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Lund Concept for De-airing of the Left Heart

Clinical Evaluation

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Lund Concept for De-airing of the Left Heart

Clinical Evaluation

Maya Landenhed Smith, MD

Doctoral Thesis

With due permission from the Faculty of Medicine, Lund University, to be
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Abstract Background: Residual air accumulated in the pulmonary veins constitutes a challenge to achievement of complete de-airing in open left heart surgery. To adress this problem, a conceptual method for de-airing was developed in Lund comprising bilateral opening of the pleurae to induce pulmonary collapse and a strategy with gradual pulmonary reperfusion and ventilation at weaning from cardiopulmonary bypass (CPB). Aim: To evaluate effectiveness and safety aspects of the Lund concept for de-airing. Methods and results: In the first paper a randomized controlled study was conducted comparing the Lund method to a standardized carbon dioxide (CO₂) insufflation technique in twenty patients undergoing open left heart surgery. Microembolic signals (MES) as monitored by transcranial Doppler sonography were fewer in the Lund method group during and after de-airing. Residual intracardiac air was graded by transesophageal echocardiography (TEE) and lower grades were found in the Lund method group in which de-airing times also were shorter compared to the CO₂ insufflation group. In the second paper, systemic side-effects of CO₂ insufflation were studied in the same twenty patients. Patients in the CO₂ insufflation group developed hypercapnic acidosis despite compensational higher gas flows in the oxygenator. CO₂ production increased during CPB as did the respiratory quotient secondary to insufflated CO₂. The mean blood flow velocities in both MCAs increased secondary to increasing PaCO₂ as did rSO₂ measured by near-infrared spectroscopy. Scanning electron microscope imaging of the cardiotomy suction and LV vent line tubing showed a higher fraction of morphologically abnormal red blood cells in the CO₂ insufflation group. In the third paper we aimed to study the contribution of each component constituting the Lund concept. In a randomized controlled study of twenty patients undergoing open left heart surgery, we compared a group with open pleurae and conventional pulmonary reperfusion and ventilation to a group with intact pleurae combined with staged pulmonary reperfusion and ventilation. During de-airing and in the first ten minutes after CPB, there was a lower number of MES in the group with open pleurae. A lower amount of residual intracardiac air was also registered in the group with open pleurae after CPB. The LV vent was reopened fewer times in the group with open pleurae and the de-airing time was shorter in the group with open pleurae. In the fourth paper we studied the impact of single right pulmonary collapse on the Lund method and the effectiveness of a right superior pulmonary vein vent (RSPV). Twenty patients in two prospective cohorts with right pleura open and RSPV respectively, were compared to a historical control cohort from the first paper with bilateral open pleurae and left ventricular apical vent (LVAV). We found a higher number of MES after CPB, both in the group with single right pulmonary collapse and in the group with RSPV compared to bilateral pulmonary collapse and LVAV. No differences in residual intracardiac air graded by TEE or in de-airing times was found. Conclusion: The Lund concept for de-airing was demonstrated to be an effective and safe alternative to the CO₂ insufflation technique. The effectiveness of the Lund method depends primarily on bilateral pulmonary collapse and it may preferably be combined with a left ventricular apical vent.		
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Lund Concept for De-airing of the Left Heart

Clinical Evaluation

Maya Landenhed Smith, MD



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To the patients who participated in the studies of this thesis

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List of papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals. Reprints of the papers are appended at the end of the thesis with permission from the publisher.

- I Al-Rashidi F, Landenhed M, Blomquist S, Höglund P, Karlsson P-A, Pierre L, Koul B. *Comparison of the effectiveness and safety of a new de-airing technique with a standardized carbon dioxide insufflation technique in open left heart surgery: A randomized clinical trial.* J Thorac Cardiovasc Surg. 2011 May; 141(5):1128-33.
- II Landenhed M, Al-Rashidi F, Blomquist S, Höglund P, Pierre L, Koul B. *Systemic effects of carbon dioxide insufflation technique for de-airing in left-sided cardiac surgery.* J Thorac Cardiovasc Surg. 2014 Jan; 147(1):295-300.
- III Landenhed M, Cunha-Goncalves D, Al-Rashidi F, Pierre L, Höglund P, Koul B. *Pulmonary collapse alone provides effective de-airing in cardiac surgery: A prospective randomized study.* Perfusion. 2016 May; 31(4):320-6.
- IV Landenhed Smith M, Cunha-Goncalves D, Höglund P, Koul B. *Single right versus bilateral pulmonary collapse and right superior pulmonary vein vent versus left ventricular apical vent for de-airing in open left heart surgery.* (Manuscript)

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Abbreviations

AO	aortic root
CABG	coronary artery bypass grafting
CO ₂	carbon dioxide
CPB	cardiopulmonary bypass
CVP	central venous pressure
dB	decibel
ECC	extracorporeal circulation
HITS	high-intensity transient signals
LA	left atrium
LV	left ventricle
LVAV	left ventricular apical vent
MCA	middle cerebral artery
MES	microembolic signals
NIRS	near-infrared spectroscopy
PaCO ₂	arterial partial pressure of carbon dioxide
PEEP	positive end-expiratory pressure
rSo ₂	regional cerebral oxygen saturation
RSPV	right superior pulmonary vein vent
SEM	scanning electron microscopy
TCD	transcranial Doppler sonography
TEE	transesophageal echocardiography

Introduction

Improvements in surgical and anesthetic methods and in extracorporeal perfusion technology have resulted in improved outcomes of open heart surgery in recent years. Despite increasing age and comorbidity in patients referred for heart surgery, rates of mortality and stroke have decreased.¹⁻⁴ However, neurological impairment remains a significant postoperative complication after open heart surgery. Contemporary studies have estimated the overall incidence of neurological impairment of any type present at discharge to 2.1%-2.9% in single valve surgery and 5.3%-5.4% in combined and double-valve procedures.^{4,5}

Adverse neurological events after open heart surgery can be subclassified into two broad groups: focal ischemia typically caused by solid emboli, and global neurocognitive dysfunction, to which multiple factors may contribute. The most important determinants of global neurocognitive function after cardiac surgery include cerebral hypoperfusion, systemic inflammatory response syndrome secondary to surgical trauma and extracorporeal circulation (ECC), and arterial microembolization.⁶ Efforts to reduce exposure to each of these factors are warranted to further reduce risk of neurocognitive dysfunction after heart surgery. The work described in this thesis focused on surgical methods to reduce arterial microembolization, specifically by targeting gaseous microemboli.

Arterial microemboli

Arterial microemboli may be solid or gaseous in composition, both of which to some extent are associated with most invasive cardiac procedures. Solid microemboli may consist of blood clots, lipids, atherosclerotic plaque debris, or other tissue components.⁷ Gaseous microemboli may have various gas compositions, such as nitrogen (N₂), oxygen (O₂), carbon dioxide (CO₂), nitrous oxide (N₂O) or air (mainly consisting of N₂, O₂, CO₂ and argon).⁸

Gaseous microemboli may from the heart be redistributed through the systemic circulation to all tissues in the body.

Some tissues are more vulnerable to ischemia than others. For example, embolization from the heart to the coronary arteries may result in coronary occlusion and rapid development of cardiac ischemia and infarction, manifesting on the electrocardiogram as ST-segment elevation or depression and ultimately resulting in pump failure or ventricular arrhythmia.⁹ Neurons are even more sensitive to ischemia than cardiac muscle cells, resulting in necrosis within minutes. Large emboli may result in occlusion of cerebral arteries and rapid development of cerebral ischemia and infarction manifesting clinically as ischemic stroke. Most investigators agree that both solid and gaseous microembolization to the brain can result in damage to brain tissues, although the acute clinical consequences of cerebral microembolism may be discrete and difficult to measure.

The definition of microemboli reflects the ability of the emboli to enter the microcirculation. Although a suggested upper size limit to 1000 μm for the distinction between micro- and macroemboli, particularly in the context of gaseous microemboli, the majority of gaseous microemboli reaching the middle cerebral arteries (MCAs) during cardiac surgical procedures are estimated to approximately 20 to 70 μm .¹⁰ The finest capillaries have a diameter of down to 4 μm , and despite a larger diameter, gaseous microemboli may deform and pass through the capillary from the arteriole to the venule.

Several negative effects of microemboli to the brain have been described. First, microemboli lodged in a vessel may result in occlusion causing ischemic neuronal damage. Sodium and water then enters the neuron as metabolic functions fail and cytotoxic edema develops.¹¹ Second, the movement of the microemboli through the capillary may result in mechanical stress to the endothelial lining and cause vasogenic edema and inflammation.¹² This mechanism has been suggested to explain why gaseous microemboli, even if passing through the capillary network, can impose damage, and that such damage can extend beyond the area immediately surrounding the affected vessel.⁸

Gaseous microemboli and postoperative neurocognitive dysfunction

Open cardiac surgical procedures are associated with higher numbers of MES than CABG surgery.¹³ The major part of MES is gaseous while a lesser proportion is solid in composition.^{13, 14} The gaseous microemboli observed during cardiac surgery mainly originate from the ECC circuit¹⁵ or from the cardiac chambers and the pulmonary veins as a consequence of the opening of the left heart during the surgical procedure.¹⁶ Arterial filters incorporated in the ECC circuit can weed out gaseous microemboli larger than 40 μm , leaving smaller microemboli to freely circulate.

As gaseous emboli eventually resolve, they are often considered to be less harmful than solid emboli.¹⁷ An air bubble with a diameter of 4000 μm is estimated to be absorbed in 560 minutes when surrounded by flowing blood.¹⁶ However, most cerebral microemboli are thought to be smaller than 40 μm , and thus should be absorbed considerably faster.¹⁸ However, there is evidence that the process of absorption of the gaseous microemboli by surrounding blood may be slowed down, as the microbubble becomes coated with proteins, platelets and leukocytes aggregating to its surface.¹⁹ In addition, small microbubbles may fuse together and create larger bubbles, a process called coalescence.^{8, 20}

Although the hazards of introduction of air into the circulatory system are obvious, there is ongoing controversy as to whether association of gaseous microemboli with brain damage reflects causality.²¹ Massive air embolism rapidly results in seizures, coma, circulatory collapse and often death,²² but proving the deleterious effects of small amounts of intravascular air is more difficult.⁸ A complicating factor when addressing the potential causality of gaseous microemboli to postoperative neurocognitive dysfunction after heart surgery is the difficulties in separating the impact of the often correlated cerebral stressors from each other, i.e. cerebral hypotension, effects of extracorporeal circulation and solid and gaseous microembolism.

Symptoms of postoperative neurocognitive dysfunction described in the literature include loss of memory, concentration difficulties and in some cases also acute confusional and delirious states.¹⁶ In a common classification, initially described in a multicenter study of coronary artery bypass surgery (CABG), neurocognitive outcomes after CABG were categorized in two types of deficits.²³ Type I outcomes were defined as focal neurological deficits, stupor or coma present at discharge. Type II outcomes

were defined as deterioration in intellectual function, disorientation, memory loss or seizures without evident focal injury. Neurocognitive deficits associated with gaseous microemboli are categorized as type II. Other terms used to express the global encephalopathy encountered in the context of gaseous microemboli are postoperative cognitive decline (POCD) and transient neurological dysfunction (TND).²⁴⁻²⁶ POCD and TND are typically most severe in the first weeks after surgery and diminish gradually at repeated cognitive tests during 4–6 months after surgery.²⁷ Although these neurocognitive symptoms are mostly transient, postoperative impairments are associated with increased morbidity and mortality.⁵

In these studies, it has been difficult to prove a causal effect between the load of cerebral microemboli and neurological type II outcomes. Furthermore, although studies based on neurocognitive testing often have failed to find associations with MES, findings from investigation by functional or diffusion weighted magnetic resonance imaging have been shown to correlate with intraoperative findings of MES.^{13,28}

Methods for visualization of gaseous microemboli

Transesophageal echocardiography

Transesophageal echocardiography (TEE) was developed as an extension of transthoracic echocardiography with transesophageal positioning of the probe with the initial intention of allowing improved visualization of the heart and aorta in patients with severe obstructive pulmonary disease and emphysema, thus avoiding the negative influence of intrapulmonary air on the image quality.²⁹ TEE is considered a semi-invasive investigation, with a reported incidence of the most serious complication, namely esophageal rupture, of between 0.01% - 0.09%.³⁰ The initial reports on how air in the cardiac chambers and aorta could be visualized by one-dimensional M-mode echocardiography during cardiopulmonary bypass were published in the early 1980s.^{31, 32} Two-dimensional (2-D) echocardiography provides anatomic images of cross-sections of the heart chambers making interpretation during surgery more accessible. Large quantities of pooled intracardiac air creates acoustic shadowing as ultrasound waves are reflected at the soft tissue/air intersection.³³ Smaller quantities of air, microbubbles, are visible on 2-D echocardiography as white “flakes” against a black background as the air bubbles scatter the ultrasound waves

differently from blood.³⁴ The first reports described probe placement directly on the cardiac surface (epicardial echocardiography).^{35, 36} The development of high-frequency transducers suitable for transesophageal placement followed, and now enables TEE in routine practice, which is recommended by current clinical practice guidelines during open heart procedures.^{37, 38}

When the aorta is cross-clamped, circulating microemboli can be visualized by TEE pulse wave Doppler in a long-axis view of the thoracic descending aorta.³⁹ Observation for the occurrence of microbubbles in the cardiac chambers and the aortic root, is relevant mainly after cross-clamp removal, as the heart otherwise is empty. The sensitivity and specificity of TEE for detection of intracardiac air has in animal studies proven to be complete (100%) when 1 mL of air was injected into the left ventricle generating detectable microbubbles in the size of 2–125 μm .³¹ Quantification of intracardiac microbubbles for research purposes can be done by counting all visible air bubbles in the field⁴⁰, or by grading the severity of visible air.^{41, 42} Three-dimensional (3-D) echocardiography permits even more precise real-time anatomical visualization, and as the technique develops, it most likely holds future possibilities for imaging of the de-airing process.

Transcranial Doppler sonography

Detection of cerebral gaseous microembolic signals (MES) during cardiac surgery was described by Spencer and Sauvage in 1969, when they applied Doppler ultrasonic sensors to the ECC circuit lines, directly on the innominate artery and transcutaneously on the carotid arteries.⁴³ Aaslid and colleagues later (1982) introduced monitoring of intracranial vessels, through insonation of the temporal acoustic window.⁴⁴ Transcranial Doppler sonography combines ultrasound and Doppler technique to assess the velocity of blood in the intracranial vessels and to detect emboli in the blood stream. Although both the middle, anterior and posterior cerebral arteries are available for investigation through the temporal window, the middle cerebral artery (MCA) is often considered suitable for continuous monitoring during cardiac surgery as it supplies a large part of the brain. The temporal acoustic window is situated close to the temple above the lateral aspect of the zygomatic arch and 1-5 cm anterior to the ear. In approximately four individuals out of five, the thickness of the temporal skull is thin enough to allow visualization of intracerebral vessels by TCD.

In the clinical setting, TCD is used for detection and monitoring of vasospasm after subarachnoid hemorrhage, screening of stroke risk in children with sickle cell disease, and increasingly, as a complement to echocardiography in investigation of paradox embolism secondary to persistent foramen ovale (PFO). The development of multifrequency probes and signal analysis of the TCD software have enabled on-line counting of emboli and automatic rejection of artifacts.⁴⁵ MES are also referred to as high-intensity transient signals (HITS).⁴⁶ The detection of these signals is possible because embolic particles, whether they are solid or gaseous, have different acoustic impedance properties compared to the surrounding red blood cells. As the emitted ultrasound wave is scattered and returned to the receiver by the embolus, an increase in Doppler power is generated. The Doppler power is the product of the increase in relative Doppler power (dB) and its duration (ms).⁴⁵ As HITS, or MES, must be distinguished from the background noise produced by the random movements of red blood cells, a threshold must be set, such that only MES which are generating an energy increase above the background scatter are detected. A threshold for discriminating MES is often set between 3 to 9 dB above background level as the relative intensity increase of the Doppler speckle background in healthy subjects with no microemboli or artifact provocation is approximated to lie within this range.⁴⁷

The first multifrequency TCD system with an automatized counting system with artifact rejection was evaluated in vitro and in vivo. The in vitro studies resulted in a sensitivity of 100% to detect and distinguish microbubbles with a diameter of 8 to 25 μm and specificity 99.3%. In the same study, in vivo assessment of MES in patients with carotid artery stenosis and mechanical heart valves resulted in a sensitivity of 98.6% and a specificity of 97.2% to correctly distinguish MES from artifacts.⁴⁵

Except for detection of microemboli, TCD is also used for determination of blood flow velocity in cerebral arteries. The Doppler Effect is the change to a higher frequency of ultrasound waves approaching the receiver, and a lower frequency of waves moving away from the receiver. Even though TCD is not able to measure the exact quantity of cerebral blood flow, there is a good correlation between changes in cerebral blood flow and mean cerebral artery blood flow velocity if the diameter of the MCA is assumed to be constant.^{48, 49} TCD can be used for assessing physiologic vasomotor reactivity secondary to increases in PaCO_2 , either by inhalation of air with a high CO_2 content, or simply by breath holding.⁵⁰ Determination of the cerebrovascular reserve by CO_2 reactivity can be useful for example to

evaluate the risk of stroke in patients with asymptomatic carotid stenosis to help making decisions about preventive carotid endarterectomy.⁵¹

Methods for prevention of air emboli in open heart surgery

De-airing of the heart is the term describing the intentional actions undertaken to remove air trapped inside the heart chambers and the aortic root, thus preventing the formation of air emboli. Meticulous removal of air is of special importance when the left heart, meaning, the left atrium, the left ventricle or aortic root have been opened and exposed to ambient air. Residual air which is not removed from the left-sided heart chambers, is likely to escape to the systemic arterial system as air emboli and occlude ordinary blood flow in capillaries until eventually absorbed.²² The hazards of systemic air embolism were acknowledged already in the advent of cardiac surgery. Today, the prevention of air embolism during cardiac surgery is a multidisciplinary teamwork and depends on the coordinated actions of the surgeon, anesthesiologist and perfusionist.

