Effect of CO_2 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 CO_2 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 CO_2 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 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 ($P<0.001$), and 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 ($P<0.001$).

Conclusions—Insufflation of CO_2 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.[1–3] The notoriously ineffective manual de-airing techniques have proved unable to eliminate the microemboli.[4] Even if the techniques are meticulously adhered to, large numbers of microemboli still occur.[4–6] Other possibilities should therefore be explored.

Carbon dioxide (CO_2) is ≥25 times more soluble in blood and tissue than air,[7,8] and CO_2 emboli are therefore much better tolerated than are air emboli.[9–14] Moreover, the density of CO_2 (50% heavier than air) facilitates air displacement in a cavity. Despite these impressive advantages, the use of CO_2 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 CO_2 has traditionally been delivered were not effective.[15] When CO_2 was supplied in this manner, the wound still contained 20% to 80% air.[15–19] In the present study, we used a new device that can achieve a CO_2 atmosphere in the wound with <1% remaining air.[16–19] We investigated the effect of CO_2 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 CO_2, and the other group was not. Random assignment was carried out with the help of unmarked envelopes,

Received October 5, 2003; revision received November 26, 2003; accepted December 2, 2003.

From the Department of Cardiothoracic Surgery and Anesthesiology, Huddinge University Hospital (P.S., M.P., J.v.d.L.), and the Division of Medical Engineering, Department of Laboratory Medicine (M.P.), Karolinska Institute, Stockholm, Sweden.

All authors are shareholders of Cardia Innovation AB, which owns the patent and produces the gas diffuser.

Correspondence to Peter Svenarud and Jan van der Linden, Department of Cardiothoracic Surgery and Anesthesiology, M85, Karolinska Institute, Huddinge University Hospital, SE-141 86 Stockholm, Sweden. E-mail peter.svenarud@hs.se and jan.vanderlinden@hs.se

Circulation **is available at http://www.circulationaha.org** **DOI: 10.1161/01.CIR.0000118501.44474.83**

TABLE 1. Demographic and Clinical Data

Characteristic	Group Control (n=10)	Group CO_2 (n=10)	*P*
Sex, male/female	6/4	7/3	0.74
Age, y	75 (64/82)	75 (57/78)	0.48
Height, cm	169 (168/178)	175 (167/181)	0.53
Weight, kg	75 (68/82)	80 (75/88)	0.19
NYHA functional class	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 ECC	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, μg/L, day 1	0.64 (0.23/0.85)	0.44 (0.27/0.71)	0.53
s-Creatine kinase-MB, μg/L, day 1	35 (18/48)	25 (14/57)	0.85

Values are given as median (25th/75th percentile). ECC indicates extracorporeal circulation.

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 patient data are shown in Table 1, and intraoperative data are shown in Table 2. The Hospital Ethics Committee approved the study, and informed consent was obtained from all patients. The procedures followed were in accordance with institutional guidelines.

Surgery

The operations were performed through a standard complete median sternotomy with cardiopulmonary bypass (CPB) with a flow rate of $\geq$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). 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 venae 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 positioned on the right superior pulmonary vein. Myocardial preservation consisted of intermittent antegrade 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.[18]

Instrumentation

CO_2 was insufflated into the cardiothoracic wound with a recently described gas diffuser (Cardia Innovation AB) that provides an almost 100% CO_2 atmosphere in the wound.[16,18,19] 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) 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 2. No. of Microemboli According to Transesophageal Echocardiographic Evaluation of the Left Atrium and Ventricle and the Proximal Part of the Ascending Aorta

Study Period/Area of Interest	No. of Microemboli: Group Control (n=10)	No. of Microemboli: 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
First 15 minutes 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
Last 10 minutes 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
First 20 minutes 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

Values are given as median (25th/75th percentile). LA indicates left atrium; LV, left ventricle; and Ao, aorta.

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 ($P \leq 0.01$). This held true for all 4 time periods and all 3 studied locations. The total numbers of microemboli present in the different areas of

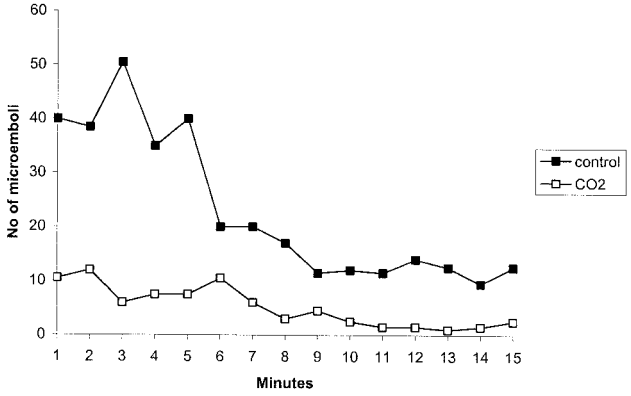

Figure 1. Median number of microemboli minute by minute during first 15 minutes after release of aortic cross-clamp in 3 areas of interest (left ventricle, left atrium, and proximal part of ascending aorta taken together shown by TEE).

