the aeration of the lungs (Fig 3), during OLC, 13±2% of the lung was atelectatic whereas in the CMV group significantly more lung tissue was atelectatic (52±3% with a HU density between -200 and 200) (Table 2). Also the amount of poorly aerated lung tissue (HU –600 to -200) was significantly higher in the OLC compared to the CMV (Table 2). The amount of good aerated lung tissue (HU -1000 to -600) was also higher in the OLC group compared to CMV (Table 2). However, OLC

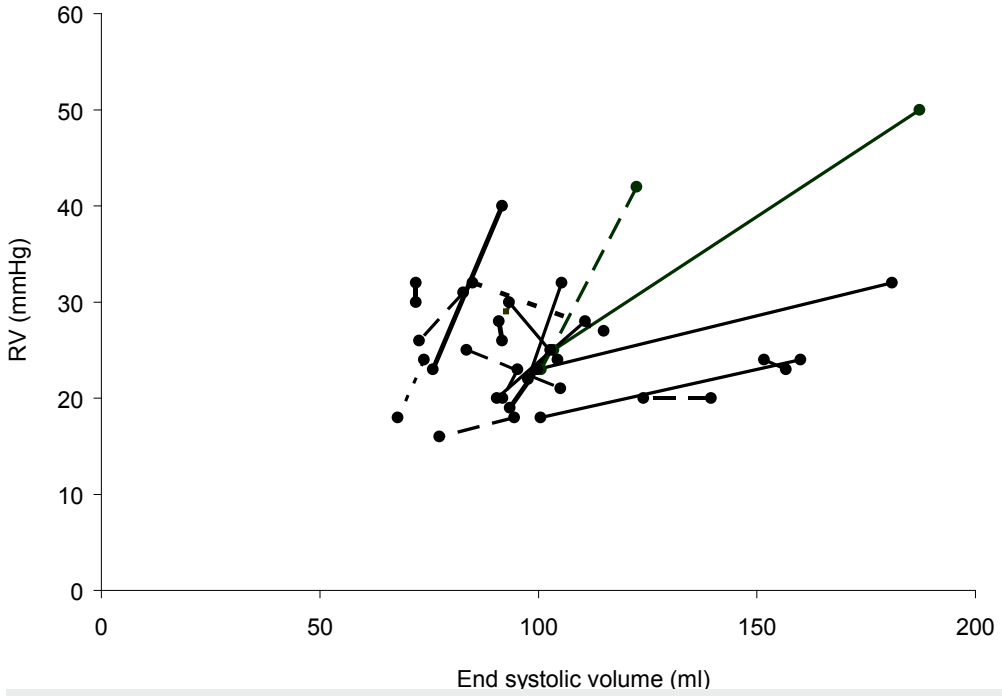

Fig 2. End-systolic pressure-volume relationship. RV= systolic right ventricular pressure. On the vertical axis right ventricular end-systolic right ventricular pressure is displayed. On the horixontal axis right ventricular end-systolic volume is displayed. End-systolic pressure, and volume with and without balloon inflation, is connected with a straight line for conventional mechanical ventilation and the interrupted line for open lung ventilation.

ventilation could not restore the area of good aerated lung tissue to baseline values (Table 2).

There was no significant correlation between PVR, CO and pressure drop through the pulmonary circulation with the amount of lung aeration (Table 3).

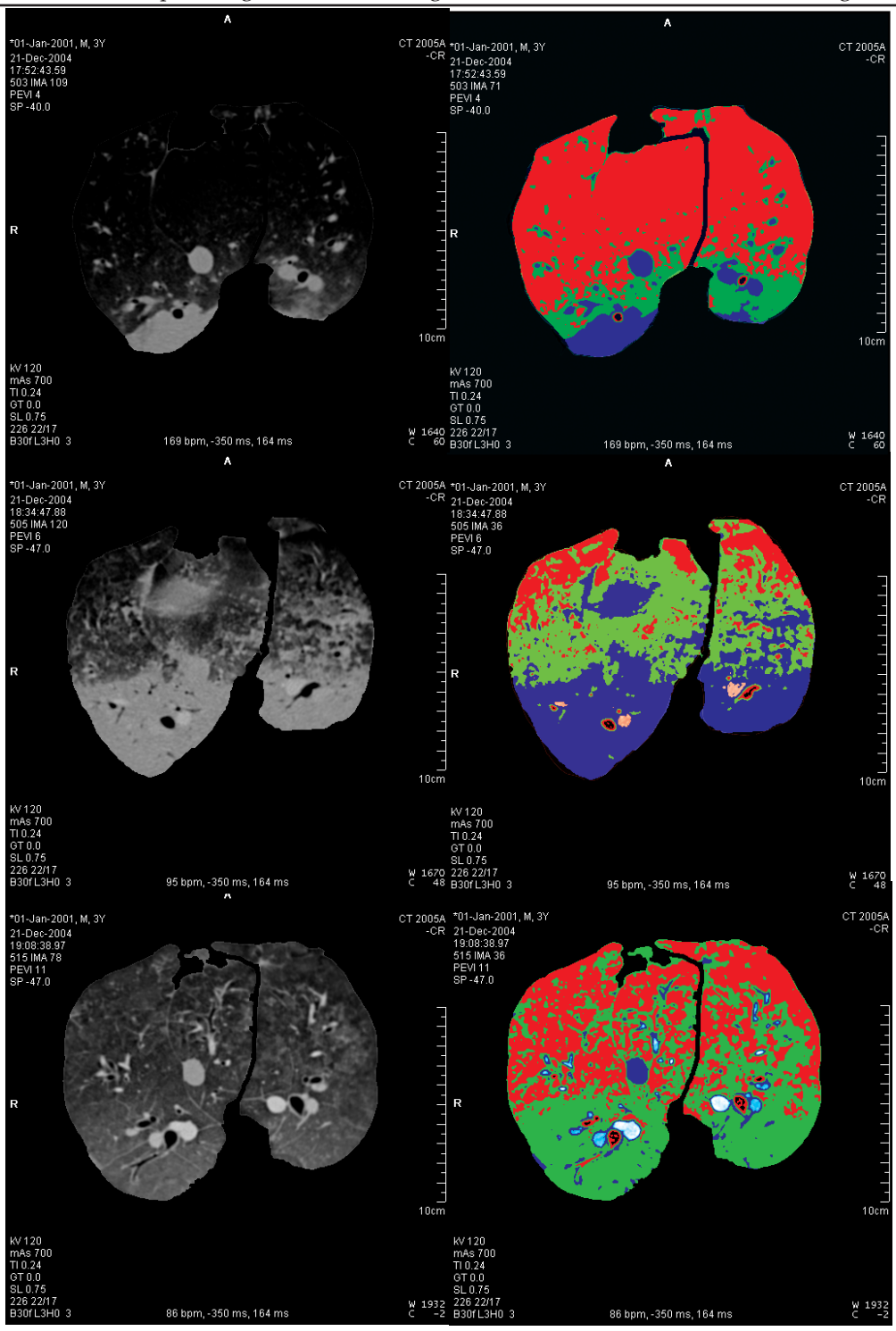

Fig 3. CT-scan examples of basal lung areas during expiration. Upper 2 scans are during baseline, before lung lavage. Middle 2 scans are CMV ventilation after lung lavage, lower 2 scans are during OLC ventilation after lung lavage. Good aerated lung areas (HU -1000 to -600) are coded red in the right-hand scans, poorly aerated areas (HU -600 to -200) are coded green, and non-aerated lung areas (HU -200 to 200) are coded blue.

Discussion

In this experimental study, the amount of atelectatic lung area was not correlated with parameters of RV afterload. OLC ventilation significantly increased the PaO_2/FiO_2 ratio and significantly reduced atelectasis compared to CMV. Indicators of RV afterload or contractility were not affected by the chosen ventilation strategy. Indicators of left ventricular afterload and contractility were also not different between the different ventilation strategies.

This study showed that ventilation according to the OLC effectively reduced atelectasis. These findings are in agreement with results of Tusman et al.[21] and Amato and colleagues[22] who found that atelectasis is greatly reduced during OLC ventilation in children and in ADRS patients. However, the present study also shows that there is still a small portion of non-aerated lung tissue during OLC ventilation. This is probably explained by the impossibility to exclude all (small) lung vasculature from lung density measurements. This falsely increases the amount of non-aerated lung tissue since lung vasculature has the same density as non-aerated lung tissue. This effect could be pronounced with this very high resolution CT technique, also measuring very small pulmonary vessels. Therefore we think that the amount of non-aerated lung tissue is negligible when considering the effect of OLC ventilation on RV contractility and afterload.

It is unlikely that OLC ventilation caused alveolar overdistention. During OLC, the lung was less aerated compared with baseline. In some studies[23-25], overdistention (or emphysema) is characterized by Houndsfield units (HU) ranging from –1000 HU to –900HU. However, the limit between air and tissue in the lungs is arbi-

trary because the spatial resolution dramatically affects the capability of the scanner to distinguish on axial slices a voxel with air from a fluid/solid one. Even with very high spatial resolution, as is the case in the present study (0.4^3mm is the highest available resolution for volumetric CT scanning), the distal part of the airways are too thin for this imaging modality. The borders of aerated lungs have recently been described as lower than –500 HU[25] while the limit for soft tissues is higher than –380 HU[26]. Therefore we decided to have three homogenous ranges of 400 HU each starting at –1000 HU and ending at +200 HU.

In the present study, ESPVR, indicating RV afterload, was not correlated with atelectasis. This relationship was described by Duggan and colleagues[9] and Creamer et al.[10] who showed experimentally that atelectasis causes a significant increase in RV afterload. This effect of atelectasis on RV afterload during mechanical ventilation could be explained by two mechanisms: 1) overdistention in aerated lung areas[27;28] and 2) local hypoxic pulmonary vasoconstriction in non-aerated lung areas[29]. In the present study, we found no correlation between atelectasis and indicators of RV afterload. The effect of avoiding atelectasis (and thereby reducing hypoxic pulmonary vasoconstriction) by means of OLC ventilation on RV afterload is probably counterbalanced by the effect of a high intrathoracic pressure.

RV afterload was not increased by the application of OLC ventilation. Mean arterial pulmonary pressure was even significantly decreased during OLC ventilation, suggesting a decreased RV afterload. However, this was not consistent with other parameters of RV afterload. This decreased PAmean might be explained by a decreased preload during OLC ventilation. During OLC ventilation, CO decreased

together with a decreased LV end diastolic volume, indicating a decreased preload. ESPVR is a load-independent afterload marker, and did not suggest a decreased RV afterload during OLC ventilation. We therefore think it is more prudent to state that RV afterload is unchanged during OLC ventilation. Pulmonary vascular resistance (PVR) is one of the parameters which indicate that RV afterload is unchanged during OLC ventilation. However, PVR as an indicator of RV afterload is heavily criticized[30]. Naeije[31] therefore proposed to use a pressure-flow diagram. On the vertical axis the pressure drop through the pulmonary circulation (PAmean minus PCWP) is displayed and on the horizontal axis CO. Changes in "PAmean minus PCWP" and CO (the latter is also preload and contractility dependent) are compared with baseline values, indicating pulmonary vasoconstriction or dilatation. Despite the reduction of CO during OLC ventilation, "PAmean minus PCWP" did not change, suggesting that RV afterload was not changed during OLC ventilation. Another parameter reflecting ventricular afterload was proposed by Pinsky using the end-systolic pressure-volume relationship (ESPVR)[14]. When afterload varies while contractility is unaltered as shown by the ESPVR, then end systolic pressure and volume varies, but along the line described by the ESPVR. End-systolic pressure and volume did not differ significantly between the two ventilation strategies. Therefore, in the case that RV contractility is not changed, RV afterload is not affected by OLC ventilation. RV contractility was comparable between both ventilation strategies. Ventricular contractility was assessed by the slope of the ESPVR and by the slope of the preload recruitable stroke work (PRSW)[32-34]. Both parameters adequately reflect contractility[13;32-34] and seem generally to be considered to be preload inde-

pendent[13-16]. In addition, ESPVR even correlated with myocardial oxygen consumption[35]. The slopes of both parameters were comparable, indicating an unchanged RV contractility during OLC ventilation. As RV contractility did not change, parameters for RV afterload were not affected by RV contractility and we therefore conclude that RV afterload was not increased by application of OLC.

OLC also did not affect LV contractility and tended to decrease LV afterload. ESPVR, representing LV contractility was not influenced by the applied ventilation strategy. Systemic vascular resistance (SVR), representing LV afterload, even tended to decrease during OLC ventilation. However, cardiac output and subsequently MAP did decrease during OLC ventilation. Cardiac output is preload, contractility and afterload dependent[14]. Indicators of LV preload left ventricular end-diastolic volume (LEDV), contractility and afterload did not change significantly during OLC ventilation compared to CMV. However, LEDV was significantly lower during OLC ventilation compared to baseline whereas LEDV during CMV was comparable with baseline. Therefore, we assume that a decrease of cardiac output during OLC ventilation is primarily attributable to a preload effect. This hypothesis is supported by Wise et al.[36] and Fellahi et al.[37] who found no change of LV contractility during PEEP increment in patients with normal LV function[37].

Conclusion

In this experimental study, OLC resulted in significantly improved lung aeration. Despite the use of elevated airway pressures, no evidence was found for a negative effect of OLC on right or left ventricular afterload which might be associated with a

loss of hypoxic pulmonary vasoconstriction due to alveolar recruitment. The reduction in cardiac output and mean pulmonary artery pressure were consequences of a reduced preload.

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4

The open lung concept: effects on right ventricular afterload after cardiac surgery

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Abstract

BACKGROUND: The open lung concept (OLC) is a method of ventilation to keep expiratory lung volume increased by increased airway pressure, which might increase right ventricular afterload. We investigated the effect this method on right ventricular afterload in patients after cardiac surgery.

METHODS: We studied 24 stable patients after coronary artery surgery and/or valve surgery with cardiopulmonary bypass. Patients were randomly assigned to OLC or conventional mechanical ventilation (CMV). In the OLC group, recruitment manoeuvres were applied until PaO_2/F_IO_2 >50 kPa was achieved (reflecting an open lung) and maintained by sufficient positive airway pressure (PEEP). In the CMV group, volume-controlled ventilation was used with a PEEP of 5 cm H_2O.

Cardiac index (CI), right ventricular preload, contractility and afterload were measured with a pulmonary artery thermodilution catheter during the 3-hour observation period. Blood gases were monitored continuously.

RESULTS: To achieve PaO_2/ F_IO_2 >50 kPa, 5.3$\pm$3 recruitment attempts were performed with a peak pressure of 45.5$\pm$2 cmH_2O. To keep the lung open, PEEP of 17.$\pm$3 cm H_2O was required. Compared with baseline, pulmonary vascular resistance and right ventricular ejection fraction did not change significantly during the observation period in either group.

CONCLUSION: No evidence was found that ventilation according to the OLC affects right ventricular afterload.

The open lung concept (OLC) is a method of ventilation to reduce shear forces caused by repeated opening and closing of atelectatic lung tissue[1;2]. This is done with a recruitment manoeuvre and application of sufficient positive end-expiratory pressure (PEEP) to counterbalance retractive forces, and ventilation with the smallest possible pressure amplitude to prevent lung overdistention[3]. However, this strategy causes increased intrathoracic pressure, which may impair right ventricular afterload, possibly limiting the safety of this ventilation strategy.

Coronary bypass grafting (CABG) can be complicated by pulmonary dysfunction[4] or by reduced right ventricular function[5], so that patients could be vulnerable to increased right ventricular afterload. However, Dyhr and colleagues[6] found that a lung recruitment manoeuvre followed by PEEP did not reduce cardiac output in volume-loaded patients after CABG. However, an increased right ventricular afterload may have been offset by an increase in end diastolic volume, since other effects of PEEP on cardiac output can be offset by preload augmentation[7-9].

We set out to study the effect of ventilation according to the OLC on right ventricular afterload in patients ventilated after CABG and/or valve surgery.

Methods

The study was approved by the local Human Ethics Research Committee and written informed consent was given by each patient. We prospectively studied 24 stable patients who had undergone CABG and/or valve surgery with use of cardiopulmonary bypass (CPB). The patients we studied often need prolonged ventilatory

support after cardiac surgery because of co-morbidity and/or extensive surgery. We exclude patients with severe airways obstruction (forced expired volume in 1 sec or vital capacity below 2 times the standard deviation of predicted value) or those who required re-operation within the first 72 hours (as blood loss requiring re-operation could cause tamponade and affect the circulation).

Preoperative risk factors were scored with the European System for Cardiac Operative Risk Evaluation (Euroscore), a scoring system to predict mortality in cardiac surgery patients, and is expressed in percentage[10].

Anaesthesia was induced with midazolam (0.1 mg kg^{-1}) i.v. and sufentanil (2 µg kg^{-1}). Muscle relaxation was achieved with pancuronium (0.1-0.2 mg kg^{-1}) and was not reversed. Administration of enoximone (0.5 mg kg^{-1}) (effective for 3-6 hours) was used routinely to reduce myocardial stunning after CPB. After induction of anaesthesia a pulmonary artery catheter (CCO 774HF75 series, Edwards, Irvine, CA, USA) was inserted through the right internal jugular vein. Anaesthesia was maintained with midazolam (0.1 mg kg^{-1}) and sufentanil (1 mcg kg^{-1}) as needed. None of the patients received corticosteroids. During operation the lungs were ventilated with the following settings: volume control mode, tidal volume 6-8 ml kg^{-1}, PEEP 5 cm H_2O, I/E ratio 1:2, F_IO_2 0.35-0.50, and respiratory rate was adjusted to achieve a $PaCO_2$ between 4.5 and 6.5 kPa. These settings were called conventional mechanical ventilation (CMV). During CPB the lungs were not ventilated. After CPB lungs were re-expanded by manual inflation and ventilation was continued with the same settings until randomization. After surgery the pericardium was not closed. After sternum closure patients were given iv fluids until left ventricular function did not increase

further. Left ventricular function was assessed by transesophageal echocardiogram used by an experienced operator, who assessed fractional area change on the transgastric midpapillary short-axis view. At optimal left ventricular function, right ventricular end volume index (EDVI) measured by the pulmonary artery catheter was defined as optimal EDVI.