Filtration of blood in the extracorporeal circulation circuit

Gaseous microemboli during cardiac surgery originates from several sources including the surgical field, the venous line, the cardiotomy reservoir and oxygenator, from the process of cavitation in the ECC lines and from infusions given into central venous catheters or directly in the ECC circuit.⁵² The extracorporeal circulation circuit has an integrated system of filters, inserted at different levels of the system to decrease the number of both solid and gaseous microemboli circulating in the blood during cardiopulmonary bypass. Very briefly, a low level sensor on the venous reservoir and a bubble detector encircles the tubing of the arterial line alarm and stops the circulation in the heart-lung machine at the occurrence of large scale air emboli. The venous reservoir contains a filter which collects air bubbles and debris in the blood from the venous returns. The hollow fiber membrane oxygenator effectively removes the vast majority of gaseous microemboli. In addition, an air filter in the oxygenator may be integrated, or a standalone arterial filter may be used instead, ranging in screen pore size from 21 to 40 μm . The reduction of gaseous microemboli by in vitro testing of these filters when injecting 10 mL of air

directly in to the filter inlets, showed that the smaller the pore size the greater the ability of removing gaseous microemboli.⁵³ Arterial filters of 40 μm pore size with coating applied to attract activated leukocytes were as effective as the smaller pore size filters of 21 μm .⁵⁴

Mechanical de-airing maneuvers

Mechanical de-airing of the heart before weaning of cardiopulmonary bypass can be performed using various techniques often involving passive filling of the heart chambers to expel air before final closure of the cardiectomy. Air trapped in the lung veins is mobilized by increasing the pressure in the pulmonary parenchyma by ventilation, thus squeezing air from the pulmonary veins to the left atrium. The aortic root is commonly de-aired passively, but may, however, be emptied from air mixed with blood through active suctioning. TEE guidance is important in identifying trapped air in the aortic root and heart chambers. Common sites of retention of pooled air are the pulmonary veins, the left atrium, under valve leaflets and between trabecula in the left ventricle (LV) and LV apex and the right coronary sinus of Valsalva.³³ In successive steps this air can be evacuated by manual manipulation of the heart or tilting of the operation table, using the up thrust forces of air in blood.⁵⁵

The Trendelenburg position, which comprises the tilting of the head in a downward position before resumption of normal circulation to redirect air to the highest point away from the cerebral circulation, is often used as a complement to other de-airing techniques. In an animal model, the volume of air injected into the aorta and hereafter reaching the carotid arteries decreased as the head was tilted to a plane below the ascending aorta.⁵⁶ However, a more recent study using TCD to assess gaseous cerebral microemboli in children undergoing left-sided heart surgery failed to demonstrate any benefit for the Trendelenburg position compared to the horizontal head position at cross-clamp removal.⁵⁷ Although blood pressure often is not very high early after CPB weaning, it should be kept in mind that the efficacy of a head-down position can be insufficient in preventing cerebral emboli, if blood flow velocities are higher than the up thrusting forces of buoyancy on air.⁵⁸ Assembling air in a pocket at the highest point of the aorta by partial cross-clamping and redirecting residual air to an aortic vent can be used to aid de-airing.⁵⁹ Digital carotid compression during aortic cannulation and at aortic cross-clamp removal in patients with no hemodynamically significant carotid artery stenosis had some effect on the

reduction of solid microemboli, but not on gaseous.¹⁴ Air in the aortic root is often removed through the cardioplegic catheter if such is used for administration of antegrade cardioplegia. In addition, needle aspiration of the aorta, the left atrial appendage or the left ventricle can be required to evacuate pooled air using a vacuum device or more commonly, by a bore needle alone.⁶⁰ In addition to the techniques described above, in general, a drain is often inserted into the left ventricle to de-air the heart.

Venting of the left ventricle

A drain is often used in open heart surgery procedures to either drain the cardiac chambers from blood, creating better visualization, or to vent the chambers from air. In addition, a drain can be used to decompress the left ventricle during reperfusion. By avoiding overdistention of the heart muscle, the oxygen consumption in myocardial cells is decreased, and the subendocardial perfusion pressure is increased.⁶¹ This can enhance recovery of cardiac function after cardiopulmonary bypass. Although the possibility of venting with a drain placed in the pulmonary artery⁶² should be mentioned, the most common drain site is nevertheless the left ventricle.⁶³ A drain can be inserted directly through the aortotomy and the aortic valve orifice for temporary improvement of visualization during an aortic root procedure but for de-airing purposes, a drain through the right superior pulmonary vein or through the left ventricular apex is most suitable.⁶³ The vent may be connected to the venous line of the ECC circuit. However, a roller pump is more often used to create a slight negative pressure for the suction of blood and air.

Left Ventricular Apical Vent

The left ventricular apical vent (LVAV) is introduced into the LV by a stab wound incision in the left ventricular apex lateral to the distal part of the left anterior descending artery (Figure 1). A silicone or polyvinyl chloride (PVC) catheter; often ranging in dimension from approximately 10 to 16 French is used as LV vent. The catheter may be secured with a pledgeted purse-string suture. Excessive suctioning in the vent line can cause damage to the left ventricle and promote entry of ambient air into the heart chambers. To prevent this, a valve placed in the vent line can be used to control high negative pressure.⁶⁴ Alternatively, the vent line tubing can be pierced by a small bore needle which is left in situ during CPB (Figure 1). Advantages of the LVAV are the reliable positioning in the left ventricle and effective removal of air and blood from the left ventricular cavity

without interference with the mitral valve.⁶⁵ Several published reports describe surgical complications secondary to LVAV including serious bleeding from the stab wound incision in the ventricular apex, hematoma and dissection of the ventricular wall⁶⁵ (Figure 2) and a contained myocardial rupture resulting in a ventricular pseudoaneurysm.⁶⁶⁻⁶⁸

Right Superior Pulmonary Vein Vent

The right superior pulmonary vein vent (RSPV), is often a malleable silicone or PVC catheter, bearing several side-holes, and introduced into the left atrium through a stab wound incision in the right superior pulmonary vein and hereafter advanced over the mitral valve orifice into the left ventricle (Figure 3). It is secured in position by a purse-string suture in the right superior pulmonary vein. The dimension of the catheter often ranges from 15 to 20 French. The position of the catheter in the left ventricle is preferentially controlled manually or by TEE as dislocation to the left atrium will result in dysfunctional LV venting. The benefit of the RSPV is its relative ease of insertion and less risk of surgical bleeding after its removal. A few cases have been reported of iatrogenic rupture of the left ventricle wall secondary to a RSPV being advanced too far into the LV.⁶⁹

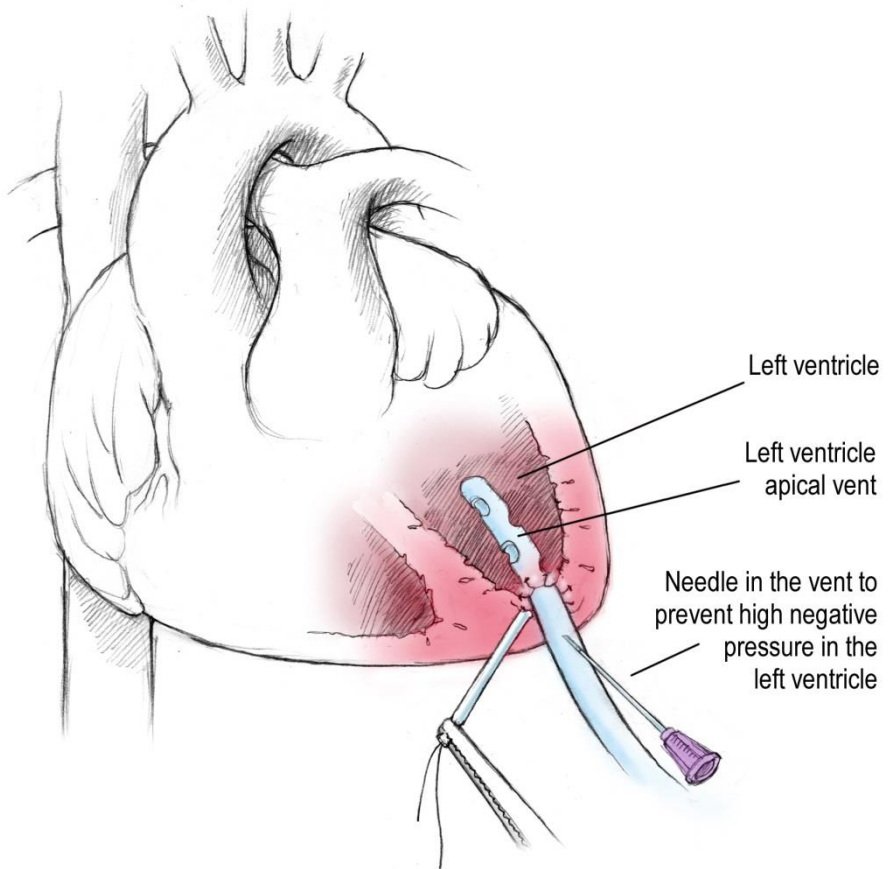


Figure 1. A left ventricular apical vent is positioned in the left ventricle through a stab wound incision in the left ventricular apex. A bore needle is used to pierce the vent or vent line tubing in order to prevent high negative pressure in the system that may damage the left ventricle.

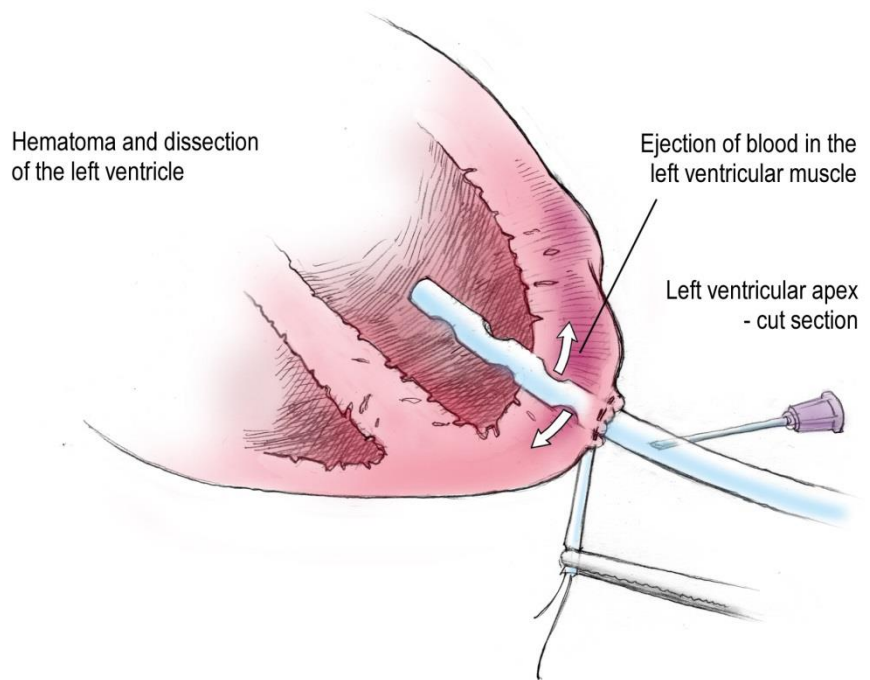


Figure 2. Hematoma and dissection of the left ventricular apical muscle caused by the ejection of blood through the side-holes of a displaced vent in the left ventricle.

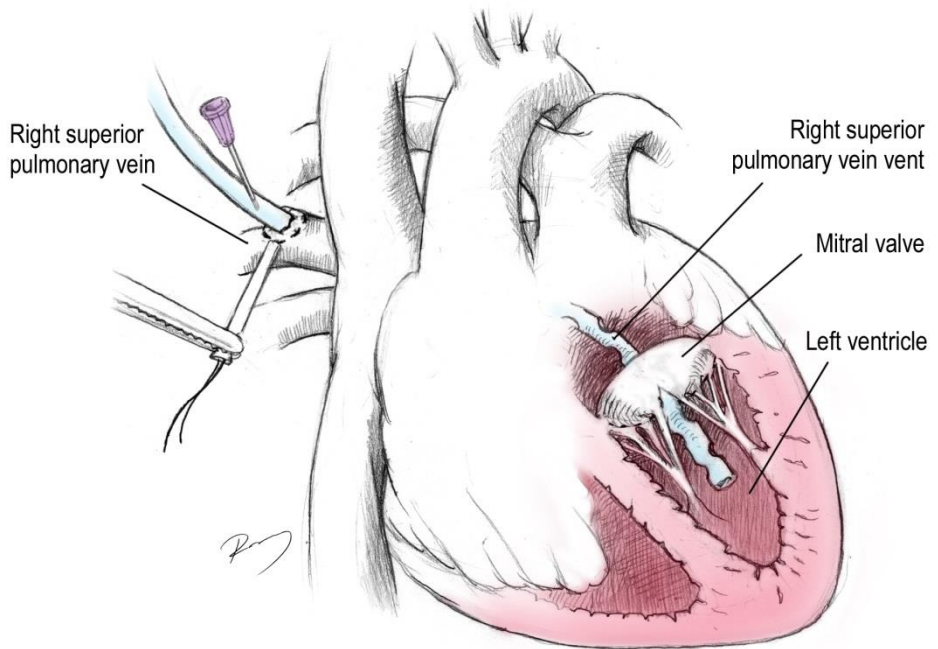


Figure 3. A right superior pulmonary vein vent is inserted into the left ventricle through a stab wound incision in the right superior pulmonary vein and advanced from the left atrium through the mitral valve to its final position in the left ventricle. The vent is pierced by a bore needle to control negative pressure in the left ventricle. Note how the side-hole bearing part of the vent is situated on both sides of the mitral valve, thus prioritising evacuation of air from the left atrium over to the left ventricle.

Carbon dioxide insufflation for cardiac de-airing

In addition to mechanical de-airing maneuvers, carbon dioxide (CO₂) insufflation of the open pericardial cavity is frequently used in cardiac surgery to reduce systemic arterial embolization during open heart surgery and even more frequently during minimal invasive open procedures. By flooding the pericardial cavity with carbon dioxide, air is prevented from entering the heart chambers because of the greater density of CO₂. Modern gas diffusion techniques provide effective topical CO₂ concentrations leaving less than 1% of ambient air in the gas-filled pericardial cavity.⁷⁰⁻⁷² In addition, the greater solubility of CO₂ in blood compared to ambient air entails faster resorption of CO₂ gas emboli, and thus decreases the duration of blockage of end capillaries and hereby prevents or decreases ischemia in organs.⁷³

Although first described in the late 1950s⁷⁴, only a few controlled clinical trials investigating the efficacy of CO₂ insufflation are available. In several of these studies, beneficial effects of CO₂ insufflation were demonstrated, as insufflation resulted in a significant reduction in residual intracardiac air emboli as observed by intraoperative TEE.^{40, 42, 75} Despite the clear findings of reduced systemic arterial air emboli and the appealing properties of CO₂, it has proven difficult to demonstrate that the CO₂ insufflation technique reduces postoperative neurological dysfunction. Three relatively large randomized controlled trials have evaluated the effect of CO₂ insufflation on postoperative neurocognitive function.^{41, 76, 77} In two of the studies, concentrations of CO₂ in the pericardial sac sufficient for effective displacement of the air content could be ensured.^{41, 77} No benefit of CO₂ insufflation could be demonstrated with neurocognitive testing.

However, a surrogate variable measuring the latency of auditory-evoked potentials indirectly succeeded in demonstrating a benefit of CO₂ insufflation to achieve neurocognitive protection.⁷⁷ CO₂ insufflation has been associated with hypercapnia in some reports, leading to the potential hazard of acidosis.^{78, 79} Other reports observed no such development despite adequate concentrations of CO₂ to the cardiothoracic wound.^{75, 80} However, there is wide agreement on active monitoring of the acid-base balance and preparedness for actions to counteract development of acidosis when using CO₂ insufflation for de-airing purposes.⁸¹

Lund concept for cardiac de-airing

The Lund concept for de-airing of the left heart was first described in 2009.⁸² It was evaluated in a controlled clinical study in which it was found to be clinically applicable.⁸³ The idea behind the Lund concept, developed by Dr. Bansi Koul, came from intraoperative observations, of how temporary occlusion of the pulmonary veins before opening of the left heart, and hereby preventing air from entering the pulmonary veins, had a positive effect on de-airing of the left heart. The theory underlying the Lund method was further supported by echocardiographic studies, which demonstrated that residual air following open heart surgery, which in particular emanates from the pulmonary veins, could be reduced.

The Lund concept for de-airing comprises of the following steps and assumptions; first, after sternotomy the mediastinal pleurae are opened. After institution of cardiopulmonary bypass, the patient is disconnected from the ventilator. This leads to bilateral collapse of the lungs, and as the patient is lying in the supine position, the lungs tend to fall dorsally in the empty pleurae. As the lungs fall backwards, a functional kink of the pulmonary veins may be created at the level of the pulmonary hili. Theoretically, this kink would function as a mechanical obstacle, or similar to a water seal, to prevent air from entering the lung veins. In addition, the anterior, non-dependent segments of the lung, like the rest of the lung, are minimized in volume during collapse and the vessels cannot accommodate as much air as if lungs were left in an expanded state. At the end of the surgical procedure, the aortic root is emptied from air by application of active suction followed by the release of the aortic cross-clamp. The heart and lungs are gradually refilled with blood from the ECC circuit under the direct visual guidance of TEE. In order to empty the pulmonary vessels from air that have gotten past the kinked pulmonary hili, the right ventricle is required to produce enough pulmonary artery pressure to overcome the vertical height of the collapsed pulmonary vascular bed in relation to the position of the right ventricle. In order to completely fill the entire pulmonary vasculature with blood in an expanded lung state, the right ventricle must manage to eject almost the full cardiac output of blood to push all air forward into the left atrium and left ventricle where it can be evacuated by an appropriate vent. In a collapsed lung the non-dependent parts of the lungs are situated in a more posterior plane than normal. Because of these circumstances, a lower pulmonary artery pressure and a lower right heart cardiac output is required to flush out all air from the entire pulmonary vasculature. This reduces the work load of the right ventricle,

which often during the early phase of weaning from CPB, is temporarily less efficient.

The next step of the de-airing procedure is commenced after the lungs are well filled with blood and heart chambers and aortic root are free from air as visualized by TEE. The patient is now connected to the ventilator and ventilation is successively increased in a stepwise manner that includes positive end-expiratory pressure (PEEP) of 5 cm H₂O in order to evacuate any residual air emanating from the pulmonary veins in a slow controlled and effective manner through the LV vent.

Aims

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| Study I | To evaluate the effectiveness with regard to gaseous microemboli as measured by TCD and TEE, safety and procedure time of the Lund concept for de-airing by comparison to a state-of-the-art reference method with CO ₂ insufflation. |
| Study II | To study potential side-effects of the CO ₂ insufflation technique, specifically intraoperative acid-base balance, gas dynamics, and cerebral hemodynamics measured by TCD and NIRS. |
| Study III | To investigate the impact of individual components for the effectiveness of the Lund concept for de-airing, including a) bilateral opening of the pleurae and b) gradual pulmonary reperfusion and ventilation during weaning from CPB. |
| Study IV | To evaluate the effectiveness of opening of the right pleura as compared to bilateral opening of the pleurae as part of the Lund concept. In addition, to compare the effectiveness of a right superior pulmonary vein vent to a left ventricular apical vent as part of the Lund concept. |

Material and Methods

Patients scheduled for elective open left heart surgery were considered for inclusion into the four studies. Preoperative exclusion criteria were a history of carotid artery disease (study I and II), chronic obstructive pulmonary disease or emphysema, prior cardiothoracic surgery or trauma potentially resulting in pleural adhesions and patients who were considered for left internal mammary artery harvesting. Failure to obtain bilateral TCD signals from the MCAs at preoperative examination excluded patients from study participation.

Intraoperative exclusion criteria were; accidental opening of pleurae in groups requiring intact pleurae, the finding of adherent pleurae that prevented the lungs from collapse, failure to obtain bilateral TCD signals and failure to wean from CPB.

Treatment group allocation in each study was randomized and achieved for each patient using computer-generated randomization lists. Sealed envelopes with allocation to the de-airing technique to be used were opened in the operation room during induction of anesthesia.

