The dynamic air bubble trap reduces cerebral microembolism during cardiopulmonary bypass

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Objective: Neuropsychologic disorders are common after coronary artery bypass operations. Air microbubbles are identified as a contributing factor. A dynamic bubble trap might reduce the number of gaseous microemboli.

Methods: A total of 50 patients undergoing coronary artery bypass operation were recruited for this study. In 26 patients a dynamic bubble trap was placed between the arterial filter and the aortic cannula (group 1), and in 24 patients a placebo dynamic bubble trap was used (group 2). The number of high-intensity transient signals within the proximal middle cerebral artery was continuously measured on both sides during bypass, which was separated into 4 periods: phase 1, start of bypass until aortic clamping; phase 2, aortic clamping until rewarming; phase 3, rewarming until clamp removal; and phase 4, clamp removal until end of bypass. S100 β values were measured before, immediately after, and 6 and 48 hours after the operation and before hospital discharge.

Results: The bubble elimination rate during bypass was 77% in group 1 and 28% in group 2 ($P < .0001$). The number of high-intensity signals was lower in group 1 during phase 1 (5.8 ± 7.3 vs 16 ± 15.4 , $P < .05$ vs group 2) and phase 2 (6.9 ± 7.3 vs 24.2 ± 27.3 , $P < .05$ vs group 2) but not during phases 3 and 4. Serum S100 β values were equally increased in both groups immediately after the operation. Group 2 patients had higher S100 β values 6 hours after the operation and significantly higher S100 β values 48 hours after the operation (0.06 ± 0.14 vs 0.18 ± 0.24 , $P = .0133$ vs group 2). Age and S100 β values were correlated in group 2 but not in group 1.

Conclusion: Gaseous microemboli can be removed with a dynamic bubble trap. Subclinical cerebral injury detectable by increases of S100 β disappears earlier after surgical intervention.

Cerebral injury and neuropsychologic deficits after cardiopulmonary bypass are well established in patients undergoing cardiac surgery.^{1,2} Macroemboli and microemboli have both been implicated in the cause of adverse cerebral outcomes.²⁻⁴ Emboli occur during extracorporeal circulation (ECC), are caused by manipulations of the aorta,^{5,6} and are associated with the technique of cardioplegia⁷ and the type of oxygenator^{8,9} or hardshell venous reservoir¹⁰ used. Air embolism is more common after open-chamber procedures¹¹; however, evidence exists that the majority of microemboli during closed cardiac surgery consists of air.^{12,13} Trans-

Figure 1. Cardiopulmonary bypass circuit with implementation of DBT. Oxy, Oxygenator; AF, conventional 40- μ m arterial line filter; measure probe, Doppler device. For further explanation, see text.

esophageal echocardiography, carotid ultrasonography,¹⁴ and transcranial Doppler ultrasonography were used during cardiac procedures^{6,11,15,16} to detect embolic signals within the aorta^{17,18} and the arteries supplying the brain. These embolic events could lead to increased S100 β levels.^{19,20} Clinical and laboratory studies showed a significant reduction of cerebral microembolic load by using an arterial filter.^{7,21,22} In the present study the efficacy of a dynamic bubble trap (DBT) was investigated in patients undergoing on-pump coronary artery bypass operations.

Methods

Patients

Fifty patients scheduled for elective coronary artery bypass surgery were randomly assigned in a double-blind manner to one of 2 groups. In group 1 ($n = 26$) a DBT was incorporated in the arterial line after a common 40- μ m arterial filter. One patient was eliminated from the study because of recurring ventricular tachycardia and fibrillation. Group 2 ($n = 24$) was perfused with a DBT placebo, which was also placed after a 40- μ m arterial line filter. Exclusion criteria were as follows: age greater than 75 years; combined procedures; ejection fraction of less than 35%; atherosclerosis of the carotid arteries; combined severe lung, renal, or cerebral diseases; drug or alcohol abuse; diabetes mellitus; emergency status; and early postoperative complications requiring prolonged artificial ventilation and sedation. The investigation interval was 10 months. The state ethics committee approved the protocol. Participating patients provided written informed consent.

Transcranial Doppler Ultrasonography

During the operation, bilateral transcranial detection of high-intensity transient signals (HITS) within the proximal middle cerebral artery was performed continuously from the beginning to end of cardiopulmonary bypass with a 2-MHz pulse-wave TCD device (CDS Neuroguard Plus, Neuroguard Inc). The flat monitoring Doppler probes were fixed before the ear above the zygomatic

bone (posterior temporal window) with a head frame (Marc 500, Spencer Technologies). In group 1 middle cerebral artery insonation of both sides was successful in 25 patients, and in group 2 such insonation was successful in 21 patients. In the other 4 patients only the right medial cerebral artery was insonatable (1 in group 1 and 3 in group 2). The mean insonation depth in group 1 was 50.5 mm (range, 35-68 mm) on the left side and 52.3 mm (range, 35-68) on the right side; in group 2 the corresponding depths were 53.6 mm (range, 41-62 mm) and 52.8 (range, 39-62 mm), respectively.