After surgery, patients were sedated with propofol 2-4 mg kg^{-1} h^{-1}. An indwelling bloodgas analyzer probe was inserted in the a. radialis for continuous bloodgas analyses (ParaTrend 7+, Philips, Boblingen, Germany). Fluid management was guided by EDVI, aiming at optimal EDVI as assessed during operation. Hypovolemia was treated with a set plan using starch colloids. When a maximum daily dosage is reached, pasteurized plasma is used. If mean arterial pressure was less than 45 mmHg, not caused by hypovolemia, dobutamine or phenylephrine was started iv.

Cardiovascular and respiratory measurements were made every 30 min for 3 h. Measurements before randomization were considered baseline measurements. Patients were randomly assigned by envelope to the OLC group or CMV group. Randomization was not stratified for type of operation. The study group was ventilated according to the OLC and in the CMV group ventilation was continued as described above.

Ventilation according to the OLC was initiated by switching the ventilator to pressure control mode, PEEP of 10 cm H_2O, F_IO_2 0.35-0.40, I/E ratio of 1:1 and a pressure to obtain a tidal volume of 4 to 6 ml kg^{-1} aiming at a $PaCO_2$ of 4.5 to 6.5 kPa. A respiratory frequency of 40 min^{-1} was chosen to achieve a good CO_2 elimination with a low tidal volume. A lung recruitment manoeuvre was applied by increas-

Table 1 Characteristics of the groups

Characteristics	OLC (n=10)	CMV (n=10)
Age (yr)	66.3±6.9	57.5±16.3
Weight (kg)	78.7±17.6	78.5±10.2
Male/Female	6/4	9/1
CABG	6	4
Valve repairs or replacement	5	9
Euroscore (%)*	2.5±2	2.0±0.9
P_aO_2 (kPa)	10.5±1.8	10.7±1.7
Operation time (h)	5.49±0.59	5.41±0.49
Aortic clamp time (min)	76.2±25.6	102.0±39.1
Temperature at baseline (°C)	35.0±0.48	34.8±0.56
FEV_1 (%)	101±13	93±12
FVC (%)	102+16	93+10

* The euroscore is expressed in median (1st quartile). CABG= Coronary artery bypass graft, FEV1= Forced expired volume in 1 sec, expressed as percentage of normal value, FVC= Forced expired vital capacity, expressed as percentage of value.

ing peak pressure to 40 cm H_2O for 40 to increase the PaO_2/F_IO_2 ratio greater than 50 kPa. If not, a recruitment manoeuvre was repeated by increasing peak pressure 5 cm H_2O greater than before, up to a maximum peak pressure of 60 cm H_2O until the P_aO_2/F_IO_2 ratio became greater than 50 kPa. If the P_aO_2/F_IO_2 ratio decreased slowly below 50 kPa after recruitment, PEEP was increased by 2 cm H_2O and a recruitment manoeuvre (beginning at 40 cm H_2O) was repeated.

Cardiovascular measurements consisted of right atrial pressure (RAP), mean pulmonary arterial pressure (PAmean), and pulmonary capillary wedge pressure (PCWP). A cardiac output computer (Vigilence, Edwards, Irvine, CA, USA), connected to the pulmonary artery catheter and the monitor recorded heart rate and calculated cardiac index (CI), EDVI and right ventricular ejection fraction (REF). From these values pulmonary vascular resistance (PVR) was calculated.

After the 3-hour study period and if temperature and cardiovascular measurements were satisfactory, sedation was stopped and the patients were weaned from ventilation. Data on outcome were not obtained in this study.

Statistics

To adjust for differences between patients, the changes from baseline measurements were calculated and used to compare the two groups.

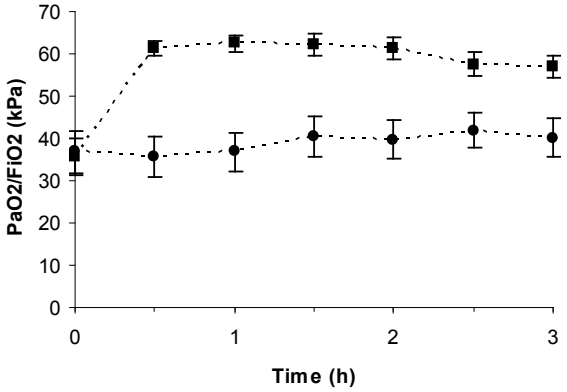

Fig 1 Changes in PaO_2/FiO_2 ratio with time. Baseline values are given at t=0. Closed squares = open lung ventilation, closed circles = conventional mechanical ventilation. Mean±SEM.

Blood gas and cardiovascular measurements, as changes from baseline, were compared using analysis of variance (ANOVA) for repeated measurements (PROC MIXED procedures from SAS[11]).

Characteristics of the patients were analyzed using the Student's t-test and the Fisher's exact test. Results are presented as means±SD unless otherwise stated. *P*- values given are two-sided, and a *P*-value below 0.05 was considered significant.

Results

We enrolled 24 patients in the study; however, because four patients were excluded retrospectively data of 20 patients were analyzed. Three patients had to be re-operated and were excluded: one in the CMV group where re-operation occurred within 2 hours, and two in the OLC group where re-operation occurred at 3 and 7 hours. One other patient (OLC) was excluded because the continuous blood gas ana-

Table 2 Cardiovascular measurements at baseline and during the study.

Parameter		Baseline	30 min	60 min	90 min	120 min	150 min	180 min	Mean change from baseline
HR (min-1)	OLC	82±13	84±10	82±10	84±10	82±13	89±16	89±16	2±3
	CMV	90±10	89±6	90±10	92±6	95±10	94±13	94±13	3±3
MAP (mmHg)	OLC	78±9	81±11	79±14	75±8	81±13	86±12	83±12	2±6
	CMV	76±13	77±10	83±13	81±10	82±13	80±10	78±10	4±6
CI (l min-1 m-2)	OLC	2.7±0.5	2.4±0.4	2.6±0.4	2.6±0.5	2.8±0.5	2.7±0.5	3.0±0.6	0.0±0.3
	CMV	3.2±1.0	3.2±0.7	3.2±0.6	3.3±0.7	3.4±0.8	3.6±0.7	3.6±0.7	0.3±0.3
REF (%)	OLC	37±14	29±6	34±9	31±6	37±10	36±10	41±13	-1.5±7.9
	CMV	33±10	35±11	34±13	34±13	33±11	38±12	34±11	1.1±7.6
PVR (dynes. cm.m2)	OLC	149±40	167±35	160±37	154±47	151±56	147±55	141±32	2.0±41
	CMV	125±87	146±82	138±68	118±47	122±51	128±51	109±47	0.9±41
RAP (mmHg)	OLC	10±2	14±2	14±3	14±4	15±3	15±3	17±7	5.1±3†
	CMV	9±3	9±2	10±2	10±2	10±3	10±3	10±3	0.6±3‡
PAmean (mmHg)	OLC	19±2	24±3	24±3	24±5	25±4	26±5	27±8	5.2±4†
	CMV	19±5	20±5	21±6	21±5	21±5	21±4	20±3	2.0±4
PCWP (mmHg)	OLC	10±2	14±3	14±3	15±2	15±5	17±6	18±8	6.0±4†
	CMV	10±3	10±2	11±3	11±3	11±4	10±4	11±3	0.8±4‡
EDVI (ml.m-2)	OLC	93±21	95±18	95±15	102±17	97±12	90±5	87±19	-1.5±8
	CMV	107±22	112±21	111±26	118±32	122±30	110±21	117±27	1.1±8

† $P<0.05$ different from zero, ‡$p<0.05$ difference OLC vs CMV. HR= Heart rate, MAP= Mean arterial pressure, CI= cardiac index, REF= right ventricular ejection fraction, PVR= Pulmonary vascular resistance, PCWP= pulmonary capillary wedge pressure, RAP= Right atrial pressure, EDVI= right ventricular end diastolic volume index.

lyzer failed. No myocardial infarction or pneumothorax occurred.

The Euroscore was slightly greater in the OLC group than in the CMV group. In the OLC group more patients were operated for CABG. Other baseline characteristics were comparable between both groups (Table 1). In the CMV group, two patients required a higher F_IO_2 to maintain PaO_2 greater than 10 kPa. In the OLC group, 5.3±3 recruitment attempts were made with a mean peak pressure

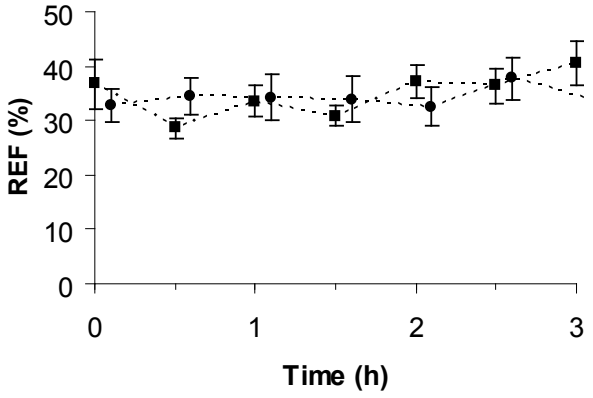

Fig 2 Changes in right ventricular ejection fraction (REF) with time. Baseline values are given at t=0. Closed squares = open lung ventilation, closed circles = conventional mechanical venilation.

Table 3 Data on respiratory parameters during the study

		Baseline	30 min	60 min	90 min	120 min	150 min	180 min
$PaCO_2$	OLC	4.5±0.3	4.8±0.5	4.7±0.4	4.8±0.5	4.7±0.5	4.9±0.8	4.9±0.8
(kPa)	CMV	5.1±0.7	4.8±0.5	5.0±0.5	5.0±0.5	5.0±0.3	5.0±0.3	5.0±0.3
Ppeak	OLC	21.8±3	25.3±5	25.2±5	25.3±4	24.5±4	25.6±4	24.4±4
(cmH_20)	CMV	21.9±4	22.1±3	22.0±4	22.5±4	21.7±5	21.9±4	21.0±4
dP	OLC	17±3	8±2	9±3	10±4	9±3	10±4	9±2
(cmH_2O)	CMV	17±4	17±3	17±4	17±4	17±4	17±4	16±4
PEEPtot	OLC	4.9±0.4	18.1±3.7	18.6±2.7	16.6±2.0	16.7±2.6	16.0±2.6	15.4±1.7
(cmH_20)	CMV	4.9±0.3	5.1±0.3	5.2±0.6	5.2±0.6	5.2±0.6	5.0±0.0	5.0±0.0
Resp rate	OLC	12±1	41±13	45±16	45±15	43±14	45±14	43±11
(min^{-1})	CMV	11±0.7	11±0.7	11±0.8	11±0.8	11±0.8	11±0.8	11±0.7
MV	OLC	7.6±1	14±5	14±4	15±4	15±4	14±3	14±2
(l/min)	CMV	8±0	7±2	8±0	7±1	7±1	7±1	7±3

Ppeak= peak pressure, PEEPtot=external PEEP+intrinsic PEEP,Resp rate= respiratory rate, dP= Driving pressure (Ppeak-PEEPtot), MV=minute ventilation

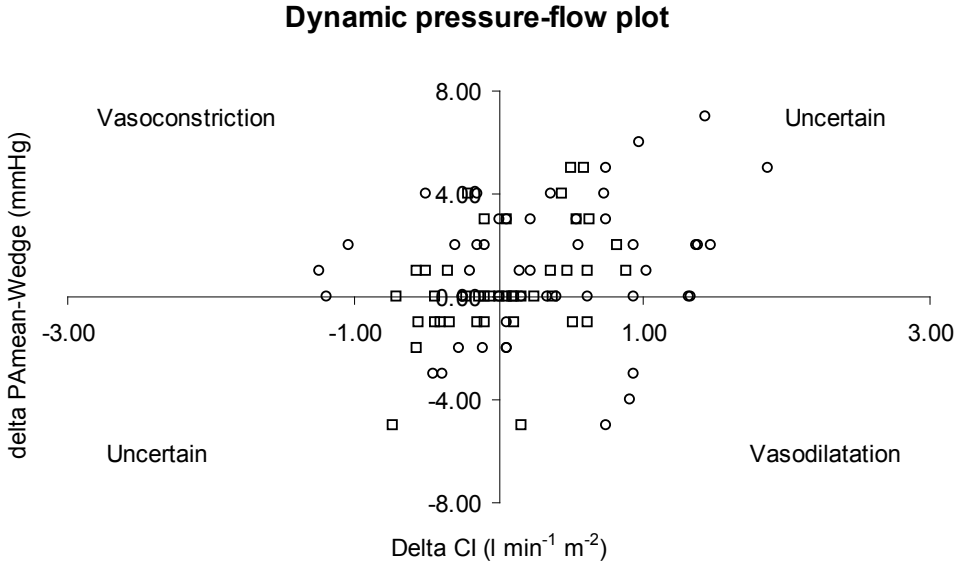

Fig 3 Dynamic pressure–flow diagram indicating changes in pulmonary vascular resistance. Baseline values of CI and the pressure decrease through the pulmonary circulation are placed at the intersection of the axes. Measurements at 60, 90, 120, 150 and 180 min are plotted as differences from baseline for each patient. Open squares= open lung ventilation, open circles= conventional ventilation.

of 45.5±2 cm H_2O to open the lung (Fig. 1). To keep the lung open, a total PEEP of 17.0±2.7 cm H_2O had to be applied in the OLC group.

Compared with baseline REF (Fig. 2), CI and PVR did not differ between groups at any time (Table 2). In the OLC group PAmean and PCWP increased significantly during treatment compared to baseline(Table 2). The increase of PCWP, not of PAmean, was in the OLC group significantly greater than in the CMV group(Table 2). The difference between baseline and treatment period in the decrease in pressure through the pulmonary circulation (PAmean-PCWP) was not significant between groups (Fig 3).

Tidal volume in the OLC group was 4.5±2 ml kg^{-1} while $PaCO_2$ remained in the target range (4.5 to 6.5 kPa). This resulted in comparable peak inspiratory pres-

sures between both groups despite the high PEEP levels in the OLC group (Table 3).

There was no significant difference in fluid balance (fluid administrated minus fluid loss) between the groups during the 3-hour study period (OLC: 230±635 ml $hour^{-1}$ vs CMV: 11±413 ml $hour^{-1}$). In each group, 5 patients received phenylephrine (0.4 mcg kg^{-1} min^{-1}) and 2 patients received dobutamine.

Discussion

We found that increased PEEP following lung recruitment did not significantly affect PVR or REF in patients after cardiac surgery. Because baseline values were different, we analysed changes from baseline. These baseline differences are probably because of differences in the patients' characteristics. These differences may perhaps be explained by a chance difference in patient severity, preoperatively; the OLC group tended to have a slight greater predicted mortality (Euroscore). Factors that could affect the hemodynamic parameters, for instance dobutamine, phenylephrine, propofol and enoximone were used in both groups comparably. Because of the long operating times, the effect of enoximone would be almost over when the patients were studied.

To study the effects of ventilation on right ventricular performance, cardiac function is best considered in processes that affect right ventricular preload, afterload and contractility[12].

Efforts were made to maintain right ventricular preload constant. Fluid management was not based on wedge pressure, because this varied with intratho-

racic pressure, but on the right ventricular EDVI. Compared with baseline, EDVI was comparable between the groups suggesting comparable right ventricular preload. However, cardiac output is dependent on right as well as left ventricular preload. Since the ventricles share a common interventricular septum and are housed in a common pericardial sac which limits their volume, right ventricular EDVI will affect left ventricle EDVI[12]. In particular, increased PEEP can restrict left ventricular filling by leftward displacement of the interventricular septum[13]. However, ventricular interdependency can be ruled out in our patients because the pericardial sac was not closed after surgery, and therefore could not limit ventricular volume.

Right ventricular afterload is difficult to assess, since the variables that would be used are not easy to measure and do not only depend on afterload. Commonly used measures of afterload are PVR and REF.

PVR is often criticized because the calculation of resistance assumes that the vessels have rigid walles. Because the pulmonary vessels can collapse their pressure-flow relationship is not linear, and a linear relationship is only likely when left atrial pressure equals or is greater than pleural pressure (West zone 3). To assess pulmonary vascular resistance, Naeije[14] suggests a pressure-flow diagram (Fig. 3). The pressure decrease across the pulmonary circulation is displayed on the vertical axis and cardiac index on the horizontal axis. If changes in this plot are compared with baseline values, then pulmonary vasoconstriction or dilatation may be inferred.

REF is inversely related to right ventricular afterload. In the present study, REF did not differ between groups, suggesting that the OLC treatment did not affect afterload.

Our findings contrast with previous clinical studies, in which afterload was greater when PEEP was greater[15-19]. In these studies, however, greater PEEP was used without a recruitment manoeuvre, so that atelectasis would persist[20]. Experimentally, atelectasis can increase right ventricular afterload, causing right ventricular failure in the longer term[21]. Thus, a greater PEEP without recruitment may increase right ventricular afterload by effects on: atelectatic lung regions, or by overdistending healthy lung parts[22]. Recruitment manoeuvres, could re-expand atelectatic regions and if combined with low tidal volumes, this would reduce increment in the right ventricular afterload during ventilation with elevated PEEP. In healthy, un-intubated volunteers without atelectasis, 12.5 cm H_2O PEEP did not increase right ventricular afterload[23], supporting our results. The open lung concept advocates recruitment manoeuvres followed by elevated PEEP levels as well as low driving pressures, resulting in low tidal volumes[3].

We found no evidence of increased right ventricular afterload during ventilation according to the OLC in patients after cardiac surgery. The question remains whether these results can be generalized to patients with an intact pericardium, and this question warrants further investigation.

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5

Open lung ventilation does not increase right ventricular afterload: an echo-Doppler study

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Abstract

OBJECTIVE: Ventilation according to the open lung concept (OLC) consists of recruitment maneuvers, followed by low tidal volume and elevated positive end-expiratory pressure (PEEP). Elevated PEEP is associated with an increased right ventricular (RV) afterload. We investigated the effect of OLC ventilation on RV outflow impedance during inspiration and expiration in patients after cardiac surgery using transesophageal echo-Doppler.

DESIGN: A prospective, single center cross-over randomized controlled clinical study.