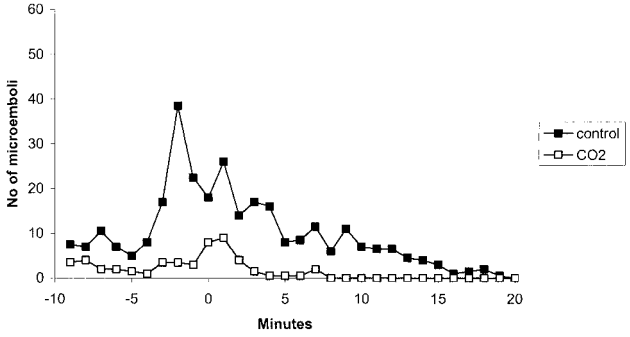

Figure 2. Median number of microemboli minute by minute from 10 minutes before to 20 minutes after discontinuation of CPB in 3 areas of interest (left ventricle, left atrium, and proximal part of ascending aorta taken together shown by TEE).

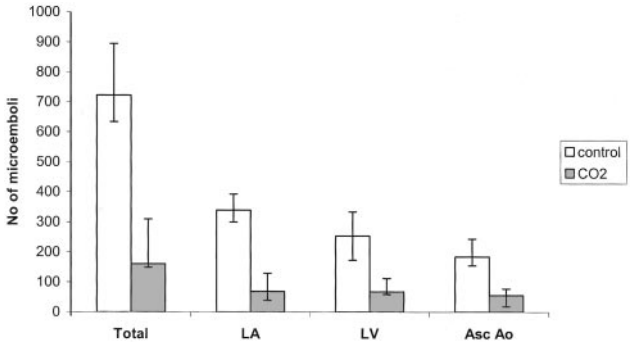

Figure 3. Total numbers of microemboli present in different areas of interest (left ventricle, left atrium, and proximal part of ascending aorta, and in all 3 areas taken together during whole study shown by TEE).

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 CO_2-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,[6] who found intracardiac microbubbles in 15 of 15 patients after release of the aortic cross-clamp (100%). After CPB, however, they[6] observed such bubbles in only 12 of their 15 patients (80%), and the figures reported by others are even lower. Rodigas et al[21] 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, 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 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.

CO_2 dissolves in blood more than 25 times faster than does air. To reduce the risk of air embolism, insufflation of CO_2 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 CO_2 into the wound, not one single study has appeared that convincingly showed its value, ie, 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.[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 CO_2 insufflation into the open surgical wound with the new device. Several important factors may influence CO_2 de-airing during cardiac surgery. Among these factors are type of insufflation device, CO_2 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 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 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 CO_2-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 CO_2-treated patients and the controls comes to the fore.[5] Moreover, it should be kept in mind that in the CO_2-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 CO_2 and not of air. Several old studies have shown that gas bubbles containing CO_2 are much better tolerated than air.[9–14] In studies on cats, injection of 0.5 cm^3 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 CO_2 were tolerated. Even the injection of 12 times the fatal dose of air (6 cm^3/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 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 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 CO_2. In this context, the results of Pugsley et al[1] 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 al[2] and Borger et al[3] 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 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 definitive confirmation of the neuropsychological benefits of CO_2 insufflation has to be given by a phase III study involving neuropsychological tests.

Acknowledgments

This study was funded by the Karolinska Institute and the Swedish Heart Lung Foundation. Thanks are due to Professor Emeritus Willem van der Linden for help with the preparation of the manuscript.

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. 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.
5. 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.
6. Tingleff J, Joyce FS, Pettersson G. Intraoperative echocardiographic study of air embolism during cardiac operations. *Ann Thorac Surg*. 1995;60:673–677.
7. Mitz MA. CO_2 biodynamics: a new concept of cellular control. *J Theor Biol*. 1979;80:537–551.
8. Ng SW, Rosen M. Carbon dioxide in the prevention of air embolism during open-heart surgery. *Thorax*. 1968;23:194–196.
9. Kunkler A, King H. Comparison of air, oxygen and carbon dioxide embolization. *Ann Surg*. 1959;149:95–99.
10. 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.
11. 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.

12. 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.
13. Eguchi S, Bosher LH Jr. Myocardial dysfunction resulting from coronary air embolism. *Surgery*. 1962;51:103–111.
14. Moore RM, Braselton CW Jr. Injection of air and of carbon dioxide into a pulmonary vein. *Ann Surg*. 1940;112:212–218.
15. 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.
16. 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.
17. 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? *J Cardiothorac Vasc Anesth*. In press.
18. 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. *J Thorac Cardiovasc Surg*. 2003;125:1043–1049.
19. 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. *Anesth Analg*. 2003;96:321–327.
20. 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.
21. 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.