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CARBON DIOXIDE DE-AIRING IN CARDIAC SURGERY

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Carbon Dioxide De-Airing in Cardiac Surgery

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" This is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning."

Sir Winston Leonard Spencer Churchill (1874-1965)

Abstract (Eng)

Background: The risks connected with the presence of air microemboli in open-heart surgery, have recently been emphasized by reports that their number is correlated with the degree of postoperative neuropsychological disorder. Insufflation of carbon dioxide (CO_2) into the chest wound is used in open-heart surgery to de-air the heart and great vessels. A new insufflation device, a gas-diffuser, was compared with traditional devices for de-airing in an experimental wound model. Finally, to assess the clinical value of CO_2 insufflation into the cardiothoracic wound, the effect of such insufflation on the incidence and behavior of microemboli in the heart and ascending aorta was studied under the conditions of a randomized clinical trial.

Methods: In a cardiothoracic wound model, a full-size torso, the degree of air displacement achieved by the gas-diffuser, was compared with that of a 2.5 mm open-ended tube, a 6.35 mm open-ended tube, a multi-perforated catheter, and a gauze sponge, respectively, during steady state. The influence of suction, varying CO_2 flow rates, an open pleural cavity, exposure to fluids and the position of the device were also evaluated. De-airing was assessed by measuring the remaining air content at the right atrium. In the trial, twenty (20) patients undergoing single valve surgery were randomly divided into two groups. Ten patients were insufflated with CO_2 via a gas-diffuser and ten were not. Microemboli were ascertained by intraoperative transesophageal echocardiography (TEE) from release of the aortic cross-clamp until 20 minutes after end of cardiopulmonary bypass (CPB).

Results: During steady state, the gas-diffuser produced efficient air displacement in the wound cavity model at CO_2 flows of ≥5 l/min (≤0.65% remaining air), while the 2.5mm and 6.35mm open-ended tube were much less efficient with ≥82% and >19.5% remaining air, respectively, at 2.5–10 l/min CO_2 flows ($p<0.001$). When using the gas-diffuser, an open pleural cavity prolonged the time needed to obtain a high degree of air displacement in the wound cavity ($p=0.001$). With suction of 10 l/min the median air content was still low (≤0.50%) at a simultaneous CO_2 flow of 10 l/min. Conversely, suction of 25 l/min caused a marked increase in air content both at a CO_2 flow of 5 and 10 l/min ($p<0.001$). When exposed to fluid, the gauze sponge and the multi-perforated catheter immediately became inefficient (70% and 96% air, respectively), whereas the gas-diffuser remained efficient (0.4% air). The two patient groups did not differ in clinical parameters. The median number of microemboli registered during the whole study period was 161 in the CO_2 group versus 723 in the control-group ($p<0.001$). Corresponding numbers for the left atrium were 69 versus 340 ($p<0.001$), left ventricle 68 versus 254 ($p<0.001$), ascending aorta 56 versus 185 ($p<0.001$). In the CO_2 group the median number of detectable microemboli after CPB fell to zero 7 minutes after CPB versus 19 minutes in the control group ($p<0.001$).

Conclusion: The most efficient de-airing (≤1% remaining air) in a cardiothoracic wound model was provided by a gas-diffuser at a CO_2 flow of 10 l/min. For efficient de-airing, CO_2 has to be delivered from within the wound cavity. Additional suction impaired air displacement with the gas-diffuser only when suction exceeded CO_2 inflow. The gas-diffuser remained efficient after exposure to fluid, while both the gauze sponge and the multi-perforated catheter lost their function when they got wet. Insufflation of CO_2 into the thoracic wound markedly decreases the incidence of microemboli during valve surgery.

ABSTRACT (SWE)

Avluftning med Koldioxid vid Hjärtkirurgi

Bakgrund

Vid öppen hjärtkirurgi drabbas 2-5 % av patienterna av stroke, medan subtila hjärnskador – minnesförsämring och emotionell instabilitet förekommer hos 30-80 % av patienterna. En viktig orsak tros vara att luft tränger in i cirkulationen i samband med att aorta och/eller hjärtat öppnas under operationen. Luft består till huvuddelen av kväve, som har låg löslighet i blod och vävnader. Trots omfattande avluftningsmanövrar av kirurgen kvarstannar alltid luft i kroppspulsådern, vänster kammare, vänster förmak och lungvener. När hjärt-lungmaskinen avvecklas förs luftbubblorna ut i artärsystemet och blockerar små artärer och kapillärer i bland annat hjärnan och hjärtat, vilket leder till endotelskador och syrgasbrist. Ett sätt att förhindra att luft kommer ut i cirkulationen vid dessa ingrepp är att skapa och underhålla en hundraprocentig koldioxidatmosfär i operationssåret. Koldioxid (CO_2) är betydligt mer lättlöslig än luft och hinner därför lösa sig innan syrgasbrist uppstår. Viktiga faktorer för avluftning som användandet av sugar, öppnande av en lungsäck samt avluftningsinstrumentets placering har tidigare inte undersökts. Målsättningen var att utröna ifall en ny avluftningsmetod kan minska förekomsten av luftembolier vid hjärtklaffsoperationer.

Metoder

I avhandlingen jämfördes effektiviteten hos traditionella instrument för avluftning med den hos ett nykonstruerat instrument, en s.k. gas-diffusor. I delarbeten I-III utfördes denna utvärdering i en fullskalig hjärtkirurgisk sårmodell. Denna modell består av en egentillverkad anatomisk torso med en sårhåla innehållande ett silikonhjärta samt en öppningsbar lungsäck. I delarbete III och IV utfördes mätningarna hos patienter som genomgick hjärtklaffkirurgi.

Resultat

Delarbete I

Gas-diffusorn var mycket effektiv med ≤0.65% kvarvarande luft i sårhålan vid ett CO_2 flöde på ≥5 l/min, medan den tunna slangen var ineffektiv med en kvarvarande lufthalt på ≥82% luft. En öppen vänstersidig lungsäck förlängde tiden som behövdes för att uppnå en hög grad av avluftning.

Delarbete II

Med en kvarttumsslang kvarstod en lufthalt på 19.5-51.7%. Med gas-diffusorn var mängden kvarvarande luft <1.2% vid 5 l/min och <0.31% vid 10 l/min. Sugning med 1.5 l/min påverkade inte avluftningen. Vid sugning med 10 l/min var mängden kvarvarande luft fortfarande låg (≤0.5%) vid en CO_2 tillförsel på 10 l/min. Sugning med 25 l/min orsakade däremot en påtaglig ökning av luft i sårhålan både vid ett CO_2 flöde på 5 och 10 l/min.

Delarbete III

Gas-diffusorn bör placeras några centimeter under sårkanten för att vara effektiv. En multiperforerad kateter och en bomullstork placerad i slutet av en tunn slang (2.5 mm) var bägge effektiva när de var torra, men så fort de utsattes för vätska blev de ineffektiva. Endast gas-diffusorn behöll sin funktion när den utsattes för väta. Dessutom visade sig gas-diffusorn ge en nära 100%-ig avluftning av sårkaviteten när den testades hos patienter under pågående hjärtoperationer.

Delarbete IV

I en klinisk studie lottades 20 patienter som skulle genomgå hjärtklaffoperationer till behandling med koldioxid, tillfört via gas-diffusorn, eller ej. Den i hjärtat och kärlen befintliga luftmängden bestämdes genom videoupptagning från en ultraljudsregistrering av hjärtat under operationen. Vid senare analys av videobanden fastställdes förekomsten av det maximala antalet bubblor varje minut. Sammanfattningsvis ledde avluftning med CO_2 via gas-diffusorn till en avsevärd minskning av antalet luftbubblor i hjärtat och kroppspulsådern.

Slutsatser

Endast gas-diffusorn gav en effektiv avluftning av sårmodellen. För att vara effektiv måste den dock placeras i sårhålan och CO_2 måste tillföras med ett flöde på minst 5 l/min. En öppen lungsäck förlänger den initiala uppfyllningen av CO_2 i sårhålan, men förändrar inte betingelserna därefter. Ifall en sug används kommer avluftningen försämras om sugeffekten överstiger koldioxidtillflödet. Den nyutvecklade tekniken resulterade i en påtaglig minskning av antalet luftbubblor i hjärtat och kroppspulsådern hos patienter som genomgår hjärtklaffoperationer.

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LIST OF ORIGINAL ARTICLES

This thesis is based on the following papers that are referred to by their roman numerals I-IV in the text:

I. **Svenarud P,** Persson M, van der Linden J
Intermittent or Continuous Carbon Dioxide Insufflation for De-Airing of the Cardiothoracic Wound Cavity? An Experimental Study with a New Gas-Diffuser.
Anesthesia and Analgesia 2003;96(2):321-7

II. **Svenarud P**, Persson M, van der Linden J.
Efficiency of a Gas-Diffuser and Influence of Suction in Carbon Dioxide De-airing of a Cardiothoracic Wound Cavity Model.
Journal of Thoracic and Cardiovascular Surgery 2003;125(5):1043-9

III. Persson M, **Svenarud P**, van der Linden J.
Which is the Optimal Device for Carbon Dioxide De-airing of the Cardiothoracic Wound and How Should it be Positioned?
Journal of Cardiothoracic and Vascular Anesthesia (Accepted for publication)

IV. **Svenarud P**, Persson M, van der Linden J.
The Effect of CO_2 Insufflation on the Number and Behavior of Air Microemboli in Open-Heart Surgery. A Randomized Clinical Trial.
Circulation (Accepted for publication)

LIST OF ABBREVIATIONS

AVR	Aortic valve replacement
CABG	Coronary artery bypass grafting
CO_2	Carbon dioxide
CPB	Cardiopulmonary bypass
ECC	Extra corporeal circulation
N_2	Nitrogen
O_2	Oxygen
TEE	Transesophageal Echocardiography

INTRODUCTION

Cardiac surgery often involves the opening of the heart and great vessels. When these vital structures have to be opened, they will inevitably be pervaded by air. As a rule the air gets entrapped and tends to accumulate in the highest parts of the heart and vessels (Figure 1). Thus, it is found in the left ventricular apex, the lung veins, the left atrial appendix, the upper wall of the left atrium, and the right coronary sinus of the ascending aorta. There the air will stay until it is mobilized into the arterial bed during and after weaning from cardiopulmonary bypass (CPB). In this stage it appears as intravascular air bubbles, which may obstruct blood vessels and thus cause distal tissue ischemia. This in its turn triggers endothelial damage, which may indirectly lead to permanent obstruction by activated leucocytes and the ensuing inflammatory response. Since air, and especially its main component nitrogen, does not easily dissolve in blood, arterial air embolism is among the most dreaded complications in open-heart surgery. It may lead to cerebral injury, myocardial dysfunction and arrhythmia. The great risk that the presence of air microemboli in open-heart surgery implies, have recently been emphasized by reports that their number correlates with the degree of postoperative neuropsychological disorder.[1-3] Borger et al[3] even found postoperative neuropsychological impairment to be directly correlated with the number of perfusionist interventions that caused arterial air microemboli.

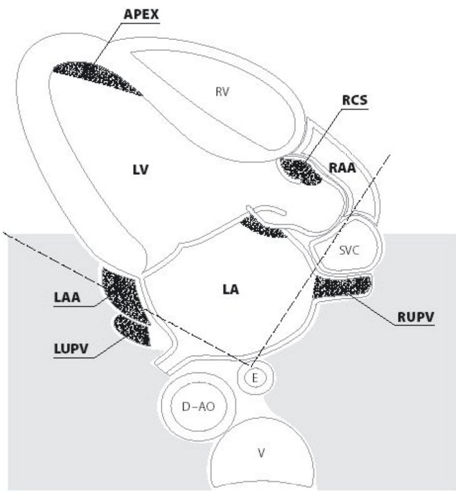

Figure 1. The entrapped air tends to accumulate in the highest parts of the heart and vessels (underlined areas in the figure). RCS=right coronary sinus, RUPV=right upper pulmonary vein, LA=left atrium, LAA=left atrial appendage, LUPV=left upper pulmonary vein, RV=right ventricle, LV=left ventricle, RAA=right atrial appendage, SVC=superior vena cava, vein, E=esophagus, D-AO=descending aorta, V=vertebra.

Cerebral air microemboli usually obstruct arterioles with inner diameters of 30-60 µm. When the bubble is slowly being resorbed, it will dislodge, move downstream and cause further damage. Even bubbles as small as 25 µL obstructing an arteriole for less than 30 seconds will disrupt brain function.[4,5] To prevent this from happening or at the very least reduce the risk de-airing techniques have been introduced. The usual de-airing maneuvers include venting of the ascending aorta, pulmonary compression with the patient in Trendelenburg’s position, shaking of the heart, venting of the left atrium through the right pulmonary vein vent, and venting through the left atrial incision in mitral valve surgery. Unfortunately, these manual de-airing techniques have proved unable to eliminate retained air.[6] It has been found that, even if these techniques are meticulously adhered to, large numbers of microemboli still occur.[6-8] Consequently, other methods should be explored to rid the heart and the arteries of air bubbles.