SETTING: Cardiothoracic intensive care unit (ICU) of a university hospital.

PATIENTS: Twenty eight patients scheduled for elective cardiac surgery with cardiopulmonary bypass.

INTERVENTIONS: In the intensive care unit, each patient was ventilated for approximately 30 minutes according to both OLC and conventional ventilation (CV). During OLC ventilation, recruitment maneuvers were applied until $PaO_2/FiO_2 > 375$ Torr (50 kPa); during CV no recruitment maneuvers were performed.

MEASUREMENTS: Transesophageal echo-Doppler measurements were performed at end-inspiration and end-expiration in a steady state condition, 20 minutes after initiation of a ventilation strategy. Mean Acceleration (Ac_{mean}) of flow was determined in the long axis of the pulmonary artery in a transverse axis view.

RESULTS: During OLC ventilation, a total PEEP of 14±4 cm H_2O was applied vs. 5 cm H_2O during CV. Ac_{mean} during expiration was comparable between groups. During

inspiration, OLC ventilation did not cause a decrease of Ac_{mean} compared to expiration, whereas this did occur during CV.

CONCLUSIONS: Despite the use of elevated PEEP levels, ventilation according to OLC does not change RV outflow impedance during expiration and decreases RV outflow impedance during inspiration.

Mechanical ventilation using elevated positive end-expiratory pressure (PEEP) is especially known to increase right ventricular afterload (RV)[1-3]. Several studies demonstrated that 15 cm H_2O of PEEP increased RV afterload[4;5], but did not affect RV contractility[6]. This might be explained by overdistention of aerated lung areas in the presence of atelectatic lung areas. In this regard, ventilation according to the open lung concept (OLC) has been introduced to avoid atelectasis[7]. This is achieved by short periods of high inspiratory pressures to open up collapsed alveoli followed by elevated levels of PEEP to keep the alveoli open. While maintaining the lung open, the lowest possible pressure amplitude is used, in order to minimize overdistention.

Recently, we showed that this ventilation strategy had several beneficial effects[8] and did not affect pulmonary vascular resistance or right ventricular ejection fraction, assessed with a pulmonary artery catheter (PAC)[9]. In this latter study, however, these volumetric measurements obtained with the PAC were averaged over 5 minutes. Therefore, the separate effects of PEEP and tidal volume on RV afterload during OLC ventilation remained unknown.

As RV afterload was not affected by OLC ventilation measured with PAC[9], we hypothesized that OLC ventilation does not affect RV afterload during the entire respiratory cycle. From echocardiographic studies, it is shown that elevated PEEP leads to elevate RV outflow impedance mainly during inspiration[2], and less during expiration[10;11]. We therefore conducted a study assessing RV outflow impedance by the echo-Doppler flow signal in the pulmonary artery during OLC ventilation and we compared this to conventional ventilation. Doppler echocardiography allows beat-

to-beat measurements, allowing inspiratory and expiratory measurements of the right ventricular impedance[2;10;12].

Methods

The local Human Ethics Research Committee approved this study and each patient gave written informed consent. We prospectively enrolled 28 patients scheduled for cardiac surgery with use of cardiopulmonary bypass (CPB) using a median sternotomy, without suspicion of pulmonary hypertension (assessed by preoperative echocardiography) or severe airway obstruction (forced expired volume in 1 sec or vital capacity in the predicted normal range, taken as predicted value ± 2 SD). Patient characteristics are given in Table 1.

Anesthesia was induced with midazolam (0.1 mg kg^{-1}) i.v. and sufentanil (2 µg kg^{-1}). Pancuronium was given only at induction of anesthesia to facilitate endotracheal intubation (0.1-0.2 mg kg^{-1}). During operation, the lungs were ventilated in pressure control mode with a respiratory frequency adjusted to maintain $PaCO_2$ between 34 and 49 Torr (4.5 and 6.5 kPa), tidal volume 8-10 ml/kg (ideal body weight), I/E ratio 1:1 and PEEP of 5 cm H_2O. FiO_2 was adjusted to achieve a PaO_2 of 75-98 Torr (10-13 kPa). The pericardium was not closed. After surgery, patients were sedated with midazolam 0.05-0.1 mg kg^{-1} h^{-1} and analgesia was achieved with morphine 5-10 mcg kg^{-1} h^{-1}. Patients did not receive inhaled nitric oxide or phosphodiesterase inhibitors.

Thirty minutes after arrival in the ICU, each ventilation strategy was applied once on each patient in a cross-over design to minimize the effect of confounding

variables. The order of the applied ventilation strategies was randomized by sealed envelopes. Each ventilation strategy commenced after disconnection from the ventilator for 15 seconds, which has been shown to result in an immediate lung collapse[13]. Each ventilation strategy was maintained for 30 min. Conventional Ventilation (CV) was started with volume control ventilation at the following settings: tidal volume of 8 mL/kg (ideal body weight), PEEP of 5 cm H_2O, I/E ratio of 1:2; FiO_2 was set to achieve a PaO_2 between 75 and 98 Torr (10-13 kPa) and respiratory rate was adjusted to achieve a $PaCO_2$ between 34 and 49 Torr (4.5-6.5 kPa).

Ventilation according to the OLC was started by switching the ventilator to a pressure controlled mode with a respiratory frequency of 40/min. FiO_2 was set to achieve a PaO_2 between 75 and 98 Torr (10-13 kPa), PEEP of 10 cm H_2O, I/E ratio of 1:1 and a driving pressure to obtain a tidal volume of 4-6 mL/kg aiming at a $PaCO_2$ of 34 and 49 Torr (4.5-6.5 kPa). A lung recruitment maneuver was performed by increasing peak inspiratory pressure (PIP) to 40 cm H_2O during 15 s in order to increase the PaO_2/FiO_2 ratio to a value greater than 375 Torr (50 kPa), as this mimics an open lung[14;15]. If this value was not reached, a recruitment maneuver was repeated by adding 5 cm H_2O to the previous PIP, up to a maximum PIP of 60 cm H_2O. If the PaO_2/FiO_2 ratio decreased slowly below 375 Torr (50 kPa) after recruitment, PEEP was increased with 2 cm H_2O and the recruitment maneuver (beginning at 40 cm H_2O) was repeated. If PaO_2/FiO_2 ratio decreased below 375 Torr (50 kPa) after an (accidental) disconnection, PEEP was not increased and a new recruitment maneuver was performed.

Echo-Doppler studies were performed by one investigator with a System Five Ultrasound (GE Vingmed, Holten, Norway) with a KN100062, 5 MHz trans-

Table 1 Patient characteristics

Age (years)		64±11
Male/Female		16/12
Weight (kg)		76±16
BMI (kg/m^2)		26±4
FEV1 (% predicted)		92±19
FVC (% predicted)		92±15
OR	CABG	12
	CABG±Valve	3
	AVR	5
	MVR	3
	MVP	2
	ASD	1
	MAZE	1
	Extirpation myxoma	1
Aortic clamp time (min)		95±41

FEV1 = forced expired volume in 1 sec, BMI= Body mass index, FVC= forced vital capacity, CABG= coronary artery bypass graft, AVR= aortic valve replacement, MVR= mitral valve replacement, MVP= mitral valvuloplasty, ASD= atrium septum defect repair, MAZE= atrial compartmentalization.

esophageal probe (GE Medical, Holten, Norway). Airway pressure was measured at the end of the endotracheal tube and the signal was displayed on the electrocardiogram channel of the echo device. During both ventilation strategies, echo-Doppler was performed after 20 minutes of steady state ventilation. End-expiratory images, defined as the last beat before inspiration, and end-inspiratory images, defined as the last beat before expiration, were stored electronically and on video tape. All images were reviewed by a cardiologist. Measurements were performed off-line by one investigator in triplicate and averaged.

RV outflow impedance was assessed by the mean acceleration (Ac_{mean}) of the pulmonary artery flow, measured with the ultrasound beam parallel to the long axis of the main pulmonary artery. The Doppler sample volume was placed beyond the pulmonary valve in the midlumen of the main pulmonary artery to record the pulmonary artery flow (Fig.1). The pulsed Doppler spectrum was measured at a high sweep speed of 100 mm/s. Ac_{mean} was calculated by dividing the peak velocity (V_{max}) by the acceleration time (AcT) (Fig.1). We also measured the velocity time

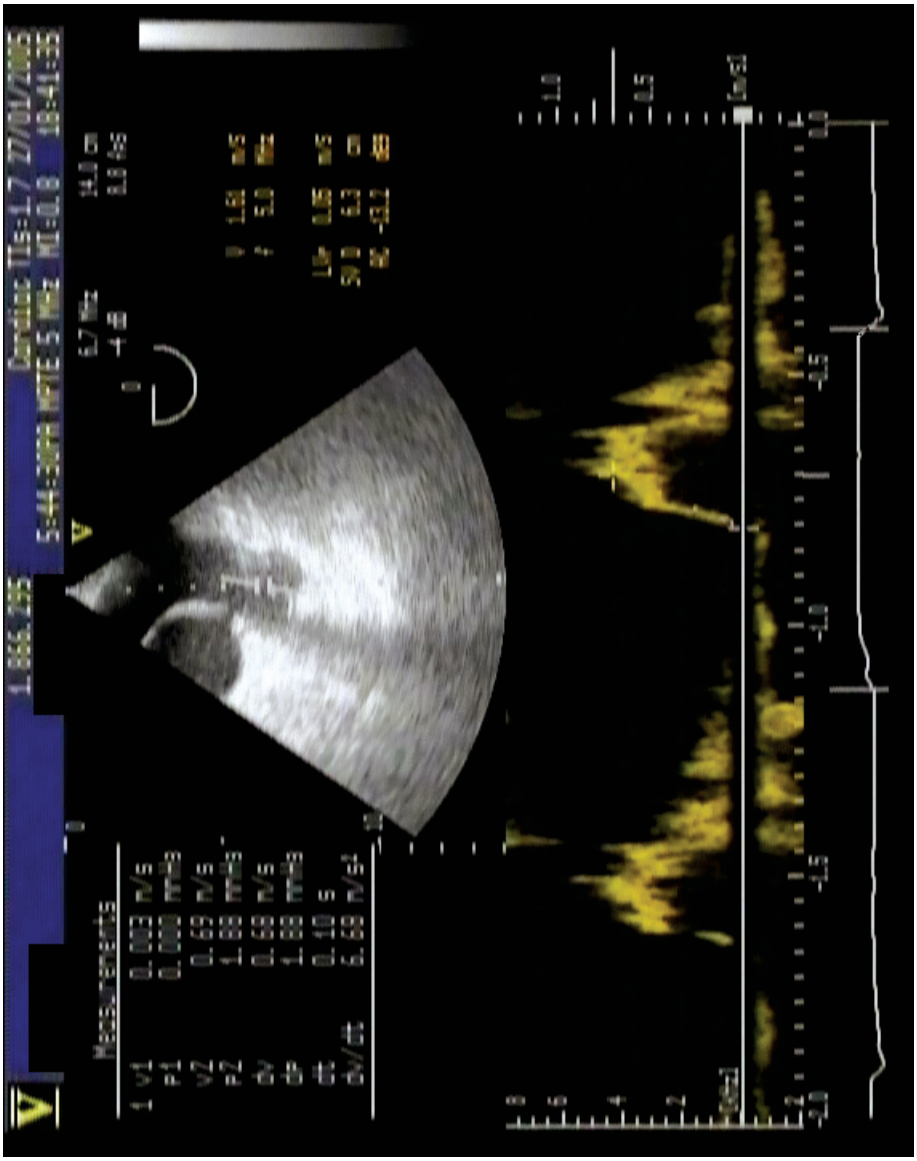

Fig. 1. Example of mean acceleration measurement of the pulmonary artery on high-speed Doppler recording. The bottom line represents airway pressure. The measured beat on the right is during inspiration.

integral (VTI), which is the area under the flow curve of the pulmonary artery and which reflects the stroke volume. The superior vena cava (SVC) was examined in a long- and short axis view. The maximal diameter during inspiration and expiration was measured in the short axis view using M-mode.

Fluid management during the study was guided by the collapsibility of the SVC. The SVC collapsibility index (VCI) was calculated as: diameter of the SVC during expiration minus diameter of the SVC during inspiration divided by diameter of the SVC during expiration times 100. A VCI greater than 20% was taken to indicate hypovolemia[16;17]. Hypovolemia was treated with starch colloids (Voluven®) with a bolus of 250 ml. Thereafter, measurement of the VCI was repeated until the VCI was less than 20%.

Cardiovascular and respiratory measurements were made just before acquiring the echocardiographic images. After finishing acquiring the echocardiographic images, patients were conventionally ventilated. Patients were weaned according to the local protocol, which is briefly described in a previous study[8].

Statistics

This randomized clinical trial was designed to detect a 25% difference in mean acceleration of the Doppler flow signal in the pulmonary artery between OLC ventilation and CV during expiration. Under the assumption that the standard deviation of the mean acceleration is about 3.4 m/s^2 [10], power analysis established that a sample size of 28 patients would have 80% power of detecting a difference of the mean accel-

Table 2, main results

		Mean (n=28)		OLC 1st strategy (n=14)		OLC 2nd strategy (n=14)	
		Exp	Insp	Exp	Insp	Exp	Insp
Ac_{mean}	OLC	9.6±2.2	10.0±2.9*	9.5±2.5	10.6±3.6*†	9.8±1.9	9.4±2.0
	CV	10.2±3.3	8.6±2.9†	10.3±4.4	8.5±3.2†	10.0±1.9	8.7±2.8†
VTI	OLC	15.1±3.9	15.4±4.1	14.1±4.1	14.8±4.5	16.1±3.7	15.9±3.6
	CV	16.1±4.0	15.1±4.2†	15.4±4.3	14.5±4.7	16.9±3.7	15.7±3.8†
AcT	OLC	0.08±.003*	0.08±0.03*	0.08±0.02*	0.08±0.03*	0.09±0.03	
	CV	0.10±0.02	0.10±.002	0.09±0.02	0.1±0.02	0.1±0.02	0.1±0.02
Vmax	OLC	0.80±0.22	0.76±0.19†	0.76±0.2*	0.74±0.2†	0.84±0.2	0.79±0.2
	CV	0.84±0.20	0.80±0.25	0.80±0.2	0.79±0.3	0.87±.2	0.82±0.3
HR	OLC	87±13		85±13		88±14	
	CV	85±12		85±14		86±10	
MAP	OLC	80±13		76±10		85±14	
	CV	82±11		83±12		81±9	
RAP	OLC	14±3*		13.6±2.5		14±3*	
	CV	11±3		11.6±17		11±4	
RR	OLC	38±4		38±4		38±4	
	CV	13±1		13±1		13±1	
Vt/kg	OLC	5.1±0.9		5.1±1.0		5.1±0.8	
	CV	8.4±1.1		8.3±1.1		8.6±1.1	
PIP	OLC	25±3*		26±4		24±4	
Pplat	CV	17±3		18±3		17±4	
Pmap	OLC	18.5±2.3*		19.0±2.4*		17.8±2.3	
	CV	10.4±2.2		10.8±2.6		9.6±1.5	
PEEPext	OLC	12±2* (3±1)*		13±2* (3±1)*		12±2* (3±2)*	
(int)							
	CV	5±0 (0±0)		5±0		5±0	
Crs	OLC	38±10		35±10		40±10	
	CV	34±6		33±5		35±7	
PaO_2/FiO_2	OLC	422±62* (56±8)*		408±66* (54±9)*		437±58 (58±8)*	
	CV	343±97* (45±12)		342±83 (45±11)		358±106 (48±14)	
$PaCO_2$	OLC	(38±6) 5.0±0.7		39±6 (5.2±0.8)		36±4 (4.9±0.6)	
	CV	(38±5) 5.1±0.8		39±6 (5.2±0.9)		37±5 (4.9±0.7)	

Table 2. OLC= Open lung concept, CV= conventional mechanical ventilation. Insp= end inspiratory, Exp= end expiratory. Acmean= Mean acceleration (m/s2), VTI= Velocity time integral (cm), AcT= acceleration time (s), Vmax= Maximal flow velocity (m/s). HR= heart rate (beats/min), MAP= mean arterial pressure (mmHg), RAP= right atrial pressure (mmHg). RR= respiratory rate (min-1). Vt/kg= tidal volume divided by ideal body weight (ml/kg), PIP= end-inspiratory pressure (cmH2O). For the OLC group (pressure controlled ventilation), this was the peak inspiratory pressure, for the CV group (volume controlled ventilation), this was the plateau pressure (Pplat, cm H2O). Pmap= mean airway pressure (cm H2O). PEEPext= PEEP, (in parenthesis intrinsic PEEP (cm H2O). Crs= Compliance respiratory system (ml/cm H2O). PaO2/FiO2 ratio is the PaO2 divided by fractional FiO2 (Torr, in parenthesis kPa). PaCO2 expressed in Torr (kPa) * $p<0.05$ OLC vs CV, † $p<0.05$ Insp vs Exp.

eration in the pulmonary artery of 25% at a significance level of $\alpha < 0.05$ between the two groups.

Between groups differences for hemodynamic parameters were tested with a paired Student *t*-test. Results are presented as mean ± SD.