Cerebral Embolus Detection

Automated embolus detection software (EMBOTec Version 5.2, STAC GmbH) was used. Axial extension of the sample volume was fixed at 7 mm (high-pass filter at 150 Hz). The color-coded power spectra of the audible Doppler shift were visualized on screen (after calculation of a 128-point fast-Fourier transformation) by using an overlap of 75%.²³ Power and gain were individually adjusted to minimize the intensity of the background color spectrum and to allow the embolic signals to be completely displayed within the dynamic range of the instrument. The audible Doppler signal was recorded with a digital audio recorder (Tascam DA-30 MKII, Teac Corp) on digital audiotapes (DT 90RA, Sony Corp). Two observers manually registered microembolic signals both online and, if necessary, offline and noted corresponding surgical events and stages of the operation. The following acoustic and visual criteria for embolic signals were used: typical visible high intensity (at least 3 db higher than that of the background blood-flow signal), typical audible sound (click, chirp, bloop), and short duration (<200 ms). Because the EMBOTec software has not yet been able to reliably indicate differences between artifacts and microemboli automatically,²⁴ especially during conditions of ECC, the investigators arbitrarily rejected signals above and below the baseline at the presence of obvious artifact. The recording time was determined on the basis of the duration of bypass. Bypass time was separated into 4 periods: phase 1, start of ECC until aortic clamping; phase 2, aortic clamping until rewarming; phase 3, rewarming until clamp removal; and phase 4, clamp removal until the end of ECC.

Arterial Line Embolus Detection

A 2-channel Doppler ultrasonography device ultrasonic bubble counter (Martin Luther University, Halle, Germany) was used to detect microbubbles before and after the DBT.²⁵ The device counts microbubbles ranging from 5 to 120 μ m. Particulate emboli do not influence the count result. Because of minor clinical relevance, only bubbles larger than 10 μ m were taken into account. Hard disk registration of online data was performed for offline investigation.

Dynamic Bubble Trap

The DBT, which efficiently removes microbubbles, was developed to reduce the number of microbubbles in the arterial line.^{26,27} The DBT was placed in the arterial line between the arterial filter and arterial cannula (Figure 1). The shape of the DBT is tubular (Figure 2). It consists of a 3/8-in inlet, a separation chamber, a tube with a 3/8-in outlet, and a site for collecting microbubbles where a recirculation line is also connected. Inside the separation chamber there is a 3-channel helix. As blood passes through the helix,

it is converted into a rotating stream. The shape of the separation chamber causes the centrifugal forces to direct air microbubbles to the center of the flow line. After the blood passes through the tube, the process stabilizes, with the largest percentage of bubbles now in the central blood-flow line. The collection site, which is situated in the center of the distal end of the tube, diverts the central blood-flow line and returns it together with all bubbles to the cardiotomy reservoir. Because of the special hydrodynamic features of the device, the diversion of flow to the cardiotomy reservoir is constant at 400 to 450 mL/min. The efficiency of the bubble trap depends on many parameters (eg, blood viscosity, temperature, and position of a microbubble in the blood stream) but mostly on microbubble size and blood-flow velocity. The mathematic model, which was set up for the in vitro tests, showed that at least 70% of bubbles with a diameter of 15 μm and at least 90% of larger bubbles ($>25 \mu\text{m}$) were removed. Before clinical use, the biocompatibility of the DBT was tested in an in vitro study.^{28,29} There was no difference between the DBT group and the control group. The DBT placebo was a DBT without a helix but with a collection site and recirculation line to protect the blindness of the study for the investigators.

Anesthesia Technique

After premedication with flunitrazepam, total intravenous general anesthesia was induced and maintained with sufentanil and propofol. No volatile anesthetic gases were used. After relaxation with pancuronium bromide, the trachea was intubated, and controlled normocapnic ventilation with an air-oxygen mixture was started. Before or during anesthesia, standard monitors were applied, including pulse oximetry, mainstream capnometry, and peripheral and central body temperature sensors, as well as arterial and pulmonary artery catheters. Blood for arterial blood gas, electrolytes, and glucose measurement, as well as activated clotting time ascertainment, was sampled according to a standard anesthesia protocol.

Protein S100 β

Blood samples were taken before, immediately after, and 24 and 48 hours after the end of the operation, as well as before discharge from the hospital. All blood samples were cooled and centrifuged immediately and were measured by using a monoclonal 2-sided immunoradiometric assay (Sangtec 100, AB Sangtec Medical).