CARBON DIOXIDE DE-AIRING

Carbon dioxide (CO_2) insufflated into the chest wound cavity is held to improve the de-airing. The theoretical background of CO_2 de-airing is simple. CO_2 dissolves in blood and tissues ≥25 times faster than air.[9,10] If the atmosphere in the wound would consist of CO_2 instead of air, we would deal with CO_2 bubbles rather than with air bubbles. The CO_2 bubbles would disappear much more quickly and this would greatly reduce the risk of neurological and myocardial complications.[11-16] CO_2 seemed eminently suitable for the purpose of displacing air because of what was seen as another very convenient quality. It is 50% heavier than air. Thus it was thought that the difference in density might facilitate the displacement of air with CO_2 in the wound cavity. In a mixture of air and CO_2 the air would stay on top while the CO_2 was expected to sink deep into the wound, there to attain its beneficial effect. It was not until very much later that these lofty expectations were definitely dashed. When CO_2 was supplied in the manner, which was then in common use, the wound was still found to contain 20% to 80% air.[17,18] Already much earlier the clinical impression had been that insufflation with CO_2 did not seem to make much difference and this is perhaps the reason why up to now the use of CO_2 insufflation is not wide spread.

FACTORS INFLUENCING CO_2 DE-AIRING

Several factors may influence the efficiency of CO_2 de-airing during cardiac surgery, i.e., type of insufflation device, CO_2 flow, and coronary and rough suction. These three factors were investigated in the present thesis.

Devices for CO_2 de-airing

Not until fairly recently has the crucial role been recognized that the delivery device plays in the creation of an air-free atmosphere in the wound. For many years the general view seems to have been that any device through which gas could be pumped would do the trick. The open-ended tube which has the great advantages of being cheap as well as easily obtainable, became on account of these qualities more or less the delivery device of choice.[9,17,19,20] Much later it was found that the conventional open-ended tube signally fails to provide efficient de-airing. The probable reason of its failure to do so is its high outflow velocity which leads to turbulent mixing with ambient air.[18] Modified devices have therefore been introduced to improve the de-airing. Most common among them are a multi-perforated catheter placed at the bottom of the pericardial well,[21] a gauze sponge[22] and a diffuser of polyurethane foam.[18] Thus, there is at present an urgent need for a comparative evaluation of these three devices' efficiency in de-airing a wound cavity with CO_2. Such an evaluation has to take into account that the devices have to stay efficient even when they are exposed to moisture and fluids, as is often the case in clinical practice.

CO_2 flows

Earlier experimental and clinical studies of de-airing with CO_2 have used flows between 2 and 10 L/min. The choice of flow is of importance since it may be assumed that at low CO_2 flow, disturbing factors of whatever kind they may be will have a greater influence. In a simple wound model with an opening area similar to the standard cardiothoracic wound cavity we have earlier found that a CO_2 flow of at least 5 L/min is needed to compensate for the influence of diffusion.[18] In the present thesis we therefore restricted the CO_2 flow variation to the range 2.5 to 10 L/min.

Suction

To improve visibility in the operating field suction is commonly used in all forms of surgery for the removal of fluids, including blood. The need of suction is especially compelling in heart surgery, due to the excessive bleeding that occurs when the heart or vessels are opened. Contributing to the bleeding is the heparinization that is routinely instituted before the start of extracorporeal circulation (ECC). It is therefore common practice among cardiac surgeons to reuse blood from the operating field by sucking it into the cardiotomy reservoir. Here, blood is filtered and mixed with venous blood from the body during ECC. Coronary suction flows are kept as low as possible, usually between 0.5 and 1.5 L/min, to avoid hemolysis. In contrast, rough suction is used to evacuate non-heparinized blood, other fluids and surgical debris. The effect of rough suction is usually approximately 20-25 L/min. Given this very high suction rate, it seems reasonable to assume that suction might influence the de-airing efficiency of CO_2 insufflation and it is somewhat surprising that this aspect has so far not attracted any attention.

Open pleural cavity

During the opening of the sternum one pleural cavity is sometimes opened incidentally. When the internal thoracic artery is being harvested during combined procedures, the left pleural cavity is usually opened. Moreover, many surgeons prefer to open both pleural cavities more or less routinely. Thus, the lungs collapse and a negative pleural pressure is avoided during the operation. Since opening of the pleural cavities occurs so often it seemed of interest to study what effect the enlargement of the wound cavity that ensues, might have on the efficiency of CO_2 de-airing. This is an aspect that so far has not been investigated either.

CO_2 MEASUREMENTS

In order to evaluate the above-mentioned factors the CO_2 concentration in the wound cavity has to be measured with a method that is accurate. The method also has to be fast. Speed is of the essence in the study of fast fluctuations in CO_2 concentration that occur due to turbulence or intermittent CO_2 insufflation. Finally, the sampling volume needed should be as small as possible to avoid interference with the CO_2 de-airing. Most previous studies have failed to fulfill these requirements.

CLINICAL EVALUATION OF CO_2 DE-AIRING

It is no doubt a sobering thought that, although CO_2 insufflation has been practiced for half a century already, the treatment has never been evaluated according to the rigorous demands of the randomized controlled trial. One can only speculate about why this was never done. The strength of the theoretical argument, based on the physical properties of CO_2, has probably played a role. So has the convincing evidence from animal experiments. To prove the obvious did not seem a very exciting task. However, in the preparatory phase of such a trial when the gas-delivery device had to be evaluated and the technique's pitfalls had to be explored **(Study I-III)**, we found that this task had been grossly underestimated. Gas cannot simply be blown into a wound by pointing an open-ended tube at its centre. One cannot even do so with a fluid. In retrospect this is quite clear, at the time it was not. When the unexpected problems pertaining to the gas-delivery technique were finally solved, the preferred device could be tested in patients and its efficiency under clinical conditions could be investigated (**Study III**).

A randomized clinical trial

Clinical evaluation could not be considered until after the insufflation device had been meticulously tested and the whole delivery technique had been tried out. In order to be classified as effective the technique should be able to create a CO_2 atmosphere in the wound with less than 1% remaining air. When this had been accomplished the conditions for clinical evaluation were present and such an evaluation should preferably be performed according to the rules of the randomized controlled trial **(Study IV)**. The clinical evaluation of the de-airing efficiency of a CO_2 insufflation device or of any other de-airing technique will have to be carried out in patients subjected to open-heart surgery, where the heart and vessels are being opened. As a first step in a clinical evaluation, the effect of CO_2 on the number and behavior of microemboli in heart and aorta should be investigated. This can be achieved with the help of intraoperative transesophageal echocardiographic (TEE) examinations during mitral or aortic valve operations. If an appropriate and generally recognized TEE view is kept constant during the vital part of the operation and recorded continuously, a blinded observer can later evaluate the examination. The use of video recordings may also allow for a more accurate discrimination between air and moving heart tissue, thus reducing variation due to random observer variability.

AIMS OF THE THESIS

The aims of this thesis were:

- to investigate to what degree a new insufflation device, a gas diffuser, can displace air in a cardiothoracic wound model.

- to study air displacement at the start, during steady state, and after discontinuation of CO_2 insufflation with the gas-diffuser in a cardiothoracic wound model.

- to evaluate the influence of an open pleural cavity on air displacement by CO_2 insufflation in a cardiothoracic wound cavity model.

- to assess the influence of suction on air displacement in a cardiothoracic wound model.

- to examine if a CO_2 insufflation device can be positioned at the level of the wound opening or if it has to be positioned in the wound in order to be efficient.

- to test the efficiency of CO_2 insufflation devices after exposure to fluid.

- to investigate the effect of CO_2 insufflation with a gas-diffuser on the number and behavior of microemboli in the heart and in the aorta with the help of intraoperative transesophageal echocardiographic (TEE) examinations in patients during valve operations.

METHODS

GAS-DIFFUSER (STUDY I-IV)

The new gas-diffuser (patented by Cardia Innovation AB, Stockholm, Sweden; www.cardia-innovation.com), consists of a ¼" gas line with a 0.2 μm bacterial filter, and a fixable plastic 2.5-mm tube with a diffuser (18x14 mm) at its end (Figure 2). The diffuser is made of soft polyurethane foam with open cells (density 30 kg/m^3).

Figure 2. The new gas-diffuser consists of a fixable PVC tube with an inner diameter of 2.5 mm, and a soft polyurethane diffuser (14x18 mm) at the end of the tube.

CONVENTIONAL DEVICES FOR DE-AIRING (STUDY I-III)

An open-ended tube with an inner diameter of 2.5 mm served as a control in **Study I**, and in **Study II** we used an open-ended tube with an inner diameter of ¼ inch (6.35 mm) for the same purpose. In **Study III** two additional devices were used, a multiperforated catheter and a gauze sponge.

The multi-perforated silicone catheter had a length of 50 cm and an inner diameter of 3 mm. It had an open end and consisted of 20 elliptical holes, 3x5 mm wide, placed in a spiral that wound itself five times around the distal 25 cm of the catheter. Thus, the holes were positioned at 90 degrees from each other. The second device consisted of a gauze sponge (Standard gauze, Size 1, approximately 20x20 mm, Klinidrape, Mölnlycke Health Care AB, Sweden) attached in front of a 2.5-mm tube.

INSTRUMENTATION (STUDY I-III)

The CO_2 flow was measured with a backpressure compensated oxygen (O_2) flowmeter since a flowmeter for medical CO_2 was unavailable at the time of the study. The O_2 reading scale was adjusted for CO_2 by a universal flowmeter (ABB/Fisher & Porter, Göttingen, Germany), because of the higher density of CO_2 gas. The universal flowmeter consisted of a measuring tube (FP ¼-16 G-5/81) with a spherical stainless steal float (SS-14). The universal flowmeter was not used for measurements in the study on account of its lack of backpressure compensation. This problem was avoided during the calibration by measuring the CO_2 outflow distal to the end of the insufflation device. The reading scale of the universal flowmeter was calculated for the gas used (medical CO_2, AGA Gas AB, Stockholm, Sweden) at 20°C and at 1013 mbar with a computer program (FlowSelect version 2.0, ABB/Fisher & Porter, Göttingen, Germany).

Air displacement in the wound cavity model was assessed by analyzing the remaining air content (*%Air*), which is given by:

$$\%Air = \frac{\%O_2}{\%O_2(ref)} \cdot 100$$

where $\%O_2$ is the measured O_2 concentration and $\%O_2$[23] is the O_2 concentration in atmospheric air near sea-level (20.95%)[23]. The O_2 concentration was measured with an O_2 sensor (CheckMate 9900, PBI Dansensor, Denmark), which has a gas sampling volume of <2 ml, a response time of <2 seconds (>20.95% change in O_2 concentration in both directions), a range of measurement of 0.0001% to 100% O_2, and an accuracy of 1% of the measured value. The sampling probe was a 1.5 mm thick Teflon tube. The O_2 instrument was connected to a personal computer for recording of data.

Torso with a Cardiothoracic Wound Cavity (Study I-III)

Air displacement was studied in an anatomical torso model, with an open cardiothoracic wound containing a silicone replica of the heart and great vessels (Figure 3). The shape of the model was based on the maximal measurements of the open chest wounds of five adults undergoing cardiac surgery (standard sternotomy and during cardiopulmonary bypass with empty heart). We presumed that due to increased diffusion a wound cavity with a large opening would be more difficult to de-air. The torso was placed on the operating table of a normally ventilated operating theater for cardiac surgery (downward laminar airflow from the ceiling above the operating table, approximately 2500 m^3/hour). The wound opening was 20 cm long (midline) and 12 cm wide. The volume of the wound cavity without the

Figure 3. The anatomical torso model, with an open cardiothoracic wound containing a silicone replica of the heart and great vessels.

artificial heart was 2.5 liter. The external volume of the artificial heart including the great vessels was 1.0 liter giving a residual cavity volume of 1.5 liter. Furthermore, the torso's cavity could be extended with an additional volume of 2.5 liters, corresponding to an opened left pleural cavity with a collapsed lung (Figure 4).

Figure 4. The posterior aspect of the anatomical torso model including pleural cavities.

EXPERIMENTAL SET-UP AND MEASUREMENTS

Study I

The orifices of the insufflation devices were positioned 5 cm below the wound opening adjacent to the diaphragm. The tube was pointed towards the center of the wound cavity, and not towards the site of O_2 measurements. CO_2 was insufflated at a flow of 2.5, 5, 7.5, and 10 liters per minute (l/min). The remaining air content was measured at the highest part of the right atrium, 5 cm below the wound opening, close to the site of the atrial incision in mitral valve surgery.

The air displacement efficiency of the two insufflation devices (Figure 5) was assessed during steady state. A stable O_2 concentration was considered to be present when values were fluctuating around a constant value over a period of 30 seconds. After that, the O_2 concentration was recorded ten times in succession, once every 5 seconds (n=10). Furthermore, the air content was recorded every 5 seconds during the first 60 seconds of initial CO_2 filling, and after termination of continuous CO_2 insufflation, using the gas-diffuser. These recordings were repeated ten times (n=10). All measurements were made with and without an open left pleural cavity. The remaining CO_2 in

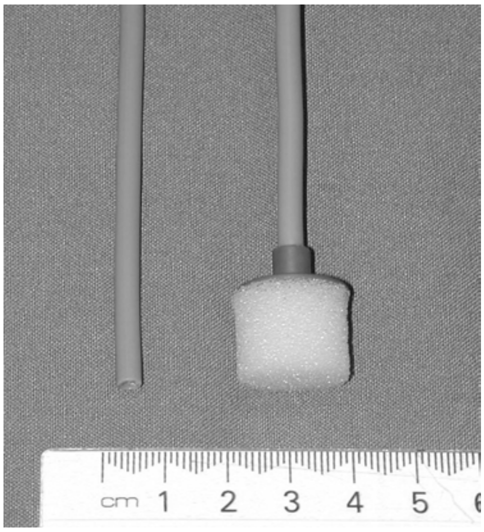

Figure 5. A thin open ended tube with a 2.5 mm cross-sectional diameter and the gas-diffuser.

the model was removed with the help of a rough sucker before every change of CO_2 flow or insufflation device, whereupon air movements around the model were left to settle for one minute.