Results

Patient characteristics are displayed in Table 1. Ten patients were on ß-blockade pre-operatively. During OLC ventilation, 2.0±1.3 recruitment maneuvers were applied to open the lung, with a mean PIP of 45±5 cm H_2O. A PEEP of 14±4 cm H_2O was used to keep the lung open. Other respiratory data are given in Table 2. All patients had a regular rhythm (either sinus or sequential atrio-ventricular pacing) and no pulmonary valve regurgitation. Three patients had trivial tricuspid regurgitation and five patients had mild tricuspid regurgitation. Tricuspid regurgitation was not

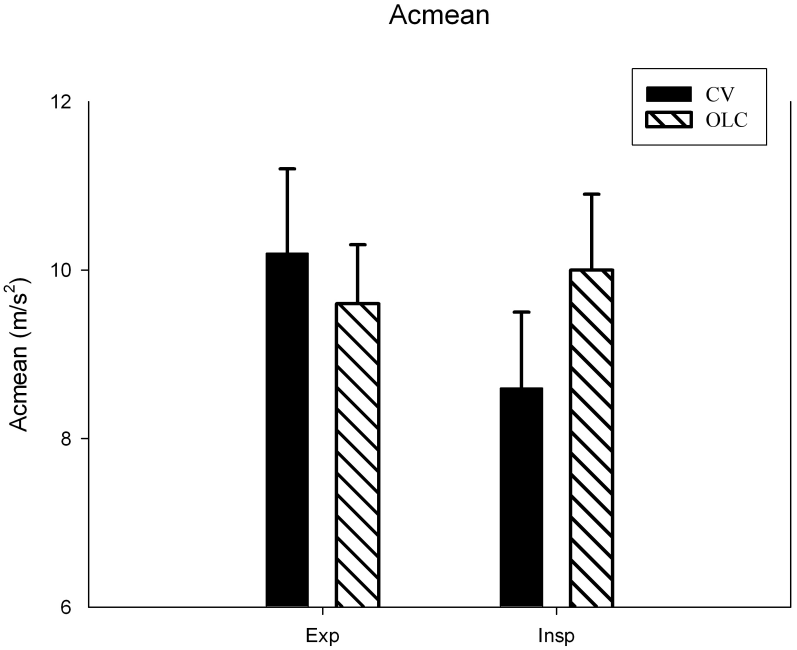

Fig 2, Acmean= mean acceleration of the pulmonary flow, high value reflects low RV afterload. CV= conventional mechanical ventilation, OLC= Open lung concept. Exp= expiration, Insp= inspiration, * p<0.05 vs CV, # p<0.05 vs exp.

affected by the ventilation strategy in any patient. No patient required re-operation within the first 72 hours.

Ac_{mean} during expiration was comparable between both ventilation strategies. Inspiration did not cause a significant decrease in Ac_{mean} compared to expiration during OLC ventilation but did do so during CV (Fig 2). Ac_{mean} during inspiration was significantly lower during CV compared to OLC ventilation.

During CV, VTI showed a significant difference between inspiration and expiration, but not during OLC (Table 2). There were no significant differences in any parameter when OLC as first strategy was compared to OLC as second strategy (Table 2).

Heart rate, mean arterial pressure and right atrial pressure were comparable between both ventilation strategies (Table 2). Throughout the entire study period, 9 patients received dobutamine (4.3±1.5 µg/kg/min) which was combined with phenylephrine in 2 patients (0.15±0.07 µg/kg/min). No changes in any drugs dosages occurred during the study period. During OLC ventilation, 2 patients received a total of 3 fluid boluses and during CV, 4 patients received a total of 6 fluid boluses.

One patient developed subcutaneous emphysema, six hours after concluding the study, due to obstruction of the chest tube. Air leakage from the chest tube was present before initiation of the study and was not increased by recruitment maneuvers.

Discussion

This study shows that a elevated PEEP during open lung concept (OLC) ventilation did not affect Ac_{mean} during expiration in cardiac surgery patients. Furthermore, inspiration did not change Ac_{mean} during OLC ventilation compared to expiration, whereas this did occur during CV.

In this study, mean acceleration of the pulmonary flow is used as marker of right ventricular outflow impedance. This impedance reflects ventricular afterload, which is defined as the ventricular wall tension during systole. The tension in the ventricular wall that the sarcomeres must overcome to shorten is not only related to the transmural pressure during systole, but also to the cavity size through the Laplace relation. However, obtaining reproducible right ventricular cavity diameters using echocardiographic measurements is difficult. Aortic or pulmonary impedance have also been used to measure accurately afterload. The impedance is the pressure divided by the flow at that instant, so that this index of the afterload varies at each stage of the contraction cycle. Factors reducing flow, such as a high arterial pressure or outlet valve stenosis or loss of arterial compliance, will increase impedance and hence the afterload. An approximation can be made by using echocardiography to determine the blood flow at any instant during systole. Therefore, an average value for the impedance can be calculated by dividing the maximum velocity by the time from the onset of flow until the peak velocity is reached, the so-called mean acceleration (Ac_{mean}). Ac_{mean} of the aortic flow is reduced by afterloading[18] and increased by unloading[19]. In contrast to the left ventricle, studies validating Ac_{mean} for the right ventricle are still lacking. Though not formally validated, several authors have used

Ac_{mean} to describe the changes during the respiratory cycle as a marker to good effect [2;10;12]. As Ac_{mean} allows dynamic measurements during the respiratory cycle, we used Ac_{mean} as marker for RV outflow impedance.

This study shows that the use of OLC ventilation with a higher PEEP level than CV is not associated with an elevation of RV outflow impedance during expiration. Elevated PEEP levels do not resolve atelectasis[15], but recruitment maneuvers followed by sufficient levels of PEEP avoid atelectasis in cardiac surgery patients[13;20]. Duggan and colleagues[21] showed that atelectasis causes a significant increase in RV afterload (assessed with PAC and echocardiography), and that this may even lead to RV failure in healthy rats. This effect of atelectasis on RV afterload can be explained by two mechanisms: 1) local hypoxic pulmonary vasoconstriction in non-aerated lung areas[22-24] and 2) overdistention in aerated lung areas. High tidal volume ventilation in aerated lung areas occurs in the presence of atelectasis, compressing the surrounding vasculature and thus increasing RV afterload. This could explain the results of Huemer et al.[12], who found no increased RV afterload using 12 cm H_2O continuous positive airway pressure in healthy volunteers (without atelectasis), assessed by echo-Doppler. In the present study, atelectasis was avoided by OLC ventilation and could explain the fact that the RV outflow impedance during expiration is comparable between the two ventilation strategies.

During CV, RV outflow impedance (as assessed by Ac_{mean}) increased significantly during inspiration. These changes in RV outflow impedance during the respiratory cycle were also found by Poelart et al[11] in cardiac surgery patients and by Vieillard-Baron et al.[10] in patients with acute respiratory distress syndrome (ARDS).

High PEEP levels even enhance this RV outflow impedance increment during inspiration in ARDS patients[2]. In contrast to these studies, OLC ventilation did not increase RV outflow impedance during inspiration in the present study. In the present study, the tidal volume used was lower during OLC ventilation compared to CV, which may explain the lack of increase in RV outflow impedance during inspiration. On the other hand, alveolar overdistention during inspiration is even reduced by application of OLC ventilation, despite the use of elevated PEEP levels. The group of Amato[25] demonstrated in ARDS patients that the degree of overdistention during inspiration decreased when a recruitment maneuver was performed first, followed by high PEEP levels. This implies that during OLC ventilation RV outflow impedance is not increased during inspiration due to: 1) the reduction of tidal volume ventilation in aerated lung areas due to homogenization of pulmonary gas distribution, and 2) the use of lower tidal volume, set on the ventilator. Furthermore, these two effects of OLC ventilation act in synergy: homogenization of pulmonary gas distribution reduces tidal volume ventilation of aerated lung areas which is reduced even further by the lower tidal volume ventilation set on the ventilator.

Ventilation according to the OLC is a ventilation strategy designed for ARDS patients[7]. In a previous study, we showed that this ventilation strategy had beneficial effect on postoperative lung volumes and oxygenation in cardiac surgery patients[8]. Interleukin release was also attenuated by application of OLC[26]; in this latter study no increased incidence of myocardial infarction or pneumothorax was seen. OLC also did not lead to an increased duration of ventilation or an increased weaning time[8]. Also other studies using recruitment maneuvers followed by elevated PEEP

levels do not report an increased rate of these complications in cardiac surgery patients[9;13;20;27;28]. In this study, however, one patient with a proven pneumothorax before recruitment developed subcutaneous emphysema 6 hours after recruitment. The link between subcutaneous emphysema and a recruitment maneuver can not be excluded, but is unlikely: air leakage did not increase after recruitment and a chest tube obstruction during the fast development of subcutaneous emphysema was observed. The ongoing development of subcutaneous emphysema stopped after relieving the obstruction.

The aim of this study was not to investigate the hemodynamic effect of recruitment maneuvers but to evaluate the effect of a ventilation strategy. Experimental[29] and clinical[30] studies suggest that during a recruitment maneuver RV outflow impedance is increased for 1-2 minutes. We supported these findings in an earlier study: RV contractility was not affected 30 minutes after a recruitment maneuver[9] in cardiac surgery patients and in this present study, RV afterload was not increased 20 minutes after a recruitment maneuver. While a potential effect of a recruitment maneuver on RV afterload is very transient in cardiac surgery patients without known RV failure, it is questionable whether this can be extrapolated to patients with RV failure. The safety of recruitment maneuvers in patients with RV failure remains to be established. In addition, in patients after cardiac surgery the pericardium has been opened. Therefore, the effect of OLC ventilation on RV outflow impedance with an intact pericardium (such as ARDS patients) still remains unknown.

Conclusion:

Despite the use of elevated PEEP levels, ventilation according to OLC does not change RV outflow impedance during expiration and decreases RV outflow impedance during inspiration.

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6

Open lung ventilation improves functional residual capacity after extubation in cardiac surgery

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Abstract

OBJECTIVE: After cardiac surgery functional residual capacity (FRC) after extubation is reduced significantly. We hypothesized that ventilation according to the open lung concept (OLC) attenuates FRC reduction after extubation.

DESIGN: A prospective, single center randomized controlled clinical study.

SETTING: Cardiothoracic operating room and intensive care unit (ICU) of a university hospital.

PATIENTS: 69 patients scheduled for elective coronary artery bypass graft and/or valve surgery with cardiopulmonary bypass.

INTERVENTIONS: Before surgery, patients were randomly assigned to three groups; 1) conventional ventilation (CV), 2) OLC started after arrival on the ICU (Late Open Lung, LOL), and 3) OLC started directly after intubation (Early Open Lung, EOL). In both OLC groups, recruitment maneuvers were applied until $PaO_2/FiO_2 > 375$ Torr (=50 kPa). The CV group received no recruitment maneuvers.

MEASUREMENTS: FRC was measured pre-operatively and 1, 3 and 5 days after extubation. Peripheral hemoglobin saturation (SpO_2) was measured daily till the third day after extubation while breathing room air. $SpO_2 \leq 90\%$ was defined as hypoxemia.

RESULTS: Averaged over the five postoperative days, FRC was significantly higher in the EOL group and tended to be higher in the LOL group groups compared to the CV group (CV: 1.8 ± 0.1, LOL: 1.9 ± 0.1 and EOL: 2.2 ± 0.1 l, mean$\pm$SEM). In the CV group, 37% of the patients were hypoxic on the

third day after extubation, compared to none of the patients in both OLC groups.

CONCLUSIONS: After cardiac surgery, earlier application of OLC resulted in a significantly higher FRC and fewer episodes of hypoxemia compared to CV after extubation.

Postoperative atelectasis is frequently observed after cardiac surgery and this may lead to postoperative pulmonary complications (PPC)[1]. Several studies have demonstrated that reduction in postoperative functional residual capacity (FRC) is associated with the development of PPC[2-4]. Fast-track extubation or epidural analgesia did not prevent postoperative FRC reduction in cardiac surgery patients[5;6]. Whether application of continuous positive airway pressure (CPAP) after extubation increases postoperative FRC, is not known in cardiac surgery patients. When CPAP is compared to non invasive positive pressure ventilation (NIPPV), atelectasis is reduced in the NIPPV group in cardiac surgery patients[7]. However, in that study oxygenation or pulmonary function was not improved by NIPPV[7].

Ventilation according to the open lung concept (OLC) aims at avoiding atelectasis and thereby attenuating ventilator-induced lung injury[8;9]. This is achieved by short periods of high inspiratory pressures to open up collapsed alveoli followed by a relatively high level of positive end-expiratory pressure (PEEP) to keep the alveoli open. Recently, Schreiter and colleagues[10] showed that OLC reduces atelectasis, examined by CT scanning, in trauma patients with severe chest injury. When applied before lung injury, we have shown in an experimental study that ventilation according to the OLC was able to prevent lung injury[11].

Assuming that cardiac surgery causes lung injury, we designed a study containing three groups; 1) conventional ventilation (CV); 2) OLC started after cardiac surgery (LOL); and 3) OLC started before cardiac surgery (EOL). We hypoth-

esize that early rather than late application of OLC attenuates FRC reduction after extubation compared to conventional ventilation.

Methods

The local Human Ethics Research Committee approved this study and each patient gave informed written consent. We prospectively studied 69 patients scheduled for coronary artery bypass graft and/or valve surgery with use of cardiopulmonary bypass (CPB). Patients with severe airway obstruction, defined as forced expired volume in 1 sec or vital capacity below predicted value minus 2SD were not included. Excluded were patients who required re-operation within the first 72 hours (as re-operation was caused by hemothorax, affecting FRC). Preoperative risk factors were scored with the Euroscore, a scoring system to predict mortality in cardiac surgery patients[12-15].

Anesthesia was induced by midazolam (0.1 mg/kg) and sufentanil (2 µg/kg). Muscle relaxation was with pancuronium (0.1-0.2 mg/kg) and was not reversed. After intubation, all patients were ventilated using a Siemens ventilator (900C, Solena, Sweden) during anesthesia and on the intensive care unit (ICU). A pulmonary artery catheter (777HF8, Edwards, Irvine, CA, USA) was inserted through the right internal jugular vein. Anesthesia was maintained with propofol (2-4 mg/kg/hr) and sufentanil (1 µg/kg) as needed. Antibiotic prophylaxis was given with cefazoline for 24 hours. None of the patients received corticosteroids.

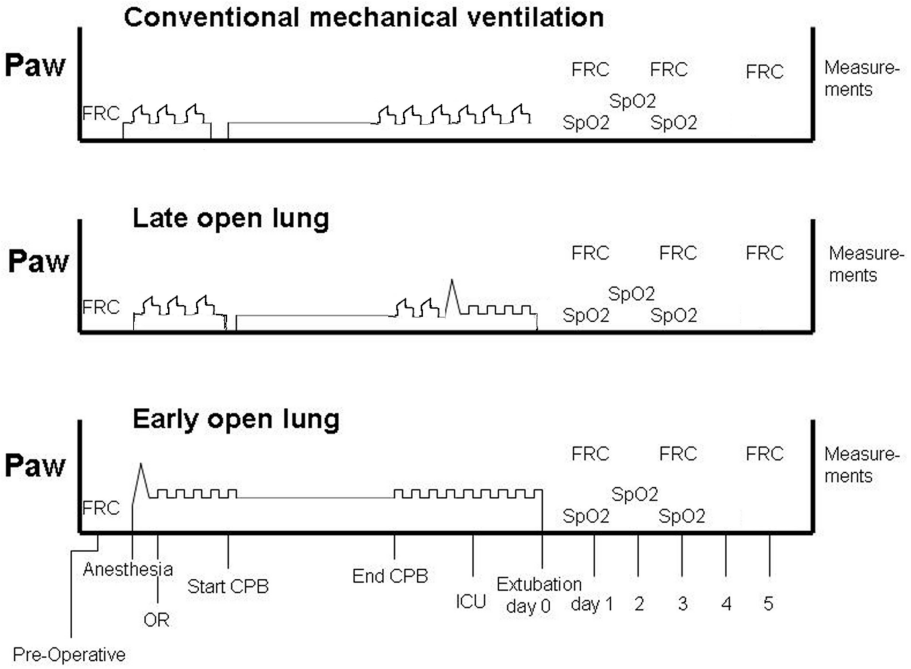

Figure 1. Graphic summary of interventions and measurements. On the right vertical axis airway pressure (Paw) during mechanical ventilation is displayed. On the left vertical axis measurements are displayed. On the horizontal axis a time bar is shown. FRC= functional residual capacity, SpO_2= peripheral oxygen saturation, CPB= cardiopulmonary bypass, OR=entry into operating theater and start of surgery. A peak in airway pressure reflects the first recruitment maneuver.

Randomization by envelope occurred after induction of anesthesia. Three groups were formed (Fig 1): the first group received Conventional Ventilation (CV) and served as control group. After intubation, mechanical ventilation was started with volume control ventilation at the following settings: tidal volume of 6-8 mL/kg, PEEP of 5 cm H_2O, I/E ratio of 1:2, FiO_2 was set to achieve a PaO_2 between 75 and 98 Torr (=10 resp 13 kPa) and respiratory rate was adjusted to achieve a $PaCO_2$ between 34 and 49 Torr (4.5 resp 6.5 kPa). During CPB, the lungs were briefly disconnected from the ventilator. Thereafter lung expansion

was maintained using CPAP 3-5 cm H_2O with 50% oxygen and 50% nitrogen. After CPB, lungs were re-expanded for 10 seconds by manual bagging (with a pop-up valve at 35 cm H_2O) with 100% oxygen to remove air from the heart and ventilation was continued with the same settings as described above until extubation.

The second group (Late Open Lung, LOL) was ventilated in the same way as the CV group after intubation. During CPB, the lungs were briefly disconnected from the ventilator. Thereafter lung expansion was maintained using CPAP 3-5 cm H_2O with 50% oxygen and 50% nitrogen, similar to the CV group. After CPB, lungs were re-expanded as described above and ventilation was continued with the same settings. Thirty minutes after arrival on the ICU, CV was switched to OLC and this was continued until extubation. Ventilation according to the OLC was started by switching the ventilator to a pressure controlled mode with a respiratory frequency of 40/min. FiO_2 was set to achieve a PaO_2 between 75 and 98 Torr (10 and 13 kPa, respectively), PEEP of 10 cm H_2O, I/E ratio of 1:1 and a driving pressure to obtain a tidal volume of 4-6 mL/kg aiming at a $PaCO_2$ of 34 and 49 Torr (4.5 and 6.5 kPa, respectively). A lung recruitment maneuver was applied by increasing peak inspiratory pressure (PIP) to 40 cm H_2O during 15 s to increase the PaO_2/FiO_2 ratio to a value greater than 375 Torr (=50 kPa). If not reaching this value, a recruitment maneuver was repeated by increasing PIP 5 cm H_2O greater than before, up to a maximum PIP of 60 cm H_2O until the PaO_2/FiO_2 ratio became greater than 375 Torr. If the PaO_2/FiO_2 ratio decreased slowly below 375 Torr after recruitment, PEEP was increased by 2 cm H_2O and a recruitment maneuver (beginning at 40 cm H_2O) was repeated. If PaO_2/FiO_2

ratio decreased below 375 Torr after an (accidental) disconnection, a new recruitment maneuver was performed.