Informed written consent was obtained from all patients. Approval to conduct the studies was obtained from the Regional Ethical Committee in Lund. The studies were also registered by the on-line protocol registration system at Clinical Trials.gov with identification numbers; NCT00934596 (Study I and II), NCT01757704 (Study III) and NCT02119871 (Study IV).

Intraoperative procedure

The patients received intravenous anesthesia and were ventilated using a SERVO-i ventilator (Maquet Inc, Solna, Sweden). In study I and II the ventilator was equipped with a module for calculation of CO₂ minute production (Capnostat, Respirationics Novametrix Inc, Wallingford, CT, US).

Surgery was performed through a median sternotomy in all patients. CPB was established using a membrane oxygenator (study I and II: Compact Flow EVO Phiso, Sorin Group USA Inc, Arvada, CO; study III and IV: Medos Hilite 7000, Rheoparin, Medos AG, Stolberg, Germany), an arterial filter (study I and II: Cobe Sentry, Sorin Group USA Inc, Arvada, CO; study III and IV: PALL AL6 Filter, Terumo Sweden AB, Gothenburg, Sweden). PVC tubing was used except for in pump heads where silicone tubing was used. Roller pumps (study I and II: Stöckert S3, Sorin Group USA Inc, Arvada, CO; study III and IV: Stöckert S5, Sorin Group, Mirandola, Italy) and a heat exchanger (T3, Sorin Group USA Inc, Arvada, CO) were used in all patients. Manufacturing site for Sorin Group products was changed from USA to Mirandola in Italy or to Munich in Germany throughout the study period.

The right atrium was cannulated for venous drainage. CPB was maintained with a nonpulsatile blood flow rate of approximately 2.4 - 2.5 L/min/m². During CPB, patients were cooled to 25°C to 28°C. Body temperature was measured in the urinary bladder or tympanic membrane depending on whether the aortic arc was replaced or not, respectively. Antegrade cold blood cardioplegia was used for myocardial protection in all patients.

All patients were continuously monitored for regional cerebral oxygen saturation (rSo₂) bilaterally by near-infrared spectroscopy (INVOS 3100, Somanetics Corp., Troy, MI, USA).

Study protocol

All studies followed the same predefined protocol for data collection as follows.

Patients were continuously monitored for MES in the middle cerebral arteries (MCAs) during the de-airing procedure using TCD. Patients were also monitored continuously for gas emboli in the left side of the heart and MES from the MCAs for the first ten minutes after weaning from CPB using TEE and TCD, respectively. During this period, the LV vent and CPB cannulas were left clamped in situ. After the ten-minute period, CPB was restarted to allow safe removal of the LV vent followed by venous and arterial cannulas. Pleural drains were placed only if pleurae were widely opened for reasons other than de-airing.

The total duration of the de-airing procedure was registered and this time period was divided into “de-airing time before cardiac ejection”, defined as t_2-t_1 , and “de-airing time after cardiac ejection”, defined as t_3-t_2 . TCD recordings and automatic counting of cerebral microemboli was commenced at cross-clamp release (t_1). After weaning from CPB (t_3), a 10-minute post-CPB observation period was commenced during which the LV vent was reopened over a variable time period if air emboli seen on the TEE exceeded grade II.

Primary efficacy endpoints were the number of MES registered from both MCAs during the de-airing procedure itself and the severity of retained intracardiac air during the first ten minutes after CPB assessed by TCD and TEE. Secondary endpoints were the duration of the de-airing procedure and the frequency of reopenings of the LV vent for evacuation of excessive residual intracardiac air observed on TEE during the first ten minutes after CPB.

Transesophageal echocardiography

Directly after weaning from CPB, the left atrium, LV, and ascending aorta were monitored continuously for ten minutes by TEE (study I and II: Philips HP Sonos 5500, Andover, MA, US; study III and IV: Philips iE33 xMatrix, Bothell, WA, US) using a three-chamber view for residual air. The echocardiogram for each individual was recorded and analyzed at the end of the study by one senior cardiac anesthesiologist who was blinded to the de-airing technique used. In study IV, the intraoperative original assessment of TEE grade decided on through agreement by the surgeon and the anesthesiologist were used for analysis. The severity of air emboli observed on TEE was classified in four grades based on the appearance of air in the left atrium (LA), left ventricle (LV) and aortic root (AO):

- Grade 0 = no residual air/gas emboli
- Grade I = air/gas emboli observed in one of the three left heart chambers (LA, LV or AO) during one cardiac cycle
- Grade II = air/gas emboli observed simultaneously in two of three left heart chambers during one cardiac cycle
- Grade III = air/gas emboli observed simultaneously in all three of the left heart chambers during one cardiac cycle

To assess the severity and progress of air emboli, the ten-minute observation period was further subdivided into three time intervals: the first three minutes (0-3 min), the second three minutes (4-6 min) and the last four minutes (7-10 min). During the de-airing, the LV was vented intermittently whenever the TEE air emboli exceeded grade II, and the events were noted for each individual patient.

Transcranial Doppler sonography

The middle cerebral arteries on both sides were monitored continuously for MES using multifrequency TCD sonography (Doppler Box; Compumedics DWL, Singen, Germany) during the de-airing procedure itself and for the first ten minutes after weaning from CPB. 2 + 2.5 MHz Click & Stay monitoring probes (EmboDop; Compumedics DWL, Singen Germany) were fixed to the temporal regions by headsets. In study II, blood flow velocities from the MCAs were registered from start of CBP to ten minutes after CPB. MES were counted on-line by the TCD machine with automatic artifact rejection. We set the threshold for detection of MES at 10 dB and registered all MES lasting for more than 4 ms with a relative energy intensity increase of 10-20 dB above the background. The insonation and reference gate depths were between 50–60 mm, sample volume was 10 mm, filter setting was 150 Hz, power was 180 mW and gain was 10 in accordance with previous protocols.^{47, 83}

Monitoring of arterial blood gases and gas dynamics

Arterial blood samples were drawn from the radial arterial line and venous samples drawn from the central venous catheter intermittently every 15 minutes for analysis of arterial and mixed venous blood gases (ABL800 FLEX; Radiometer, Copenhagen, Denmark). For study purposes, the results of the blood gas analysis were corrected to the actual temperature of the patients by calculation performed by the ABL800 blood gas machine. Arterial blood gas parameters including pH and arterial partial pressure of CO₂ (PaCO₂) were also monitored continuously using an in-line blood gas monitor (CDI Blood Parameter Monitoring System 500; Terumo Cardiovascular System, Ann Arbor, MI, USA) attached to a shunt on the arterial line and set to present values measured at the actual temperature of the patient. PaCO₂ was targeted to 5.5 to 6.5 kPa for both groups and the gas

flow in the oxygenator was readjusted when PaCO_2 diverged from this interval. Alpha-stat pH management was used.

The carbon dioxide concentration at the gas outlet on the oxygenator was measured using a capnograph (IRMA CO_2 ; Phasein AB; Danderyd, Sweden). CO_2 minute production (VCO_2 mL/min) from the oxygenator was calculated by multiplying the gas flow in the oxygenator with the concentration of CO_2 measured at the oxygenator gas outlet. The total volume of CO_2 in the CO_2 insufflation group was thus the sum of CO_2 from dead space ventilation measured in the ventilator and CO_2 measured at the oxygenator gas outlet. In the Lund concept group, CO_2 minute production was measured only at the oxygenator gas outlet and not from dead space ventilation as the ventilator was disconnected in this group during CPB. For clinical comparison an upper cut-off value at 60 minutes of CPB time was chosen for two reasons: (1) to retain adequate number of observations in both groups for statistical comparison, and (2) to permit comparison between the groups when all patients are in cooling or early rewarming phase of surgery.

Calculations

Arterial oxygen content and mixed venous oxygen content in blood was calculated according to the following formula:

$$C_{O_2} = C_{Hb} \times 1.36 \times \frac{S_{O_2}}{100} + P_{O_2} \times 0.0031$$

where C_{O_2} is oxygen content (mL/L), C_{Hb} is the concentration of Hemoglobin (g/L), the constant 1.36 is the amount of oxygen bound per gram of Hemoglobin (mL at 1 atmosphere), S_{O_2} is the oxygen saturation (%) and P_{O_2} is the oxygen tension (mmHg). The constant 0.0031 represents the amount of oxygen dissolved in plasma.

Oxygen consumption was calculated according to the Fick principle:

$$\dot{V}_{O_2} = (C_{aO_2} - C_{vO_2}) \times Q$$

where $\dot{V}_{O_2}$ is oxygen consumption (mL/min), C_{aO_2} - C_{vO_2} is the arteriovenous oxygen content difference (mL/L) and Q is pump flow (L/min).

The respiratory quotient was calculated according to the formula:

$$RQ = \frac{\dot{V}_{CO_2}}{\dot{V}_{O_2}}$$

where RQ is the respiratory quotient, $\dot{V}_{CO_2}$ is the volume of produced CO_2 (mL/min), $\dot{V}_{O_2}$ is oxygen consumption (mL/min).

Scanning Electron Microscopy

At the conclusion of CPB in patients with inclusion number four and five in the group with CO₂ insufflation, clot formation was suspected in the tubing of the cardiotomy suction close to the pump head of the CPB machine. For closer investigation, samples of the PVC tubing from these patients were taken for study in a Scanning Electron Microscope (SEM). The SEM imaging showed no clot formation, but varying degrees of damaged red blood cells at the tube surface were observed. To further follow up this finding, segments of the PVC cardiotomy suctions and vent tubing immediately proximal to the respective pump heads, were hereafter consequently sent for SEM study in ten of the remaining patients (Lund group, n = 5 and CO₂ insufflation group, n = 5). Two 15-mm long sections from each tubing sample were fixed in 2% glutaraldehyde in Sorensen buffer at pH 7 for two hours. Each tubing segment was then cut in half along the long axis and dehydrated in a series of graded ethanol concentrations until an ethanol critical drying point was reached. Each section was mounted on stub, sputter-coated with 20 nm gold and examined under a Scanning Electron Microscope, (Philips SEM 515, Eindhoven, the Netherlands) by one expert who was blinded to intervention groups. All images were recorded at the same magnification. Four representative images from each individual, resulting in a total of 20 images from each group were thus available for comparison. Five images from each group were randomly selected for detailed calculation of the proportion of damaged red blood cells in each image.

De-airing protocols

Study I and II

Twenty patients were randomized to de-airing with (1) the Lund concept for de-airing (Lund group, n=10) or (2) the CO₂ insufflation technique (CO₂ group, n=10).

Lund method for de-airing: bilateral pleurae opened, gradual pulmonary reperfusion and ventilation, LVAV

Before CPB was started, both pleural cavities were exposed to atmospheric air through small openings in the mediastinal pleurae. After CPB was

established the patient was disconnected from the ventilator, allowing both lungs to collapse. After completion of the surgical procedure and closure of the heart, the LV vent was clamped and the aortic root was de-aired by applying active suction of the aortic root until complete collapse was achieved. The aortic cross-clamp was then released and the LV vent opened again. The heart was then defibrillated to a sinus or pacemaker-induced rhythm. After good cardiac contractions and normal central hemodynamics was obtained, the LV preload was gradually and successively increased by reducing the venous return to the CPB circuit, and the vent in the LV-apex increased under TEE monitoring to prevent cardiac ejection. When no air emboli were observed in the left side of the heart, the patient was reconnected to the ventilator and the lungs were ventilated with half of the estimated minute volume using 100% oxygen and 5 cm H₂O PEEP. The de-airing was continued, and when no air emboli were observed in the left side of the heart, the lungs were ventilated to full capacity and the heart was allowed to eject by reducing the LV vent. The time from the release of the aortic cross-clamp (t1) to cardiac ejection (t2) was noted (t2-t1 = de-airing time before cardiac ejection). The de-airing was continued and provided that the TEE continued to show no air emboli in the left side of the heart, the patient was weaned from CPB (t3) and the LV vent was clamped in situ (t3-t2 = de-airing time after cardiac ejection).

Carbon dioxide insufflation technique: CO₂ insufflated, intact pleurae, conventional pulmonary reperfusion and ventilation, LVAV

The pleural cavities were left intact in the CO₂ group. During CPB, the patient was ventilated with a minute volume of 1L, at a frequency of 5 breaths per minute and with a PEEP of 5 cm H₂O. Before the cannulation for CPB, the CO₂ insufflation was accomplished as follows: CO₂ was insufflated into the cardiothoracic wound through a gas diffuser (Cardia Innovation AB, Stockholm, Sweden) that is constructed to create an approximately 100% CO₂ atmosphere in the wound. The diffuser was placed in the sternotomy wound at a depth of 5 cm below the skin adjacent to the diaphragm. CO₂ flow was set at 10 L/min and continued until ten minutes after the end of CPB. Use of coronary and vent suction was restricted to a minimum to maintain adequate CO₂ concentration in the cardiothoracic cavity. Care was also taken to ensure that the diffuser was not soaked with blood during the course of surgery. After completion of the surgical procedure and closure of the heart, the heart and lungs were passively filled with blood from the CPB circuit. The heart was massaged gently, and the left side was de-aired continuously through the LV apical vent. Full ventilation was then resumed, the LV vent was clamped and the

aortic root de-aired by active suctioning until it collapsed completely. The aortic cross-clamp was then released (t1), and the LV vent was opened again. The heart was defibrillated to sinus- or pacemaker-induced rhythm. After good cardiac contractions and normal central hemodynamics were achieved, the LV preload was gradually and successively increased by reducing the venous return to the CPB circuit, and the de-airing continued through the vent in the LV apex under TEE monitoring. When no gas emboli were observed in the left side of the heart, the LV vent was reduced and the heart was allowed to eject (t2), (t2-t1 = de-airing before cardiac ejection). De-airing was continued, and when no further gas emboli were observed in the left side of the heart, the patient was weaned from CPB (t3) and the LV vent was clamped in situ, (t3-t2 = de-airing time after cardiac ejection).

Study III

Twenty patients were randomized to de-airing with (1) open pleurae (collapsed lungs, n=10) or (2) intact pleurae (expanded lungs, n=10).

Open pleurae with collapsed lungs, conventional pulmonary reperfusion and ventilation, LVAV

After sternotomy, both pleural cavities were exposed to atmospheric pressure through openings in the mediastinal pleurae. After the establishment of CPB and before cardioplegic arrest, the ventilator was disconnected from the patient, allowing both lungs to collapse. At the end of cardioplegic arrest and at about 35°C core temperature, the aortic root was de-aired by active catheter suction, the LV preload gradually increased by reducing the venous return to the CPB circuit and the central venous pressure (CVP) increased to 5-10 cm H₂O. The calculated minute ventilation with 100% oxygen and PEEP of 5 cm H₂O was restored. The aortic cross-clamp was now released (t1). The heart was defibrillated to sinus or pacemaker-induced rhythm and the de-airing continued through the LV vent. When no air was seen in the left heart on the TEE and the heart showed visibly good contractions, the heart was allowed to eject in the systematic circulation by decreasing the LV vent (t2). When no air was seen on the TEE, the de-airing was considered complete and the patient completely weaned from CPB (t3).

Intact pleurae with expanded lungs, gradual pulmonary reperfusion and ventilation, LVAV

The pleurae were left intact and after establishment of CPB, the ventilator was disconnected from the patient. At the end of cardioplegic arrest and at a core temperature around 35°C, the aortic root was de-aired by active catheter suction and the aortic cross-clamp was released (t1). The heart was defibrillated to sinus or pacemaker-induced rhythm. When visibly good cardiac contractions were restored, the LV pre-load was increased by slowly reducing the venous return to the CPB circuit, thereby, raising the CVP to 5-10 cm H₂O. When no air was seen in the heart on the TEE, half of the calculated minute ventilation was resumed with 100% oxygen and a PEEP of 5 cm H₂O. De-airing was continued under the guidance of the TEE and when minimal or no residual air was seen on the TEE, full ventilation was restored and the heart was allowed to eject by reducing the LV vent (t2). After de-airing was deemed complete and the patient was weaned from CPB (t3), the remaining procedure was continued in the same way as in the group with open pleurae.

Study IV

Twenty patients were allocated in a randomized controlled manner to two cohorts. Ten patients underwent de-airing with single right open pleura together with a LVAV (single right open pleura and LVAV, n=10). Ten patients were assigned to de-airing with bilateral open pleurae but with the left ventricle (LV) vented with a RSPV (bilateral open pleurae and LVAV, n=10). In both cohorts, pulmonary reperfusion and ventilation was administered in a gradual manner. The two groups were compared to a historical control cohort of ten patients from study I with bilateral open pleurae, LVAV and in whom pulmonary reperfusion and ventilation was also administered in a gradual increasing manner. In all three cohorts, the ventilator was disconnected after the initiation of CPB and prior to cardioplegic arrest to obtain the desired collapse of one or both lungs.

Single right open pleura with collapsed right lung and LVAV

After sternotomy, only the right pleural cavity was exposed to ambient atmosphere through a small opening in the anterior mediastinal pleura. After establishing complete CPB and before cardioplegic arrest, the ventilator was disconnected from the patient, allowing the right lung to collapse. Pulmonary collapse was ascertained by the visual inspection of lung through the opening in pleura. The LV was vented by a 16 French PVC catheter

inserted through the apex (CalMed Laboratories, Costa Mesa, CA, US). At the end of cardioplegic arrest, and at core temperature of about 35°C, the aortic root was de-aired by active suction, followed by the release of the aortic cross clamp. The remaining de-airing procedure was performed according to the Lund concept protocol with gradual pulmonary reperfusion and ventilation.

Bilateral open pleurae with collapsed lungs and RSPV

These patients were treated in a manner similar to those in the single right open pleura cohort, except that both pleurae were opened by small holes in the mediastinal pleurae. Moreover, in this cohort, a 16 French silicone RSPV catheter with malleable introducer (Medtronic Inc., Minneapolis, MN, US) was inserted in the interatrial groove near the right superior pulmonary vein, and guided into the LV across the posterior left atrioventricular groove by the surgeon's left hand. At the end of cardioplegic arrest, and at core temperature of about 35°C, the aortic root was de-aired by active suction, followed by the release of the aortic cross clamp. The remaining de-airing procedure was performed according to the Lund method protocol with gradual pulmonary reperfusion and ventilation.

Bilateral open pleurae with collapsed lungs and LVAV

Both pleurae were opened by small holes in the mediastinal pleurae and de-airing followed the Lund method protocol described in Study I-II above.

Statistics

The randomization lists were computer-generated using the PLAN procedure of the Statistical Analysis System (SAS, SAS Institute, Cary, NC, US) version 8.2 (study I) or version 9.2 (study III and IV).

Power calculations were performed in study III for estimation of the needed sample size by simulation of the assumed clinically relevant difference in MES during the first ten minutes after CPB based on observed MES rates in study I. Occurrence of MES in all patients during the study period was assumed. The power was set to 0.8 (80%) to detect a significant difference in MES during the first ten minutes after CPB of group medians of 5 versus 15 at a level of significance of 5% with equal numbers of patients in each arm. In these simulations, ten patients in each arm were determined necessary.