Study II

Coronary suction, which is usually set at an effect of 1-1.5 liters per minute (l/min), was set at 1.5 l/min, and was provided by a standard roller pump and calibrated according to the manual of the manufacturer (CAPS, Stöckert, Freiburg, Germany). The rough suction was set at 10 and 25 l/min (maximum) and was controlled by two flowmeters with regulators coupled in parallel. These flowmeters were also calibrated with the universal flowmeter.

The orifices of the two insufflation devices, the gas-diffuser and a conventional 0.25-inch tube, (Figure 6) were positioned 5 cm below the wound opening adjacent to the diaphragm. The tube was pointed to the center of the wound cavity, and not towards the site of measurements. CO_2 was insufflated into the wound cavity at a flow of 5 and 10 l/min. The remaining air content was measured at the highest part of the right atrium, 5 cm below the wound opening, and at the highest part of the ascending aorta, 3 cm below the wound opening. These positions are close to the sites of the atrial and aortic incisions in valve surgery.

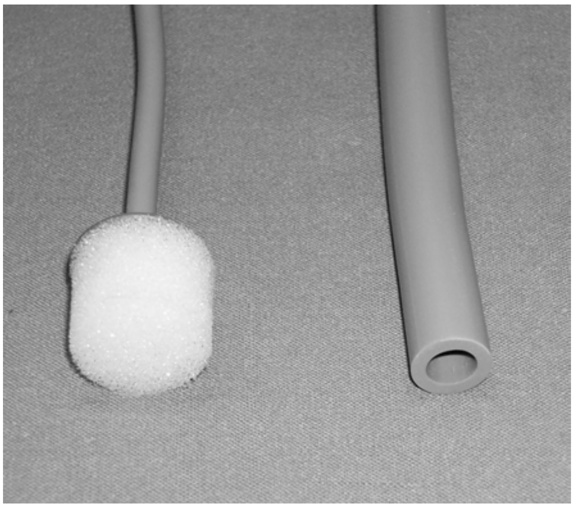

Figure 6. The gas-diffuser and a conventional 6,35 mm (1/4 inch) tube.

First, the air displacement efficiency of the two insufflation devices was assessed without suction. A stable O_2 concentration was considered to be present when values were fluctuating around a constant value over a period of 30 seconds. After that the O_2 concentration was recorded ten times in succession, once every 5 seconds (n=10). We then studied the influence of varying degrees of continuous suction, i.e., 1.5, 10, and 25 l/min applied at the site of the artificial left atrial appendix, on the efficiency of the gas-diffuser. When a stable O_2 concentration as defined above was present, suction was applied and the O_2 concentration was recorded once every 5 seconds during 60 seconds. Each recording procedure with suction was repeated ten times (n=10). Before every change of CO_2 flow or insufflation device the gas mixture remaining in the model was removed with the rough sucker and air movements around the model were left to settle for one minute.

Study III

Torso measurements

First, the de-airing efficiency of the three insufflation devices i.e., 1) a multi-perforated catheter, 2) a 2.5-mm tube with a gauze sponge at its end, and 3) a 2.5-mm tube with a gas-diffuser of polyurethane foam at its end (Figure 7) was studied when they were positioned at the level of the wound opening. The end of each insufflation device, except the multi-perforated catheter, was positioned at the level of the wound opening above the diaphragm, pointing into the center of the wound cavity but not towards the site of O_2 measurement. The multi-perforated catheter was attached along the edge of the sternotomy, starting on the patient's right side and extending cranially and back on the left side. Secondly, the de-airing efficiency was studied with the devices positioned inside the wound cavity. The end of the first two insufflation devices was positioned 5 cm below the wound opening adjacent to the diaphragm, pointing to the center of the wound cavity but not towards the site of O_2 measurements. The multi-perforated catheter was positioned at the bottom of the pericardial well, starting inferiorly on the patient's right side and extending above the aortic cannulation site and down the left side, as described by Webb et al.[21] The distance between the end of the first two insufflation devices and the site of O_2 measurement was always 8 cm.

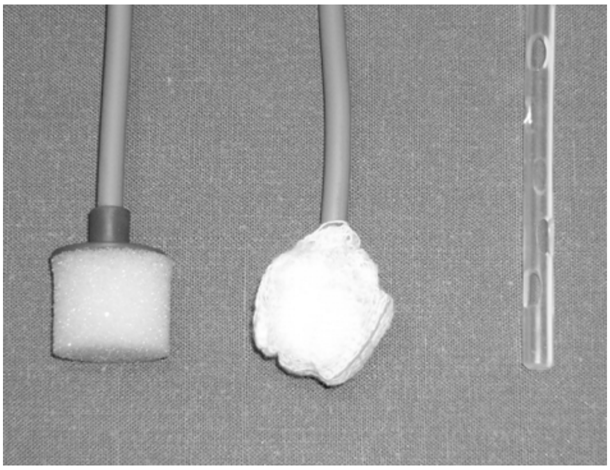

Figure 7. A gas-diffuser, a 2.5-mm tube with a gauze sponge at its end, and a multi-perforated catheter.

CO_2 was insufflated at a flow of 2.5, 5, 7.5, and 10 liters per minute (l/min). Furthermore, the de-airing efficiency of the gauze sponge and the gas-diffuser was assessed after having been temporarily immersed into water during CO_2 insufflation. The multi-perforated catheter was exposed to water at the bottom of the wound cavity during CO_2 insufflation. On that occasion the CO_2 flow was set at 10 l/min since it was considered likely that the studied devices would resist fluid exposure better at a high flow.

The air content was measured during steady state at the highest part of the right atrium, 5 cm below the sternal wound edge, close to the site of the atrial incision in mitral valve surgery. No surgical maneuvers were employed during the measurements. A stable O_2 concentration was considered to be present when values were fluctuating around a constant value over a period of 30 seconds. Subsequently, the O_2 concentration was recorded ten times in succession, once every 5 seconds (n=10). Before every change of CO_2 flow or insufflation device the remaining CO_2 in the model was removed with the help of a surgical rough sucker.

Patient measurements

The gas-diffuser, the most efficient insufflation device was further studied in ten patients undergoing cardiac surgery with complete sternotomy. Eight patients underwent coronary bypass surgery, and two underwent aortic valve replacement. There were six men and four women with a median age of 66.5 years (range 49-74). Their wound opening had a median length and width of 18 cm (range 16-22 cm) and 10 cm (range 9-11 cm), respectively. We positioned the gas-diffuser inside the wound cavity as described above. CO_2 was supplied to the wound at a flow of 5 and 10 l/min. The air content was measured immediately above the right atrium at a median depth of 5 cm (range 3-7 cm) below the wound edge, during full cardiopulmonary bypass when the heart was empty. The measurements were carried out during active surgery without use of suction. When a stable O_2 concentration, as defined above, was present the O_2 concentration was measured and recorded five times in succession, once every 5 seconds. The mean of these five values represented the recorded air content for that particular patient. Just as in the torso experiment, the remaining CO_2 in the wound cavity was removed with the help of the rough sucker before changing the CO_2 flow.

Study IV

Patient recruitment

Twenty (20) patients scheduled for isolated valve surgery at Huddinge University Hospital were included in this prospective study. All patients were first time candidates for cardiac surgery. Six (6) patients underwent mitral valve repair and 14 underwent aortic valve surgery. Eight (8) patients had coronary bypass grafting in addition to the valve procedure. Six (6) senior surgeons performed the operations. Immediately before the start of surgery the patients were randomized to one of two groups. One group was operated with intraoperative wound insufflation of CO_2 and the other group was not. Random assignment was carried out with the help of unmarked envelopes, each of which contained a card indicating CO_2 treatment in the wound or not. The patients were stratified according to type of valve procedure. Preoperative patients data are shown in Table 1.

Table 1.
Demographic and clinical data (median, 25th/75th percentile)

Characteristic	Group Control n=10	Group CO_2 n=10	P
Sex (M/F)	6/4	7/3	0.74
Age (yrs)	75 (64/82)	75 (57/78)	0.48
Length (cm)	169 (168/178)	175 (167/181)	0.53
Weight (kg)	75 (68/82)	80 (75/88)	0.19
NYHA	II (II/III)	II (II/III)	0.48
Euroscore	6.5 (5/8)	6 (3.8/7.5)	0.63
Aortic valve replacement	7	7	1.0
Mitral valve repair	3	3	1.0
CABG	3	5	0.48
ECC (min)	116 (90/136)	113 (90/138)	1.0
Aortic cross clamping (min)	84 (64/105)	85 (62/101)	0.97
Minutes from release of cross clamp until discontinuation of CPB	*42 (40/45)*	42 (38/45)	0.80
Intubation in intensive care unit (h)	7.8 (4.8/11.1)	6.5 (5.6/7.8)	0.44
s-troponin-t (microgram/liter) day 1	0.64 (0.23/0.85)	0.44 (0.27/0.71)	0.53
s-creatine kinase-MB (microgram/liter) day 1	35 (18/48)	25 (14/57)	0.85

CABG=Coronary artery bypass grafting, ECC=Extra corporeal circulation, CPB=Cardiopulmonary bypass

Surgery

The operations were performed through a standard complete median sternotomy with CPB with a flow rate of ≥2.4 L/m^2 and mild hypothermia at 34°C. CPB was instituted with a standard kit and a hollow fiber membrane oxygenator (Dideco Simplex D708, Dideco, Mirandola, Italy). The CPB-circuit was primed with Ringer's acetate and mannitol, and carefully de-aired. Standard cannulation consisted of arterial cannulation in the distal part of ascending aorta, and a two stage venous cannula inserted into the right atrium and the inferior vena cava. An exception was made for mitral valve operations, where bicaval cannulation was used. In all aortic valve operations a vent was inserted through a purse-string stitch positioned on the right superior pulmonary vein. Myocardial preservation consisted of intermittent ante- and retrograde cold blood cardioplegia. Cardiotomy suction, 1.5 l/min, was used intermittently throughout the CPB period. Rough suction was set to 10 l/min (**Study II**).

Instrumentation
CO_2 was insufflated into the cardiothoracic wound with a gas-diffuser. The diffuser was placed 5 cm below the wound opening adjacent to the diaphragm and the CO_2 flow was set at 10 l/min. Intraoperative TEE (Vivid Five, Vingmed-GE, Horten, Norway) examinations were performed by the same experienced anesthesiologist in all patients. The TEE probe was positioned in such a manner that a mid-esophageal long axis view could be kept. That view included three areas of interest, i.e., the left atrium, the left ventricle and the proximal part of the ascending aorta.[24] Video-recordings of this view were started from the release of the aortic cross clamp until 20 minutes after CPB was discontinued. After the study was finished an examiner, who was unaware of the treatment given, analyzed the videotapes of all the patients. The maximal number of microemboli in the left atrium, the left ventricle and the proximal part of the ascending aorta that appeared on one frame, was determined for each minute by scrolling the tape back and forth in slow motion. Thus, microemboli could be differentiated from moving heart tissue including the valve structures.

Four different time periods were analyzed: 1) from release of the aortic cross clamp until 20 minutes after end of CPB, 2) the first 15 minutes after release of the aortic cross clamp, 3) the last 10 min of CPB, 4) the first 20 min after end of CPB. At the end of CPB de-airing of the heart and great vessels was performed according to the routine of our department. This routine included venting of the ascending aorta, pulmonary compression with the patient in Trendelenburg's position, shaking of the heart, venting of the left atrium through the right pulmonary vein vent, and venting through the left atrial incision in mitral valve surgery. The right pulmonary vein vent was removed while the dependent part of the thoracic cavity was filled with blood in order to avoid entrapment of air. The aortic vent was removed 10 min after end of CPB. Due to his position at the table the surgeon was unable to observe the degree of air entrapment in the heart and the ascending aorta shown by echocardiography during the operations. Thus, the surgeon's decisions concerning de-airing could not be influenced by the echocardiographic findings. Arterial troponin-t and creatine kinase-MB as markers of myocardial damage were sampled in the morning of the first postoperative day.

ETHICS

The Hospital Ethical Committee approved the study, and informed consent was obtained from all patients. The procedures followed were in accordance with institutional guidelines (**Study III and IV**).

STATISTICS

In **Study I** data are presented as medians and ranges. Mann-Whitney U and Wilcoxon's tests were used whenever appropriate. Pair wise comparison ANOVA was used for comparison between groups with repeated measures. ANOVA with Bonferroni's correction was used for multiple comparisons within a group.

An analysis of variance design should theoretically be used in **Study II,** but due to unsuitable distribution characteristics a more simple and conservative nonparametric analysis was chosen. Mann-Whitney U and Wilcoxon's tests were used whenever appropriate. Differences were considered to be statistically significant if $p<0.05$. Data in the diagrams are presented as median and range.

In **Study III** differences were considered to be statistically significant if $p<0.05$. Data are presented as medians and ranges. Mann-Whitney U and Wilcoxon's tests were used when appropriate.

The data in **Study IV** were tested for normality with the Kolmogorov–Smirnov test and found to be not normally distributed. Therefore conventional nonparametric tests were used and results are expressed as median and $25^{th}/75^{th}$ percentiles. Differences were considered significant at $p<0.05$.

All Data were analyzed with SPSS version 11.0 statistical program (http://www.spss.com).

