Effect of CO₂ Insufflation on the Number and Behavior of Air Microemboli in Open-Heart Surgery

A Randomized Clinical Trial

P. Svenarud, MD; M. Persson, PhD; J. van der Linden, MD, PhD

Background—The risks that the presence of air microemboli implies in open-heart surgery have recently been emphasized by reports that their number is correlated with the degree of postoperative neuropsychological disorder. Therefore, we studied the effect of CO₂ insufflation into the cardiothoracic wound on the incidence and behavior of microemboli in the heart and ascending aorta.

Methods and Results—Twenty patients undergoing single-valve surgery were randomly divided into 2 groups. Ten patients were insufflated with CO₂ via a gas diffuser, and 10 were not. Microemboli were ascertained by intraoperative transesophageal echocardiography (TEE) and recorded on videotape from the moment that the aortic cross-clamp was released until 20 minutes after end of cardiopulmonary bypass (CPB). The surgeon performed standard de-airing maneuvers without being aware of TEE findings. Postoperatively, a blinded assessor determined the maximal number of gas emboli during each consecutive minute in the left atrium, left ventricle, and ascending aorta. The 2 groups did not differ in the usual clinical parameters. The median number of microemboli registered during the whole study period was 161 in the CO₂ 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), and ascending aorta 56 versus 185 (P<0.001). In the CO₂ 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).

Conclusions—Insufflation of CO₂ into the thoracic wound markedly decreases the incidence of microemboli. (Circulation. 2004;109:1127-1132.)

Key Words: microemboli ■ surgery ■ carbon dioxide ■ echocardiography

The great risks 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. The notoriously ineffective manual de-airing techniques have proved unable to eliminate the microemboli. Even if the techniques are meticulously adhered to, large numbers of microemboli still occur. Other possibilities should therefore be explored.

Carbon dioxide (CO₂) is 25 times more soluble in blood and tissue than air, and CO₂ emboli are therefore much better tolerated than are air emboli. Moreover, the density of CO₂ (50% heavier than air) facilitates air displacement in a cavity. Despite these impressive advantages, the use of CO₂ insufflation is not widespread. The reason for its lack of success has only recently become clear, when it was found that the devices through which CO₂ has traditionally been delivered were not effective. In the present study, we used a new device that can achieve a CO₂ atmosphere in the wound with >1% remaining air. We investigated the effect of CO₂ so delivered on the number and behavior of microemboli in heart and aorta. We did so with the help of intraoperative transesophageal echocardiographic (TEE) examinations during mitral or aortic valve operations.

Methods

Patient Recruitment

Twenty patients scheduled for single valve surgery at Huddinge University Hospital were included in this prospective study. All patients were first-time candidates for cardiac surgery. Six patients underwent mitral valve surgery, and 14 underwent aortic valve surgery. Eight patients had coronary bypass grafting in addition to the valve procedure. Six senior surgeons operated on the patients. Immediately before the start of surgery, the patients were randomized to 1 of 2 groups. One group was operated on with intraoperative wound insufflation of CO₂, and the other group was not. Random assignment was carried out with the help of unmarked envelopes.
each of which contained a card indicating CO2 treatment in the wound or not. The patients were stratified according to type of valve procedure. Preoperative patient data are shown in Table 1, and intraoperative data are shown in Table 2. The operations were performed through a standard complete median sternotomy with cardiopulmonary bypass (CPB) with a flow rate of ≥2.4 L/min and mild hypothermia at 34°C. CPB was instituted with a standard kit and a hollow-fiber membrane oxygenator (Dideco Simplex D708, Dideco). 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 the ascending aorta and a 2-stage venous cannula inserted into the right atrium and the inferior vena cavae. An exception was made for mitral valve operations, in which bicaval cannulation was used. In all aortic valve operations, a vent was inserted through a purse-string stitch position on the right superior pulmonary vein. Myocardial preservation consisted of intermittent antegrade and retrograde cold blood cardioplegia. Cardiopulmonary bypass, 1.5 L/min, was used intermittently throughout the CPB period. Rough suction was set to 10 L/min.18

**Surgery**

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**Instrumentation**

CO2 was insufflated into the cardiothoracic wound with a recently described gas diffuser (Cardia Innovation AB) that provides an almost 100% CO2 atmosphere in the wound.16,18,19 The diffuser was placed 5 cm below the wound opening adjacent to the diaphragm, and the CO2 flow was set at 10 L/min. Intraoperative TEE (Vivid Five, Vingmed-GE) examinations were performed by the same experienced anesthesiologist in all patients. The TEE probe was positioned in such a manner that a midesophageal long-axis view could be kept. That view included 3 areas of interest, ie, the left atrium, the left ventricle, and the proximal part of the ascending aorta.20 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 1 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 the end of CPB, (2) the first 15 minutes after release of the aortic cross-clamp, (3) the last 10 minutes of CPB, and (4) the first 20 minutes after the 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 inflation with the patient in the Trendelenburg 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 to avoid entrapment of air. The aortic vent was removed 10 minutes after the end of CPB. Because of 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.