For each study, descriptive data on continuous variables were presented as medians and quartiles, and the Wilcoxon rank sum test was used to test for differences between treatment arms. Categorical data were presented as counts and percentages, and Fishers exact test was used to test for differences. Poisson regression was used to test for differences in the number of times the LV vent was opened during the first ten minutes after CPB termination for the evacuation of intracardiac gas emboli. The results were presented as the cumulative incidence of openings of the LV vent per individual and as means with 95% confidence intervals.

P-values ≤ 0.05 were considered statistically significant.

All data were analyzed using Sigma Plot version 11.2 (study II, III and IV), (Systat Software, Inc, San Jose, CA, US) or the R software (R Foundation for Statistical Computing, Vienna, Austria) version 2.6.0 (study I, II and III) or version 3.0.2 (study IV).

Results

Study I

Patient demography and preoperative characteristics are presented in Table 1. Patient characteristics were similar in the two groups at baseline except for a higher level of ASAT preoperatively in the Lund method group. Intra- and postoperative characteristics are summarized in Table 2. The total de-airing time was shorter with the Lund method compared to the carbon dioxide method, ($p=0.001$). The difference was due to shorter duration of the de-airing procedure in the period after cardiac ejection to the end of the de-airing procedure (Table 2). The number of MES as registered with TCD was lower with the Lund method, both during the de-airing period, ($p<0.001$) and in the first ten minutes after termination of CPB, ($p<0.001$), (Figure 4).

Table 1. Patient demography and preoperative clinical characteristics by group

	Lund method n=10	CO ₂ method n=10	p-value
Age (y)	70 (59-77)	71 (56-78)	0.942
Male/female	5/5	5/5	1.000
Weight (kg)	72 (65-86)	80 (71-90)	0.511
Height (cm)	176 (169-182)	172 (162-181)	0.487
Body surface area (m ²)	1.85 (1.76-2.06)	2.0 (1.76-2.16)	0.743
Plasma creatinine preoperative (μmol/L)	73 (67-84)	66 (64-83)	0.559
Plasma ASAT preoperative (μkat/L)	0.49 (0.44-0.54)	0.36 (0.32-0.44)	0.006
Plasma ALAT preoperative (μkat/L)	0.50 (0.42-0.59)	0.29 (0.26-0.41)	0.030

Median values with upper and lower quartiles are shown for continuous variables. ASAT = Aspartate amino transaminase; ALAT = Alanine amino transaminase.

Table 2. Perioperative clinical characteristics by group).

	Lund method n=10	CO ₂ method n=10	p-value
Original surgical procedures:			
Aortic valve replacement	7 (70%)	6 (60%)	
Aortic valve repair	1 (10%)	3 (30%)	
Bentall operation	2 (20%)	1 (10%)	
Concomitant procedures:			
Ascending aorta replacement	2 (20%)	1 (10%)	
Aortic arch replacement	0	1 (10%)	
Aortic annulus enlargement	2 (20%)	0	
Coronary artery bypass grafting	2 (20%)	1 (10%)	
Maze procedure	1 (10%)	0	
CPB time (minutes)	117 (105-135)	94 (84-154)	0.252
Aortic cross-clamp time (min)	89 (77-108)	59 (52-88)	0.074
Total de-airing time (min)	9 (8-10)	15 (11-16)	0.001
De-airing time before cardiac ejection (min)	6 (4-7)	7 (5-10)	0.334
De-airing time after cardiac ejection (min)	3 (2-3)	5 (4-8)	0.002
Ventilator time (h)	6 (4-8)	6 (4-7)	0.882
Intensive care unit stay (d)	21 (20-22)	22 (21-24)	0.293
Hospital stay (d)	7 (7-8)	7 (6-7)	0.239
Plasma creatinine postoperative (μmol/L)	72 (64-87)	55 (52-74)	0.155
Plasma ASAT postoperative (μkat/L)	1.13 (0.87-1.48)	0.83 (0.79-0.95)	0.180
Plasma ALAT postoperative (μkat/L)	0.73 (0.44-1.08)	0.32 (0.29-0.39)	0.056

Median values with upper and lower quartiles are shown for continuous variables. ASAT = Aspartate amino transaminase; ALAT = Alanine amino transaminase; CPB = cardiopulmonary bypass.

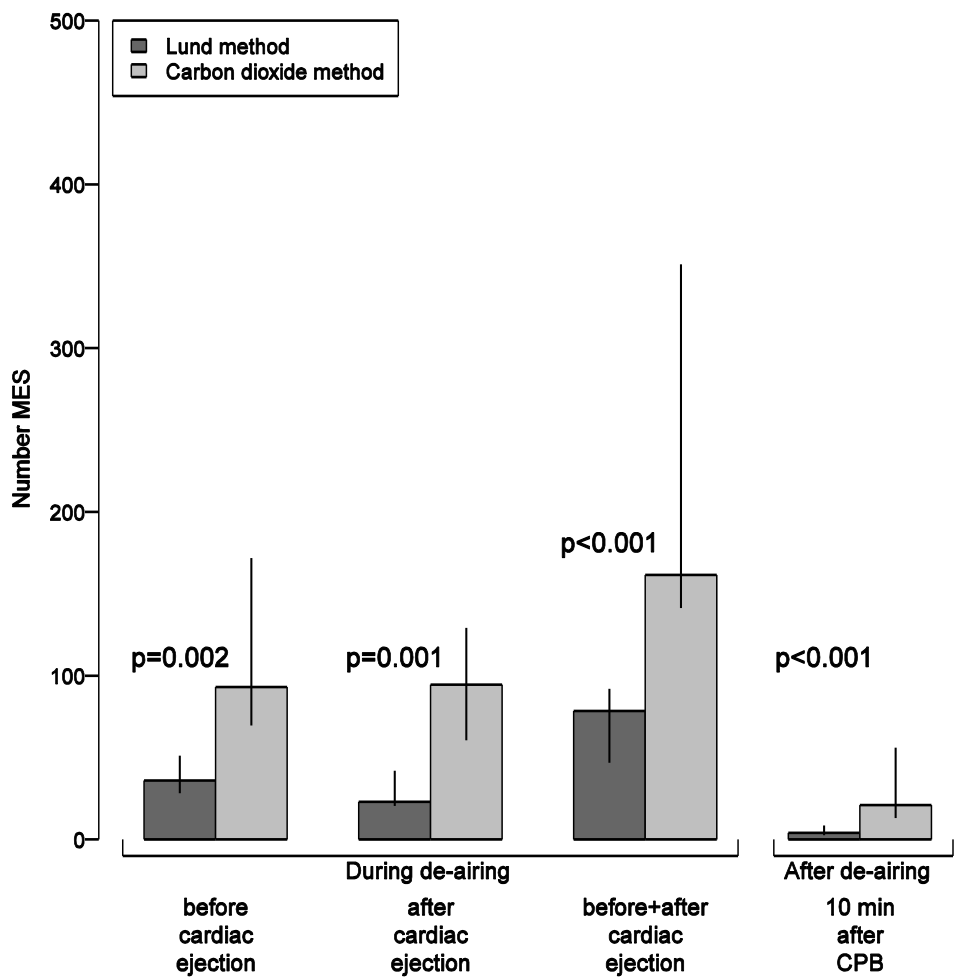


Figure 4. Number of microembolic signals as registered by Transcranial Doppler sonography from both middle cerebral arteries. MES = microembolic signals, CPB = cardiopulmonary bypass.

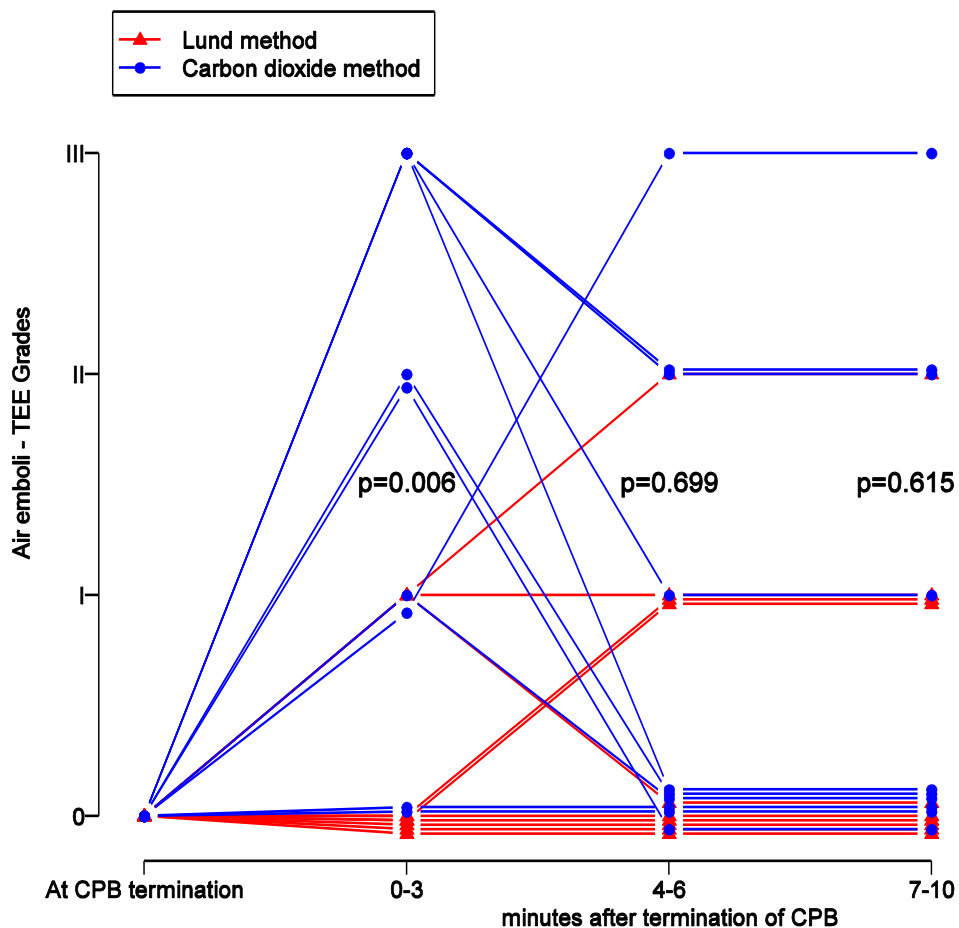


Figure 5. TEE three-chamber view monitoring of gas emboli during the first ten minutes after termination of CPB in each study individual (n=20). Grade 0: no residual air/gas emboli; Grade I: air/gas emboli detected in one of three left heart chambers (LA, LV or AO) during one cardiac cycle; Grade II: air/gas emboli detected simultaneously in two of three left heart chambers during one cardiac cycle; Grade III: air/gas emboli detected simultaneously in all three left heart chambers during one cardiac cycle. TEE = transesophageal echocardiography, CPB = cardiopulmonary bypass.

In the Lund method group, all ten patients (100%) had intracardiac residual air of TEE grade I or lower during the first three minutes after CPB termination compared to four patients (40%) in the carbon dioxide method group (CO₂ group, $p=0.006$), (Figure 5). In the interval 4-6 minutes after CPB termination, nine patients (90%) had TEE grade I or lower compared to the CO₂ group, ($p=0.699$). In the third interval after CPB termination, nine patients (90%) with the Lund method continued to have TEE grade I or lower compared to seven patients (70%) in the CO₂ group ($p=0.615$).

During the first ten minutes after termination of CPB, the LV vent was reopened in one patient with grade II - III air emboli (10%, 95% CI=0.3% - 45%) in the Lund group compared to four patients with grade III air emboli (40%, 95% CI= 12% - 74%) in the CO₂ group. Poisson regression on the number of times the LV vent was reopened was (2,0,0,0,0,0,0,0,0) in the Lund method group (mean 0.2) and (3,2,1,1,0,0,0,0,0) in the CO₂ group (mean 0.7, $p=0.0816$).

In the Lund method group, a mild degree of right-sided transient weakness developed in one patient on the second postoperative day. This patient had received mediastinal radiotherapy previously for lymphoma, and his lungs failed to collapse and drop posteriorly when the respirator was disconnected. This was the only patient in the Lund method group for whom the LV vent was reopened for the evacuation of intracardiac air during the first ten minutes after CPB.

In the CO₂ insufflation group, one patient developed transient weakness of the right arm on the first postoperative day. This was one of the four patients in the CO₂ insufflation group in whom the LV vent was reopened to evacuate intracardiac air during the first ten minutes after CPB.

Study II

Preoperative and intraoperative characteristics are summarized in Table 1 and Table 2, respectively. One patient in the Lund method group was excluded from calculation of CO₂ volume and respiratory quotient due to failure to obtain data from the gas outlet on the oxygenator (Table 3). There was no difference in CO₂ partial pressure (PaCO₂) between groups before institution of CPB (Figure 6). In the CO₂ group, PaCO₂ increased significantly at 15- and 30-minute intervals compared to the Lund method group. PaCO₂ could be kept within the targeted normal levels in the CO₂ group at the expense of a significant increase in gas flow through the oxygenator at 30-, 45- and 60-minute time intervals (Figure 6). At 45 minutes the gas flow in the CO₂ group was more than twice as high as in the Lund method group: 2.20 (1.63-3.10) versus 0.64 (0.60-1.25) L/minute. Similarly, at 60 minutes the gas flow in the CO₂ group was 2.65 (1.78-3.38) L/minute compared with 0.80 (0.70-1.45) L/minute in the Lund group.

There was no difference in arterial blood pH between groups before initiation of CPB. After initiation of CPB, pH decreased to significantly lower levels at 15-, 30-, and 45-minute time intervals in the CO₂ group (Figure 6). No significant difference in concentration of blood lactate was found between groups. In the CO₂ group the highest level of lactate during CPB was 1.10 (0.90-1.60) mmol/L at 60 minutes and in the Lund group it was 1.00 (0.60-1.20) mmol/L at 45 minutes. CO₂ volume during CPB was at all times higher in the CO₂ group compared with the Lund method group (Figure 6).

However, differences in CO₂ volume between the groups were statistically significant at 30-, 45-, and 60-minute intervals only. At 60 minutes, the CO₂ volume in the CO₂ group was 198 (152-229) mL/minute. In the Lund method group VCO₂ was 70 (39-106) mL/minute. In contrast, the amount of CO₂ measured from dead space in the ventilator was 4.5 (4.0-8.0) mL/minute at 15 minutes, 5.0 (3.0-6.0) mL/minute at 30 minutes, 5.0 (4.0-6.0) mL/minute at 45 minutes, and 5.0 (3.8-6.5) mL/minute at 60-minute intervals in the CO₂ group.

No significant difference in oxygen consumption was found during CPB between the groups (Table 3). The fraction of inspired oxygen administered during CPB was similar for both groups at all intervals. In the CO₂ group, the respiratory quotient was significantly higher at 30-, 45-, and 60-minute intervals during CPB than in the Lund method group (Table 3).

Blood gas values obtained from intermittent sampling of blood from the CPB circuit and the in-line blood gas monitoring showed a common trend. No statistically significant differences in PaCO₂ and pH measurements were observed between the two methods at any time interval. Blood flow velocity measured in the middle cerebral artery during CPB was higher bilaterally in the CO₂ group than in the Lund method group (Figure 7). There was a significant increase in velocity in both hemispheres in the CO₂ group from 30 minutes on CPB ($p<0.01$) until the end of CPB ($p<0.001$).

In the right hemisphere, statistically significant differences in blood flow velocity were seen after 30 minutes on CPB and onward in the CO₂ group. In the left hemisphere these differences were significantly different already at 15 minutes on CPB and onward. Regional cerebral oxygen saturation (rSo₂) is presented in absolute values (Figure 7). In the CO₂ group significantly higher rSo₂ values were recorded from both cerebral hemispheres until CPB was terminated when compared with the Lund group. No statistically significant difference in hematocrit was found between the two groups at corresponding time intervals.

Table 3. Oxygen consumption and respiratory quotient.

Time on CPB (min)	Lund method n=9	CO ₂ method n=10	p-value
Oxygen consumption (mL/min)			
15	118.3 (77.4-152.6)	109.8 (72.9-134.5)	0.912
30	114.9 (76.6-139.6)	115.8 (77.0-120.5)	0.481
45	109.7 (91.4-151.2)	100.6 (84.5-150.9)	0.579
60	109.2 (101.9-151.5)	125.9 (97.2-137.4)	0.905
Respiratory quotient			
15	0.52 (0.39-0.69)	0.78 (0.56-1.01)	0.065
30	0.44 (0.27-0.59)	1.01 (0.85-1.45)	<0.001
45	0.45 (0.27-0.66)	1.47 (1.29-1.66)	<0.001
60	0.61 (0.49-0.67)	1.47 (1.16-2.36)	<0.001

Continuous variables are presented as median with upper and lower quartiles. CPB = cardiopulmonary bypass.

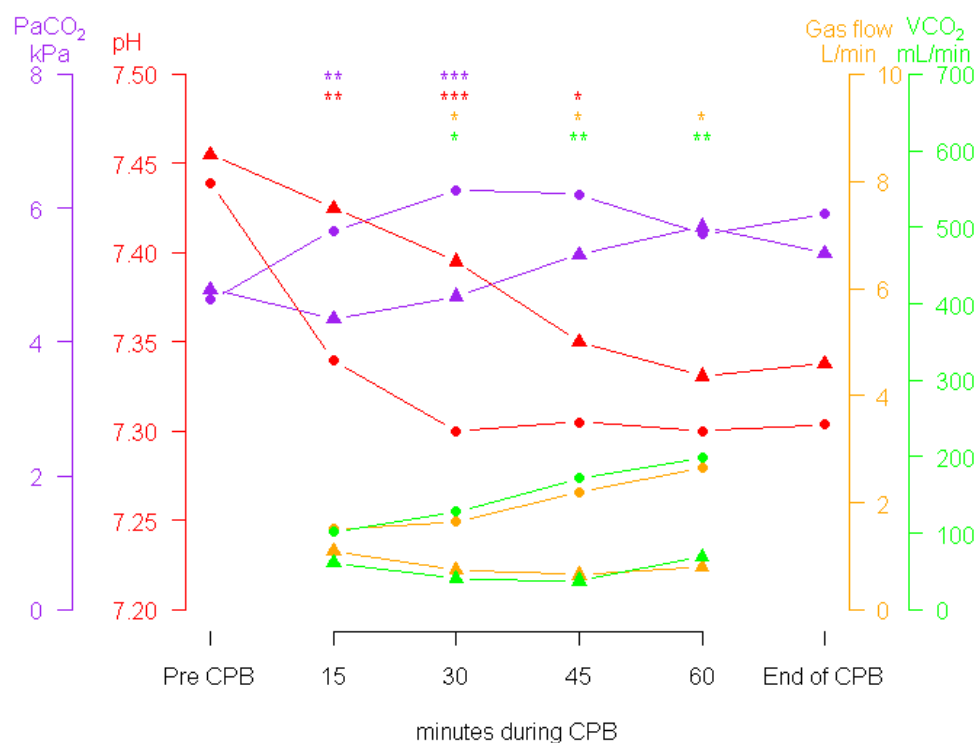


Figure 6. Arterial blood gases and extracorporeal gas dynamics before, during, and at the end of cardiopulmonary bypass (CPB). Circles indicate the carbon dioxide group, triangles indicate the Lund group. PaCO₂ = Arterial partial pressure of carbon dioxide; VCO₂ = volume of carbon dioxide produced. *p<0.05; **p<0.01; ***p<0.001 for between-group comparison.