RESULTS

STUDY I

Figure 8 depicts the air content (steady state) in the model with a closed (A) and an open (B) left pleura, when CO_2 was insufflated through the 2.5 mm tube and the gas-diffuser. When the cavity was insufflated with CO_2 through the 2.5 mm tube the median air content was between

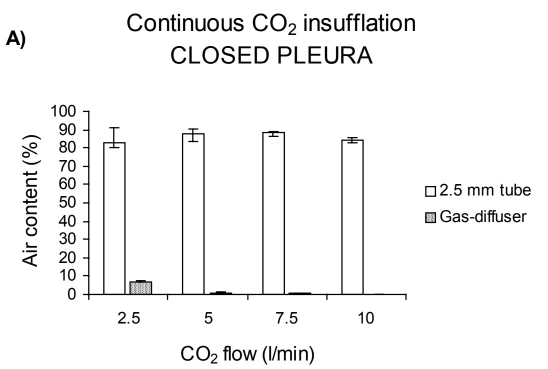

Figure 8A. Median and range of air content in a cardiothoracic wound cavity model, with a closed pleural cavity, insufflated with a 2.5 mm tube, and a gas-diffuser.

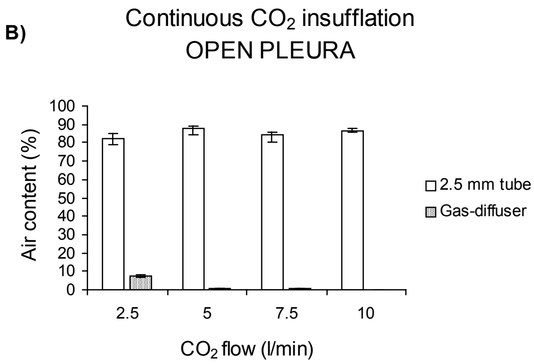

Figure 8B. Median and range of air content in a cardiothoracic wound cavity model, with an open pleural cavity, insufflated with a 2.5 mm tube, and a gas-diffuser.

82.0% and 88.2% (range 78.8-91.2%) at the studied CO_2 flows, including both a closed and an open left pleural cavity. With the gas-diffuser the air content was much lower ($p<0.001$) than with the 2.5 mm tube at all studied CO_2 flows. This striking difference between the two insufflation devices appeared when the left pleura was closed as well as when it had been opened. At a CO_2 flow of 2.5 l/min the median air content was 6.9% (range 6.6-7.3%) at a CO_2 flow of 2.5 l/min when the gas-diffuser was used and when the pleural cavity was closed. When the CO_2 flow was raised to 5 l/min under similar circumstances the corresponding figure was 0.65% (range 0.54-1.3, $p<0.001$). A further drop ($p<0.001$) in median air content to 0.38% (range 0.37-0.42%) was seen when the CO_2 flow was increased to 7.5 l/min. At a CO_2 flow of 10 l/min the median air content was 0.29% (range 0.27-0.33%, $p<0.001$). With an open left pleural cavity the corresponding median air contents were 7.2% (range 6.8-8.0%), 0.47% (range 0.38-0.53%), 0.37% (range 0.34-0.38%), and 0.18% (range 0.16-0.20%) with statistically significant differences between all flows ($p<0.001$). At a CO_2 flow of 2.5 l/min the air content was somewhat higher with an open than with a closed pleura ($p<0.001$), whereas with higher CO_2 flows the air content was slightly higher with a closed pleura ($p<0.003$).

Figure 9 depicts the air content in the model with a closed (A) and an open (B) left pleural cavity during the first 60 seconds of initial CO_2 filling, when CO_2 was insufflated with the gas-diffuser at 2.5, 5, 7.5, and 10 l/min. Paired comparison of air contents with repeated

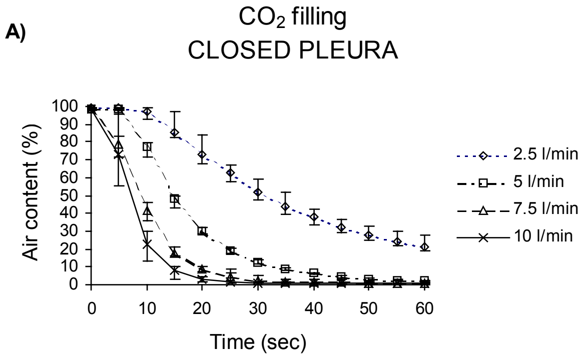

Figure 9A. Median and range of air content in a cardiothoracic wound cavity model, with closed left pleural cavity, insufflated with the gas-diffuser at 2.5, 5, 7.5, and 10 liters of carbon dioxide gas (CO_2) per minute during the first 60 seconds of CO_2 filling.

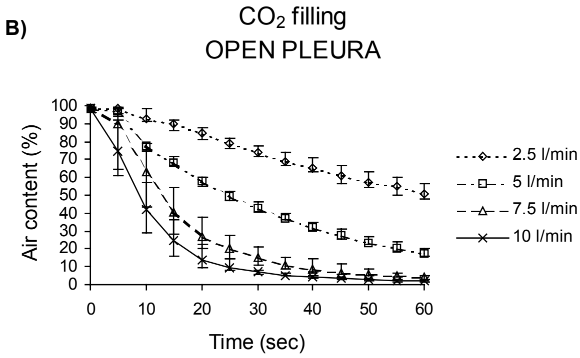

Figure 9B. Median and range of air content in a cardiothoracic wound cavity model with an open left pleural cavity, insufflated with the gas-diffuser at 2.5, 5, 7.5, and 10 liters of carbon dioxide gas (CO_2) per minute during the first 60 seconds of CO_2 filling.

measures ANOVA showed statistically significant differences ($p<0.001$) between the four CO_2 flows, both with an open and a closed left pleural cavity. Statistically significant differences ($p<0.001$) also appeared in comparisons between the open and closed left pleural cavity at the same flows. With the pleura closed a CO_2 flow of 10 l/min resulted in the quickest decrease in air content and a stable low value was reached 20 seconds after the start of CO_2 filling (tested with ANOVA including Bonferroni´s correction). At this point in time (20 seconds after start) the air content showed statistically significant differences between the four CO_2 flows ($p<0.001$). The air content reached a stable low level after 25, 50 and 55 seconds at a CO_2 flow of 7.5, 5, and 2.5 l/min, respectively. The corresponding stable air content with an open pleura was achieved after 30 and 35 seconds at a CO_2 flow of 10 and 7.5 l/min, respectively. Stable low values were not obtained with a CO_2 flow of 5 or 2.5 l/min (open pleura) within one minute of CO_2 filling. At each of the CO_2 flows used the air content was statistically lower after 20 seconds of CO_2 filling, when the left pleural cavity was closed than when it was open ($p=0.001$).

Figure 10 shows the air content in the model, with and without an open left pleural cavity filled with CO_2, during the first 60 seconds after CO_2 supply was discontinued. In paired comparisons with repeated measures ANOVA the air contents did not differ statistically ($p=0.49$) with closed and open left pleural cavity. However, the air content increased ($p<0.01$) between every 5 second interval both with an open and a closed left pleural cavity, (tested with ANOVA including Bonferroni's correction), except between 0

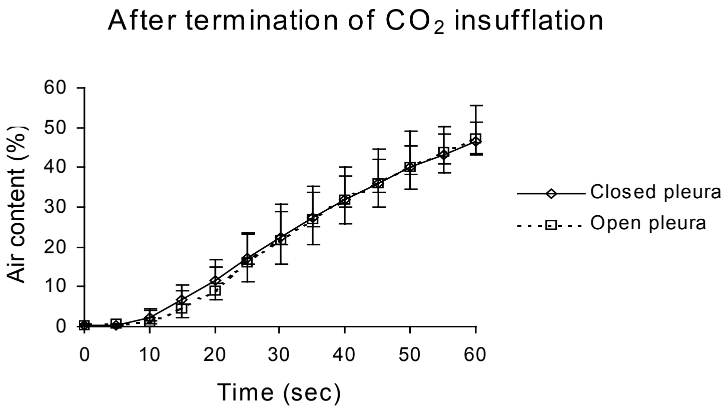

Figure 10. Median and range of air content in a cardiothoracic wound cavity model with closed and open left pleural cavity during the first 60 seconds after termination of carbon dioxide (CO_2) insufflation.

and 5 seconds with a closed pleural cavity and between 0 and 10 seconds with an open pleural cavity.

STUDY II

Figure 11 depicts the remaining air content at the right atrium (A) and at the ascending aorta (B) when the wound model was insufflated with CO_2 at a flow of 5 and 10 l/min through the ¼" tube and the gas-diffuser. With the ¼" tube the median air content at the right atrium was 28.3% (range 26.9-30.0%) and 51.7% (range 48.5-54.6%, $p<0.001$) at a CO_2 flow of 5 and 10 l/min, respectively. The corresponding values at the ascending aorta were 19.5% (range 18.1-20.5%) and 48.2% (range 35.4-52.1%, $p<0.001$). The air content was lower at the ascending aorta than at the right atrium both with a CO_2 flow of 5 l/min ($p<0.001$) and 10 l/min ($p<0.01$). With the gas-diffuser the median air content at the right atrium decreased from 0.65% (range 0.54-1.3%) at a CO_2 flow of 5 l/min to 0.29% (range 0.27-0.33%, $p<0.001$) at 10 l/min. The corresponding values at the ascending aorta were 1.2% (range 0.88-1.4%), and 0.31% (range 0.24-0.36%, $p<0.001$). The air content was lower at the right atrium than at the ascending aorta at a CO_2 flow of 5 l/min ($p=0.002$). With a CO_2 flow of 10 l/min there was no statistical difference in air content between the two positions. The air content was markedly lower with the gas-diffuser than with the ¼" tube ($p<0.001$) for both CO_2 flows both at the right atrium and at the ascending aorta.

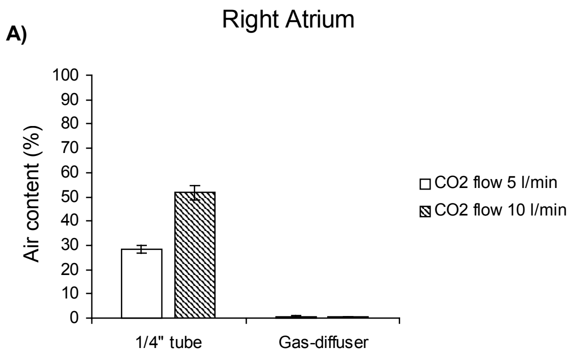

Figure 11A. The air contents (median and range, n=10) at the right atrium when the cardiothoracic wound model was continuously insufflated with carbon dioxide at a flow of 5 and 10 l/min through the ¼" tube and the gas-diffuser.

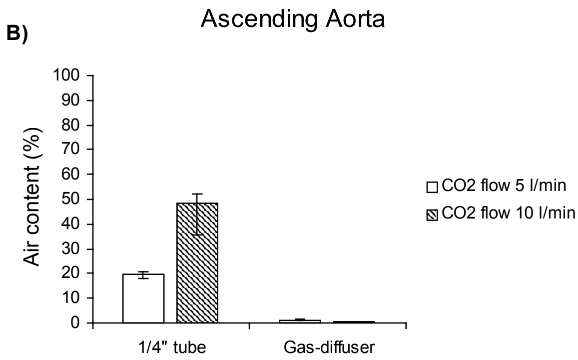

Figure 11B. The air contents (median and range, n=10) at the ascending aorta when the cardiothoracic wound model was continuously insufflated with carbon dioxide at a flow of 5 and 10 l/min through the ¼" tube and the gas-diffuser.

Figure 12 illustrates the remaining air content at the right atrium (A) and at the ascending aorta (B) after one minute of varying degrees of continuous suction, when the cavity was insufflated at CO_2 flows of 5 and 10 l/min with the gas-diffuser. A CO_2 flow of 10 l/min resulted in a lower air content than with a CO_2 flow of 5 l/min for all degrees of suction both at the right atrium and at the ascending aorta ($p<0.001$). The median air content remained very low (≤0.24% at 10 l/min and ≤1.0% at 5 l/min CO_2) both at the right atrium and at the ascending aorta, when a suction of 1.5 l/min was applied. With a CO_2 flow of 10 l/min the air content was lower than in the case when no suction was used, both at the right

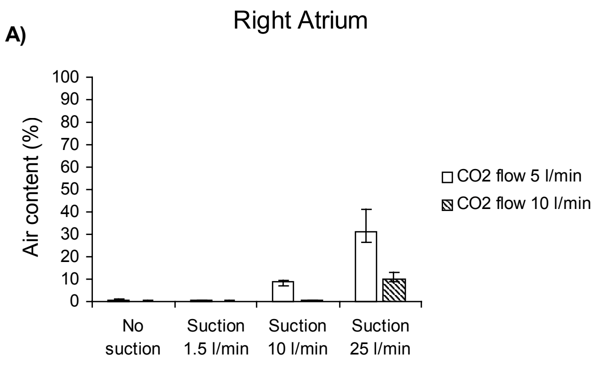

Figure 12A. The air content (median and range, n=10) at the right atrium in the cardiothoracic wound model after one minute of various degrees of continuous suction at the left atrial appendix. Carbon dioxide was supplied at a flow of 5 and 10 l/min through the gas-diffuser.