**Statistics**

Data were analyzed with the SPSS version 11.0 statistical program. The data 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 25th/75th percentiles. Differences were considered significant at a probability level of P<0.05.

**Results**

Demographic and clinical data are listed in Table 1. No significant differences were observed for any parameter. Seven and 3 patients in each group underwent aortic and mitral valve operations, respectively. The median age was 75 years in both groups. Three and 5 patients in the control group and in the treatment group, respectively, underwent additional CABG. The duration of CPB and aortic cross-clamping and the duration from release of the cross-clamp until the

**TABLE 1. Demographic and Clinical Data**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group Control (n=10)</th>
<th>Group CO2 (n=10)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male/female</td>
<td>6/4</td>
<td>7/3</td>
<td>0.74</td>
</tr>
<tr>
<td>Age, y</td>
<td>75 (64/82)</td>
<td>75 (57/78)</td>
<td>0.48</td>
</tr>
<tr>
<td>Height, cm</td>
<td>169 (168/178)</td>
<td>175 (167/181)</td>
<td>0.53</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>75 (68/82)</td>
<td>80 (75/88)</td>
<td>0.19</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td>II (I/III)</td>
<td>II (I/III)</td>
<td>0.48</td>
</tr>
<tr>
<td>Euroscore</td>
<td>6.5 (5/8)</td>
<td>6 (3.8/7.5)</td>
<td>0.63</td>
</tr>
<tr>
<td>Aortic valve replacement</td>
<td>7</td>
<td>7</td>
<td>1.0</td>
</tr>
<tr>
<td>Mitral valve repair</td>
<td>3</td>
<td>3</td>
<td>1.0</td>
</tr>
<tr>
<td>CABG</td>
<td>3</td>
<td>5</td>
<td>0.48</td>
</tr>
<tr>
<td>ECC, min</td>
<td>116 (90/136)</td>
<td>113 (90/138)</td>
<td>1.0</td>
</tr>
<tr>
<td>Aortic cross-clamping, min</td>
<td>84 (64/105)</td>
<td>85 (62/101)</td>
<td>0.97</td>
</tr>
<tr>
<td>Minutes from release of cross-clamp until discontinuation of ECC</td>
<td>42 (40/45)</td>
<td>42 (38/45)</td>
<td>0.80</td>
</tr>
<tr>
<td>Intubation in intensive care unit, h</td>
<td>7.8 (4.8/11.1)</td>
<td>6.5 (5.6/7.8)</td>
<td>0.44</td>
</tr>
<tr>
<td>s-Troponin T, μg/L, day 1</td>
<td>0.64 (0.23/0.85)</td>
<td>0.44 (0.27/0.71)</td>
<td>0.53</td>
</tr>
<tr>
<td>s-Creatine kinase-MB, μg/L, day 1</td>
<td>35 (18/48)</td>
<td>25 (14/57)</td>
<td>0.85</td>
</tr>
</tbody>
</table>

Values are given as median (25th/75th percentile). ECC indicates extracorporeal circulation.
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 1 depicts the median number of microemboli minute by minute during the first 15 minutes after release of the aortic cross-clamp in the 3 areas of interest taken together. All patients in both groups had microemboli after release of the aortic cross-clamp in all 3 areas of interest. The number of microemboli peaked during the first few minutes after release of the aortic cross-clamp. Figure 2 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 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 ($P<0.01$). This held true for all 4 time periods and all 3 studied locations. The total numbers of microemboli present in the different areas of

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Median number of microemboli minute by minute during first 15 minutes after release of aortic cross-clamp in 3 areas of interest (left ventricle, left atrium, and proximal part of ascending aorta taken together shown by TEE).

![Figure 2](https://example.com/figure2.png)

**Figure 2.** Median number of microemboli minute by minute from 10 minutes before to 20 minutes after discontinuation of CPB in 3 areas of interest (left ventricle, left atrium, and proximal part of ascending aorta taken together shown by TEE).
interest and in all 3 areas taken together are shown for the whole study in Figure 3.

The total number of microemboli per minute in the 3 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 3 areas of interest was 3 (1/9) in the control group, compared with 18 (16/26) in the CO2-treated group (P<0.001). Finally, at the end of the study, the median number of microemboli present in all 3 areas of interest taken together fell to zero 7 (0/16) minutes after discontinuation of CPB in the treatment group, compared with 19 (14/20) minutes after this was done in the control group (P<0.001).