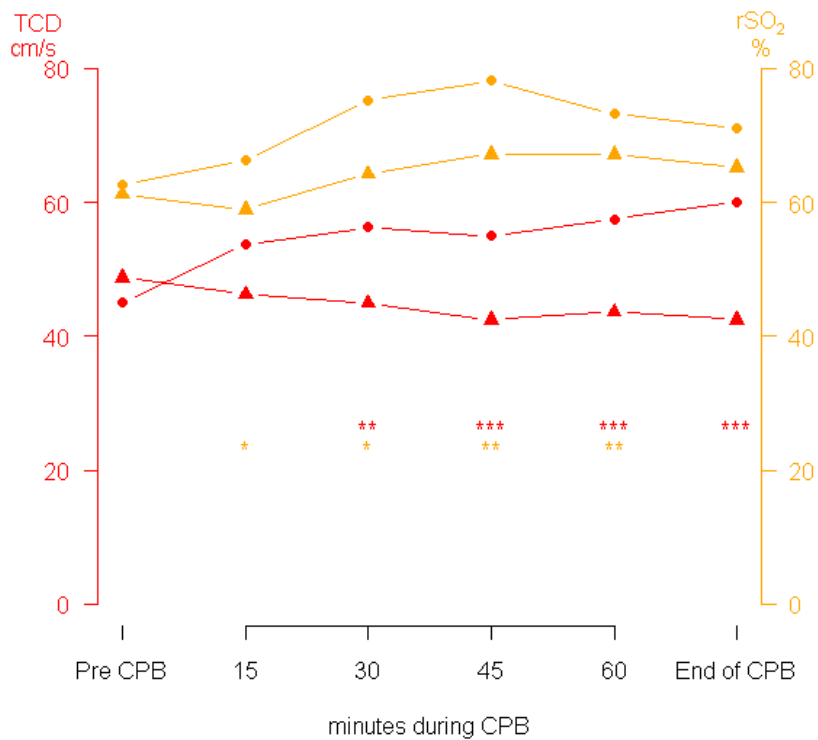


Figure 7. Mean cerebral blood flow velocity (cm/s) measured by transcranial Doppler sonography (TCD) and regional cerebral oxygen saturation (rSO₂) measured by near-infrared spectroscopy (NIRS) before, during, and at end of cardiopulmonary bypass (CPB). Circles indicate carbon dioxide group, triangles indicate Lund method group. *p<0.05; **p<0.01; ***p<0.001 for between-group comparisons.

The Scanning Electron Microscopy (SEM) images of the cardiectomy suction and LV vent tubing showed a higher degree of red blood cell damage in the CO₂ group (Figure 8). This finding was consistent in the final five patients in the CO₂ group despite restricted use of cardiectomy suction in this group. The fraction of damaged red cells in the CO₂ group was 0.97 (0.64-1.00) compared with 0.18 (0.11-0.30) in the Lund method group. In both groups the activated clotting times and the heparin concentration was within therapeutic limits throughout CPB.

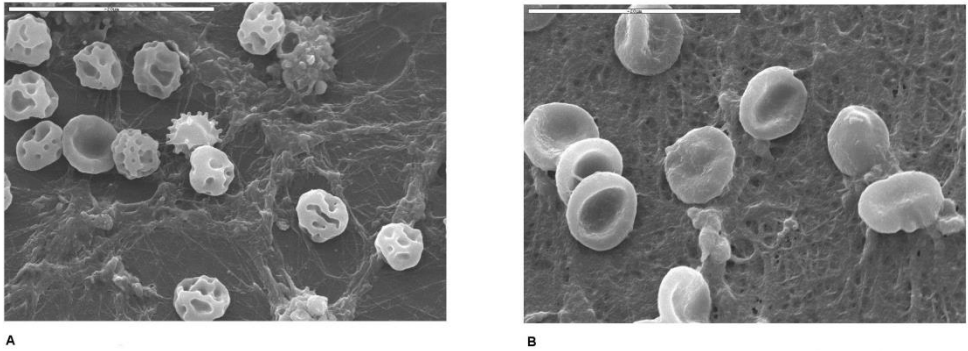


Figure 8. Scanning electron microscope pictures of the cardiectomy and/or left ventricular vent tubings showing morphology of the red blood cells in A) the CO₂ insufflation group, B) the Lund method group. The fraction of damaged red blood cells in the carbon dioxide method group was 0.97 compared with 0.18 in the Lund method group.

Study III

Preoperative demographic characteristics are presented in Table 4. The majority of surgical procedures performed were aortic valve replacements (Table 5). The total de-airing time was shorter in the group with open pleurae (Table 5). During the entire de-airing procedure, a lower number of MES, 78 (54-109) vs 190 (75-516), ($p=0.031$), was recorded in the group with open pleurae. This difference was due to a significantly lower number of MES after cardiac ejection in patients with open pleurae 28 (14-41) vs 71 (31-360; $p=0.017$). The number of MES recorded over MCA was lower in patients with open pleurae during the first ten minutes after completed de-airing 9 (6-36) vs 65 (36-210) than in the group with intact pleurae ($p=0.004$), (Figure 9).

During the first ten minutes after termination of cardiopulmonary bypass, the TEE showed a significantly higher grade of residual air in the group with intact pleurae (Figure 10). Two patients (20%) with open pleurae had air emboli Grade I or more during the first three minutes compared to ten (100%) with intact pleurae ($p=0.0002$). In the second and third time intervals, no patients with open pleurae showed residual air emboli, while those with intact pleurae, seven patients (70%), had Grade I or higher emboli during the second time interval ($p=0.002$) and three patients (30%) had Grade I or higher emboli ($p=0.078$) in the third time interval.

In patients with open pleurae, the LV vent was not opened in any patient (0%-30%, 95% confidence interval) while, in those with intact pleurae, the LV vent was opened once or more in four patients (40%, 12%-74%, 95% confidence interval). Poisson regression for the number of times the LV vent was opened in the first ten minutes after CPB was 0,0,0,0,0,0,0,0,0 (mean=0, 0-0.10, 95% confidence interval) for patients with open pleura and 0,3,1,1,0,0,0,0,5,0 (mean=1, 0.47-1.73, 95% confidence interval) for patients with intact pleurae, respectively ($p<0.001$).

The group with open pleurae and conventional pulmonary reperfusion and ventilation was compared to a historical control group from study I with open pleurae and staged filling (i.e. gradual pulmonary reperfusion and ventilation) both for MES (Figure 11) and TEE grading of intracardiac residual air (Figure 12). During de-airing itself, there were no differences in MES between the group with open pleurae and gradual reperfusion and ventilation compared to a historical control group with open pleurae and conventional filling (i.e. conventional pulmonary reperfusion and ventilation). There was significantly lower MES in the group with open

pleurae and staged filling (i.e. gradual reperfusion and ventilation) during the first ten minutes after CPB. Comparing the same groups for residual air on TEE, the group with open pleurae and conventional filling (i.e. pulmonary reperfusion and ventilation) had lower grades of air at 4-6 minutes after CPB but was not different during the other time periods after CPB.

One patient in the group with intact pleurae developed a lacunar infarction in the left cerebral hemisphere on the second postoperative day. In this patient, the LV vent was reopened once for the evacuation of intracardiac air during the first ten minutes after CPB.

Table 4. Patient demography and preoperative clinical characteristics by group.

	Open pleurae n=10	Intact pleurae n=10	p-value
Age (y)	74 (59-81)	71 (59-81)	0.733
Male/female	5/5	5/5	1.000
Weight (kg)	84 (68-100)	82 (72-96)	0.791
Height (cm)	167 (162-177)	172 (165-179)	0.520
Body surface area (m ²)	1.98 (1.71-2.21)	1.96 (1.77-2.19)	0.910
Plasma creatinine preoperative (μmol/L)	86 (67-114)	87 (69-96)	0.623
Plasma ASAT preoperative (μkat/L)	0.42 (0.37-0.47)	0.47 (0.34-0.58)	0.649
Plasma ALAT preoperative (μkat/L)	0.30 (0.24-0.45)	0.36 (0.26-0.56)	0.570

Median values with upper and lower quartiles are shown for continuous variables. ASAT = Aspartate amino transaminase; ALAT = Alanine amino transaminase.

Table 5. Perioperative clinical characteristics by group.

	Open pleurae n=10	Intact pleurae n=10	p-value
Original Surgical procedures:			
Aortic valve replacement	10 (100%)	9 (90%)	
Bentall operation	0	1 (10%)	
Concomitant procedures:			
Ascending aortic replacement	0	2 (20%)	
Aortic annulus enlargement	3 (30%)	3 (30%)	
Decalcification of aortic root	0	1 (10%)	
Myectomy and excision of subvalvular membrane	2 (20%)	0	
Cardiopulmonary bypass time (minutes)	111 (84-124)	104 (102-139)	0.677
Aortic cross-clamp time (minutes)	79 (64-91)	81 (73-96)	0.762
Total de-airing time (minutes)	8.5 (6-12)	14 (10-20)	0.034
De-airing time before cardiac ejection (minutes)	4.5 (3-6)	7 (5-10)	0.063
De-airing time after cardiac ejection (minutes)	3 (2-5)	5 (3-11)	0.093
Ventilator time (hours)	5 (4-7)	7 (5-11)	0.180
Intensive care unit stay (hours)	22 (21-32)	24 (21-53)	0.620
Plasma creatinine postoperative (μmol/L)	91 (72-114)	98 (82-113)	0.705
Plasma ASAT postoperative (μkat/L)	0.95 (0.82-1.45)	0.95 (0.73-2.23)	0.850
Plasma ALAT postoperative (μkat/L)	0.42 (0.25-1.11)	0.54 (0.29-1.45)	0.571

Median values with upper and lower quartiles are shown for continuous variables. ASAT = Aspartate amino transaminase; ALAT = Alanine amino transaminase.

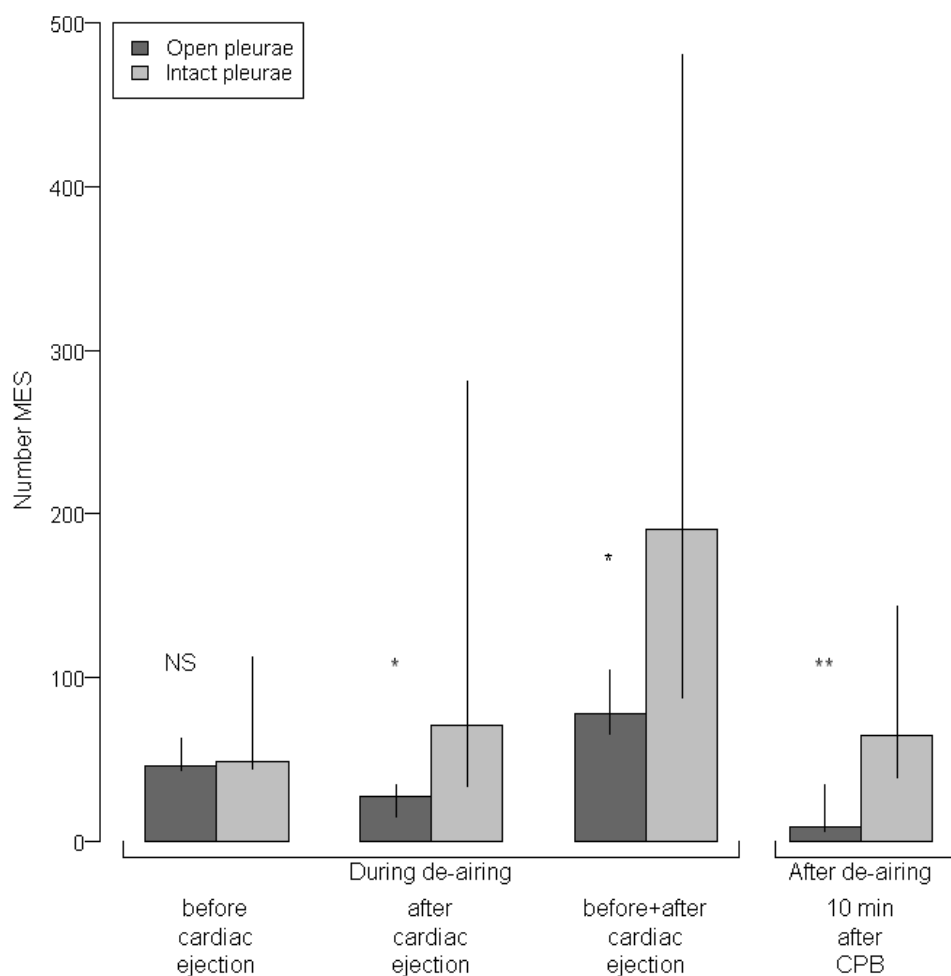


Figure 9. Number of microembolic signals as registered by transcranial Doppler sonography from both middle cerebral arteries. NS = non-significant, * $p < 0.05$, ** $p < 0.01$. CPB = cardiopulmonary bypass, MES = microembolic signals.

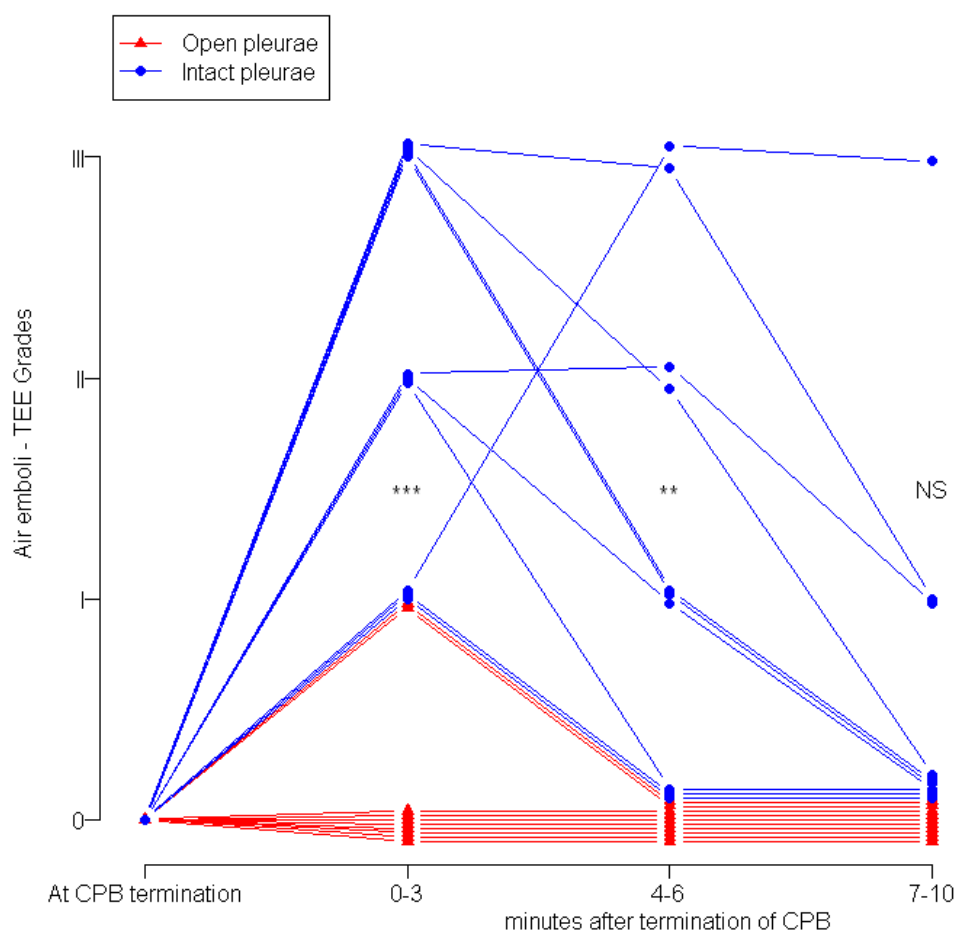


Figure 10. TEE three-chamber view monitoring of gas emboli during the first ten minutes after cardiopulmonary bypass (CPB) in each study individual (n=20). Grade 0: no residual air emboli; Grade I: air emboli detected in one of three left heart chambers (LA, LV or AO) during one cardiac cycle; Grade II: air emboli detected simultaneously in two of three left heart chambers during one cardiac cycle; Grade III: air emboli detected simultaneously in all three left heart chambers during one cardiac cycle. **p<0.01, ***p<0.001. TEE = transesophageal echocardiography.

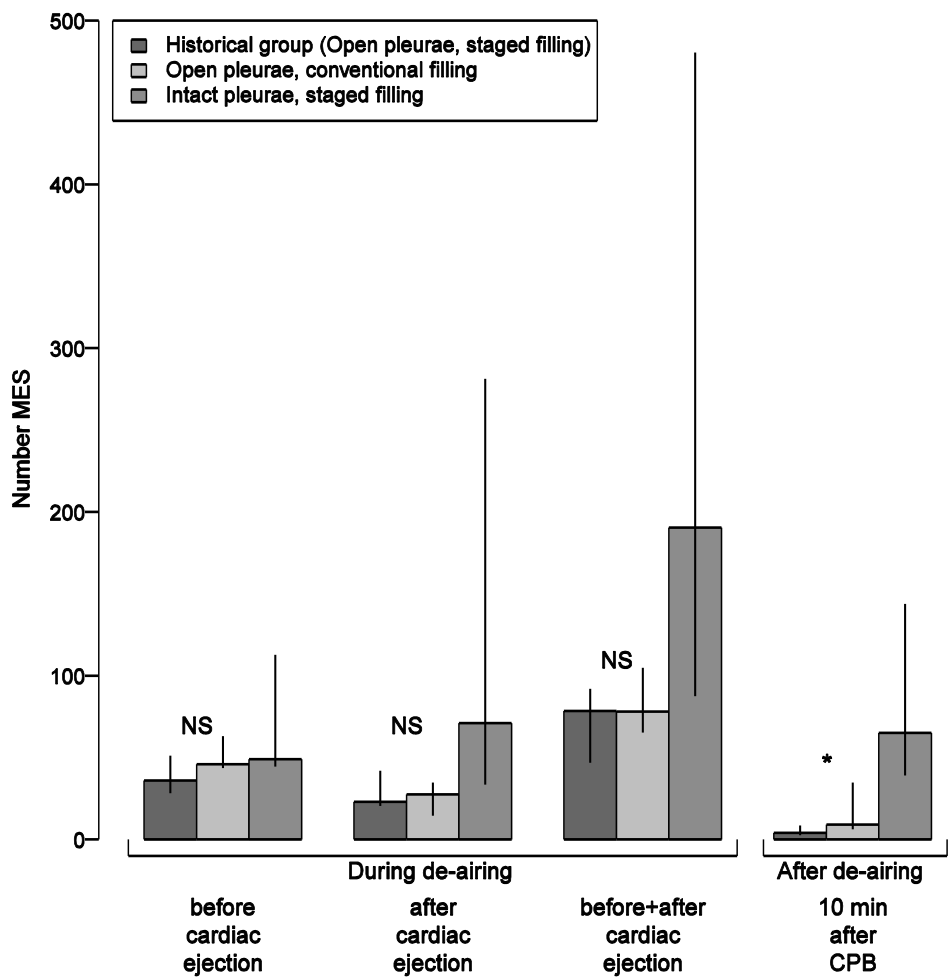


Figure 11. Number of microembolic signals in comparison to a historical control group. CPB = cardiopulmonary bypass, MES = microembolic signals. Values are medians with upper and lower quartiles. NS = non-significant, * $p < 0.05$, refers to the comparison of the group with open pleura + conventional filling to the historical control group with open pleurae + staged filling.