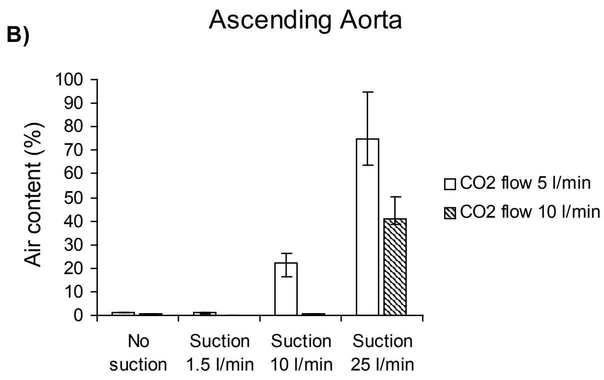

Figure 12B. The air content (median and range, n=10) at the ascending aorta in the cardiothoracic wound model after one minute of various degrees of continuous suction at the left atrial appendix. Carbon dioxide was supplied at a flow of 5 and 10 l/min through the gas-diffuser.

atrium (p=0.001) and at the ascending aorta (p<0.001). With a suction of 10 l/min the median air content was still very low both at the right atrium (0.37%) and at the ascending aorta (0.50%) with a simultaneous CO_2 flow of 10 l/min, but much higher (>8.9%, p<0.001) with a CO_2 flow of 5 l/min at both sites. A suction of 25 l/min increased the median air content at the right atrium to 9.9% (p<0.001) at a CO_2 flow of 10 l/min, and to 31.4% (p<0.001) at 5 l/min. The corresponding values at the ascending aorta were 41.1% (p<0.001) and 75.1% (p<0.001). With a suction of 10 and 25 l/min the air content at the right atrium was lower than at the ascending aorta at both CO_2 flows (p=0.001).

Figure 13 depicts the air content at the right atrium (A) and at the ascending aorta (B) during the first 30 seconds of continuous suction at 10 and 25 l/min, when the cavity was

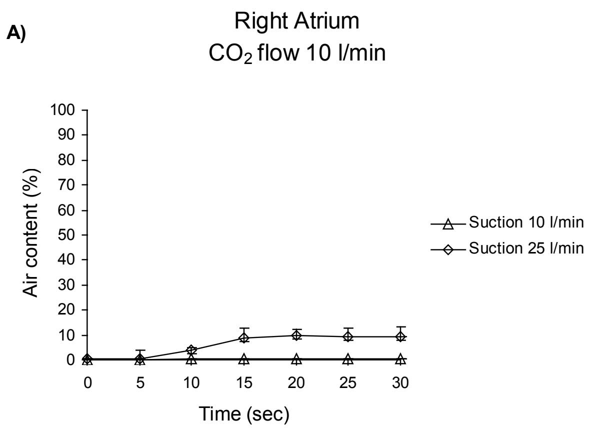

Figure 13A. The air content (median and range, n=10) at the right atrium in the cardiothoracic wound model during 30 seconds of a continuous suction at 10 and 25 l/min. Carbon dioxide was insufflated at a flow of 10 l/min with the gas-diffuser.

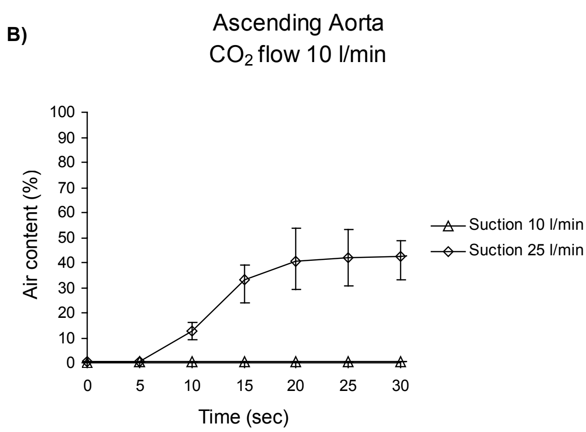

Figure 13B. The air content (median and range, n=10) at the ascending aorta in the cardiothoracic wound model during 30 seconds of a continuous suction at 10 and 25 l/min. Carbon dioxide was insufflated at a flow of 10 l/min with the gas-diffuser.

insufflated at a CO_2 flow of 10 l/min with the gas-diffuser. At a suction of 10 l/min the median air content remained very low (≤0.46%) both at the right atrium and at the ascending aorta during the measurements. After start of suction with 25 l/min the air content remained unchanged during 5 seconds at both sites, followed by an increase after 10 seconds. Stable air contents were reached after 15 and 20 seconds at the right atrium and at the ascending aorta, respectively, with a higher air content at the ascending aorta than at the right atrium ($p<0.001$).

STUDY III

Torso measurements

The multi-perforated catheter was more efficient ($p<0.001$) at all CO_2 flows when positioned inside the cavity, than at the wound opening (Figure 14). When positioned inside the cavity, the lowest median air content was 8.4% (range 7.6-10.2%) at a CO_2 flow of 2.5 l/min. The median air content increased to 18%, 24%, and 29% when the CO_2 flow was increased to 5 ($p<0.001$), 7.5 ($p<0.001$), and 10 l/min ($p=0.003$), respectively. When the multi-perforated catheter was exposed to water at the bottom of the cavity the median air content immediately increased to 96% at a CO_2 flow of 10 l/min ($p<0.001$), (Figure 15).

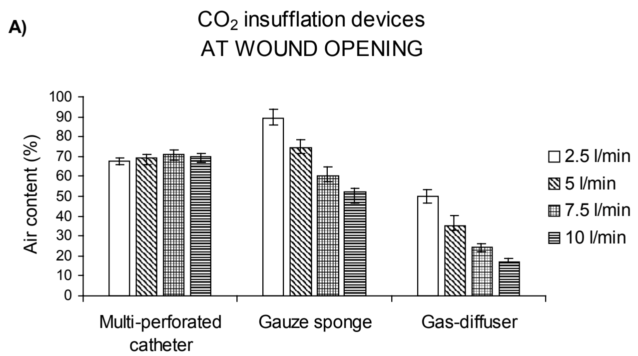

Figure 14A. Air content (median and range) measured at the topmost part of the right atrium in a cardiothoracic wound model. Carbon dioxide (CO_2) was insufflated into the cavity from the wound opening within the wound cavity using a multi-perforated catheter, a gauze sponge, and a gas-diffuser. CO_2 was insufflated at flows of 2.5, 5, 7.5, and 10 liters per minute.

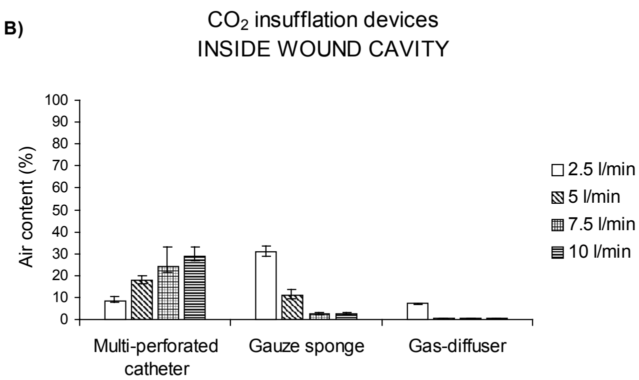

Figure 14B. Air content (median and range) measured at the topmost part of the right atrium in a cardiothoracic wound model. Carbon dioxide (CO_2) was insufflated from within the wound cavity using a multi-perforated catheter, a gauze sponge, and a gas-diffuser. CO_2 was insufflated at flows of 2.5, 5, 7.5, and 10 liters per minute.

The gauze sponge was more efficient at all CO_2 flows ($p<0.001$) when positioned inside the wound cavity, than at the wound opening (Figure 14). When positioned inside the cavity, the lowest median air contents were 2.5% (range 2.1-3.4%), and 2.6% (range 1.8-3.0%), obtained at a CO_2 flow of 7.5 and 10 l/min (n.s.), respectively. These values were lower than the lowest air content obtained with the multi-perforated catheter ($p<0.001$). After the gauze sponge had been temporarily immersed into water at a flow of 10 l/min the median air content immediately increased to 70% (range 65.8-73.5%, p<0.001), (Figure 15).

The gas-diffuser provided a more efficient de-airing at all CO_2 flows when positioned inside the wound cavity, than at the wound opening (p<0.001), (Figure 14). When the gas-diffuser was positioned inside the wound cavity the median air content was 7.4% (range 7.0-7.6%) at a CO_2 flow of 2.5 l/min, and 0.6% (range 0.5-0.6%) at a CO_2 flow of 5 l/min (p<0.001). A further drop in median air content to 0.4% (range 0.3-0.6%, p=0.002) was seen when the CO_2 flow was increased to 7.5 l/min. An increase of the CO_2 flow to 10 l/min decreased the median air content to 0.3% (range 0.2-0.3%, p<0.001). When positioned 5 cm below the wound edge, the gas-diffuser provided a more efficient de-airing than the other devices at the same CO_2 flows (p<0.001). After the gas-diffuser had been temporarily immersed into water the median air content remained low 0.4% (range 0.3-0.6%) at a flow of 10 l/min, a value that was much lower than that obtained with the wet gauze sponge (p<0.001), (Figure 15).

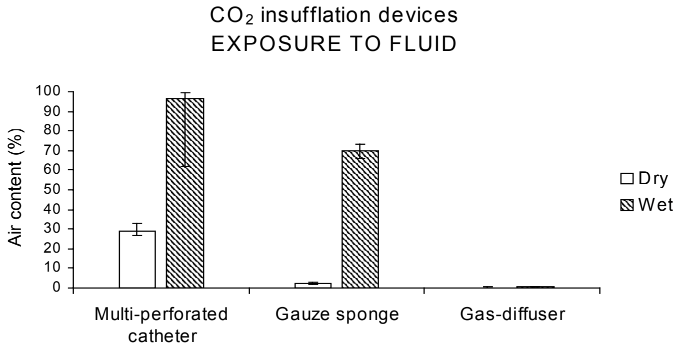

Figure 15. Air content (median and range) in a cardiothoracic wound model, insufflated with CO_2 at a flow of 10 liters per minute using a multi-perforated, and a 2.5-mm tube with a gauze sponge or a gas-diffuser of polyurethane foam at its end, before and after having been exposed to water.

Patient measurements

With the gas-diffuser in vivo the median content of remaining air in the wound cavity was 1.0% (range 0.6-6.3%) at a CO_2 flow of 5 l/min, and 0.7% (range 0.2-2.4%) at 10 l/min (n.s.). The remaining air content was statistically higher in vivo than in vitro at a CO_2 flow of 5 l/min (p<0.001), but at 10 l/min there was no statistically significant difference.

STUDY IV

Demographic and clinical data are listed in Table 1. No significant differences were observed for any parameter. All patients were first time candidates for surgery. Seven and three patients in each group underwent aortic and mitral valve surgery, respectively. The median age was 75 in both groups. Three and five patients in the control group and in the treatment group, respectively, underwent additional CABG. The duration of CPB and aortic cross clamping, as well as the duration from release of the cross-clamp until the discontinuation of CPB were similar in both groups. S-troponin-t and s-creatine kinase-MB on day 1 did not differ between the groups.

Figure 16 depicts the median number of microemboli minute by minute during the first 15 minutes after release of the aortic cross clamp in the three areas of interest taken together.

All patients in both groups had microemboli after release of the aortic cross clamp in all three areas of interests. The number of microemboli peaked during the first few minutes after release of the aortic cross clamp.

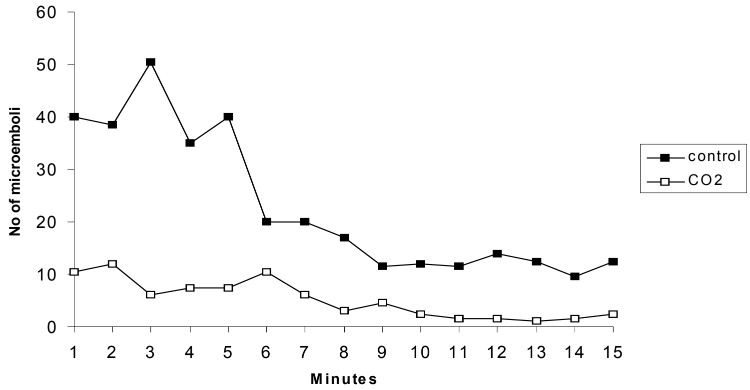

Figure 16. The median number of microemboli minute by minute during the first 15 minutes after release of the aortic cross clamp in the three areas of interest (left ventricle, left atrium, proximal part of the ascending aorta) taken together, registered by transesophageal echocardiography.

Figure 17 shows in the same manner the median number of microemboli from 10 minutes before to 20 minutes after discontinuation of CPB. During the whole procedure the

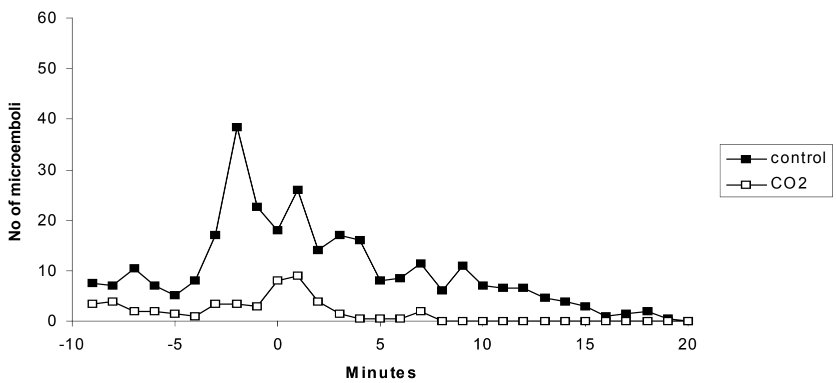

Figure 17. The median number of microemboli minute by minute from 10 minutes before to 20 minutes after discontinuation of CPB in the three areas of interest (left ventricle, left atrium, proximal part of the ascending aorta) taken together, registered by transesophageal echocardiography.

number of microemboli was constantly markedly higher in the control group. The number of microemboli peaked during the discontinuation of CPB.

Table 2 depicts the number of microemboli shown by TEE. As seen in this Table the number of microemboli was significantly lower in the treatment group than in the control group ($p \leq 0.01$). This held true for all four-time periods and all three studied locations. The total numbers of microemboli present in the different areas of interest and in all three areas taken together are shown for the whole study in Figure 18.