The third group (Early Open Lung, EOL) received pressure controlled ventilation using the OLC strategy as described in the previous paragraph, which started directly after intubation. Ventilation was maintained during cardiac surgery and on the ICU. During CPB, patients were pressure controlled ventilated with a frequency of 40/min, tidal volume of 1 mL/kg, 50% oxygen and 50% nitrogen, I/E ratio of 1:1 and PEEP of 10 cm H_2O. If the lungs obstructed the surgical exposure, CPAP was applied at 10 cm H_2O. If inadequate vision remained, the endotracheal tube was briefly disconnected and a CPAP level of 3-5 cm H_2O was applied. The duration of this low CPAP level after disconnection was recorded as lung deflation time. Ventilation settings as used before the lung deflation were restored as soon as possible. After CPB, manual bagging was performed as described above and was the ventilation strategy again guided by the PaO_2/FiO_2 ratio. Thereafter, ventilation was restarted according to the OLC as described above and was maintained until the weaning procedure was started.

FRC was measured using He-rebreathing technique (Masterscreen-PFT, Jaeger, Hoechberg, Germany). FRC was measured one day before operation and 1, 3 and 5 days after extubation in the late afternoon (Fig 1). During FRC measurements, patients were always measured in bed in the upright sitting position. Peripheral hemoglobin oxygen saturation was measured with pulse oximetry (SpO_2) (Siemens SC9000, Danvers, USA) during the first three days after extubation in the early morning and the late afternoon (Fig 1). Oxygenation was meas-

ured while breathing room air during 10 min. Measurements were terminated earlier when SpO_2 fell ≤ 90%. The latter was defined as hypoxemia and supplemental oxygen therapy was continued. Postoperative evaluators measuring FRC and SpO_2 were blinded for the groups. Pneumonia was defined as the presence of new, persistent pulmonary infiltrates not otherwise explained, appearing on chest radiographs. This in combination with at least two of the following criteria: (1) body temperature of >38 °C, (2) leukocytosis > 10,000 cells/mm^3, or (3) purulent respiratory secretions[16]. Pneumothorax was defined as leakage of air from the chest tube not otherwise explained, or a pneumothorax visible on chest radiography.

Ventilatory and hemodynamic measurements were made during the first three hours after arrival on the ICU. Ventilatory measurements consisted of PIP, total PEEP (PEEPexternal + PEEPintrinsic= PEEPtot), FiO_2, PaO_2 and $PaCO_2$. Hemodynamic measurements consisted of cardiac index (CI), right ventricular end diastolic volume index (EDVI), right ventricular ejection fraction (RVEF) and mixed venous saturation (SvO_2). The latter values were continuously measured and calculated by a Vigilance cardiac output computer (Edwards, Irvine, CA, USA), connected to a pulmonary artery catheter (PAC). Fluid balance on the ICU was defined as fluids administrated minus fluid loss.

Intravenous fluid therapy on the ICU was based on the EDVI obtained by the pulmonary artery catheter. An optimal EDVI was assessed during surgery by a transesophageal echocardiogram performed by an experienced operator. During surgery but after sternum closure, intravenous fluids were given as long as increment of left ventricular end diastolic area was accompanied by maximal left ventricular

shortening fraction. At this optimal left ventricular end diastolic area EDVI, measured by the pulmonary artery catheter, was defined as optimal EDVI. Optimal EDVI was assessed during ventilation with 10 cm H_2O PEEP in both OLC groups and 5 cm H_2O PEEP in the CV group.

On the ICU, patients were sedated (propofol 2-4 mg/kg/h) and fluid management on the ICU was guided by EDVI, aiming at the optimal EDVI as assessed during surgery. Low EDVI was treated with starch colloids (Voluven®). When maximum daily dosage starch colloids (30 ml/kg) was reached, fluid resuscitation was continued with GPO® (containing 40 g/l albumin). If mean arterial pressure was less than 45 mmHg, and optimal EDVI was reached, an infusion of dobutamine (CI<2 l/m^2) or phenylephrine (CI>2 l/m^2) was given. If body temperature and cardiovascular measurements were satisfactory, sedation was stopped. When the patient triggered the ventilator, ventilator mode was switched to pressure support. A support level was chosen to obtain a tidal volume of 6-8 ml/kg. PEEP was reduced to 10 cm H_2O in both OLC groups and was not changed during weaning. PEEP levels in the CV group were not changed. Approachable patients with pressure support levels lower 15 cm H_2O were extubated. Patients received 0.05-0.1 mg/kg morphine i.v. on demand during the first 24 postoperative hours. After extubation, patients received paracetamol 1 g 4 times a day.

Table 1. Characteristics of the study population

		CV (n=23)	LOL (n=23)	EOL (n=23)
Age (yr)		66±9	63±11	58±15
BMI (kg/m^2)		28±5	26±4	26±5
Male/Female		13/10	12/11	12/11
CABG		15(11)	11(9)	12 (8)
Valve pathology requiring surgery	AoS	8	7	6
	AoR	1	2	3
	MR	2	6	4
FEV1 (%)		98±18	91±14	82±15
FVC (%)		99±22	97±11	88±12
Euroscore (%)		3.2±2	3.8±3	4.3±3
PaO_2 preoperative (Torr and kPa)		77±2 (10±1)	79±2 (10±2)	79±2 (11±2)
Aortic crossclamp time (min)		75±36	109±37	100±51
Tbaseline (°C)		35.1±0.5	34.7±0.8	34.5±0.7

Mean ± SD. BMI= Body mass index. CABG=coronary artery bypass graft, in parentheses the number of patients receiving an internal mammary artery graft. AoS= numer of patients suffering from aortic valve stenosis, AoR= numer of patients suffering from aortic vlave regurgitation, MR= numer of patients suffering from mitral regurgitation. FEV1= forced expired volume in 1 sec expressed in percentage of predicted value. FVC= vital capacity expressed in percentage of predicted value. Euroscore= scoring system predicting mortality in cardiac surgery (%). Tbaseline= rectal temperature at arrival on the ICU.

Statistics

This randomized clinical trial was designed to detect a 0.5 L difference in the postoperative FRC using ventilation according to the OLC compared to CV. For such a difference, assuming that the FRC standard deviation is 0.5 L[5], power analysis established that a sample size of 23 patients in each group would have 80% power of detecting a FRC difference of 0.5 L at a significance level of $\alpha < 0.017$ between the three groups. A significance level of 0.05 was considered statistical significant. However, in multiple comparisons, the significance level was adjusted according to Bonferroni.

Hemodynamic and respiratory parameters were compared between groups using analysis of variance (ANOVA) for repeated measurements. In this analysis, hemodynamic values recorded after induction and preoperative FRC were taken as covariate. In case of significant differences between groups, individual time points were analyzed using ANOVA for repeated measurements. Pneumonia and postop-

erative hypoxemia were compared between groups with the Chi-square test. Duration of lung deflation time was related to FRC on the first postoperative day using Pearson's correlation. All parameters which were different between groups "by design" (PaO_2/FiO_2 ratio, FiO_2, $PaCO_2$, PEEP) were not statistically tested.

All results are expressed as mean ± SEM unless otherwise stated.

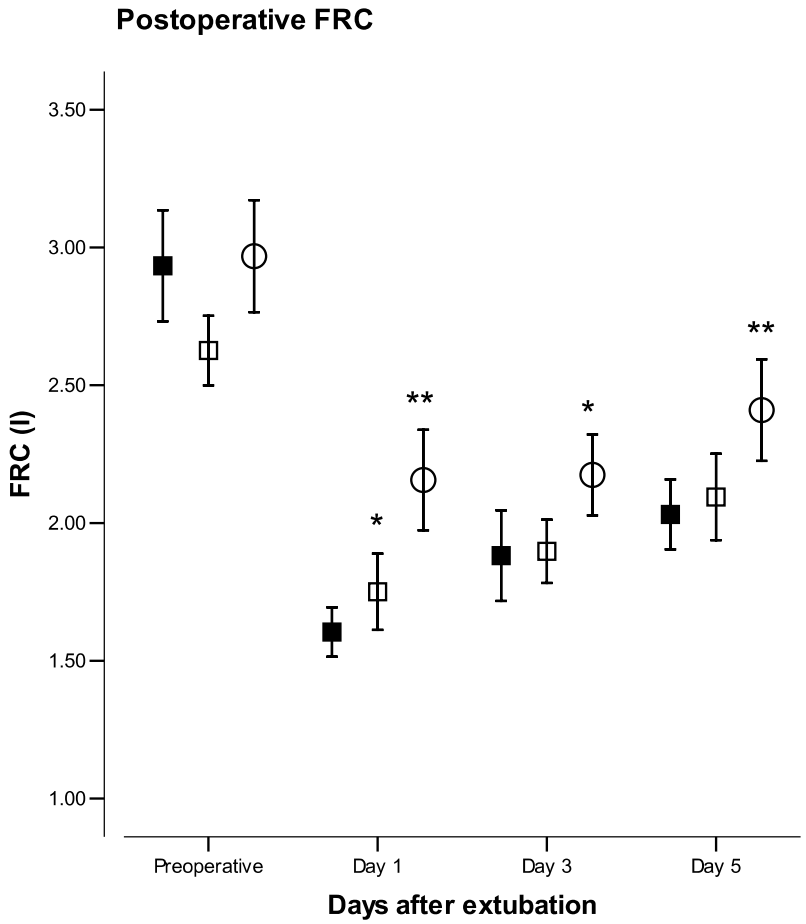

Figure 2, Mean ± SEM. Preoperative functional residual capacity (FRC) and FRC at 1,3 and 5 days after extubation. Closed squares: CV group, open squares LOL group, open circles EOL group. *= $p<0.05$, **=$p<0.017$ vs CV (adjusted for preoperative baseline values).

Results

A total of 69 patients participated in the study. Baseline characteristics are given in Table 1. In 4 patients in the CV group, FRC measurements were not done: two because of a re-thoracotomy, one because of technical failure of the FRC equipment preoperatively and one due to mental confusion impairing FRC measurement. One patient in the EOL group died due to cerebral ischemia after three days. In one patient (EOL group), paracetamol alone did not alleviate pain from the chest tube and this patient received morphine during the first 72 hours.

In all three groups, postoperative FRC was significantly reduced compared to pre-operative values. Mean postoperative FRC in the EOL group (2.2±0.1 L) was significantly higher (p=0.001) compared to the CV group (1.8±0.1 L). Mean FRC in the LOL group (1.9±0.1 L) tended

Table 2, Ventilatory data

		T=0	T=60
PEEPtot ($cm H_2O$)	CV	5±0	5±0
	LOL	5±0	15±1
	EOL	14±0	14±0
PIP ($cm H_2O$)	CV	23±1	24±1
	LOL	22±1	25±1
	EOL	22±0	24±1
Compliance ($ml/ cm H_2O$)	CV	37±2	35±2
	LOL	35±2	36±2
	EOL	44±2	41±2
$PaCO_2$ (Torr and kPa)	CV	38±1 (5.0±0.1)	39±1 (5.2±0.2)
	LOL	38±1 (5.0±0.1)	37±1 (4.9±0.2)
	EOL	39±1 (5.3±0.2)	38±1 (5.0±0.1)
PaO_2/FiO_2 (Torr and kPa)	CV	267±15 (36±2)	285±17 (38±2)
	LOL	347±26 (46±3)	438±18 (58±2)
	EOL	458±21 (61±3)	462±19 (62±3)
FiO_2 (%)	CV	40±1	42±1
	LOL	36±1	22±1
	EOL	26±2	25±2

Mean±SEM. Respiratory data on 0 and 60 minutes after arrival on the ICU. CV= conventional ventilation, LOL= late open lung group and EOL=early open lung group. PEEPtot= external PEEP + intrinsic PEEP; PIP= peak inspiratory pressure.

towards a higher FRC (p=0.031) compared to the CV group (Fig. 2). In the EOL group, FRC was significantly higher than CV group at all time points (Fig. 2).

During mechanical ventilation on the ICU, less recruitment maneuvers had to be performed in the EOL group compared with the LOL group to maintain PaO_2/FiO_2 ratio>375 Torr (=50 kPa) (1.6 $\pm$ 0.2 vs 2.8 $\pm$ 0.2, p<0.05). Also the maximum pressure needed to open up the lung during the recruitment maneuvers was significantly lower in the EOL group compared to the LOL group (43.2 $\pm$ 2 and 50.0 $\pm$ 2 cm H_2O, respectively, p<0.05).

Ventilatory data are given in Table 2. Ventilation time on the ICU was comparable between groups (CV:11 h 28min$\pm$3 h 01min LOL 9 h 22 min$\pm$1 h 13 min and EOL: 12 h 04 min$\pm$2 h 41 min). Weaning time, defined as time on pres-

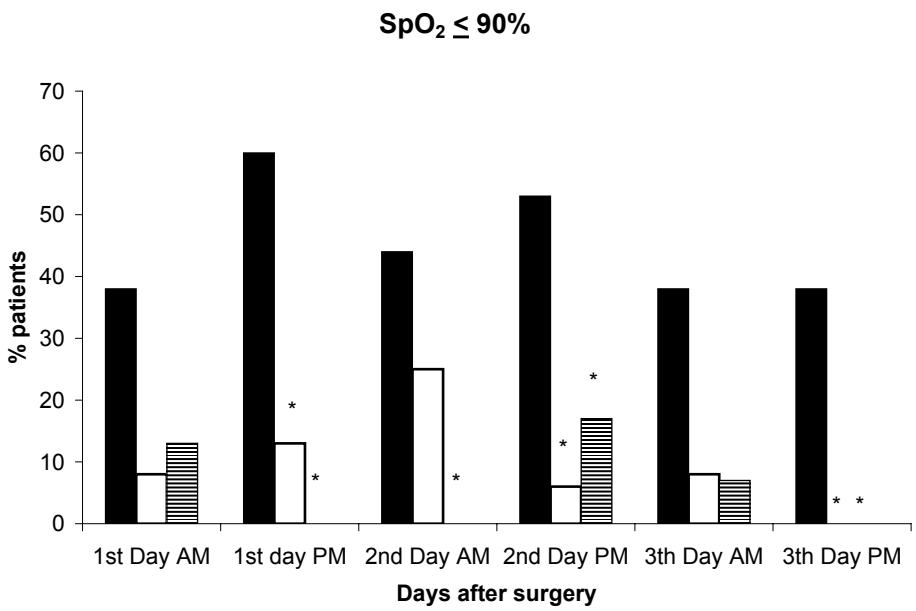

Figure 3, Percentage of patients with peripheral hemoglobin saturation (SpO_2) equal to or below 90% breathing room air during the first three days after extubation. CV= solid bars, LOL= open bars, EOL= striped pattern bars. AM= measured in the morning, PM= measured in the afternoon. * p<0.017 vs CV.

sure support ventilation was also comparable between groups (CV 1 h 43 min±18 min LOL 1 h 33 min±16 min EOL 1 h 17±20 min). PIP was comparable between all groups while PEEP was higher in the open lung groups. PEEP levels were comparable between both open lung groups. In the EOL group, lung deflation during CPB occurred in 6 cases and lasted 47 ± 19 min. The duration of lung deflation did not correlate with the postoperative FRC at any time (r=-0.38, p=0.25). Postoperative oxygenation, occurrence of pneumothorax, or the occurrence of pneumonia was not influenced by lung deflation during CPB in the EOL group.

In the CV group significantly more hypoxic episodes were recorded compared to both OLC groups (Fig.3). There was no significant difference in hypoxia between the EOL and LOL group (Fig.3).

Pneumothorax occurred in two patients in the CV group, two patients in the EOL group and in one patient in the LOL group. Pneumonia occurred in 5 patients in the CV group versus 3 patients in each open lung group (p=0.23).

CI (CV: 2.7±0.1, LOL 3.0±0.2 and EOL 2.6±0.2 l/m^2), REF (CV: 30±3, LOL: 40±3 and EOL 39±3%) and EDVI (CV 112±5, LOL 117±8 and EOL 99±5 ml/m^2) was comparable between groups after induction of anesthesia and did not change significantly on the ICU. SvO_2 at induction was again comparable between groups (CV: 76±1, LOL: 77±2 and EOL 77±2%). On the ICU, SvO_2 was significantly lower in the EOL group compared to the CV group (CV: 71±1, LOL 70±1 and EOL 67±1%). However, when each time point is analyzed, SvO2 was significantly lower in the EOL group compared to the CV group at 120 minutes after arrival on the ICU. On the ICU fluid balance was comparable between groups (CV 91±71, LOL 189±71 and EOL 255±51

ml/hr). Administered crystalloids (83 ml/hr in all groups) and blood products were equally divided between groups (CV: 1.8±0.3, LOL 1.7±0.3 and EOL 1.5±0.1 number of products per patient).

Discussion

Early application of open lung concept (OLC) significantly attenuated functional residual capacity (FRC) reduction after cardiac surgery when compared to conventional ventilation (CV). Three days after surgery, none of the patients ventilated according to the OLC had hypoxemia whereas 40% of the control patients still had hypoxic episodes. The use of high levels of PEEP in the OLC groups, did not affect cardiac output or right ventricular ejection fraction. Also the use of recruitment maneuvers together with the high level of PEEP did not increase the rate of barotraumas.

Hedenstierna[17] reported that general anesthesia causes atelectasis during surgery by three possible mechanisms: 1) compression atelectasis, mainly caused by displacement of the diaphragm, 2) gas absorption, mainly caused by high inspiratory oxygen fraction, and 3) impeded surfactant function. These mechanisms can reduce postoperative FRC by 20-30%. In cardiac surgery, however, FRC reductions up to 40-50% during the first 24 hours after extubation have been reported[5]. In the present study, similar FRC reductions were observed in our control group on the first day after extubation. The precise mechanism for the increased FRC reduction after cardiac surgery is not yet fully elucidated. Cardiopulmonary bypass leads to significant inflammatory mediator release,

likely to cause pulmonary dysfunction[18-22]. However, no differences in pulmonary function have been found between on- and off-pump surgery[18;21]. Therefore, it has been suggested that the exaggerated decrease in FRC after cardiac surgery is due to surgical and anesthetic procedures rather than the use of the CPB. The cardiac surgical procedure itself causes lung inflammation as shown by higher level of mediators[23]. In addition, it has been shown that CV of healthy lungs with atelectasis, as seen after cardiac surgery, leads to lung injury as a result of repetitive reopening of collapsed alveoli. This so-called ventilator induced lung injury leads to surfactant inactivation with reduction of FRC[24-26]. Therefore, our hypothesis was that the exaggerated decrease of FRC after cardiac surgery is probably due to the combination of the inflammatory environment caused by the surgical procedure and its enhancement caused by ventilator-induced lung injury.