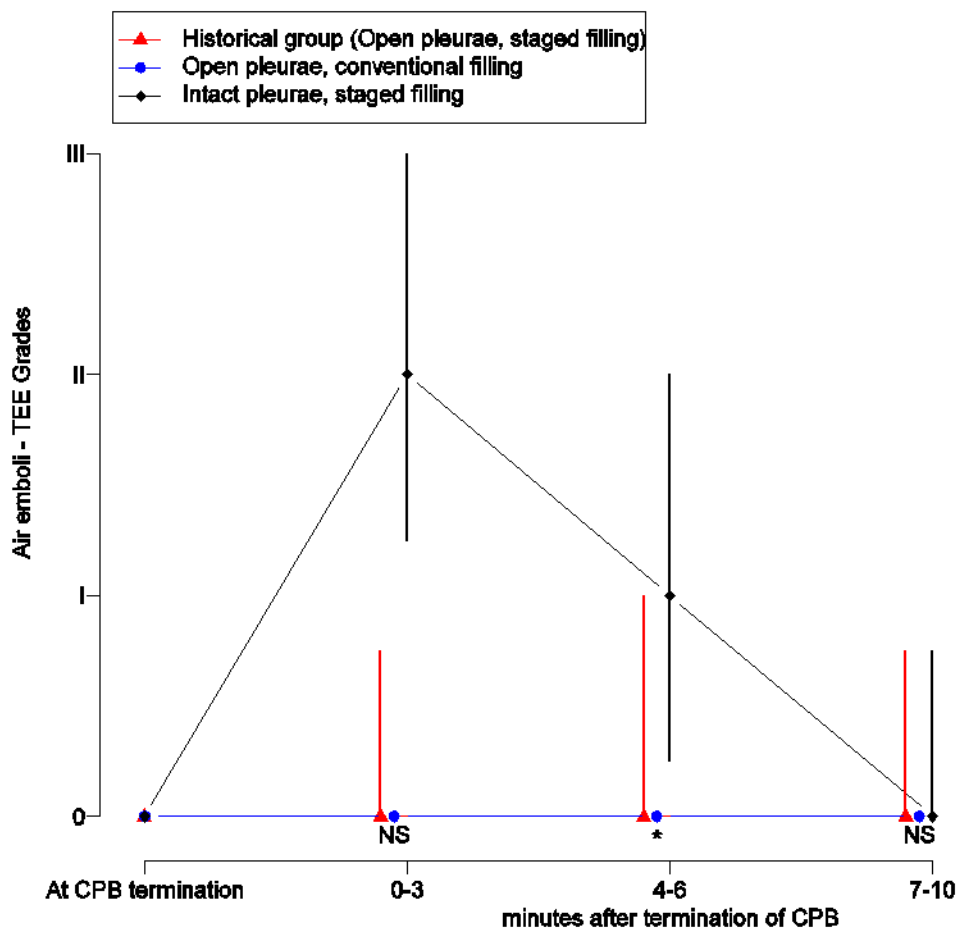


Figure 12. TEE three-chamber view monitoring of air emboli during the 10-minute post-CPB observation period compared to a historical control group. Grade 0, no residual air emboli; Grade I, air emboli observed in one of the three left heart chambers (LA, LV or AO) during one cardiac cycle; Grade II, air emboli observed simultaneously in two of three left heart chambers during one cardiac cycle; Grade III, air emboli observed simultaneously in all three left heart chambers during one cardiac cycle. CPB = cardiopulmonary bypass, TEE = transesophageal echocardiography. Values are medians with upper and lower quartiles, NS = non-significant, * $p < 0.05$, refers to the comparison of the group with open pleurae + conventional filling to the historical control group with open pleurae + staged filling).

Study IV

Preoperative demographic characteristics were similar across all three cohorts and the majority of surgical procedures performed were aortic valve replacements (Table 6). The de-airing time and other intraoperative and early postoperative variables were also similar in the three cohorts (Table 7). No intraoperative surgical complications, directly or indirectly, related to the venting techniques, were observed.

Single right open pleura versus bilateral open pleurae

The number of MES registered in the MCAs by TCD was statistically similar in the two cohorts during the de-airing procedure itself. However, in the first ten minutes after CPB, there was a significantly higher number of MES registered in the group with right open pleura 34 (14-43) compared to the group with bilateral open pleurae 4 (2-10, $p<0.001$), (Figure 13). TEE monitoring during the period of the first ten minutes after CPB was dominated by grade zero intracardiac retained air in both groups. In the group with the right pleura open, the LV vent was not reopened in any patient (0%, 95% CI=0%-31%), while in the group with bilateral open pleurae, the LV vent was reopened twice in one patient (10%, 95% CI=0.3%-45%), (Table 7). 12 TEE recordings (right open pleura $n=5$, bilateral open pleurae $n=7$) were available for postoperative assessment blinded to groups. In ten of the cases (83%) the grading of retained intracardiac air corresponded well to the intraoperative grading.

Right superior pulmonary vein vent versus left ventricular apical vent

In the first ten minutes after CPB, the number of MES was significantly higher in the RSPV group 30 (9-75) than in the LVAV group 4 (2-10, $p=0.003$), (Figure 14). The grading of the severity of the TEE-recorded retained intracardiac air emboli showed no significant differences between the two groups during the first ten minutes after CPB. In the RSPV group, the LV vent was reopened in two patients (20%, 95% CI=3%-57%) to evacuate residual intracardiac air exceeding grade II (Table 7). In the RSPV cohort, one patient with a history of cerebrovascular insult showed delayed awakening and confusion on the first postoperative day and was kept an additional 24 hours in the intensive care unit. One patient in the historical control cohort developed a mild and transient right-sided weakness on the second postoperative day as described in study I.

Table 6. Patient demography and surgical procedures performed by cohort

	Right open pleura + LVAV n=10	p- value ¹	Bilateral open pleurae + LVAV n=10	p- value ²	Bilateral open pleurae + RSPV n=10
Age (y)	71 (64-79)	0.760	70 (59-77)	0.970	69 (65-74)
Male/female	6/4	1.000	5/5	0.670	7/3
Body surface area (m ²)	1.93 (1.79- 2.11)	0.148	1.85 (1.76- 2.06)	0.910	1.97 (1.71- 2.13)
Plasma creatinine preoperative (µmol/L)	92 (82-102)	0.093	73 (67-84)	0.762	74 (66-92)
Plasma ASAT preoperative (µkat/L)	0.44 (0.36- 0.50)	0.139	0.49 (0.44- 0.54)	0.031	0.41 (0.34- 0.47)
Plasma ALAT preoperative (µkat/L)	0.42 (0.32- 0.43)	0.075	0.50 (0.42- 0.59)	0.140	0.42 (0.37- 0.44)
Original surgical procedures:					
Aortic valve replacement	7 (70%)		7 (70%)		8 (80%)
Bentall operation	2 (20%)		2 (20%)		2 (20%)
Aortic valve repair	1 (10%)		1 (10%)		0
Concomitant procedures:					
Ascending aortic replacement	0		2 (20%)		1 (10%)
Aortic annulus enlargement	1 (10%)		2 (20%)		1 (10%)
Decalcification of aortic root	1 (10%)		0		0
CABG	1 (10%)		2 (20%)		0
Amputation of the LAA	2 (20%)		0		0
MAZE procedure	0		1 (10%)		0

Median values with upper and lower quartiles are shown for continuous variables. LVAV = Left ventricular apical vent, RSPV = Right superior pulmonary vein vent, LAA = Left atrial appendage. P-value¹ refers to comparison between Right open pleura + LVAV versus Bilateral open pleurae + LVAV. P-value² refers to comparison between Bilateral open pleurae + LVAV versus Bilateral open pleurae + RSPV.

Table 7. Perioperative data by cohort

	Right open pleura LVAV n=10	p- value ¹	Bilateral open pleurae + LVAV n=10	p- value ²	Bilateral open pleurae + RSPV n=10
Cardiopulmonary bypass time (minutes)	114 (103- 118)	0.508	117 (105- 135)	0.075	90 (81-120)
Aortic cross clamp time (minutes)	92 (81-99)	0.799	89 (77-108)	0.064	67 (57-94)
Total de-airing time (minutes)	10 (7-11)	0.944	9 (8-10)	0.469	8 (6-12)
De-airing time before cardiac ejection (minutes)	7 (3-7)	0.624	6 (4-7)	0.849	5 (3-10)
De-airing time after cardiac ejection (minutes)	4 (2-4)	0.953	3 (2-3)	0.843	3 (2-4)
Ventilator time (hours)	6 (4-6)	0.529	6 (4-8)	0.070	8 (6-10)
Intensive care unit stay (hours)	19 (17-24)	0.683	21 (20-22)	0.486	20 (18-47)
Plasma creatinine postoperative ($\mu\text{mol/L}$)	82 (77- 105)	0.169	72 (64-87)	0.096	89 (76-111)
Plasma ASAT postoperative ($\mu\text{kat/L}$)	0.86 (0.47- 1.43)	0.132	1.13 (0.87- 1.48)	0.059	0.80 (0.58- 0.87)
Plasma ALAT postoperative ($\mu\text{kat/L}$)	0.53 (0.38- 0.69)	0.851	0.73 (0.44- 1.08)	0.273	0.48 (0.32- 0.67)
Frequency of re- opening of LV vent during first ten minutes after CPB mean, (95%CI)	0 (0-0.10)	0.045	0.2 (0.02- 0.58)	0.082	0.7 (0.27- 1.33)
Reopenings of LV vent per study individual	0,0,0,0,0, 0,0,0,0,0		2*,0,0,0,0, 0,0,0,0,0		6,0,1,0,0, 0,0,0,0,0

Median values with upper and lower quartiles are shown for continuous variables. LVAV = Left ventricular apical vent, RSPV = Right superior pulmonary vein vent. P-value¹ refers to comparison between Right open pleura + LVAV versus Bilateral open pleurae + LVAV. P-value² refers to comparison between Bilateral open pleurae + LVAV versus Bilateral open pleurae + RSPV. CPB = cardiopulmonary bypass. *In this patient both lungs failed to collapse due to previous mediastinal radiotherapy.

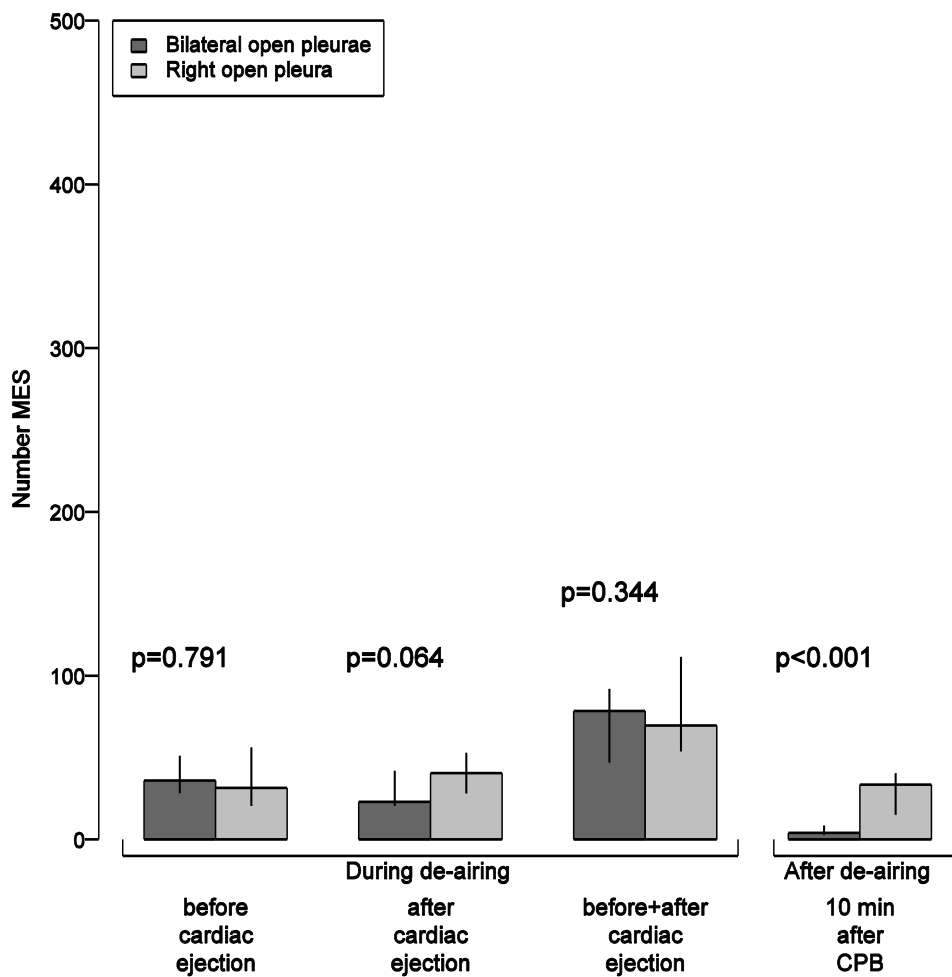


Figure 13. Number of microembolic signals in two cohorts with unilateral right open pleura and bilateral open pleurae as registered by transcranial Doppler sonography from both middle cerebral arteries. Left apical ventricular vent and gradual pulmonary reperfusion and ventilation were administered to both groups. Values are medians with upper and lower quartiles. CPB = cardiopulmonary bypass, MES = microembolic signals.

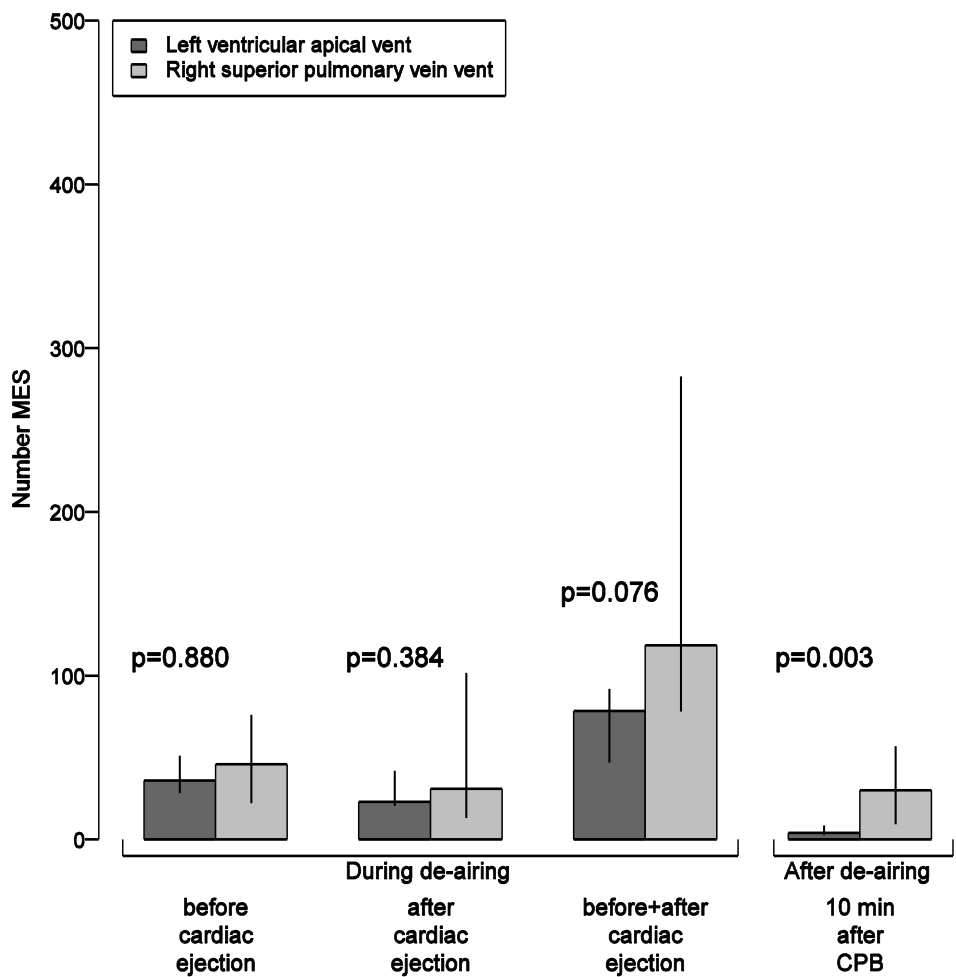


Figure 14. Number of microembolic signals as registered by transcranial Doppler sonography from both middle cerebral arteries in two patient groups with right superior pulmonary vein vent and left ventricular apical vent respectively. Bilateral open pleurae and gradual pulmonary reperfusion and ventilation were administered to both groups. Values are medians with upper and lower quartiles. CPB = cardiopulmonary bypass, MES = microembolic signals.

Discussion

In this thesis, a method for de-airing in open left heart surgery has been evaluated for its ability to reduce gaseous microemboli. The method is based on opening of pleural cavities, disconnection of the ventilator during cardiopulmonary bypass, and gradual and successive pulmonary reperfusion and ventilation.

In summary, we observed that the method appears to be a safe and accessible method for de-airing. In comparison with a standardized reference method with CO₂ insufflation, the Lund method in our study resulted in fewer MES, lower grades of intracardiac residual air emboli and shorter de-airing times. The method can be used without extra equipment needed provided that the condition of the patients lungs allow satisfactory pulmonary collapse. We argue that these advantages make the Lund method attractive as a first choice for de-airing in many situations.

During the evaluation of the Lund concept, we identified some important issues which contributed to further development of the method. The Lund method was modified in study I based on the finding of a relatively high number of MES in the pre-ejection phase of de-airing in a previous study.⁸³ As MES registered during this part of de-airing are believed to largely originate from air in the aortic root, application of active suctioning of the aortic root before cross-clamp removal was added to all de-airing protocols in our subsequent studies. After this modification we expected no difference in the number of MES in the pre-ejection phase, but yet we found a higher number of MES in the control group in study I. This difference could possibly be explained by the fact that that in the CO₂ group, the left side of the heart was passively filled with blood from the extracorporeal circuit first, and the aortic cross-clamp released thereafter. In the Lund method group, filling of the left ventricle was commenced after de-airing of the aortic root and cross-clamp. Therefore, aortic root suction may not completely empty the aortic root, as it was continuously fed with blood mixed with air or gas emboli from the LV. The pre-ejection phase of the de-airing procedure, we believe reflect de-airing of the aortic root, LA and LV. The de-airing phase after cardiac ejection, on the other hand, should

represent a more complex part of the de-airing procedure, namely, the de-airing of residual air trapped in the pulmonary veins.

Understanding the Lund concept

How does bilateral lung collapse facilitate effective de-airing?