Table 2.
Number of microemboli according to transesophageal echocardiographic evaluation of the left atrium and ventricle, and the proximal part of the ascending aorta (median, 25th/75th percentile).

Number of microemboli

Study period	Area of interest	Group Control n=10	Group CO_2 n=10	P
From release of cross clamp until 20 minutes after end of CPB	LA	340 (300/393)	69 (39/129)	<0.001
	LV	254 (173/334)	68 (59/112)	<0.001
	Ao	184 (155/244)	56 (19/78)	<0.001
	LA+LV+Ao	723 (634/895)	161 (149/310)	<0.001
The first 15 min after release of cross clamp	LA	224 (108/336)	36 (16/69)	<0.01
	LV	131 (77/170)	43 (24/61)	<0.001
	Ao	81 (71/111)	25 (11/33)	<0.001
	LA+LV+Ao	414 (316/597)	101 (67/143)	<0.001
The last 10 min of CPB	LA	72 (27/193)	17 (9/41)	<0.01
	LV	50 (36/82)	21 (9/30)	<0.001
	Ao	47 (30/87)	16 (5/26)	<0.01
	LA+LV+Ao	179 (92/327)	66 (22/88)	<0.001
The first 20 min after end of CPB	LA	94 (40/141)	8 (4/32)	<0.01
	LV	73 (14/175)	12 (2/33)	0.01
	Ao	56 (16/105)	13 (1/19)	<0.01
	LA+LV+Ao	221 (67/418)	32 (8/77)	<0.01

CPB=Cardiopulmonary bypass

The total number of microemboli per minute in the three areas of interest during the study period was 18.2 (16/21) in the control group and 4.6 (4/8) in the treatment group ($p<0.01$). The total number of minutes with no microemboli in any of the three areas of interest was 18 (16/26) in the control group as compared with 3 (1/9) in the CO_2 treated group ($p<0.001$).

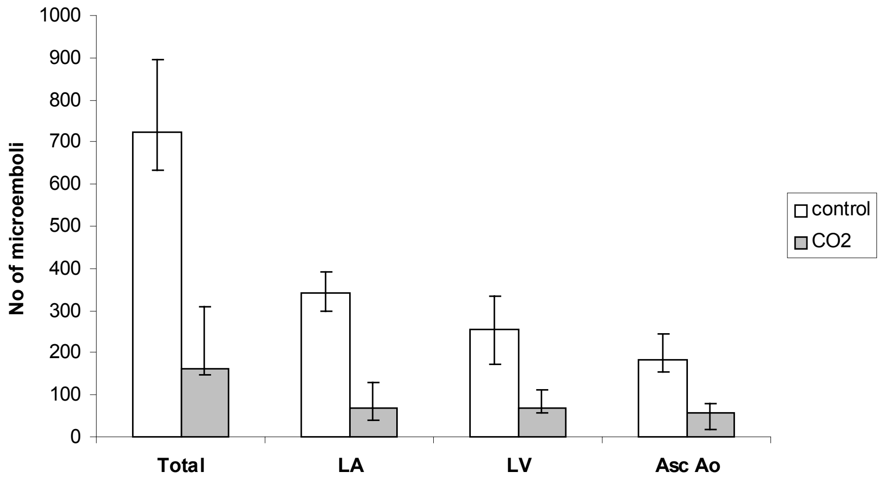

Figure 18. The total numbers of microemboli present in the three areas of interest taken together are shown for the whole study.

Finally, at the end of the study the median number of microemboli present in all three areas of interest taken together, fell to zero 7 (0/16) minutes after discontinuation of CPB in the treatment group as compared with 19 (14/20) minutes after this was done in the control group ($p<0.001$).

GENERAL DISCUSSION

To reduce the risk of air embolism, insufflation of CO_2 into the wound cavity was introduced in the 1950's. This form of insufflation has been practiced for almost fifty years now and it is certainly worthy of note that during this whole half century of blowing CO_2 into the wound there has not appeared one single study that convincingly showed its value, i.e., could show less air embolism with CO_2 insufflation. The reason why this has never been possible has only recently become apparent. Not until the last few years did it finally become clear that the insufflation devices used for so long, mainly open ended tubes, catheters, and the like, were unable to provide a true CO_2 atmosphere in the wound.[17,18]

Most surgeons try to prevent air embolism during open-heart surgery. Usual surgical measures include atrial venting, vent suction, Trendelenburg's position, ventricle emptying by compression, evacuation of trapped air (diagnosed by TEE) by gravitation or aspiration, and the insufflation of the cardothoracic wound with CO_2. The value of all these maneuvers is of limited value. In fact the only randomized clinical study of these interventions found that whatever the Trendelenburg's position was used or not, made no difference at all.[25] Earlier experimental animal studies[11-16] have shown that arterial embolization of air (injected) to the brain and heart may not only cause cerebral and myocardial dysfunction but may also lead to convulsions, infarctions, ventricular fibrillation and increased mortality. In contrast, animal studies have shown that injection of carbon dioxide into the pulmonary veins or the left ventricle is much better tolerated than injection of air.[11-16]

We are only aware of one single study, where insufflation of the cardiothoracic wound with CO_2 has been shown to be advantageous. In an experimental study in dogs Eguchi et al[12] exposed the mitral valve to the open cardiothoracic wound by opening the left atrium widely for 2 minutes. "In the control group, air appeared in the coronary arteries within a few seconds following atriotomy and produced arterial obstruction, and evidence of coronary insufficiency appeared. Once the air embolus ceased to move, it remained permanently in that position". "The heart became dilated and the cardiac action became so weak that cardiac massage was necessary to maintain the circulation in 70% of the control group". In the treatment group, where the cardiothoracic wound cavity was insufflated with CO_2, "the bubbles of carbon dioxide gas would rapidly traverse the extent of the artery and disappear. The cardiac action was satisfactory and cardiac massage was not necessary except in one case". Ventricular fibrillation occurred in 37.5% of the control group, but in none of the CO_2 group. Electrocardiographic changes were seen in 87.5% of the control group versus 28.6% in the treatment group. The gross and microscopic examination revealed pathologic findings in 75% in the control group versus 28.6% in the CO_2 group. Of particular interest were the measures taken to achieve a high content of CO_2 in the open cardiothoracic wound. "In the experimental animals carbon dioxide gas was flooded across the operative field at the flow rate of 5 liter per minute in a closed room, since the concentration of carbon dioxide in the chest cavity decreases when the wind blows in". Unfortunately, the insufflation device was not described. Only with these measures were they able to achieve a CO_2 content of approximately 80 to 90%. However, we are not aware of any clinical study where insufflation of the cardiothoracic wound with CO_2 through a traditional tube has been shown to reduce morbidity. In fact, in a recent clinical study in open-heart surgery Martens et al.[17] used an open-ended perfusion line with an inner diameter of 2 mm for CO_2 insufflation at a flow of 2 l/min. They did not find any difference in neuropsychological outcome between patients in whom the cardiothoracic cavity had been insufflated with CO_2 and controls in whom it was not. Neither did they achieve efficient air displacement (mean air content 56%, range 14-92%), and they concluded: “For effective reduction of cerebral and coronary artery emboli, higher levels of CO_2 must be achieved in the operating field by more sophisticated means of application”.

HOW SHOULD AIR DISPLACEMENT BE MEASURED?

Before evaluating more sophisticated means of application for CO_2 one has to select an appropriate method to evaluate air displacement. Most earlier studies of de-airing have used direct measurement of the CO_2 content in the wound cavity. However, it may be advantageous to measure the air content, i.e., the gas component we want to get rid of, instead. We analyzed the air content indirectly by measuring the O_2 concentration,[9,21,26] which is about one fifth of air (20.95% near sea level).[23] Although air is a mixture of several gases, including O_2, it acts as one gas at normal pressure and temperature. Furthermore, Avogadro's law states, “At constant pressure and temperature equal volumes of different gases contain equal amounts of gas molecules”. This implies that for every five CO_2 molecules that are supplied to a wound cavity, five air molecules are displaced and approximately one of these five is an O_2 molecule. Thus, when the content of O_2 is measured, the content of air and CO_2 is measured at the same time.

The O_2 instrument used is equipped with a heated ceramic sensor, which can assess air displacement more accurately than commonly used CO_2 sensors that utilize an optical infrared sensor technique to measure CO_2 concentrations up to 100%. The O_2 sensor’s accuracy was 1% of the measured value in the range 0.0001%-100% O_2, which means that the accuracy increases when the O_2 concentration and consequently the air content decreases. Moreover, the O_2 sensor requires only a 2 ml gas sample and has a response time of <2 seconds. The smaller the gas sample needed, the less will the gas measurements interfere with CO_2 de-airing. In contrast, CO_2 sensors using the infrared technique usually have a constant accuracy (which must not be confused with the resolution of the instrument’s figure display) of approximately ±2% units CO_2 over the entire range of measurement 0-100% CO_2. They also have a larger required sampling volume and response time. Nitrogen (N_2) is the major constituent of air (78%). This is a valid argument in favor of direct measurement of the N_2 content instead of the O_2 content. However, N_2 is difficult to detect and practical instruments for intraoperative measurements are not available. N_2 gas is inert and the N_2 molecule is not a dipole and does not absorb energy from electromagnetic radiation in the infrared or the ultraviolet range. Therefore, conventional chemical, magnetic, and optical sensor techniques cannot be used. Thus, we consider the used O_2 sensor the most suitable device to assess de-airing of the wound cavity.

EXPERIMENTAL SETUP

In order to reduce the number of measurements in patients, the greater part of the thesis was carried out with a full-scale torso. The size and form of the wound model were based on measurements in vivo **(Study I)**. We therefore feel justified in assuming that the model enabled us to perform a controlled and standardized study of air displacement with CO_2 insufflation in a realistic clinical set-up. As part of our efforts to reproduce the conditions existing in practice as carefully as possible, measurements were carried out on the same operating table in the same fully ventilated operating theatre as used for surgery **(Study I-III)**.

WHERE SHOULD DE-AIRING BE MEASURED?

Since the size of the wound cavity including the opening area is about the same, we performed our measurements in coronary bypass as well as in valve surgery cases. Both in patients **(Study III)** and in the torso **(Study I-III)**, the air content was measured at the upper level of the right atrium, which is close to the atrial incision during mitral valve replacement. The air content was also measured at the upper level of the ascending aorta **(Study II)**. Measuring the air content at the bottom of the wound cavity, as reported by Webb et al.,[21] may lead to an overestimation of the de-airing efficiency, since CO_2 is heavier than air and tends to accumulate at the lowest point.[18]

INSUFFLATION DEVICES

Open-ended tube

2.5 mm open-ended

There was a striking difference in efficiency between the 2.5 mm open-ended tube and the gas-diffuser at all CO_2 flows studied (**Study I**, Figure 8). CO_2 insufflation with the 2.5 mm tube resulted in median air contents between 82% and 88% at the studied flows. A thin tube's apparent failure to displace air with CO_2 is probably due to turbulence induced by the CO_2 jet. The same phenomenon occurs when one tries to fill a pail with water using a garden hose. Most of the water splashes out of the pail. By contrast, the pail is quickly filled if the hose is provided with a multi-perforated nozzle resulting in a reduced flow velocity (Figure 19 A-C). In comparison, the gas-diffuser produced very low levels of air ($\leq$0.65%) in the cardiothoracic wound cavity at a CO_2 flow of 5 l/min. At higher CO_2 flows the air content decreased further and reached values as low as $\leq$0.29% at 10 l/min, both with and without an open left pleural cavity, indicating minimal turbulence despite a high CO_2 flow.

Open-ended tube with an inner diameter of ¼"

We also studied an open-ended tube with an inner diameter of ¼", since tubes with the same size have been used for CO_2 insufflation in our clinic as well as in earlier studies.[9,20,26] The air displacement efficiency of the ¼" tube was compared with a new device, a gas-diffuser. **Study II** revealed a striking difference in efficiency between the conventional ¼" open-ended tube and the gas-diffuser at the studied CO_2 flows (Figure 11). CO_2 insufflation with the ¼" tube resulted in median air contents between 19.5-28.3% and 48.2-51.7% at CO_2 flows of 5 and 10 l/min, respectively. The insufficient air displacement with the ¼" got even worse with increased CO_2 flow. The ¼" tube's apparent failure to displace air with CO_2 was probably due to the high velocity of the CO_2 jet and to the induced turbulence in the wound.

Figure 19A. A thin tube's apparent failure to displace air with CO_2 is probably due to turbulence induced by the CO_2 jet.

Figure 19B. The same phenomenon occurs when one tries to fill a pail with water using a garden hose. Most of the water splashes out of the pail.

Figure 19C. By contrast, the pail is quickly filled if the hose is provided with a multi-perforated nozzle resulting in a reduced flow velocity.

Multi-perforated catheter

Webb et al.[21] made a valuable contribution to the search for an efficient insufflation device by suggesting the use of a multi-perforated catheter. In contrast to an open-ended tube, the multi-perforated catheter delivers CO_2 from multiple holes, which reduces gas velocity and turbulence. A drawback is that this catheter is bulkier than the other devices.

The mean outflow velocity is considered a suitable yardstick for the comparison of insufflation devices. Its calculation is simple. Assuming the outflow to be equally distributed over the whole dispersion surface, the CO_2 flow is divided by the total gas dispersing area of the device. Thus, a multi-perforated catheter would theoretically need to consist of more than 80 holes, each 3x5 mm wide, to provide a gas velocity corresponding to that of the gas-diffuser. However, the assumption of equal distribution is not fulfilled when the multi-perforated catheter gets curved. This is due to pressure drop at the holes along the multi-perforated catheter and due to inertia. The explanation of the latter phenomenon is very simple. Any object that is set in motion tends to continue in the direction in which it is propelled. This is the reason why it is difficult to keep your car on the road when you suddenly meet a sharp curve. The car tends to continue in its original direction. The same holds true for a gas that is blown through a bent multi-perforated catheter. When CO_2 meets a curve in the multi-perforated catheter the gas will tend to escape through the first holes in the outer side of the curve.