Ventilation according to the OLC reduces atelectasis[27-29] and thereby probably prevents shear stress. Several studies have shown that this ventilation strategy leads to a reduction of surfactant inactivation[24;26] and pulmonary inflammation[30;31] in different acute respiratory distress syndrome models. When we used this strategy in healthy lungs, we were also able to protect the lung against an experimental induced inflammatory insult[11]. It is therefore conceivable that the significant attenuated FRC reduction found in the EOL group is attributable to the prevention of additional lung injury caused by mechanical ventilation. In contrast, postoperative FRC in the LOL group did not significantly differ from the CV group, despite the application of OLC on the ICU. The reason for this is not known, but the greatest differences between the LOL and the EOL group occurred in the first 1 to 2 hours after CPB. In

this period, patients in the LOL group received conventional ventilation in the inflammatory environment caused by cardiac surgery. Therefore, we believe that in the LOL group, additional surfactant inactivation has occurred during this period, leading to a reduction in FRC. This indicates that lung injury is best attenuated by early application of OLC, as indicated by an attenuated FRC reduction in the early postoperative phase. In this early postoperative phase, EOL affected mainly FRC on the first postoperative day. The subsequent trend in FRC recovery during the five postoperative days is comparable between groups. Westerdahl and colleagues[32] found that conventionally ventilated patients recovered to 94% of their preoperative FRC, 4 months after cardiac surgery. Our patients in the EOL group, however, already reached 85% of their preoperative FRC on their fifth postoperative day.

Both OLC groups received only a mean of 25% oxygen whereas the CV group received a mean FiO_2 of 42%. Rothen et al. and Agarwal et al. showed that FiO_2 of 40% does not cause absorption atelectasis. Therefore, the beneficial effect of OLC on FRC can probably not be attributed to the difference in FiO_2 concentrations.

To avoid surgical complications during surgery while ventilating (1 ml/kg) the lungs during CPB, a good understanding between the surgeon and the anesthetist was essential. As aortic crossclamp time was comparable between groups, we believe that early application of the OLC did not lead to surgical difficulties. However, on the other hand, lung deflation in the EOL group did not affect mean postoperative FRC. This could be due to the low number of patients

undergoing lung deflation (6 out of 23). Another explanation for this result could be that due to our chosen strategy (application of CPAP 5 cm H_2O after lung deflation) no additional lung injury occurs during CPB in this group of patients. If only CPAP is applied in a lung with atelectatic regions, no shear forces may occur and therefore no additional lung injury is to be expected. Further studies focusing on the effectiveness of CPAP levels during CPB on postoperative FRC are warranted.

Hypoxemia occurred in 54% of our patients in the CV group on the second day after extubation. These results are comparable with the results of Taggart and colleagues[23] who report that after cardiac surgery, 66% of the patients had a PaO_2<60 Torr within the first two days after extubation. On the third day, hypoxemia was still observed in 40% of the patients in the CV group. In both OLC groups, hypoxemia was not observed in any patient in the afternoon of the third postoperative day. Limiting hypoxemia could lead to earlier discharge from hospital. However, the use of a protocolized discharge regimen is needed to evaluate the effect of early application of OLC on length of hospital stay.

It is conceivable that severe pain causes impairment of deep breaths and therefore could enhance formation of atelectasis. However, somatic pain particularly affects vital capacity, more than FRC[2]. In addition, these somatic pain levels are usually low after cardiac surgery and may not explain the decrease in FRC[32]. Furthermore, pain treatment was for all groups equal, making an important effect of pain on postoperative FRC unlikely.

One of the arguments for not applying OLC in cardiac patients is the use of relatively high PEEP levels. It has been demonstrated that PEEP levels above 15 cm

H_2O can increase right ventricular afterload[33-37]. However, when high PEEP levels are preceded by a recruitment maneuver, Dyhr and colleagues[38] found that cardiac output was not affected by these high PEEP levels in cardiac surgery patients. We have confirmed these results in a previous study in which OLC ventilation (using 17 cm H_2O PEEP) did not increase right ventricular afterload compared with CV in cardiac surgery patients[39]. The exact mechanism is not yet clear. Duggan et al.[40] found a significant right ventricular afterload increment caused by atelectasis in healthy rat lungs. Therefore, we speculate that avoidance of atelectasis during OLC may counterbalance the possible negative effect of high PEEP on right ventricular afterload.

Ventilation according to the OLC was not accompanied by an increased risk of barotrauma; the occurrence of pneumothorax was comparable between all groups. By applying OLC directly after intubation (EOL group), the number of recruitments and the maximal pressure needed for recruitment maneuver were even lower compared to the late OLC group indicating less atelectasis in the EOL group.

Conclusion

This study shows that early application of ventilation according to the OLC was associated with a higher postoperative FRC as compared to conventional ventilation. The occurrence of postoperative hypoxemia was significantly lower in both OLC groups as compared to the control group (CV).

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7

Ventilation according to the open lung concept attenuates pulmonary inflammatory response in cardiac surgery

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Abstract

OBJECTIVE: Cardiac surgery with cardiopulmonary bypass (CPB) is associated with a systemic inflammatory response, which is correlated with outcome. We hypothesized that ventilation according to the open lung concept (OLC) attenuates cytokine release.

METHODS: A prospective, single center randomized controlled clinical study containing sixty-two patients scheduled for elective coronary artery bypass graft and/or valve surgery with cardiopulmonary bypass. Before surgery, patients were randomly assigned to three groups; 1) conventional mechanical ventilation (CV), 2) OLC started after arrival on the ICU (Late Open Lung, LOL), and 3) OLC started directly after intubation (Early Open Lung, EOL). In both OLC groups, recruitment maneuvers were applied until $PaO_2/FiO_2 > 50$ kPa. The CV group received no recruitment maneuvers. Interleukin (IL)-6, IL-8, IL-10, tumor necrosis factor (TNF)-α and interferon (IFN)-γ were measured pre-operatively, immediately after cessation of CPB, and 3h, 5h, 24h, 2 and 3 days after cessation of CPB.

RESULTS: CPB caused a significant increase of IL-6, IL-8 and IL-10 in all groups. Thereafter, IL-8 decreased significantly more rapidly in both OLC groups compared to CV. IL-10 decreased significantly more rapidly after CPB only in the EOL group, compared with CV. Three hours after cessation of the CPB, IL-10 was already comparable with preoperative levels in the EOL group, but not in the LOL or CV group. IL-6, TNF-α and IFN-γ did not differ significantly between groups.

CONCLUSIONS: OLC ventilation leads to an attenuated inflammatory response, presumably by reducing additional lung injury after cardiac surgery. Studies on cytokines after cardiac surgery should take these findings into account.

Cardiac surgery with cardiopulmonary bypass (CPB) is associated with a systemic inflammatory response syndrome. It has been shown that cytokine release is correlated with outcome after cardiac surgery[1]. This cytokine release is caused by contact of blood with the artificial surface of the cardiopulmonary bypass (CPB), but also by the surgical trauma and ischemia/reperfusion injury from the heart. Furthermore, mechanical ventilation with abnormal shear stress may be responsible for eliciting cytokine release from the lung[2].

In acute respiratory distress syndrome (ARDS) patients, plasma interleukin (IL)-8 but also IL-6 and tumor necrosis factor (TNF)-α concentrations increase during conventional ventilation (CV)[3;4]. The inflammatory response from the lung during mechanical ventilation originates at the alveolar membrane as a result of mechanical stress, enhanced by repetitive re-opening of atelectatic lung areas[3]. Ventilation according to the open lung concept (OLC) has been introduced to avoid atelectasis and thereby attenuating ventilator-induced lung injury[5]. This is achieved by short periods of high inspiratory pressures to open up collapsed alveoli followed by a relatively high level of positive end-expiratory pressure (PEEP) to keep the alveoli open. Using this strategy, we were able to reduce cytokine release compared to conventional ventilation in an experimental ARDS model[6;7].

As ventilation according to the OLC aims at decreasing alveolar mechanical stress, we hypothesized that OLC would attenuate pulmonary inflammation after cardiac surgery. We have previously shown that this ventilation strategy attenuates the reduction of functional residual capacity (FRC) and the occurrence of hypoxemia, at least until three days after extubation[8]. Especially early application of OLC appears

to be the most effective way to attenuate FRC loss after extubation. Therefore, we studied the effect of OLC on pulmonary inflammation and the influence of the timing with which OLC was initiated (before or after cardiac surgery).

Methods

The local Human Ethics Research Committee approved this study and each patient gave written informed consent. Sixty-nine patients were enrolled in this study, the effect of OLC on FRC in this patient group was reported previously[8]. In this study; patients scheduled for coronary artery bypass graft and/or valve surgery with use of CPB were included. Patients with severe airway obstruction (defined as forced expired volume in 1 sec or vital capacity more than two standard deviations below the predicted value) were not included.

After intubation, all patients were ventilated using a Siemens 900C ventilator (Siemens, Solena, Sweden) during anesthesia and during their postoperative ICU stay. Anesthesia was maintained with propofol (2-4 mg/kg/hr) and sufentanil (1 µg/kg) as needed. Antibiotic prophylaxis was given with cefazolin for 24 hours. None of the patients received corticosteroids or phosphodiesterase inhibitors in the perioperative period.

Randomization by envelope occurred after induction of anesthesia. Patients were randomized to one of three groups: Group 1 received CV. After intubation, mechanical ventilation was guided by the results of the ARDS network group[9], entailing volume control ventilation at the following settings: tidal volume of 6-8 mL/kg, PEEP of 5 cm H_2O, I/E ratio of 1:2, FiO_2 was set to achieve a PaO_2 between 75

and 98 mmHg and respiratory rate was adjusted to achieve a $PaCO_2$ between 34 and 49 mmHg. During CPB, the lungs were briefly disconnected from the ventilator. Thereafter lung expansion was maintained using CPAP 3-5 cm H_2O with 50% oxygen and 50% nitrogen. After CPB, ventilation was continued with the same settings as described above until the weaning procedure was started.

The second group (Late Open Lung, LOL) was ventilated in the same way as the CV group after intubation. During CPB, the lungs were briefly disconnected from the ventilator. Thereafter lung expansion was maintained using CPAP 3-5 cm H_2O with 50% oxygen and 50% nitrogen, similar to the CV group. After CPB, ventilation was continued with the same settings. Thirty minutes after arrival on the ICU, CV was switched to OLC and this was continued until extubation. Ventilation according to the OLC was started by switching the ventilator to a pressure controlled mode with a respiratory frequency of 40/min. FiO_2 was set to achieve a PaO_2 between 75 and 98 mmHg, PEEP of 10 cm H_2O, I/E ratio of 1:1 and a driving pressure to obtain a tidal volume of 4-6 mL/kg aiming at a $PaCO_2$ of 34 and 49 mmHg. A lung recruitment maneuver was applied by increasing peak inspiratory pressure (PIP) to 40 cm H_2O during 15 s to increase the PaO_2/FiO_2 ratio to a value greater than 375 mmHg. If not reaching this value, a recruitment maneuver was repeated by increasing PIP 5 cm H_2O greater than before, up to a maximum PIP of 60 cm H_2O until the PaO_2/FiO_2 ratio became greater than 375 mmHg. If the PaO_2/FiO_2 ratio decreased slowly below 375 mmHg after recruitment, PEEP was increased by 2 cm H_2O and a recruitment maneuver (beginning at 40 cm H_2O) was repeated. If PaO_2/FiO_2 ratio decreased

below 375 mmHg after an (accidental) disconnection, a new recruitment maneuver was performed.

The third group (Early Open Lung, EOL) received pressure controlled ventilation using the OLC strategy as described in the previous paragraph, which started directly after intubation. Ventilation was maintained during cardiac surgery and on the ICU. During CPB, patients were pressure controlled ventilated with a frequency of 40/min, tidal volume of 1 mL/kg, 50% oxygen and 50% nitrogen, I/E ratio of 1:1 and PEEP of 10 cm H_2O. If the lungs obstructed the surgical exposure, CPAP was applied at 10 cm H_2O. If inadequate vision remained, the endotracheal tube was briefly disconnected and a CPAP level of 3-5 cm H_2O was applied. Ventilation settings as used before the lung deflation were restored as soon as possible. After CPB, ventilation was according to the OLC until the weaning procedure was started.

If body temperature and cardiovascular measurements were satisfactory, sedation was stopped. When the patient triggered the ventilator, ventilator mode was switched to pressure support. A support level was chosen to obtain a tidal volume of 6-8 ml/kg. PEEP was reduced to 10 cm H_2O in both OLC groups and was not changed during weaning. PEEP levels in the CV group were not changed. Approachable patients with pressure support levels lower 15 cm H_2O were extubated

Before initiating CPB, heparin 3 mg/kg was administered. For CPB, a non-pulsatile roller-pump was used for all patients, containing a flat sheet membrane oxygenator. The use of aprotinin (1.5×10^6 KIU) in the pump priming was left to the discretion of the surgeon. Surgery was performed with a core temperature of 28-32

°C. Heparin was reversed with 4-5 mg/kg protamine, immediately after separation of CPB in all patients. Packed red cells were administered if the hemoglobin concentration was lower than 6.0 mmol/l. To correct coagulation, fresh frozen plasma and platelet concentrates were given as indicated.

Blood samples were drawn preoperatively (before induction of anesthesia), after cessation of CPB (T=0) and 3h, 5h, 24h, 2, and 3 days after cessation of CPB. After the blood sample was taken, blood was immediately centrifuged at a speed of 3500 rpm and at a temperature of 4 °C. After centrifugation, plasma was frozen at a temperature of -20°C. A commercially available Pelikine Compact enzyme-linked immunosorbent assay kit (Central laboratory of the Netherlands Red Cross, Amsterdam, The Netherlands) was used to determine plasma IL-6, IL-8, IL-10, TNF-α and interferon (IFN)-γ concentrations in one batch.

To determine peri-operative myocardial infarction, creatine kinase subfraction MB (CK-MB) was determined directly after arrival on the ICU, and 8, 12 and 24 h after arrival on the ICU. A 12-lead electrocardiogram (ECG) was recorded 4, 16 and 24 h after admission on the ICU. CK-MB and the ECGs were evaluated by an experienced cardiologist (JM) who was blinded to the applied ventilation strategy. Perioperative myocardial infarction was diagnosed if: a) the CK-MB fraction increased to more than five times the upper normal limit or b) new Q waves appeared in a postoperative ECG[10]. New Q waves were defined as a 2-grade worsening on the Minnesota code or a 1-grade Q wave worsening with major ST segment elevation or depression.

Table 1: Patient characteristics.

	CV (n=22)	LOL (n=18)	EOL (n=22)
Age (yr)	65±2	59±3 (p=0.12)	63±2 (p=1.0)
Male/Female	13/9	10/8	12/10
Weight (kg)	83±4	74±3 (p=0.29)	76±3 (p=0.70)
FEV1 (%)	98±18	91±14 (p=0.91)	82±15 (p=0.07)
FVC (%)	99±22	97±11 (p=0.31)	88±12 (p=0.14)
CABG	11	7	9
Valve surgery	7	8	10
CABG+valve	4	3	3
Aprotinin	7	9	6
Aortic crossclamp time (min)	75±8	106±13 (p=0.19)	100±8 (p=0.37)
Intubation time (hrs)	11±3	8±1 (p=1.0)	12±3 (p=1.0)
Lowest core temp (°C)	30.9±1.9	30.2±2.6 (p=0.88)	30.1±2.3 (p=0.79)

Mean±SEM. FEV1= forced expired volume in 1 sec expressed in percentage of predicted value. FVC= vital capacity expressed in percentage of predicted value. CABG= cononary artery bypass graft. Aprotinin= number of patients receiving aprotinin. *p* values: vs CV.

Statistics

The changes from baseline (= end of CPB) measurements on cytokines were calculated and used to compare the three groups using analysis of variance for repeated measurements. The difference between the different time points and pre-operative values were compared using a paired Student's T-test. The incidence of myocardial infarction in each group was compared with a Chi-square test. Data are presented as mean±SEM.

Results

The patient characteristics were comparable between the groups and are given in Table 1. Failure to adequately collect blood samples occurred in 7 patients; these patients were only excluded for the cytokine analyses (1 CV, 5 LOL, 1 EOL). Detailed cardiovascular parameters and pulmonary complication rates are described previously[8]. In summary, no differences between cardiovascular parameters were detected and occurrence of pneumonia (CV 5 patients, LOL 3 patients, EOL 3 patients) and

pneumothorax (CV 2 patients, LOL 1 patients and EOL 2 patients) were comparable between groups.

The overall decrease in IL-8 after CPB was significantly greater in both OLC groups compared to the CV group (Fig 1). Immediately after cessation of CPB (T=0), IL-8 were significantly elevated compared to preoperative values, but these concentrations were comparable between the groups (Fig 2). In the CV group, IL-8 concentrations remained significantly elevated until 72 h after CPB compared to the preoperative values (Fig 2). In both OLC groups, however, IL-8 concentrations were only significantly elevated until 24 h after CPB (Fig 2).

The overall decrease in IL-10 after CPB was only significantly greater in the EOL group (Fig 1). At T=0, IL-10 concentrations were significantly elevated compared to preoperative values, but were comparable between the groups (Fig. 2). After T=0, IL-10 was comparable to preoperative values in the EOL group. In the LOL and CV group, however, IL-10 concentrations remained significantly elevated until 5 h after CPB (Fig 2).

IL-6 concentrations were comparable between all groups (Fig 2).

Directly after CPB (T=0), TNF-α and IFN-γ concentrations did not differ significantly between the three groups throughout the study period (Fig 1). Postoperative C-reactive protein concentrations were comparable between the groups (Fig 3).