After observing successful de-airing with our Lund concept in study I, we considered whether it was the collapse of the lungs, or the strategy of a gradual pulmonary reperfusion and ventilation that was of larger importance for de-airing, or whether they were of equal importance. This question is important, as collapse of the lungs is difficult to achieve in a subset of patients, with pleural adhesions or pulmonary disease resulting in inadequate pulmonary collapse. Therefore, we aimed to assess in study III the relative importance of each component of the Lund method. We found that opening of the pleura and associated bilateral pulmonary collapse, significantly reduced the total number of cerebral microemboli ($p=0.004$) and the amount of residual intracardiac air measured by intraoperative TEE ($p=0.0002$, $p=0.002$, $p=0.078$ for first, second and third interval, respectively) during the first ten minutes after weaning from CPB. The LV vent was also opened on significantly more occasions to evacuate residual air emanating from the pulmonary veins during this period ($p<0.001$). Also, the total de-airing time was shorter in the group with open pleurae ($p=0.034$). These findings strongly suggest that the opening of the pleurae is the most important factor for the effectiveness of the Lund method for de-airing.

The primary aim of opening the pleurae is to allow bilateral pulmonary collapse and, thus, letting the lungs drop posteriorly in the empty pleural spaces. We believe that the pulmonary veins, as a result of this posterior drop, get kinked at the level of the pulmonary hili, thereby preventing ambient air from entering them. The collapsed lungs fall posteriorly in the open pleural cavities, and the atelectasis formed in the non-dependent parts of the lungs may reduce the amount of ambient air that can enter into the pulmonary veins. The circulating blood volume that needs to pass through the collapsed lungs to flush out all residual air from the pulmonary veins should be less than that needed for fully ventilated lungs and may be

achieved early during the de-airing phase. The pulmonary artery pressure needed to be generated by the right ventricle to fill the entire pulmonary vascular bed, seems likely to be lower when the non-dependent parts of the lungs are collapsed and closer to the heart than if fully expanded.

Is it sufficient to collapse only the right lung?

TEE studies have shown that most of the residual air after open cardiac surgery emanates from the right pulmonary veins.^{33, 34} In study IV, we therefore aimed to investigate whether single right pulmonary collapse with gradual pulmonary reperfusion and ventilation is as effective as bilateral pulmonary collapse for de-airing of the left heart. The right pulmonary veins open more anteriorly in the LA than the left pulmonary veins when the patient is lying in the supine position on the operating table which may facilitate entry of more air into the right pulmonary veins. This topic has clinical implications in situations when the left lung cannot be collapsed because of pleural adhesions, for example due to previous surgery, trauma or pleural infection, or if the left lung is non-compliant, as in some cases after previous radiotherapy. Also, when surgical access to the left pleura is limited as in minimal aortic valve replacement, the right pleura may be relatively easily accessed.

The counted MES as registered by on-line TCD in study III showed large inter-patient variation in magnitude in the group with intact pleura. We believe that the higher number of MES and the higher grade of residual air emboli in the observational period in the first ten minutes after CPB in patients with intact pleurae are directly related to the circulating blood volume that should pass extended and fully ventilated lungs before all residual air emboli can be flushed from the pulmonary veins. The severity of residual air emboli may, therefore, vary in these patients, depending upon post-CPB right and left ventricular pre- and afterload in each individual patient in the first ten minutes or longer after the termination of CPB.

In study IV, we found that unilateral right pulmonary collapse provided nearly equipotent de-airing of the left heart with respect to the number of MES registered during the de-airing procedure and the severity of retained intracardiac air emboli as graded by TEE during the first ten minutes after CPB and also by a shorter total de-airing time. However, the number of MES recorded by TCD during the first ten minutes after CPB was significantly higher in the group with unilateral right pulmonary collapse as

an expression of more retained intracardiac air in this group after finished de-airing.

Are there any risks associated with collapse of lungs during cardioplegic arrest?

In our studies, which all had relatively short aortic occlusion times, we did not find overt clinical signs of postoperative pulmonary injury due to pulmonary collapse during CPB. The de-airing method with open pleurae and pulmonary collapse has also been used by us in patients undergoing the Ross operation. Despite long CPB and aortic occlusion times for those patients, the postoperative ventilator times and the duration of the patients stay in the intensive care unit postoperatively were similar to those in the present study.⁸⁴ Cold ischemic pulmonary collapse over extended periods of time is also employed routinely for the transport of donor lungs for clinical lung transplantation and these lungs also lack bronchial circulation in the early post-transplant period.⁸⁵

Does gradual pulmonary reperfusion and ventilation matter?

We re-evaluated the original Lund concept in study I. Besides bilateral pulmonary collapse, the Lund concept also comprises of a gradual increase in cardiac output coupled with delayed and staged ventilation at the end of cardioplegic arrest. In study III we attempted to assess whether these efforts of a controlled and stepwise strategy for pulmonary reperfusion and ventilation contributed to the overall efficacy of the Lund concept. The general results for the group with open pleurae and conventional pulmonary reperfusion and ventilation were better than for the group with intact pleurae and gradual pulmonary reperfusion and ventilation. Based on these results and findings from our earlier studies, we concluded that the strategy for filling and ventilation added little benefit to the overall efficacy of the Lund concept. In a comparison to a historical control group with bilateral open pleurae and staged pulmonary reperfusion and ventilation, the gradual technique was superior in the first ten minutes after CPB with respect to MES, although contradictory results were found for residual air as graded by TEE (Figures 11 and 12).

However, despite this, we do believe that gradual reperfusion and ventilation have a role in adding safety to the de-airing procedure at a fairly low expense, although bilateral pulmonary induced collapse is the key

factor for effective de-airing. A gradual increase in the right ventricular preload and ejection, followed by staged increase in pulmonary ventilation allow us to evacuate the air effectively in a gradual and controlled manner through the LV vent under continuous TEE control. Conventional filling of the lungs with blood from the CPB circuit while the ascending aorta is clamped and the lungs fully ventilated, with or without PEEP, may cause right ventricular volume overload, right ventricular distention and transient atrio-ventricular conduction problems, resulting in delayed weaning of the heart from CPB. Moreover, this part of the de-airing procedure cannot be monitored by TEE and there is a theoretical risk of air embolizing into the coronary arteries during this phase, in spite of active suction of the aortic root. Gradual reperfusion and ventilation of the lungs after the heart has assumed a strong beat may help to avoid these problems.

Benefits and drawbacks of CO₂ insufflation

We used CO₂ insufflation as a golden standard reference method for cardiac de-airing in our evaluation of the Lund concept. It is important to underline that CO₂ insufflation for de-airing can be used in various ways. One de-airing protocol with CO₂ insufflation might not be identical to the other. In our studies, CO₂ insufflation of the operative field was used employing a standardized and recommended protocol.⁷² For the effectivity of the method, it is important to achieve a high local concentration of CO₂ in the surgical field, ideally displacing all air. To achieve this, we consistently used a gas diffuser validated to provide optimal concentration of CO₂ in the open pericardial sac.⁷⁰ Further, we attempted to restrict the use of suction and excessive movement in the field, factors which could contribute to the wash out of CO₂.

Carbon dioxide insufflation is a widely used technique for de-airing and the recommended method for de-airing in minimal invasive procedures where access to the heart and lungs is limited. In study II we studied the occurrence of possible side effects associated with CO₂ insufflation. The insufflation of CO₂ induced hypercapnic acidosis despite early and continuous corrections by increasing the gas flows to the oxygenator based on in-line monitoring of blood gases. The increase in PaCO₂ corroborated the observed concomitant increase in produced volumes of CO₂ in the group with CO₂ insufflation. This illustrates the rapid uptake of CO₂ in the open mediastinum and the necessity of compensational increases in the oxygenator gas flows as described in several reports.^{42, 78, 79, 81} The volume of CO₂ produced by the bronchial circulation in the CO₂ group, consisted only of a small fraction of total volume of CO₂, indicating that the increased volume of CO₂ derived from gas insufflation.

The use of a capnograph at the oxygenator gas outlet is a simple adjuvant in controlling appropriate gas flows to avoid adverse effects of CO₂ insufflation.^{81, 86} Also, the in-line blood gas monitoring system can be a beneficial complement or alternative to conventional blood gas analysis as it reports rapid fluctuations in acid base balance in real time. In our study we compared data collected from in-line monitoring of blood gases to conventional intermittent blood gas samples drawn from the arterial and central venous lines of the patient and found the methods concordant.

Effect on cerebral hemodynamics

In study II we found influence on cerebral hemodynamics by CO₂ insufflation, as the mean blood flow velocities in both MCAs were higher in the CO₂ group compared with Lund method group. The increase in cerebral blood flow velocity seems to occur early after initiation of CO₂ but velocities are hereafter stabilized as the CO₂ partial pressure is controlled within targeted limits by adjustments of the sweep rates of the oxygenator. Increased velocities in the MCA can theoretically be caused by increased intracranial vascular resistance, or by increased blood flow to the brain secondary to vasodilation.⁸⁷ In this study, rSo₂ measured by near-infrared spectroscopy (NIRS), did also increase significantly during CO₂ exposure, suggesting that the increased blood flow velocity to most likely be due to vasodilation secondary to increasing PaCO₂. The immediate response in vasoreactivity of the MCAs from changes in PaCO₂ is well described.⁸⁸

Exact assessment of cerebral blood flow with the TCD technique was not feasible because of the unknown diameter of the MCA. However, although not knowing the diameter of the MCA, one can estimate a diameter and assume that it remains unchanged, provided that the vasomotor action is confined to resistance arteries and arterioles.⁴⁸ Under such circumstances, there is strong correlation between changes in MCA blood flow velocity and cerebral blood flow why TCD can be useful to monitor changes in cerebral hemodynamics during CPB.⁴⁸ The normal blood flow velocities in the MCAs at rest ranges from 35–90 cm/s with a mean velocity of 60 cm/s.⁴⁹ The mean blood flow velocity in patients in the CO₂ group during CPB was significantly higher than in the group without CO₂ but did not exceed normal values. Potential negative effects of this increase, if any, might theoretically be an increase in MES reaching the cerebral circulation secondary to a putative increase in cerebral blood flow. Experimental studies suggested that reduction in PaCO₂ during CPB could decrease cerebral microembolization.⁸⁹ However, no evidence supporting this theory could be demonstrated in humans.⁹⁰

Effect on red blood cells

The normal erythrocyte is 6-8 µm in diameter and can undergo structural deformation and squeeze through the smallest capillaries with a diameter of 3 µm in the microcirculatory system.⁹¹ Several factors during the cardiopulmonary bypass affect both the structure and the function of the red

blood cells.⁹¹⁻⁹³ As reported in study II, suspicion of thrombus formation in the tubing close to the pump head in two patients, led to the incidental finding of a morphological change in 97% of the counted red blood cells in the CO₂ group compared to 18% in the Lund group. Despite restricted use of the cardiectomy suction, affected red cells were found both in samples from the cardiectomy and the vent line tubing, both containing blood immediately exposed to the atmosphere in the open pericardium during surgery. We undertook no further functional analysis of the red blood cells, but by inspection it appears as if the cells have undergone the type of crenation that can be seen secondary to dehydration. The finding of the morphologically altered red blood cells was not anticipated and we did not find this phenomenon in association to CPB and CO₂ insufflation described elsewhere in the literature. A recent study reported observation of thrombus formation in the pericardium and in the cardiectomy reservoir after CO₂ insufflation in 20 patients over a three year period.⁹⁴ In a subsequent in-vitro study, the same authors found that acidosis secondary to CO₂ insufflation, could decrease the anticoagulant potency of heparin, thus predisposing patients to thrombus formation in stagnant blood.⁹⁴ In our study the activated clotting time and heparin concentration in both groups were within therapeutic limits throughout CPB. We also did not find signs of affected oxygen consumption in our study with relatively short periods of CPB and aortic cross-clamping. It is likely, although unknown, that the affected erythrocytes are not present in the venous and arterial line tubing in which circulating blood is less stagnant and CO₂ concentrations are lower due to the gas exchange in the oxygenator and due to the low exposure of CO₂ compared to the cardiectomy suction and vent tubing. The accidental findings of affected red blood cells in our study should be considered as reported observations as this was not an endpoint we primarily aimed at studying in detail.

Effect of LV vent type for de-airing

In prior reports describing and evaluating the Lund method,^{82, 83} as well as in the current study I and III, a left ventricular apical vent (LVAV) was used for de-airing of the left ventricle. A LVAV was chosen in order not to manipulate the junction of the right superior pulmonary vein and the left atrium surgically, and thereby, possibly preventing any trapped air in the left atrium from again entering the right pulmonary veins after achieving complete evacuation of air from these during the de-airing process.

However, the use of a right superior pulmonary vein vent (RSPV) is a commonly used alternative in the clinical setting. Both types of LV vents have benefits and disadvantages. We therefore aimed to investigate whether a RSPV in conjunction with bilateral pulmonary collapse would be as effective as a LVAV for de-airing of the left heart.

In study IV, we compared a group with RSPV with a historical control group with LVAV. In both groups, the lungs were bilaterally collapsed and the patients were disconnected from the ventilator during cardioplegic arrest. Gradual pulmonary perfusion and ventilation was applied to both groups. We found a higher number of MES during the first ten minutes after CPB in the group with RSPV compared to the historical control group in which LVAV was used to vent the left ventricle (30 vs 4, $p=0.003$). The findings of this study suggest that LVAV is superior to RSPV in de-airing of the left heart. One explanation for why RSPV performed less effective than LVAV in our study may be that the RSPV catheter positioned through the mitral valve facilitates entry of air from the empty cardioplegic LV into the empty LA. Furthermore, the RSPV may also mechanically undo the functional kink or closure in the distal right pulmonary veins and let the air in the LA enter the non-dependent anterior segments of the collapsed right lung. It is also possible that the RSPV preferentially empties the LA over the LV depending on the length of the side hole bearing part of the catheter tip that ends up in the LA. RSPV is prone to dislocation from its position in the LV to the LA or into one of the pulmonary veins while LVAV may accidentally dislocate upwards into the aortic root or into the LA. We closely monitored correct positioning of all LV vents with TEE guidance, manual palpation or by direct visual control of the catheters in the LV through the exposed aortic valve orifices.

In our studies, no intraoperative surgical complications were observed with any of the two venting techniques. The use of a LVAV may, however, be attended by postoperative bleeding from the LV incision site, tear, or dissection and hematoma of the LV apical muscle⁶⁵ (Figure 2). The late formation of a pseudoaneurysm at the venting site is also considered to be a potential risk associated with LVAV usage.⁶⁶⁻⁶⁸ Injury to the left anterior descending artery is another potential complication. These surgical risks can be avoided with the use of an RSPV, although an RSPV catheter may sometimes perforate a thin and weak LV wall.⁶⁹

TCD monitoring in studies of cardiac de-airing

Improvements in TCD technology now enables automatic on-line counting of emboli and artifact rejection by the TCD software, based on a stepwise binary decision tree involving complex mathematical models.^{95, 96} This development has led to a more user-friendly technique, and opened for potential use of TCD as intraoperative monitoring of cerebral perfusion and emboli. However, successful analyses require proper insonation of the intracranial vessel of interest. Maintaining a strong signal throughout critical periods of surgery and anesthesia can be challenging. In addition, insonation of the MCAs, most likely measures only a fraction of the total air embolism reaching the arterial circulation.

In our studies, we set the threshold at 10 dB and registered all MES lasting for more than 4 ms with a relative energy intensity increase of 10-20 dB above the threshold. The interobserver agreement between observers in different hospitals has been graded as high in multicenter studies and suggests the modern TCD technique to be reproducible⁹⁷ although it is important that all investigators follow the same protocols and perform analyses in accordance with recommended guidelines for emboli detection.⁴⁷ In our studies of de-airing, we did not adopt the possibility of using software for differentiation of MES in gaseous or solid microemboli. A small part of all MES registered during de-airing were likely solid. After de-airing however, we expected the majority of MES measured in our studies to be of gaseous composition as the aorta was not manipulated during the ten minute observational period.⁹⁸⁻¹⁰⁰ However, we performed a small pilot survey of three patients, from study IV, in which emboli differentiation was attempted, and confirmed the results of other studies which showed the majority of MES during cardiac surgery to be gaseous (Table 8).^{13, 14}

Table 8. Differentiation between solid and gaseous microembolic signals in three individuals from Study IV.

Before and After cardiac ejection			0-10 minutes after CPB		
Solid	Gaseous	Total	Solid	Gaseous	Total
0 (0%)	40 (100%)	40	0 (0%)	13 (100%)	13
0 (0%)	49 (100%)	49	0 (0%)	11 (100%)	11
15 (12%)	115 (88%)	130	2 (5%)	39 (95%)	41

Figures represent number of microembolic signals (percentage) recorded at an relative signal intensity increase of 10-20 dB above background. CPB=cardiopulmonary bypass.

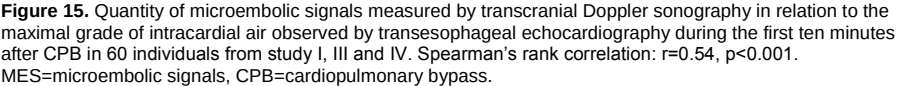
TEE and TCD as complementary methods of MES detection

Studies of gaseous microemboli in the context of cardiac de-airing typically use TEE^{33, 34, 40-42, 55, 75} or TCD^{14, 43} and occasionally combine both methods as they to some extent provide complementary information^{39, 57, 83}. Quantification of intracardiac air by TEE grading of retained intracardiac seems to be a more blunt measure of microemboli whereas counting the number of MES by TCD provides a more fine-grained estimate. Figure 15 depicts the distribution of MES in relation to TEE findings during the first ten minutes after CPB from study I, III and IV, (n=60). In individuals with none or small quantities of intracardiac air (grade 0 or I), the amount of MES is consistently in the lower range of observations. As the grading of intracardiac air increases, a discrete corresponding increase in MES is seen, with very high numbers of MES observed only in a few individuals. A potential explanation to this might be found in the design of our studies where the LV vent was always purposely left in situ and clamped after the first termination of CPB since we did not want any interference or disturbance in the collection of data in the immediate ten-minute post-CPB period, during which we recorded cerebral microemboli on-line by TCD and residual air in the left heart by TEE. Also, the occurrence of higher grades of air on TEE resulted in prompt reopening of the LV vent to evacuate the air and hereby prevent it from being converted to MES. The evacuation of air from the LV is likely to affect the amount of measured MES in these individuals, in part explaining why an individual with the higher grades of intracardiac air upon TEE assessment presented with a relatively low amount of MES.

Some studies on cardiac de-airing defined their primary endpoint as the amount of intracardiac air emboli determined by TEE. In study I and III, the amount of intracardiac air seemed to correlate well with our MES findings and seemed sufficient to serve as a primary endpoint together with quantification of MES. However, in study IV, these associations became weaker, and we were doubtful as to whether TEE was sensitive enough to register small differences in air emboli. In study IV, we found more MES in the group with only the right pleura open during the ten first minutes after CPB. However, this difference in microemboli could not be confirmed by higher grades of intracardiac air as visualized on TEE, nor did we need to open the LV vent in this group. The discordance between TEE and TCD findings in this study was unexpected. The distribution of blood and air to

the LA from the right and left pulmonary veins, in a situation with single right pulmonary collapse, could be different from, the for us, more familiar situation with bilateral pulmonary collapse. A single plane TEE three-chamber view was employed for monitoring of retained intracardiac air in this study similar to all our previous de-airing studies. It is possible that the TEE view, which visualizes three chambers but in a single plane, may not show retained intracardiac air emboli present in the heart anterior or posterior to the plane set at the start of the TEE recordings.