Moreover, a multi-perforated catheter or a commercial drain is designed to effectively remove blood, which will easily occur when the catheter is placed at the bottom of the pericardial well, as described by Webb et al.[21] Once fluid enters the multi-perforated catheter the distal part of the catheter will be blocked and inactivated. According to the law of least resistance, the CO_2 gas will then exit through the proximal holes with an increased velocity, producing increased turbulence and impaired CO_2 de-airing. This was confirmed in **Study III**.

Gauze sponge

The use of the gauze sponge[22] presumes the tortuous paths inside it to distribute the CO_2 gas uniformly over a much larger surface, thus reducing gas velocity. Because of their hydrophilic properties gauze sponges are used to absorb fluids. When the gauze sponge gets wet, its structure collapses and its function as a diffuser is lost (**Study III**, Figure 15). Thus, an undetected absorption of fluid by the gauze sponge will within seconds lead to a significant rise in air content and thus a risk of air trapping. Furthermore, since almost any surgical wound is wet, one would have to measure the CO_2/air content continuously in order to know when to exchange the gauze sponge. This is not practical.

Gas-diffuser

A thin conventional tube is a small and simple insufflation device, which does not take up much space in the wound. A small diffuser added to the end, to divert the CO_2 stream, does not increase the size or decrease the flexibility of the insufflation device to any appreciable degree. However, the de-airing efficiency is considerably improved. The principle of a diffuser is that the tortuous paths inside the diffuser will distribute the CO_2 gas uniformly over the much larger surface of the diffuser. This substantially reduces the gas velocity and minimizes turbulence in the wound. During dry conditions, the gas-diffuser produced a higher degree of air displacement than the other devices studied.

In contrast to the gauze sponge, the gas-diffuser remained efficient when wet **(Study III).** The gas-diffuser is made of soft polyurethane foam with open cells (Figure 2). Due to its elastic properties the foam does not collapse even when soaked, and when gas is blown through the diffuser, large parts of its cell structure will remain open. If the gas-diffuser gets partly covered with tissue or blood, which occurred in our patient studies **(Study III-IV)**, its function will remain unaffected. According to the law of least resistance, the CO_2 gas will, automatically be redirected inside the diffuser foam to exit through an open part. Thus, the hydrophobic and elastic properties of the gas-diffuser will enable it to retain its function, even if it is in direct contact with the wet inner wound. Although the foam material is hydrophobic the foam may absorb and store a liquid by capillary forces, but only if it is completely drowned and at the same time compressed in the liquid, just as a car wash sponge would. If the gas-diffuser unexpectedly becomes soaked through with blood or water, a short compression with the tip of a finger will evacuate the fluid and restore the full function of the gas-diffuser. Due to its lack of hydrophobic and elastic properties, the same does not hold true for a wet gauze sponge **(Study III)**.

What is the most efficient device?

Of all studied insufflation devices the gas-diffuser produced the highest degree of air displacement in the wound cavity **(Study I-III)**. The inverse relationship between remaining air content and CO_2 flow suggests that CO_2 insufflation occurs with minimal turbulence even at high flows. In terms of lowest median air content, the gas-diffuser was approximately 30 times more efficient than the dry multi-perforated catheter and 8 times more efficient than the dry gauze sponge **(Study III)**.

CO_2 has to be delivered from within the wound cavity, in order to provide a high degree of de-airing **(Study III)**. Therefore, an insufflation device has to remain efficient also when there is fluid present in the cardiothoracic wound cavity. Only the gas-diffuser remained efficient when exposed to a fluid. The multi-perforated catheter and the gauze sponge are unsuitable for CO_2 de-airing since they stop functioning when they get wet **(Study III)**.

CONTINUOUS OR INTERMITTENT CO_2 INSUFFLATION?

As far as we know, earlier studies have only considered CO_2 de-airing of a wound cavity during steady state. This may partly be due to deficiencies of earlier used measurement techniques. The measuring technique used here has made it possible to study the rapid changes in the degree of de-airing that occur as a result of changes in CO_2 flow and the opening of the left pleural cavity **(Study I)**. As seen in Figure 8 a CO_2 flow of ≥5 l/min was required during continuous CO_2 insufflation with the gas-diffuser to reach very low levels of air in the wound cavity model. Continuous CO_2 insufflation at ≥5 l/min seems to be needed to compensate for the continuous loss of CO_2 due to diffusion as well as to the convective air currents around the wound cavity caused by the ventilation system. Figure 10 further illustrates this phenomenon. When CO_2 insufflation is discontinued the air content in the wound cavity rapidly increases. This implies that a single filling of the cardiothoracic wound cavity with CO_2 is insufficient and intermittent periods without CO_2 insufflation should be avoided.

Since CO_2 is not a liquid that remains in the wound but a gas that, although heavy, disperses into the surrounding air, CO_2 insufflation has to be continued as long as heart and vessels are open.

OPEN PLEURAL CAVITY

During heart surgery one or both pleural cavities are often opened. Furthermore, many surgeons deliberately open both pleural cavities during open-heart surgery to facilitate the collapse of the lungs and to avoid a negative pleural pressure during the operation.

The opening of the pleural cavities may impair air displacement. During CPB the lungs are as a rule not ventilated and allowed to collapse. Thus, opening the pleural cavity will markedly increase the wound cavity's volume. Such an increase was found not to have a clinically important influence on the wound cavity's air content during steady state although the differences were statistically significant **(Study I)**. Nor did discontinuation of CO_2 insufflation have any appreciable effect. It did, however, substantially delay the initial filling of the cavity with CO_2.

To sum up, CO_2 insufflation into the cardiothoracic wound cavity should be started at a flow of 10 l/min at least one minute before incision of the heart and great vessels, so that potential gas traps will be filled with CO_2 instead of air. An open pleural cavity will prolong complete filling of the cardiothoracic wound cavity with CO_2. This can be counteracted by prolonging the initial CO_2 insufflation or by increasing the CO_2 flow. CO_2 insufflation should be continued at a CO_2 flow of at least 5 l/min until surgical closure of the heart and great vessels to avoid new possible air trapping or air foam formation. This might be appropriate not only for open heart and aortic surgery, but also in conventional coronary artery bypass surgery if the single clamp technique is used.

SUCTION

The influence of suction has to be considered when aiming at efficient de-airing with CO_2 insufflation in cardiac surgery **(Study II)**. Coronary suction of 1.5 l/min did not deteriorate air displacement in the wound cavity. However, in patients continuous suction of almost pure CO_2 into the cardiotomy reservoir may affect arterial pCO_2.[20,27,28] This may be avoided by minimizing continuous suction of CO_2 and by increasing the ventilation of the oxygenator. A rough suction of 25 l/min applied in the wound cavity at CO_2 flows of 5 and 10 l/min markedly increased the air content. This was to be expected because the suction markedly exceeded the CO_2 inflow. Surprisingly, the air content did not rise towards 100%, but stabilized at lower levels. This may be explained by a partial suction of air from above the cavity. Moreover, CO_2 disperses effectively from the diffuser in multiple directions in the wound cavity and not only towards the sucker. The increase of air content to a stable level started first after 5 seconds and before 10 seconds of suction (not adjusted for the response time of the instrument, which is <2 seconds). This delay is most likely explained by the buffering effect of the volume of CO_2 within the cavity. A smaller wound cavity will hold a smaller volume of CO_2, which may make it more difficult to keep a low air content when suction is applied. When the rough suction was reduced to equal the CO_2 inflow at 10 l/min, the median air content could be kept ≤0.5% in the wound cavity.

Coronary suction did not influence CO_2 de-airing. Rough suction impaired air displacement with the gas-diffuser when suction exceeded CO_2 inflow. Only then did the proximity of the gas-diffuser to the location of interest become a factor of importance.

These findings suggest that the duration of active use of rough suction at 25 l/min is important if it is higher than the CO_2 flow. A short period of suction up to approximately 5 seconds does not affect the air content, whereas a longer period of suction will create an increase in the air content, which soon stabilizes. Thus, rough suction should be kept as short as possible. Inside the wound it will interfere with de-airing provided that it is not continuously sucking fluid. Otherwise, the sucker should either be shut off or kept outside the wound cavity.[9] Another option is to set the rough suction rate equal to or lower than the CO_2 inflow. Theoretically, the CO_2 flow could also be increased to 25 l/min, but this may not be necessary, since as a rule rough suction is only used infrequently and during short periods.

WHAT IS A SUITABLE CO_2 FLOW?

Diffusion between ambient air and CO_2 in the wound cavity, as well as convective air currents around the wound caused by the ventilation system will rapidly increase the air content in the wound unless compensated for with an increased inflow of CO_2.[18] As seen in **Study II**, Figure 8, a CO_2 flow of 5 l/min sufficed to reach a high degree of de-airing (0.6% remaining air) in vitro, but there was a decrease in air content when the CO_2 flow was increased from 5 to 10 l/min. In patients the differences between these flows were not statistically significant, although the range and the maximal air content decreased substantially **(Study III)**. Surgical hand movements may also affect CO_2 de-airing. In patients a CO_2 flow of 5 l/min sufficed to reach a high degree of de-airing (1% remaining air) during active surgery **(Study III)**. As mentioned earlier an open pleural cavity will prolong the filling of the cardiothoracic wound cavity with CO_2 unless a higher flow is used. Furthermore, the use of rough suction will also impair CO_2 de-airing unless the CO_2 flow is equal or higher than the suction rate **(Study II)**, which may require a CO_2 flow higher than 5 l/min. All in all, we are therefore inclined to recommend a CO_2 flow of 10 l/min.

Most clinicians use O_2 flowmeters to control delivery of medical CO_2, since CO_2 flowmeters are rarely available for this purpose due to the limited use of CO_2 in clinical practice. In that case one should be aware that the flowmarker, usually a spherical float, should be set at a flow that is approximately 10% higher than the CO_2 flow one aims at. This is advisable in view of the higher density of CO_2. In addition, the use of a bacterial filter in the gas line is advocated in order to prevent iatrogenic bacterial contamination, since the connection to the CO_2 cylinder is non-sterile.

WHEN AND WHERE SHOULD CO_2 BE INSUFFLATED?

All devices were more efficient when positioned inside the wound cavity than at the wound opening (**Study III**, Figure 14), where the CO_2 is more exposed to dilution with ambient air.[18] Thus, for maximal effect any device will have to be placed inside the wound where it comes into contact with fluid. The gas-diffuser was found to be efficient when the diffuser was positioned approximately 5 cm below the wound edge **(Study I-III)**. The position of the diffuser at the caudal part of the wound caused little interference with surgery **(Study III-IV)**. However, it may be advantageous to position the gas-diffuser closer to the site of interest since surgical maneuvers such as the use of rough suction may increase the air content locally **(Study II)**. Since the cranial part of the wound is usually narrower, shallower, and already occupied with surgical instruments, we suggest that the gas-diffuser set is introduced at the caudal part of the wound. The thin distal gas line that leads to the diffuser contains a stainless steel wire, which makes it easy to change and fix the diffuser's position inside the wound.

It is important that CO_2 is insufflated from incision to closure of the heart and great vessels, so that these potential air pockets are filled with CO_2. This is suitable not only for open-heart and aortic surgery, but also when the single clamp technique is used in conventional coronary artery bypass surgery.

The gas-diffuser is preferably placed where it is efficient without interfering with surgery. In this study the diffuser was positioned 5 cm below the opening, adjacent to the diaphragm. During surgery there is little activity and few if any surgical instruments at this site. In this position the gas-diffuser provided a high degree of air displacement both at the site of the right atrium as well at the ascending aorta. However, when the suction rate exceeds the CO_2 inflow the proximity of the diffuser to the location of interest (measuring point) will start to interfere with air displacement (Figure 12, 13).

A RANDOMIZED CLINICAL STUDY

Incidence of microbubbles in valve surgery

In all of the study's 20 patients intra-operative TEE examination showed cardiac/aortic microemboli **(Study IV).** The emboli were found in all the three studied locations, i.e., the left atrium, the left ventricle, and the proximal part of the ascending aorta. Moreover, they were found throughout the studied part of the operative procedure, i.e., after release of the aortic cross clamp, and before as well as after weaning from CPB. A similarly high incidence of air microemboli in valve surgery has so far only been reported by Tingleff et al[8], who found intra-cardiac microbubbles in 15 out of 15 patients after release of the aortic cross clamp (100%). After CPB, however, they[8] observed such bubbles in only 12 of their 15 patients (80%) while the figures reported by others are even lower. Rodrigas et al.[29] observed left ventricular bubbles in 39 of 58 patients (67%) and Dalmas et al.[6] using a three or four chamber TEE view did so in 25 out of 42 patients (59%).

How can these differences be explained?

Given the close contacts we have with the leading North American clinics, differences in surgical de-airing technique are not very likely. The same goes for false positives. Although allowances have to be made for the possible presence of particles of a different nature, it seems a bit far-fetched to suggest that one can see a microbubble and show it to others when there is none. The reason, which probably is multi-factorial, must therefore be sought in the method. The length of the study period, the positioning of the TEE view, and the reading of the images may all play a role.

It may be reasoned that the question whether air emboli occur in the majority of patients or in all of them is irrelevant since no one doubts that air embolism constitutes a risk. However, if one intends to study the effect of a treatment, i.e. CO_2, on the occurrence and behavior of such emboli, it is essential that all of them or at least the great majority be observed. Thus, the disturbing variation due to inaccurate registration can be reduced to a minimum.