Total PEEP values were in the CV group 5.5±0.1, in the LOL group 14.6±0.4 cm H_2O and in the EOL group 14.1±0.2 cm H_2O. PIP was 24±1 in the CV group, 25±1 in the LOL group and 24±1 cm H_2O in the EOL group. The PaO_2/FiO_2 ratio in the CV group was 285±8, in the LOL group 428±8 and in the EOL group 450±8 mmHg. $PaCO_2$ con-

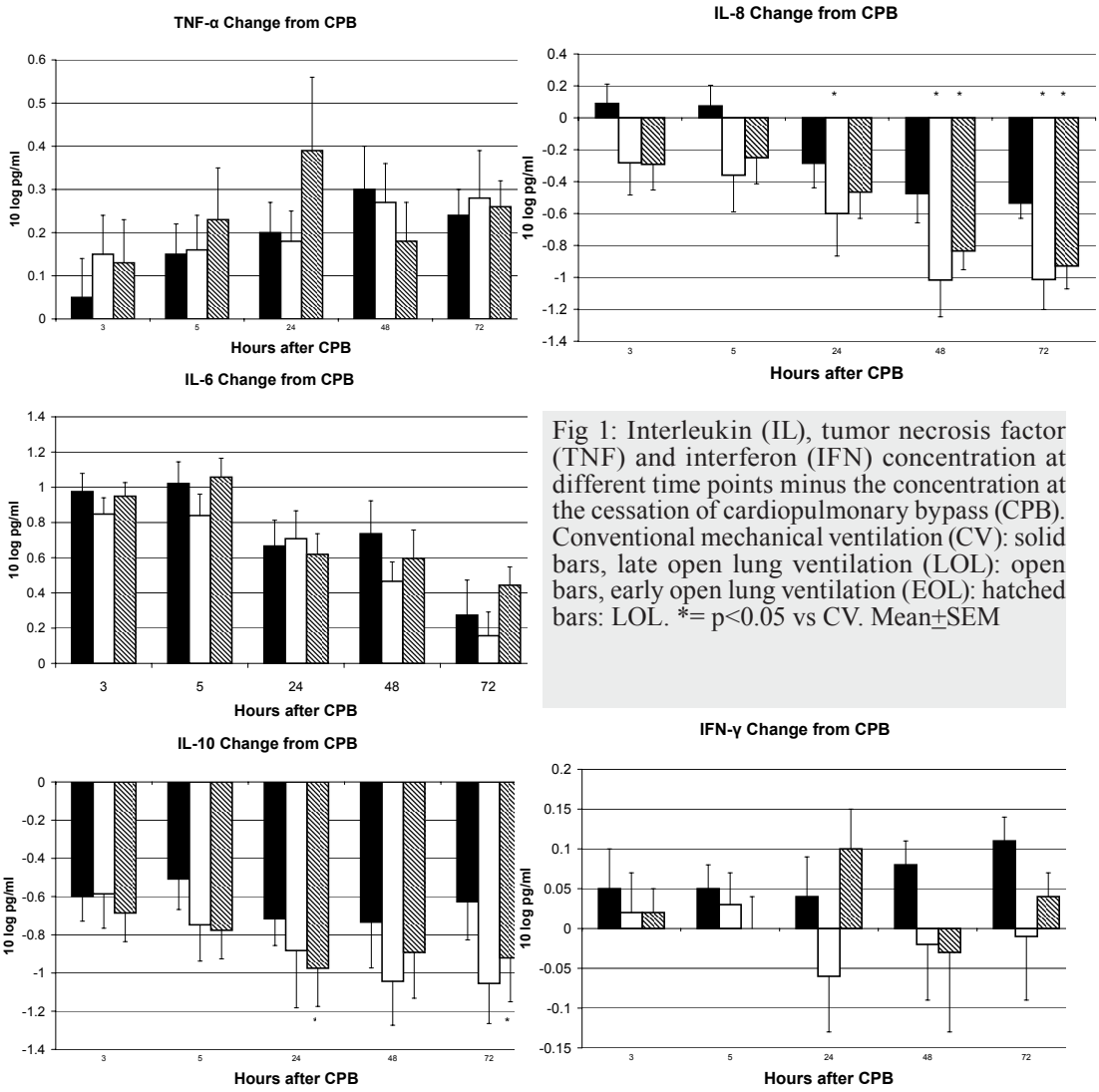

Fig 1: Interleukin (IL), tumor necrosis factor (TNF) and interferon (IFN) concentration at different time points minus the concentration at the cessation of cardiopulmonary bypass (CPB). Conventional mechanical ventilation (CV): solid bars, late open lung ventilation (LOL): open bars, early open lung ventilation (EOL): hatched bars: LOL. *= $p<0.05$ vs CV. Mean±SEM

centrations were comparable between groups (CMV: 38± 5, LOL: 37± 6, EOL: 38± 4.5 mmHg).

Myocardial infarction did not occur in the EOL group, whereas one patient in the CV group and two patients in the LOL group suffered from a peri-operative myocardial infarction (p=0.35).

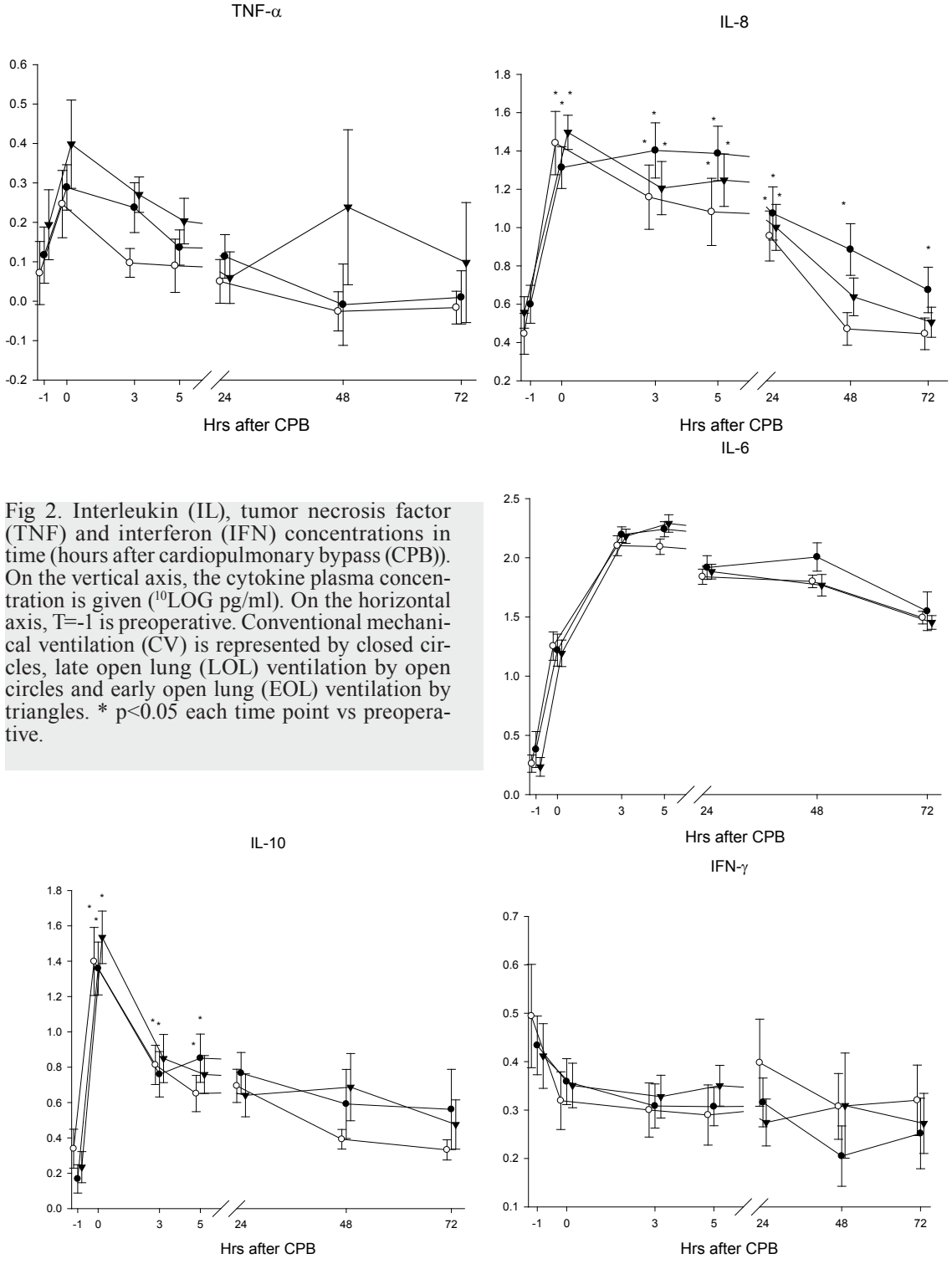

Fig 2. Interleukin (IL), tumor necrosis factor (TNF) and interferon (IFN) concentrations in time (hours after cardiopulmonary bypass (CPB)). On the vertical axis, the cytokine plasma concentration is given (^{10}LOG pg/ml). On the horizontal axis, T=-1 is preoperative. Conventional mechanical ventilation (CV) is represented by closed circles, late open lung (LOL) ventilation by open circles and early open lung (EOL) ventilation by triangles. * $p<0.05$ each time point vs preoperative.

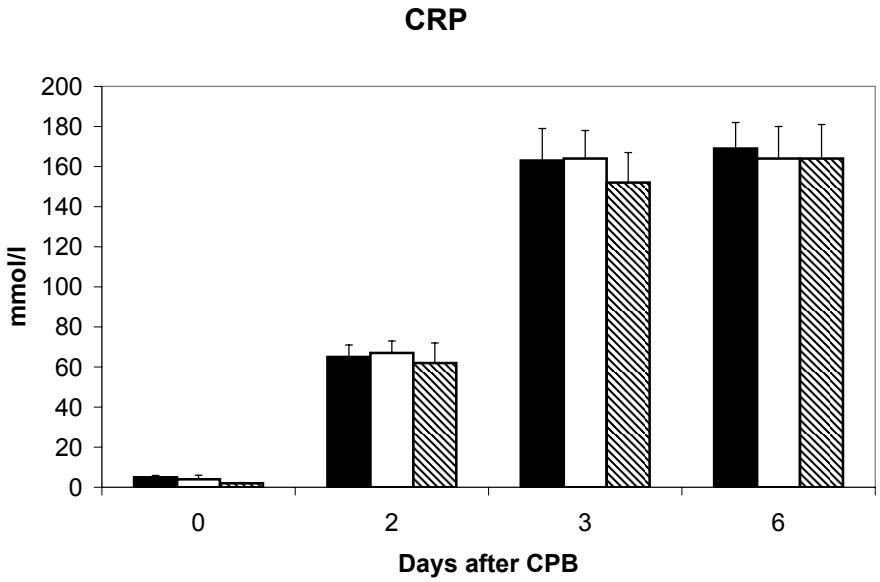

Fig 3: C-reactive protein (CRP) concentrations following CPB. T=0 is before CPB. CV group: solid bars, LOL: open bars, EOL group: hatched bars. Mean±SEM.

Administered units of blood products were equally divided between the groups (CV: 1.8±0.3, LOL 1.7±0.3 and EOL 1.5±0.1 number of products per patient).

Discussion

Our results show that the early application of OLC (EOL) is significantly associated with the decline in plasma concentrations of IL-8 and IL-10 after cardiopulmonary bypass (CPB) compared to conventional ventilation. Late application of OLC (LOL) results in a significant decrease of IL-8, but not IL-10, after CPB.

The inflammatory response after CPB is known to be mediated by several mechanisms including mechanical ventilation, extracorporeal circulation and tissue damage[11]. Cytokines initiate and coordinate the inflammatory response and act in a complex cascade. TNF-α is a proximal mediator within this cascade and induces a

second wave of cytokines such as IL-6, an important regulator of the hepatic acute phase response, and IL-8. IL-8 is a cytokine with important neutrophil-activating and chemoattractant properties and can be produced by alveolar macrophages. Other mediators of the cytokine network are the so-called T helper (Th) 1 and Th2 cytokines. Uncommitted T cells can differentiate into either the Th1 phenotype which produces cytokines like IL-2 and IFN-γ, or the Th2 phenotype which produces IL-4 and IL-10. Th1 cytokines have pro-inflammatory effects and are involved in cellular immunity, whereas Th2 cytokines have anti-inflammatory properties and are regulators of the humoral immune response[12]. There is to some extent a reciprocal cross-regulation between Th1 and Th2 cytokines.

The decrease of IL-8 after CPB as seen in the OLC groups suggests that mechanical ventilation promotes the systemic inflammatory response after cardiac surgery[13]. It has repeatedly been shown that mechanical ventilation leads to IL-8 production in the lung due to cyclic alveolar stress[14;15]. OLC, however, aims at avoiding this cyclic alveolar stress by minimizing atelectasis, and should therefore lead to a reduction of pulmonary inflammation. Our group[6] has previously shown that this ventilation strategy reduces the influx of polymorphonuclear neutrophils, IL-8 and thrombin activity in broncho-alveolar lavage (BAL) fluid in newborn piglets[6]. Ranieri and colleagues[4] measured IL-8 in BAL fluid in ARDS patients and showed a reduction of IL-8 when using a protective ventilation strategy. In contrast to the present study, Ranieri et al. [4] did not find any effect of this protective ventilation strategy on plasma IL-8 levels.

Furthermore, IL-8 probably plays an important role in the pathophysiology of myocardial ischemia and infarction. In patients with acute myocardial infarction, IL-8 concentration appeared to be correlated to complications after myocardial infarction[16]. In addition, myocardial injury could be prevented by administration of antibodies of IL-8 in an experimental model[17]. This suggests that IL-8 participates in the pathogenesis of myocardial infarction. As OLC ventilation is accompanied by a more rapid normalization of IL-8 levels, it might be speculated that this ventilation modality could have beneficial effects on the perioperative myocardial infarction rate. In the present study the incidence of myocardial infarction was comparable between the groups, however it is fortunately a relatively infrequent complication and this study was not powered to show any difference in the myocardial infarction rate.

In the present study the decrease in IL-10 after CPB was only significantly greater in the EOL group compared to the CV group. During inflammation, IL-10 levels increase, suppressing pro-inflammatory cytokine production. When the primary injury is attenuated, both pro- and anti-inflammatory cytokine responses decrease after cardiac surgery[18;19]. As stated above, ventilation according to the OLC aims at reducing shear stress in atelectatic lung areas, thus avoiding ventilator-induced lung injury[7]. Lower IL-10 levels in combination with lower IL-8 levels suggest attenuated primary injury in the lung during early application of OLC. In neither the CV group nor both OLC groups did we find an increase in plasma IFN-γ concentrations. This may indicate an absence of Th1 activation after CPB, although effects on tissue IFN-γ production cannot be excluded, nor can inhibition of the Th1 pathway by elevated IL-10 levels.

Based on these results we conclude that ventilation according to the OLC may actually protect the lung against injury and therefore is best applied early. Late application of OLC also reduced IL-8 release, but did not affect IL-10 concentrations. The greater decreases in IL-10 concentration in only the EOL group suggest that the LOL group may initially have developed a greater degree of pulmonary inflammation compared to the EOL group. That IL-8 after CPB also decreases significantly in the LOL group suggests that further development of pulmonary inflammation on the ICU is attenuated by using OLC in the ICU. The findings of the ARDS network group[20] support the suggestion that IL-10 indicates the degree of primary pulmonary inflammation[18] and IL-8 indicates the development of further pulmonary inflammation related to mechanical ventilation. This group showed in 703 patients with acute lung injury that IL-6 and IL-8, but not IL-10 decreased when a protective ventilation strategy was initiated[20]. We therefore assume that the LOL group suffered from greater primary pulmonary inflammation than the EOL group.

While early application of OLC seems to attenuate pulmonary inflammation, the optimal timing of this early initiation of OLC is unclear. In the present study it is unlikely that the protective effect of the EOL on pulmonary inflammation occurred during induction of anesthesia, before initiation of CPB. Major surgery in patients without pulmonary dysfunction does not seem to elicit significant interleukin release[21]. It is also doubtful whether this primary pulmonary dysfunction in the LOL group occurred during CPB. It could be argued that pulmonary tissue hypoxia (followed by ischemia/reperfusion injury) occurred in the LOL group, as this group was not ventilated during CPB, in contrast to the EOL group. However, non-

ventilation during CPB is not expected to cause pulmonary tissue hypoxia, as the bronchial circulation seems to meet pulmonary oxygen demands[2]. In addition, it is unlikely that mechanical ventilation with a tidal volume of 1 ml/kg would cause sufficient alveolar ventilation to avoid pulmonary tissue hypoxia. Furthermore, application of only CPAP during CPB does not cause cyclic re-opening of alveolar units and thus no additional cytokine release[22]. Therefore, it is also unlikely that the primary pulmonary inflammation in the LOL group is caused by 3-5 cm H_2O CPAP during CPB compared to the 10 cm H_2O CPAP with small tidal volume ventilation in the EOL group. The most likely cause of the accentuated primary pulmonary inflammation in the LOL group is the application of conventional ventilation immediately after CPB. Immediately after release of the aortic cross clamp, cytokine concentrations are significantly elevated, as shown in Fig 1. Cytokine release induced by conventional mechanical ventilation is in part dependent on the pro-inflammatory condition induced by CPB[23]. Therefore, the accentuated primary pulmonary inflammation in the LOL group compared to the EOL group is probably caused by the application of conventional ventilation immediately after CPB. This suggests that OLC should at the latest be initiated immediately after cessation of CPB.

IL-6 is a pro-inflammatory cytokine and is probably more influenced by the degree of surgical trauma than by specific myocardial or lung injury after cardiac surgery[24]. In several studies no reduction of IL-6 levels were found with on-pump cardiac surgery compared to off-pump surgery[18;19]. Also in the present study, no effect of OLC on IL-6 levels was observed. This might be explained by the major release of IL-6 due to surgical trauma, masking the possible effects of OLC on IL-6 production.

In this study, the influence of EOL on pulmonary inflammation is mainly based on the decrease of IL-8 and IL-10 concentrations after CPB. CPB is known to cause a firm inflammatory response and before initiation of CPB, lungs are relatively healthy. Ventilator induced lung injury does not occur in healthy lungs[21], as described above. However, ventilator induced lung injury is likely to occur when mechanical ventilation occurs in an inflammatory environment. Therefore, increment or attenuation of interleukin release after CPB could theoretically reveal the effect of ventilatory strategy on pulmonary inflammation.