Discussion

In all of the study’s 20 patients, intraoperative TEE examination showed cardiac/aortic microemboli. The emboli were found in all 3 studied locations, ie, 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, ie, 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 been reported only by Tingleff et al.8 who found intracardiac microbubbles in 15 of 15 patients after release of the aortic cross-clamp (100%). After CPB, however, they8 observed such bubbles in only 12 of their 15 patients (80%), and the figures reported by others are even lower. Rodigas et al.11 observed left ventricular bubbles in 39 of 58 patients (67%), and Dalmas et al.4 using a 3- or 4-chamber TEE view, did so in 25 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 is true 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 multifactorial, 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 of whether air emboli occur in the majority of patients or in all of them is irrelevant, because no one doubts that air embolism constitutes a risk. However, if one intends to study the effect of a treatment, ie, CO2, 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 caused by inaccurate registration can be reduced to a minimum.

Let us therefore have a closer look at how the occurrence of microbubbles was assessed. Earlier studies used arbitrary scales to grade the number of intracardiac microemboli.4,6,21 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 assess not only peaks and total numbers of microemboli but also the exact moment when they disappear from the area of interest.

CO2 dissolves in blood more than 25 times faster than does air. To reduce the risk of air embolism, insufflation of CO2 into the wound cavity was therefore introduced in the 1950s. This form of insufflation has been practiced for almost 50 years now, and it is certainly worthy of note that during this whole half century of blowing CO2 into the wound, not one single study has appeared that convincingly showed its value, ie, could show less air embolism with CO2 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 CO2 atmosphere in the wound.15–19 Because of the high outflow velocities of these devices and the air turbulence the jet generates,16–19 the remaining air concentrations in the wound cavity were found to vary between 20% and 80%.15–19 Therefore, we have developed a more effective insufflation device, a gas diffuser that in in vitro experiments was found to provide adequate de-airing with <1% remaining air in the wound model.16–19 The question now arose whether these promising results of in vitro experiments could be reproduced in clinical practice.

In the present study, we evaluated the effectiveness of CO2 insufflation into the open surgical wound with the new device. Several important factors may influence CO2 de-airing during cardiac surgery. Among these factors are type of insufflation device, CO2 flow rate, and coronary and rough suction.16–19 These factors were all controlled in the study. Twenty consecutive patients were randomized to 2 groups. Ten received treatment, and 10 served as controls. As seen in Table 1, randomization had been effective. The demographic and clinical data of the 2 groups were very similar. The 2 groups were comparable. Treatment of 1 of these 2 comparable groups with CO2 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 2 groups were apparent throughout the whole study period, ie, from release of the aortic cross-clamp until 20 minutes after the end of CPB. In addition, in the CO₂-insufflated group, microemboli disappeared much more quickly after the end of CPB. As seen in Table 2, all the differences were significant at the 0.01 or 0.001 level. Admittedly, the variables in Table 2 are all more or less strongly correlated, but even if the correlation between them were perfect, with the appropriate correlation coefficient approaching 1, this would not affect the probability value of any of the differences between the groups. Those differences would still be significant at least at the 1% level.

Because the study 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 1). Most of the microemboli were then whirling around in the left ventricle and the left atrium and were not propagated forward, whereas 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 2). 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.5 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 CO₂-treated patients and the controls comes to the fore.5 Moreover, it should be kept in mind that in the CO₂-treated patients, the microemboli were not only fewer in number but also differed from those in the untreated group as to their composition. They consisted of CO₂ and not of air. Several old studies have shown that gas bubbles containing CO₂ are much better tolerated than air.9−14 In studies on cats, injection of 0.5 cm³ of air per pound body weight into the pulmonary vein resulted in the filling of the coronary arteries with air and subsequent death in all animals.14 By contrast, similar injections of CO₂ were tolerated. Even the injection of 12 times the fatal dose of air (6 cm³/lb body wt), 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 CO₂ 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 CO₂ insufflation. Thus, it seems reasonable to assume that the number of bubbles ending up in the brain will also 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 CO₂. In this context, the results of Pugsley et al1 are of great interest. 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 al2 and Borger et al3 reported that perfusionist interventions led to cerebral air emboli and that frequent interventions increased the incidence of neuropsychological impairment.3 Thus, a mere decrease of the number of microemboli had a beneficial effect, whereas CO₂ insufflation not only decreases the number of emboli but probably also decreases the harm they can do. If this line of reasoning is correct, CO₂ insufflation, practiced for half a century on purely theoretical and experimental grounds, could finally be shown to be of clinical significance. The definitive confirmation of the neuropsychological benefits of CO₂ insufflation has to be given by a phase III study involving neuropsychological tests.

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