Assessment of microbubbles

How is the occurrence of microbubbles usually assessed? Earlier studies have used arbitrary scales to grade the amount of intracardiac microemboli.[6,8,29] The use of such scales may be convenient but loss of information is unavoidable. We have therefore tried to determine the amount of air in the left atrium, left ventricle and proximal part of the ascending aorta in a different manner. A blinded examiner counted the maximal number of microemboli minute by minute on TEE video-recordings. This was done by scrolling the videotape back and forth in slow motion. Thus, it was possible to discriminate microemboli from moving heart tissue structures that otherwise might have been confounding. In addition, by registering the number of microemboli that occur during a longer time period one may not only assess peaks and total numbers of microemboli but also the exact moment when they disappear from the area of interest.

Can the results be generalized or does the study design put limits to it?

In **Study IV**, the surgeons were not permitted to see the TEE echocardiographic results. This proviso may be criticized on ethical grounds. In addition, this protocol proviso could have explained the greater number of microbubbles seen in **Study IV** in the control group and could therefore limit the generalization of the results. CO_2 insufflation may thus be beneficial only in circumstances where the surgeon does not have a TEE available.

Firstly, for study reasons the surgeons had to be blinded. All participating surgeons were senior surgeons who had acquired a standard de-airing technique over many years of direct feedback with intraoperative TEE. Therefore, none of the participating surgeons was uncomfortable with the study design. Moreover, the study was approved by the Hospital Ethical Committee.

Secondly, according to the ACC/AHA guidelines[30] intraoperative TEE is only considered mandatory in “mitral regurgitation to establish the anatomic basis for mitral regurgitation and to guide repair”, and not for surgical de-airing guidance in valve surgery. Indeed, Dalmas et al.[6] concluded that even if TEE guided surgical de-airing was used in valve surgery, it was impossible to “clear intracardiac air”.

Were the randomized groups comparable?

Several important factors may influence CO_2 de-airing during cardiac surgery. Among these factors are: type of insufflation device, CO_2 flow rate, as well as coronary and rough suction (**Study I-III**) These factors were all controlled in **Study IV**. Twenty (20) consecutive patients were randomized to two groups. Ten (10) received treatment and ten served as controls. As seen in Table 1 randomization had been effective. The demographic and clinical data of the two groups were very similar. The two groups were comparable.

Are the differences really significant?

Treatment of one of these two comparable groups with CO_2 insufflation resulted in markedly fewer microemboli in the left atrium, the left ventricle, and the proximal part of the ascending aorta. The differences between the two groups were apparent throughout the whole study period, i.e., from release of the aortic cross-clamp until 20 minutes after end of CPB. In addition, in the CO_2 insufflated group microemboli disappeared much quicker after end of CPB. As seen in Table 2 all the differences were significant at the 0.01 or 0.001 level.

The issue of statistical analysis may be criticized of not accounting for multiple comparisons and it may be pointed out that multiple measurements may best be analyzed by a repeated measures analysis of variance. However true, this is beside the point. We do not want to contend that our serial measurements provide additional evidence of the statistical significance of our findings, and know fully well that the studied variables are all correlated and should not be viewed as independent. But, even if the correlation between them were perfect with the appropriate non-parametric coefficient approaching 1, the fact remains that all comparisons are backed up with p-values at the 1% or 1‰ level. This means that even with a perfect correlation the probability due to chance lies somewhere between these two values. Therefore we feel that the reader will not be in any doubt as to the statistical significance of the findings.

Number and behavior of air microemboli

Since the study's design enabled us to follow the movements of the microemboli over a period of time, we found that they behaved according to a characteristic pattern. One early peak occurred just after release of the aortic cross clamp (Figure 16). Most of the microemboli were then whirling around in the left ventricle and the left atrium and were not propagated forward, while only a small fraction appeared in the ascending aorta, Table 2. The second peak occurred when the beating heart was being filled and started to eject blood during weaning from CPB (Figure 17). During this phase most of the microemboli originated from the pulmonary veins. They first appeared as floating strings of pearls at the roof of the left atrium. They were then propagated forward to the left ventricle and finally ejected into the ascending aorta. Despite thorough surgical de-airing new microemboli continued to pop up in the left atrium even up to 20 minutes after end of CPB. The second peak is in accordance with our earlier transcranial Doppler study during open-heart surgery, in which we found that most microemboli reached the brain during and after weaning from CPB.[7] By contrast, only very few emboli passed the middle cerebral artery after release of the aortic clamp until the heart started to eject blood. Thus, most microemboli that appear in the heart after release of the cross-clamp stay there until the beating heart is being filled.

This is the critical moment because it is during weaning from CPB that the heart starts ejecting microemboli to the brain. Thus, it is then that the difference in the number of microemboli between the CO_2 treated patients and the controls comes to the fore.[7] Moreover, it should be kept in mind that in the CO_2 treated patients the microemboli were not only fewer in number but they also differed from those in the untreated group as to their composition. They consisted of CO_2 and not of air.

Does a reduction of air microemboli really matter?

Several old studies have shown that gas bubbles containing CO_2 are much better tolerated than air.[11-16] In studies on cats injection of 0.5 cc/lb body weight of air into the pulmonary vein resulted in the filling of the coronary arteries with air and subsequent death in all animals.[15] By contrast, similar injections of CO_2 were tolerated. Even the injection of 12 times the fatal dose of air (6 cc/lb body weight), although resulting in total obstruction of the coronaries with gas, did not lead to death. Within approximately 20 seconds the gas had disappeared and the circulation was not affected. These findings convincingly demonstrate the striking difference that exists between microemboli of air and those of CO_2 as potential health hazards.

As shown here, the number of microemboli ejected into the peripheral circulation during and after weaning from CPB can be substantially reduced with CO_2 insufflation. Thus, it seems reasonable to assume that also the number of bubbles ending up in the brain will become less. It also seems reasonable to assume that the microbubbles that do end up there are less harmful to the brain if they consist of CO_2. In this context the results of Pugsley et al. are of great interest.[1] During routine coronary bypass surgery they studied the occurrence of microemboli in the middle cerebral artery with transcranial Doppler ultrasonography and found the number of such emboli to be related to the patients' postoperative neuropsychological deficits. Moreover, Taylor et al. reported that perfusionist interventions led to cerebral air emboli[2,3] and frequent interventions increased the incidence of neuropsychological impairment.[3] Thus, a mere decrease of the number of microemboli had a beneficial effect while CO_2 insufflation not only decreases the number of emboli but probably also decreases the harm they can do. If this line of reasoning is correct, CO_2 insufflation, practiced for half a century on purely theoretical and experimental grounds, could finally be shown to be of clinical significance. The definite confirmation of the neuropsychological benefits of CO_2 has to be given by a phase III study involving neuropsychological tests.

CONCLUSIONS

This thesis concludes that:

- The gas-diffuser produced efficient de-airing of a cardiothoracic wound model at CO_2 flows of ≥5 l/min, while an open-ended tube did not.

- If CO_2 insufflation is started at a flow of 10 l/min the cardiothoracic wound cavity will be efficiently de-aired after 1 minute.

- An open pleural cavity delayed initial CO_2 de-airing, but did not have a clinically significant influence on air displacement during steady state.

- Coronary suction did not influence CO_2 de-airing. Rough suction impaired air displacement with the gas-diffuser when it exceeded the CO_2 inflow.

- In order to provide a high degree of de-airing CO_2 has to be delivered from within the wound cavity.

- When exposed to a fluid only the gas-diffuser remained efficient as a CO_2 insufflation device. In contrast, the multi-perforated catheter and the gauze sponge stopped functioning when they got wet.

- The number of microemboli ejected into the peripheral circulation during and after weaning from CPB can be substantially reduced with CO_2 insufflation.

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References

1. Pugsley W, Klinger L, Paschalis C, et al. The impact of microemboli during cardiopulmonary bypass on neuropsychological functioning. *Stroke*. 1994;25:1393-1399.

2. Taylor RL, Borger MA, Weisel RD, et al. Cerebral microemboli during cardiopulmonary bypass: increased emboli during perfusionist interventions. *Ann Thorac Surg*. 1999;68:89-93.

3. Borger MA, Peniston CM, Weisel RD, et al. Neuropsychologic impairment after coronary bypass surgery: effect of gaseous microemboli during perfusionist interventions. *J Thorac Cardiovasc Surg*. 2001;121:743-749.

4. Hindman BJ, Dexter F, Subieta A, et al. Brain injury after cerebral arterial air embolism in the rabbit as determined by triphenyltetrazolium staining. *Anesthesiology*. 1999;90:1462-1473.

5. Helps SC, Parsons DW, Reilly PL, et al. The effect of gas emboli on rabbit cerebral blood flow. *Stroke*. 1990;21:94-99.

6. Dalmas JP, Eker A, Girard C, et al. Intracardiac air clearing in valvular surgery guided by transesophageal echocardiography. *J Heart Valve Dis*. 1996;5:553-557.

7. van der Linden J, Casimir-Ahn H. When do cerebral emboli appear during open heart operations? A transcranial Doppler study. *Ann Thorac Surg*. 1991;51:237-241.

8. Tingleff J, Joyce FS, Pettersson G. Intraoperative echocardiographic study of air embolism during cardiac operations. *Ann Thorac Surg*. 1995;60:673-677.

9. Ng SW, Rosen M. Carbon dioxide in the prevention of air embolism during open-heart surgery. *Thorax*. 1968;23:194-196.

10. Mitz MA. CO_2 biodynamics: a new concept of cellular control. *J Theor Biol*. 1979;80:537-551.

11. Eguchi S, Bosher Jr LH. Myocardial dysfunction resulting from coronary air embolism. *Surgery*. 1962;51:103-111.

12. Eguchi S, Sakurai Y, Yamaguchi A. The use of carbon dioxide gas to prevent air embolism during open heart surgery. *Acta Med Biol*. 1963;11:1-13.

13. Goldfarb D, Bahnson HT. Early and late effects on the heart of small amounts of air in the coronary circulation. *J Thorac Cardiovasc Surg*. 1963;46:368-378.

14. Kunkler A, King H. Comparison of air, oxygen and carbon dioxide embolization. *Ann Surg*. 1959;149:95-99.

15. Moore RM, Braselton Jr CW. Injection of air and of carbon dioxide into a pulmonary vein. *Ann Surg*. 1940;112:212-218.

16. Spencer FC, Rossi NP, Yu S-C, et al. The significance of air embolism during cardiopulmonary bypass. *J Thorac Cardiovasc Surg*. 1965;49:615-634.

17. Martens S, Dietrich M, Wals S, et al. Conventional carbon dioxide application does not reduce cerebral or myocardial damage in open heart surgery. *Ann Thorac Surg*. 2001;72:1940-1944.

18. Persson M, van der Linden J. De-airing of a cardiothoracic wound cavity model with carbon dioxide: theory and comparison of a gas diffuser with conventional tubes. *J Cardiothorac Vasc Anesth*. 2003;17:329-335.

19. Olinger GN. Carbon dioxide displacement of left heart chambers. *J Thorac Cardiovasc Surg*. 1995;109:187-188.

20. Nadolny EM, Svensson LG. Carbon dioxide field flooding techniques for open heart surgery: monitoring and minimizing potential adverse effects. *Perfusion*. 2000;15:151-153.

21. Webb WR, Harrison LH, Jr., Helmcke FR, et al. Carbon dioxide field flooding minimizes residual intracardiac air after open heart operations. *Ann Thorac Surg*. 1997;64:1489-1491.

22. Martens S, Dietrich M, Doss M, et al. Optimal carbon dioxide application for organ protection in cardiac surgery. *J Thorac Cardiovasc Surg*. 2002;124:387-391.

23. Lindsay B. Mechanics. In: Gray DE, ed. *American Institute of Physics Handbook*. 3rd ed. New York: McGraw-Hill; 1972:134.

24. Shanewise JS, Cheung AT, Aronson S, et al. ASE/SCA guidelines for performing a comprehensive intraoperative multiplane transesophageal echocardiography examination: recommendations of the American Society of Echocardiography Council for Intraoperative Echocardiography and the Society of Cardiovascular Anesthesiologists Task Force for Certification in Perioperative Transesophageal Echocardiography. *Anesth Analg*. 1999;89:870-884.

25. Rodriguez RA, Cornel G, Weerasena NA, et al. Effect of Trendelenburg head position during cardiac deairing on cerebral microemboli in children: a randomized controlled trial. *J Thorac Cardiovasc Surg*. 2001;121:3-9.

26. Selman MW, McAlpine WA, Albregt H, et al. An effective method of replacing air in the chest with CO_2 during open-heart surgery. *J Thorac Cardiovasc Surg*. 1967;53:618-622.

27. Burbank A, Ferguson TB, Burford TH. Carbon dioxide flooding of the chest in open-heart surgery. A potential hazard. *J Thorac Cardiovasc Surg*. 1965;50:691-698.

28. O'Connor BR, Kussman BD, Park KW. Severe hypercarbia during cardiopulmonary bypass: a complication of CO2 flooding of the surgical field. *Anesth Analg*. 1998;86:264-266.

29. Rodigas PC, Meyer FJ, Haasler GB, et al. Intraoperative 2-dimensional echocardiography: ejection of microbubbles from the left ventricle after cardiac surgery. *Am J Cardiol*. 1982;50:1130-1132.

30. Bonow RO, Carabello B, de Leon AC, Jr., et al. Guidelines for the management of patients with valvular heart disease: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients with Valvular Heart Disease). *Circulation*. 1998;98:1949-1984.