A possible drawback of this study is that aprotinin was used at the discretion of the surgeon. High dose aprotinin (2 x 10^6 KIU loading dose + 2 x 10^6 KIU priming dose + infusion 5x10^5 KIU/h) significantly reduces IL-8 and IL-10 plasma levels[25]. However, the effect of aprotinin on interleukin release is dose dependent: low dose (0.5 x 10^5 KIU/kg or 2.0 x 10^6 KIU at pump priming) does not significantly affect interleukin release[26]. In this study, low dose aprotinin was used at pump priming and was equally distributed over the three groups (table 1). We therefore think that the influence of aprotinin on interleukin concentrations in this study is negligible.

Another possible drawback is that cytokine concentrations in bronchoalveolar fluid were not obtained. Cytokines obtained from a BAL are specifically produced by the lung and may reflect the intrapulmonary inflammation more accurately. However, a BAL has the potential to transiently aggravate pulmonary dysfunction. In addition, a BAL reflects a local pulmonary inflammation status of one pulmonary lobe. To avoid a possible bias of a BAL on the effect of mechanical ventilation on pulmonary inflammation, we did not perform a BAL.

Conclusion:

We conclude that in cardiac patients, OLC ventilation leads to an attenuated inflammatory response, presumably by reducing additional lung injury. In addition, early application of the OLC has a more pronounced effect on pulmonary inflammation compared to late application of this ventilation strategy. Studies on cytokines after cardiac surgery should take these findings into account.

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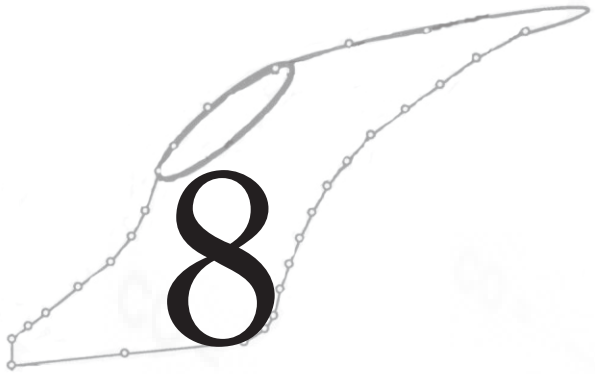

8

General discussion and prospects

Cardiac surgery is often associated with a pulmonary inflammatory response and this inflammatory reaction often develops sub-clinical. Although the functional residual capacity (FRC) of cardiac surgery patients decreases up to 40-50% during the first 24 hours after extubation, in general surgery patients the FRC decreases by only 20-30% after extubation. This exaggerated decrease of FRC after cardiac surgery is not yet fully understood, but has been attributed to pulmonary inflammation initiated by cardiac surgery (including the cardiopulmonary bypass procedure), and exacerbated by mechanical ventilation. Specifically, it is now established that conventional mechanical ventilation itself can cause damage to the lung in critically ill patients, also known as ventilator-induced lung injury (VILI).

One of the main results of the present thesis is that early initiation of mechanical ventilation according to the open lung concept leads to a significantly better preservation of FRC and better oxygenation several days after extubation when compared to conventional ventilation. A decreased FRC is associated with postoperative pulmonary dysfunction[1]. After cardiac surgery, respiratory dysfunction accounts for 40% of the readmissions on the ICU[2;3].Chung et al.[4] have shown that each percent increase of inspired oxygen fraction on discharge from the ICU, increases significantly the risk of readmission (odds ratio 1.09). Several other attempts to preserve FRC after extubation in cardiac [5] and upper abdominal surgery patients[6] have been without success. Because open lung ventilation leads to an increased FRC and reduced incidence of hypoxemia after extubation, the incidence of ICU readmission might be reduced by early application of open lung concept ventilation. Therefore,

appropriate outcome studies should be performed to investigate the effect of open lung ventilation on postoperative morbidity after cardiac surgery. In this respect, especially studies on FRC loss and recovery should improve our insight into therapeutic approaches.

The timing of initiation of the application of the open lung concept is still not clear. In this thesis, we showed that early (immediately after intubation) initiation of ventilation according to the Open Lung concept attenuated pulmonary dysfunction better than late (after arrival on the ICU) initiation. However, in the open lung theory, pulmonary dysfunction is mainly caused by cyclical collapse of alveoli, which is not expected in the non-ventilated lung during surgery. Additionally, surgical exposure may need interruption of the ventilatory strategy. Therefore, the efficacy of maintaining the lung open during cardiopulmonary bypass on pulmonary function remains to be established.

Concerns about right ventricular afterload increment (or even right ventricular failure) during open lung ventilation were in the past important reasons to not apply open lung ventilation. In this thesis, right ventricular afterload was not increased by open lung ventilation, using various methods to assess right ventricular afterload, experimentally as well as in cardiac surgery patients. These patients were not in severe right ventricular failure. Because a recruitment maneuver increases right ventricular afterload for approximately 10 seconds[7;8] it remains to be established whether this procedure can be tolerated by patients in severe right ventricular failure. This is therefore also an important marker of further studies.

We conclude that ventilation according to the Open Lung concept attenuates pulmonary dysfunction after cardiac surgery. The beneficial effect of this ventilation strategy is best when applied immediately after intubation. Ventilation according to the Open Lung concept does not affect right or left ventricular afterload or contractility.

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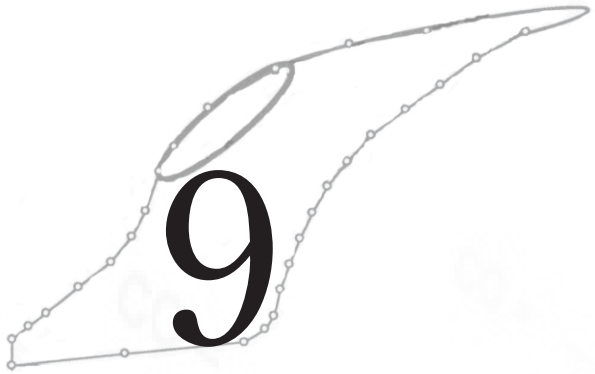

9

Summary

Samenvatting

Summary

In **Chapter 1** the mechanisms of ventilator-induced lung injury (VILI) are discussed. In this chapter, it is suggested that application of the Open lung concept (OLC) could attenuate VILI. This latter ventilation strategy avoids shear forces generated by repetitive opening and closing of atelectatic lung areas. This can be accomplished by applying a recruitment maneuver and the use of elevated positive end-expiratory pressure (PEEP).

However, elevated PEEP may increase intrathoracic pressure, which may in turn compress pulmonary capillaries, thus increasing right ventricular (RV) afterload. The right ventricle is known to be very sensitive to changes in afterload. RVafterload is a difficult concept to assess because parameters which solely depend on RV afterload are lacking. In **Chapter 2** we review how to assess RV afterload, as well as the effect of increased airway pressures on RV afterload.

The effect of OLC ventilation on both RV afterload and on left ventricular function is evaluated in an experimental model, described in **Chapter 3.** Because most afterload parameters are also dependent on contractility, this chapter focuses on RV contractility. RV contractility was measured by the load-independent parameter end-systolic pressure-volume relationship and the preload-recruitable stroke work (both explained in chapter 2). Neither RV contractility nor RV afterload were affected by OLC ventilation. Application of the OLC during and after cardiac surgery attenuated interleukin (IL) release compared to conventional mechanical ventilation.

Also in patients undergoing cardiac surgery, the RV afterload was not increased during ventilation according to the OLC. In **Chapter 4** twenty four patients were randomized to receive ventilation either according to the OLC or to CMV. Whereas patients in the OLC group received 17 cm H_2O PEEP and patients in the CMV group received 5 cm H_2O PEEP, indices of RV afterload were comparable between the two groups.

In **Chapter 5**, the separate effects of PEEP and peak inspiratory pressure on RV afterload were investigated during OLC ventilation and during CMV. RV impedance (reflecting RV afterload) was assessed by use of the echo-Doppler flow signal in the pulmonary artery. Doppler echocardiography allows beat-to-beat measurements, allowing inspiratory and expiratory measurements of the right ventricular impedance. During expiration, no differences were seen between the two ventilation strategies. Surprisingly, no increment in RV impedance during inspiration compared to expiration was seen during OLC ventilation. However, in the CMV group, inspiration significantly increased RV impedance compared to expiration. This inspiratory increase of RV impedance during CMV has also been reported others. The fact that RV impedance increment does not occur during ventilation according to the OLC may be attributed to the reduction of atelectasis and thereby the reduction of hypoxic pulmonary vasoconstriction. Another explanation for this result is the lower tidal volume used during OLC ventilation (6 versus 8 ml/kg).

In **Chapter 6**, it was demonstrated in sixty-nine cardiac surgery patients that early application of OLC ventilation attenuates pulmonary dysfunction, even days after extubation. In this study, patients were divided into three groups: 1) conven-

tional mechanical ventilation (CMV), 2) OLC started after arrival on the intensive care (Late Open Lung, LOL), and 3) OLC started directly after intubation (Early Open Lung, EOL). FRC was significantly higher in the EOL group compared to CMV. Moreover, the occurrence of hypoxemia during the first three days after extubation decreased dramatically with the application of OLC ventilation.

In the same study, it was also demonstrated that pulmonary inflammation was decreased using OLC ventilation. IL-8 (a pro-inflammatory cytokine produced by alveolar macrophages) decreased significantly in both OLC groups compared with CMV. IL-10 (which is an anti-inflammatory cytokine) decreased only in the EOL group. These results suggest an attenuated primary lung injury during early application of OLC, described in **Chapter 7**.

This thesis shows that early application of the OLC in cardiac surgery patients attenuates pulmonary dysfunction without affecting RV afterload or RV contractility.

Samenvatting

Hartchirurgie gaat gepaard met een pulmonale onstekingsproces. De gevolgen hiervan verlopen meestal subklinisch. Functionele residue capaciteit (FRC) na hartchirurgie, daalt echter wel met 40-50% gedurende de eerste 24 uur na extubatie terwijl na algemene chirurgie, FRC slechts met 20-30% daalt. Deze FRC daling na hartchirurgie is het resultaat van een pulmonale onstekingsproces, geïnitieerd door hartchirurgie zelf (inclusief de cardiopulmonale bypass procedure) of door mechanische beademing van de long. Het is de afgelopen jaren gebleken dat mechanische beademing van de long long schade kan veroorzaken in ernstig zieke patienten. Deze schade door beademing wordt ook wel "ventilator induced lung injury" (VILI) genoemd. In het **eerste hoofdstuk** worden de mechanismen van VILI besproken. Hierin wordt gesuggereerd dat beademing volgens het Open lung concept (OLC) het ontstaan van VILI verminderd. Deze beademingsstrategie voorkomt het herhaaldelijke openen en sluiten van gecollabeerde lungblaasjes. Dit kan worden bereikt door een recruitment maneuver gevolgd door relatief hoge positieve eind-expiratoire druk (PEEP).

Hoge PEEP waarden kunnen de intrathoracale druk verhogen, welke weer de pulmonale capillairen kunnen comprimeren en zo de weerstand (=afterload) voor de rechter ventrikel (RV) wordt verhoogd. De RV is zeer gevoelig voor veranderingen in afterload. Parameters die RV afterload weergeven zijn meestal moeilijk te meten omdat ze ook afhankelijk zijn van contractilieit. Hoe RV afterload te meten en

het effect van verhoogde beademingsdrukken op RV afterload wordt behandeld in **hoofdstuk 2**.

Hoofdstuk 3 beschrijft het effect van OLC beademing op de afterload van zowel de rechter ventrikel als de linker ventrikel in een experimenteel diermodel. Aangezien meeste parameters die afterload beschrijven, ook afhankelijk zijn van contractiliteit, wordt in dit hoofdstuk met name aandacht geschonken aan RV contractiliteit. RV contractiliteit was bepaald met de weerstands onafhankelijke parameter "end-systolic pressure volume relationship" en de "preload-recruitable stroke work", beide uitgelegd in hoofdstuk 2. RV contractiliteit en RV afterload veranderde in deze studie niet gedurende OLC beademing.

Ook bij patienten na hartchirurgie leidde het gebruik van beademing volgens het OLC niet tot een RV afterload stijging. In **hoofdstuk 4** zijn 24 patienten gerandomiseerd in beademing volgens het OLC en volgens CMV. Terwijl patiënten in de OLC groep 17 cm H_2O PEEP kregen en patiënten in de CMV groep 5 cm H_2O PEEP, waren de RV afterload parameters vergelijkbaar tussen de groepen.

In **hoofdstuk 5** zijn de verschillende effecten van PEEP en piek inspiratoire druk gedurende OLC beademing en CMV met elkaar vergeleken. RV afterload was bepaald met behulp van het echo-Doppler signaal in de a. Pulmonalis. Met Doppler echocardiografie kan men gedurende iedere hartslag RV belasting meten. Zodoende kan RV belasting worden gemeten gedurende inspiratie en expiratie (zie ook hoofdstuk 2). Gedurende expiratie (PEEP effect) zijn geen verschillen gevonden in RV belasting tijdens de verschillende beademings strategieën. Echter, tijdens OLC beademing is geen RV belasting stijging waargenomen gedurende inspira-

tie in vergelijking met expiratie. Gedurende CMV is deze stijging van RV belasting gedurende inspiratie wel gezien. Deze RV belasting stijging gedurende inspiratie is ook door andere autheurs gevonden gedurende CMV beademing. De verklaring dat gedurende OLC beademing de RV belasting niet stijgt gedurende inspiratie kan gelegen zijn in het feit dat gedurende OLC beademing minder atelectase is, en daardoor minder hypoxische pulmonale vasoconstrictie. Een andere verklaring is dat het teugvolume gedurende OLC beademing lager is vergeleken met CMV (6 vs 8 ml/kg).

In **hoofdstuk 6** is bij 69 patiënten na hartchirurgie gezien, dat vroege start van open long beademing, pulmonale disfunctie vermindert, zelfs dagen na extubatie. In deze studie zijn de patiënten verdeeld over 3 groepen: 1) conventionele beademing (CMV), 2) OLC gestart na aankomst op de intensive care (LOL), en 3) OLC gestart onmiddellijk na intubatie (EOL). FRC was significant hoger in de EOL groep vergeleken met de controle groep. Dit effect houdt tenminste 5 dagen na extubatie aan. FRC was ook hoger in de LOL groep vergeleken met CMV, echter, dit effect verdween 3 dagen na extubatie. In beide OLC groepen daalde het voorkomen van hypoxemie fors in vergelijking met CMV, tot tenminste 3 dagen na extubatie.

In de zelfde studie werd ook aangetoond dat pulmonale inflammatie verminderd werd door het gebruik van open long beademing. IL-8, een pro-inflammatoire cytokine geproduceerd in alveolaire macrofagen, daalde sneller in beide OLC groepen in vergelijking met CMV. IL-10, een anti-inflammatoire cytokine, daalde alleen sneller in de EOL groep. Dit suggereerd een verminderde long beschadi-

ging gedurende vroegtijdige start van beademing volgens het OLC, beschreven in **hoofdstuk 7**.

Dit proefschrift toont aan dat een vroege start van beademing volgens het OLC tot een verminderde pulmonale dysfunctie leidt, zonder RV afterload of RV contractiliteit te beinvloeden bij hart chirurgische patienten.

Dankwoord:

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Jasper van Bommel: Mix een flinke dosis vriendschap, plenty of biertjes, een mooie scheut intelligentie met nuchtere logica en Jasper is beschreven. Bedankt dat je mij bij wilt staan tijdens de openbare verdegiging en voor jou luisterend oor, sigaretten, en menig wetenschappelijke discussies tijdens hardlopen of in de kroeg. Word zeker vervolgd!

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Ronald Schepp: Jij paste het open long concept bij cardiochirurgische patiente al toe, lang voordat wij het onderzochten. Je (terechte) geloof daarin was zo groot dat je ervan baalde dat een deel van je patiënten in de controle groep zat. Ronald, het was heerlijk om met je samen te werken en bedankt voor de vele uren longfysiologie.

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Alle collega's van anesthesie: Metingen verrichten betekent vaak dat je niet beschikbaar bent voor de OK. Bedankt voor het opvullen van deze hiaten. Gert-Jan Los, jou moet ik extra bedanken dat je iedere keer maar weer het rooster hebt aangepast.

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En wie ongetwijfeld het meest geleden heeft is de vrouw wiens man zondag het vlees kwam snijden. Onze vrije tijd gedurende deze jaren hebben grotendeels 2 opties gekend: metingen doen of de resultaten daarvan opschrijven. Dat we nu nog samen zijn is merendeel aan jouw kwaliteiten te danken.

Nu dit boekwerk klaar is, ...

Curriculum Vitae

Dinis dos Reis Miranda werd op 28 september 1971 geboren in Lissabon, Portugal. Hij volgde het middelbaar onderwijs aan het Werkman College te Groningen. In 1990 begon hij met de studie Bewegingswetenschappen aan de Vrije Universiteit Amsterdam. In 1996 voltooide hij deze studie met als hoofdvak Inspanningsfysiologie. In 1992 begon hij met de studie Geneeskunde wederom aan de Vrije Universiteit Amsterdam. In 1999 werd het artsexamen behaald. Van januari 2000 tot en met november 2005 volgde hij de opleiding tot anesthesioloog aan de Erasmus Universiteit te Rotterdam (hoofd Prof. dr. J. Klein). In deze periode werd onder begeleiding van dr. D. Gommers het onderzoek uitgevoerd, waarvan de resultaten in dit proefschrift beschreven staan. In oktober 2005 beeindigde hij zijn opleiding tot anesthesioloog. Sinds 1 november 2005 is hij werkzaam als fellow Intensive Care in het Onze Lieve Vrouwe Gasthuis, te Amsterdam (hoofd Prof. dr. D. Zandsta). Een jaar later zal hij de Intensive Care opleiding voltooien en werkzaam zijn als anesthesioloog-intensivist in the ErasmusMC te Rotterdam (hoofd Prof. dr. J. Bakker).

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