Another contributing factor explaining the discordance of TEE to TCD findings in study IV might be that in the TEE three-chamber single plane view, the TEE registers residual intracardiac air emboli emanating mostly from the right pulmonary veins due probably to streamlining of higher rates of blood flow from the larger right lung into the left heart in the plane set for TEE monitoring. If this would be the case, residual air emanating from the non-collapsed left lung would not be visible on TEE during the ten-minute study period after CPB, and patients with single right lung collapse would then run the risk of being graded falsely low in the severity of residual intracardiac air. The asymmetrical pattern of blood flow from lung veins into the LA is described in echocardiographic studies and could contribute to our findings.¹⁰¹⁻¹⁰³ It appears that this represents one of the inherent diagnostic weaknesses of TEE in this setting.



Study limitations

A few questions concerning the study design merit consideration. First, the studies were not conducted double-blinded due to the nature of the study hypotheses, where blinding of the surgeon, perfusionist and anesthesiologist was not feasible. Since investigators were not blinded to the treatment allocation, a potential investigator bias cannot be ruled out. In study III, the risk of investigator bias may be low due to the study design, as one of the two main components of the Lund concept was distributed randomly to two treatment arms and each arm was assigned one of two potentially equally important underlying components of effective de-airing. In study I and III, all TEE investigations were recorded for re-evaluation retrospectively by an investigator blinded to study allocation. In study IV only 12 of 20 TEE recordings covered the full ten minutes of the observational period and thus were available for blinded re-evaluation. In ten of these cases (83%) the grading of residual intracardiac air corresponded well with the intraoperative grading used for data analysis. TCD data were obtained by on-line and automated counting of MES by the TCD software. Postoperative re-evaluation by an external assessor of TCD recordings was not applied in these studies.

Second, the comparison of study groups to a historical control group confers potential methodological problems. Study designs involving historical control groups are the lowest ranked in the category of clinical controlled trials. However, it proved difficult for the investigators to recruit the given number of patients with, in essence, isolated aortic valve stenosis in the prescribed study period on account of other aortic valve replacement procedures currently under investigation including minimal invasive sternotomy, suture less aortic valve replacements and transcatheter aortic valve implantation. Therefore historical control patients were used for comparison when feasible. The historical control group used for comparison in this thesis, was however, part of a *de novo* randomized clinical trial that was conducted by the same investigators from the same institution that conducted the subsequent trials and with identical protocols except for the investigated de-airing technique.

Third, the sample sizes of our studies are small. The number of ten patients in each group was decided on for study I after initial observations of MES in a prior study. For the conduct of study III, an estimation of the needed sample size could be performed based on the observed differences of the primary endpoint in study I. For study IV, we used the same estimation as in

study III. Despite the small sample size, we were able to detect significant differences between groups, and our power calculations indicated a statistical power of 80% to detect effects of the magnitude in which we were interested. The value of increasing the sample size to gain further power to the study for these specific hypotheses is unclear. Nonetheless, potential biases linked to a small sample size must be kept in mind.¹⁰⁴ Studies I, II and III have the strength of randomized controlled trials. In study IV, the study groups were compared to a historical control group, in a prospective controlled design.

Clinical implications

The improved techniques of contemporary cardiac surgery and associated technology have minimized the risks of gross air embolism to a minimum. Effective arterial line filters, blood level sensors and bubble traps provide high grade protection from solid and gaseous microemboli originating from the ECC circuit but do not prevent microembolization directly to the brain from the surgical field. Despite these efforts of improved neuroprotection during cardiopulmonary bypass procedures, the incidence of postoperative neurocognitive dysfunction remains an issue in a smaller proportion of patients undergoing open heart surgery. In addition to these measurable evident neurological deficits, an unclear proportion of patients is also thought to have subclinical neurocognitive dysfunction such as memory loss.⁶ Although there is a general consensus on the multifactorial nature of postoperative neurocognitive dysfunction, gaseous microemboli are a well-recognized contributing factor. We used cerebral microemboli detection as a surrogate marker¹⁰⁵ for postoperative neurocognitive injury in our interventional studies, and chose to focus on intraoperative techniques to reduce gaseous microembolism. In an elderly population of patients, the occurrence of coexisting cerebrovascular disease may be more frequent, and lead to increased vulnerability to the load of intraoperative neurological stressors.¹⁰⁶ The usually subclinical manifestations of gaseous cerebral microembolism may in patients with preexisting early dementia or with a history of cerebrovascular disease rapidly become clinically overt.¹⁰⁷ It is therefore important to prevent also small quantities of air from reaching the systemic circulation. Air in the blood, even in the form of small microbubbles, are non-physiological foreign bodies which besides causing potential ischemia also triggers an inflammatory reaction in the vessel and

surrounding tissue. Gaseous microemboli should be avoided whenever possible.

The Lund concept depends on the complete collapse of lungs, and may not be equally effective in patients in whom complete pulmonary collapse cannot be achieved, e.g., with chronic obstructive lung disease, uni- or bilateral pleural adhesions, chronic pulmonary injury following radiation of the chest and the mediastinum etc. In such cases, CO₂ insufflation of the open mediastinum is an alternative option. Single right open pleura seem to be as efficient as bilateral open pleurae as far as de-airing time and the number of cerebral MES registered during the de-airing procedure itself is concerned. It is however associated with a significantly higher number of cerebral MES during the first ten minutes after CPB. These MES are most probably emanating from the non-collapsed left lung. While bilateral open pleurae should be the method of choice, single right pulmonary collapse should be considered as an alternate to CO₂ insufflation if the left lung happens to be adherent, non-compliant, or if there is poor access to the left pleura during minimal invasive aortic valve replacement. In minimal invasive open cardiac procedures, CO₂ insufflation may prove to be the preferable option as optimal manual de-airing may not always be possible.

Conclusions

Study I The Lund method is a safe and effective method for cardiac de-airing compared to a carbon dioxide insufflation method with respect to, fewer cerebral microemboli, less retained intracardiac air emboli and shorter duration of the de-airing procedure.

The Lund method did not affect postoperative short-term pulmonary function negatively as postoperative ventilation times and intensive care stay were normal.

Study II Insufflation of CO₂ to the mediastinum caused systemic side-effects by increased PaCO₂ and decreased pH.

The rate of gas flow in the oxygenator was increased to twice the normal to counteract the developing hypercapnic acidosis.

The increase in PaCO₂ affected cerebral hemodynamics as the blood flow velocity in the MCAs increased as did rSO₂.

We found morphologically changed red blood cell morphology on SEM images of the tubing of parts of the ECC circuit exposed to high concentrations of CO₂ that mimicked a blood clot to the naked eye.

Capnography at the oxygenator outlet and in-line monitoring of arterial blood gas parameters is of importance to counteract rapid development of hypercapnic acidosis.

Study III Bilateral opening of the pleurae and associated pulmonary collapse is the most important factor of the Lund concept for achieving effective de-airing of the left heart.

Gradual pulmonary reperfusion and ventilation alone, in combination with intact pleurae and expanded lungs, do not contribute significantly to effective cardiac de-airing and thus seem to be of lesser importance for the Lund concept as long as satisfactory bilateral pulmonary collapse has been achieved in the first instance.

Study IV Bilateral pulmonary collapse is more effective than single right pulmonary collapse in cardiac de-airing.

LVAV reduces retained intracardiac air and provides better de-airing than RSPV in a scenario with bilateral pulmonary collapse and gradual pulmonary reperfusion and ventilation.

Summary in Swedish (Sammanfattning)

Luft förekommer normalt inte i blodcirkulationen men kan introduceras när vänster del av hjärtat eller kroppspulsådern öppnas under ett kirurgiskt ingrepp. Med avluftning avses de åtgärder som vidtas för att eliminera luft från hjärtat. Avluftning är i synnerhet av vikt för lungvener, vänster förmak, vänster kammare och aortaroten eftersom kvarvarande luft här efter avslutat hjärtkirurgiskt ingrepp riskerar att föras vidare ut i kroppen som så kallade luftembolier. När luftembolier skapar luftlås i blodkärlen blockeras det normala blodflödet vilket kan leda till syrebrist förorsakande övergående eller permanent skada i de exponerade organen där framför allt hjärnan är särskilt känslig.

I de fyra delarbeten som utgör den föreliggande avhandlingen studeras en konceptuell metod för avluftning som första gången beskrevs och evaluerades i Lund år 2009 av dr. Bansi Koul. Avluftsningmetoden uppkom ur intraoperativa iakttagelser av att tillfällig avstängning av lungvenerna med klämmor eller band kunde förhindra luft från att ansamlas i lungvenerna under operationen, och att detta tycktes ha en avgörande positiv betydelse för avluftsningprocessen. Lundametoden för avluftning består huvudsakligen av två delkomponenter.

Den första komponenten är öppnandet av patientens lungsäckar i början av operationen. Detta syftar till att minska mängden luft i lungvenerna som senare kan bli svår att göra sig av med. När lungsäcken öppnas mot atmosfärisk luft utjämnas det undertryck som normalt upprätthåller lungans expansion. Detta bidrar till att lungan kollaberar. För att ytterligare förstärka effekten kopplas patienten också tillfälligt bort från ventilatorn. Detta kan göras när lungornas arbete har tagits över av hjärt- lungmaskinen som under operationen tar hand om det lilla kretslopp av blod som normalt finns i hjärta och lungor. När lungorna faller bakåt i de öppna lungsäckarna knickas sannolikt lungvenerna något. Detta åstadkommer troligen ett visst mekaniskt hinder som liksom ett vattenlås hindrar luft som kommer in i vänster förmak från att vandra ut och fångas i lungvenerna. Att lungorna

kollaberar ökar samtidigt motståndet för luft att vandra ut i kärlen i de främre, och i rygggläge högst belägna lungsegmenten.

Den andra komponenten består av en gradvis återuppfyllnad av hjärta och lungor med blod från hjärt-lungmaskinen vid operationens slut och en successiv stegvis återgång till normal ventilation av lungorna syftande till att göra sig av med den luft som trots förebyggande åtgärder kan ha tagit sig in i lungvenerna. För att lungornas kärl ska kunna tömmas helt och hållet på luft, krävs det att höger kammare klarar att generera ett tillräckligt högt blodtryck i det lilla kretsloppet för att fylla upp lungkärlbädden med blod och på så vis skjuta luften framför sig genom lungvenerna ut i vänster förmak och vidare till vänster kammare där luften fångas upp av ett dränage. Tack vare att lungorna är kollaberade, och att de främre och i rygggläge högst belägna lungsegmenten nu befinner sig i ett lägre plan i förhållande till hjärtat än normalt, krävs av höger kammare en lägre blodvolym och därmed ett mindre arbete för att helt fylla den kollaberade lungkärlbädden med blod. Detta i motsats till att det krävs ett betydligt större arbete för hjärtat att generera en större hjärtminutvolym för att fylla hela lungkretsloppet vid två normalt expanderade lungor. Denna åtgärd kan således minska belastningen på högerkammaren i denna tidiga fas när hjärtat åter ska överta arbetet från hjärt-lungmaskinen. Processen övervakas med hjälp av transesophageal ekokardiografi (TEE) som visar om det finns luft kvar i hjärtat. Först när TEE visar att hjärtat är tomt på luft tar nästa del av avluftningen vid genom att de lufttomma lungorna nu åter gradvist fylls med luft och lungkärlen med mer blod. De sammanfallna lungblåsorna öppnas upp med hjälp av att ett positivt slutexpiratoriskt tryck genereras i luftvägarna med hjälp av ventilatorn.

Avhandlingens övergripande syfte är att undersöka den ovan beskrivna Lundametoden med avseende på säkerhet, effektivitet och verkningsmekanism genom att bland annat sätta metoden i relation till en väl beprövad standardiserad referensmetod där koldioxid (CO₂) används för avluftningsändamål.

I det första delarbetet jämfördes Lundametoden mot CO₂-metoden med hänsyn till säkerhet och effektivitet. I den senare fylldes den öppnade hjärtsäcken med CO₂ som på grund av sin högre densitet tränger undan luft, men som på grund av sin högre lösbarhet snabbare resorberas från blodbanan än luft, och därför i mindre grad ger upphov till skadliga blockeringar i blodcirkulationen. Avluftningsmetodernas effektivitet undersöktes genom att mäta antalet påvisade cerebrala mikroembolier (MES) i höger och vänster arteria cerebri media med transkraniell Doppler

(TCD). Som ett komplement till TCD användes TEE under de första tio minuterna efter avslutad avluftsproceduren för att gradera mängden kvarvarande luft i hjärtat efter avslutad avluftsning. Vid stora luftmängder evakuerades denna luft genom ett vänsterkammardränage och antalet öppningar av detta per patient registrerades. Durationen av avluftsproceduren tjänade också som mått för metodernas effektivitet.

Studien kunde inte påvisa ogynnsamma bieffekter associerade till att kollabera lungorna så som förlängt behov av respiratorvård efter operationen. I gruppen där Lundametoden använts uppmättes färre MES vilket kunde bekräftas med lägre grader av luft i hjärtat även mätt med TEE. Avluftsningen tog också kortare tid med den studerade avluftsningmetoden jämfört med referensmetoden.

I delarbete två studerades samma patientgrupper som i det första delarbetet, men med fokus på sidoeffekter av CO₂. Studien beskriver hur CO₂ som tillförs lokalt till mediastinum löser sig i blodet och därmed även utövar en systemisk effekt genom att surgöra blodet. I motverkande syfte ökades utvädringen av CO₂ i hjärt- lungmaskinens oxygenator men trots detta sjönk blodets pH i koldioxidgruppen. För att demonstrera att det ökade innehållet av koldioxid i blodet berodde på lokalt tillfört CO₂, och inte på en ökad ämnesomsättning, beräknades varje patients respiratoriska kvot. Denna visade sig vara förhöjd i gruppen med CO₂ som ett uttryck för att den samlade koldioxidproduktionen faktiskt översteg syrgasupptaget och alltså kunde betraktas bero på tillförseln av CO₂. I gruppen med CO₂ ökade även blodets flödes hastighet i höger och vänster arteria cerebri media sekundärt till den ökade koldioxidhalten i blodet. Samtidigt sågs också en ökning i regional cerebral syrgasmättnad, också denna sannolikt sekundär till vasodilatation. Prover från hjärt-lungmaskinens plastsslangar studerades i svepelektronmikroskop och visade att en del av de röda blodkroppar som fanns kvar på insidan av slangarna var deformerade i gruppen där CO₂ använts. Det fanns dock inga overta tecken på att blodkropparna inne i blodbanan hos patienterna var påverkade varför fyndet får sägas vara en observation där orsaksförhållande och konsekvens ej är klarlagt.

I det tredje delarbetet undersöktes om någon av de två delkomponenter som utgör Lundametoden var av större betydelse. Detta var viktigt för att närmare kunna bestämma avluftsningens användbarhet i de fall där lungorna inte går att kollabera på grund av lungsjukdom eller sammanväxningar i lungsäckarna. En grupp patienter med öppna lungsäckar och snabb återfyllnad och ventilation av lungorna jämfördes med en grupp patienter med intakta lungsäckar och gradvis återfyllnad och ventilation av

lungorna. Resultaten påvisade färre MES och mindre kvarvarande luft i hjärtat uppskattat med TEE hos gruppen med öppna lungsäckar. Durationen av avluftsprocessen var kortare i gruppen med öppna lungsäckar och likaså öppnades vänsterkammardrännet för evakuering av luft efter avslutad avluftsning färre gånger i gruppen med öppna lungsäckar. Från detta kunde vi konkludera att det är öppnandet av lungsäckarna som är den viktigaste delkomponenten för avluftsningens effektivitet förutsatt att adekvat och bilateral kollabering av lungorna uppnås. En annan intressant slutsats från detta arbete är att ventilatorn var fränkopplad i bägge grupper vilket i sig ger en viss lungkollaps. Att resultaten var bättre i gruppen med öppna lungsäckar understryker att det inte räcker att koppla bort ventilatorn utan att också lungsäckarna måste öppnas för att åstadkomma effektiv lungkollabering.

När vi nu så påvisat att öppnandet av lungsäckarna är den huvudsakliga verkningsmekanismen för den studerade avluftsningens metod vill vi i det fjärde delarbetet undersöka om metoden också skulle vara effektiv med endast höger lungsäck öppnad. Ekokardiografiska studier har visat att mer luft fastnar i de högersidiga än i de vänstersidiga lungvenerna. Detta kan bero på att höger lunga är större än vänster, men också på att de högersidiga lungvenerna mynnar ut i vänster förmak i ett högre plan sett i ryggläge vilket gör att luften som söker sig uppåt fastnar här. Frågeställningen är kliniskt relevant, eftersom att Lundametoden då också skulle kunna användas i situationer med nedsatt åtkomlighet till vänster lungsäck, som vid till exempel vissa typer av minimal invasiv kirurgi. I samma studie ville vi jämföra effektiviteten för avluftsning av två olika typer av vänsterkammardränage. Båda används för att tömma vänster kammare på blod och luft. Den ena typen läggs direkt in i vänster kammare genom kammarens vägg, så kallat apexdrän (LVAV). Den andra typen, så kallat lungvensdrän (RSPV), läggs in via en öppning i den högra övre lungvenen och förs genom vänster förmak över mitralklaffen in till vänster kammare. LVAV användes för alla patienter i studie I, II och III. RSPV, som dock används i allt större utsträckning världen över, har den fördelen att risken för skada på vänster kammare är mindre. Patienterna fördelades slumpvist till en grupp som opererades med endast höger lungsäck öppnad och LVAV eller till en grupp som opererades med båda lungsäckarna öppna och RSPV. För att besvara båda frågeställningarna jämfördes gruppernas resultat mot en historisk kontrollgrupp med båda lungsäckarna öppna och LVAV. Resultaten från studien visade att antalet MES under avluftsprocessen var lika i båda grupperna. Tidsåtgången för avluftsprocessen var också lika mellan grupperna. Däremot sågs under de första tio minuterna efter

avlufning fler MES i gruppen med endast höger lungsäck öppnad, men denna skillnad i mängden kvarvarande luft sågs inte med TEE. Att resultaten med TCD och TEE inte överensstämde kan vara ett uttryck för att den relativt lilla mängd luft som fanns att se i hjärtat med TEE inte kunde uppfattas på det endimensionella plan som ultraljudsundersökningen av hjärtat tillhandahåller. Den andra delen av studien visade på samma sätt att LVAV resulterade i färre MES efter avluftning och därför får sägas vara mer effektiv än RSPV men att fyndet inte heller kunde bekräftas med TEE.

Avhandlingens fyra delarbeten utgör tillsammans en beskrivning av Lundametoden och tillhandahåller underlag för evidensbaserad användning av metoden i ett konceptuellt sammanhang för effektiv avluftning av hjärtat efter vänstersidig öppen hjärkirurgi.

“It’s not exactly brain surgery”

That Mitchell & Webb Look, Season 3 Episode 1, BBC

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