Bypass Technique

The DBT (HPmedica) or placebo DBT was integrated into a standard ECC tubing set (HMT Medizintechnik), which contained a 40- μm heparin-coated arterial line filter (AF 1040 Gold, Baxter). Extracorporeal perfusion was performed with a roller pump (Stoeckert Instrumente) and a hollow-fiber membrane oxygenator with venous hardshell reservoir (Biocor 200 IHS, Minntech Corp) at a nonpulsatile flow rate of $2.4 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$. The circuit was primed with 1600 mL of Ringer solution, 100 mL of mannitol 20%, 100 mL of sodium bicarbonate 8.4%, 5000 units of heparin, and 2 mL of aprotinin. A standard cannulation technique was performed with a wire inlay aortic arch cannula (diameter, 0.26 in; length, 8 in; straight 3/8-in connector; Stoeckert), which was placed in the ascending aorta, as well as with a proximal and distal wire-reinforced 2-stage venous cannula (F36-32, connector 1/2 in, Medos Medizintechnik) through the right atrium after systemic

Figure 2. The DBT in detail: 1, Separation chamber; 2, 3/8-in inlet; 3, tube with 3/8-in outlet; 4, collection site; 5, 3-channel helix. For further explanation, see text.

heparinization (500 U/kg). ECC (Stoeckert Instrumente) was initiated according to the alpha-stat concept. Additional heparin was added during cardiopulmonary bypass to maintain the activated clotting time at greater than 400 seconds if necessary. The left ventricle was vented with an aortic root cannula (diameter, 14-gauge; length, 5.6 in; Stoeckert Instrumente). After reaching moderate hypothermia, distal graft anastomoses were performed during aortic crossclamping. For myocardial preservation, Bretschneider Cardioplegia (Custodiol, Dr Franz Koehler Chemie, Alsbach-Hähnlein, Germany) was administered to achieve and sustain cardiac arrest. After the removal of the crossclamp, proximal anastomoses were made after tangential clamping of the aorta during rewarming. Weaning from ECC happened after watching the reperfusion time (one third of the crossclamp time) to recover normal myocardial function and reaching normothermic core temperature. If necessary, intravenous dopamine was infused at $3 \text{ to } 5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ to enhance cardiac inotropy.

Statistical Analysis

The data were collected with a computer database (SigmaPlot 4.01, SPSS Corp). Statistical analysis was performed with the DataDesk software (v6.1, Data Description Inc). All values are expressed as mean $\pm$ SD if normally distributed or median with range. Statistical significance regarding the differences between groups was determined with a 2-sample Student *t* test for normally distributed data or with the nonparametric Mann-Whitney rank sum test.

Results

According to the study design, one female patient of group 1 was excluded because of hemodynamic instability caused by recurring ventricular tachycardia and fibrillation. Postoperative records of all patients were uncomplicated. They could be extubated within 12 hours and left the intensive care unit after 1 day (mean intensive care unit stay, 1.04 days). Neurologic examinations of all patients on the second and third day postoperatively were normal. The biometric data of the 2 groups did not differ concerning sex and key body figures. Overall, 41 men and 8 women were included in both groups. Intraoperative data are summarized in Table 1. The bubble elimination rate of the DBT (defined as $\text{Elimination rate} = [\text{Bubbles before DBT} - \text{Bubbles after DBT}] / \text{Bubbles before DBT}$) was 81% in group 1 and 36% in group 2.

TABLE 1. Biometric and intraoperative data of both groups (DBT = group 1, Dummy = group 2)

Parameter	Group	Mean	SD	Median	Range	P value
Age (y)	DBT	63.8	8.5	66.3	33.3	.118
	Dummy	60.1	7.7	59.9	32.1	
BSA (m ²)	DBT	1.94	0.18	1.95	33.3	.193
	Dummy	2.01	0.2	1.98	32.1	
ECC time (min)	DBT	71	17	71	73	.069
	Dummy	82	23	77	91	
Body temperature (°C)	DBT	27	1.3	27	5.9	.955
	Dummy	26.9	1.5	26.6	7	
No. of arterial grafts	DBT	1.32	0.748	1	3	.167
	Dummy	1.7	0.91	1.5	3	
No. of venous grafts	DBT	1.76	0.88	2	4	.342
	Dummy	2.04	1.16	2	4	
pH	DBT	7.369	0.041	7.41	0.18	.117
	Dummy	7.365	0.086	7.375	0.44	
Pco ₂ (mm Hg)	DBT	44.13	3.314	34	22	.369
	Dummy	45.13	4.266	44.5	13	
Po ₂ (mm Hg)	DBT	273	107	246	396	.375
	Dummy	282	98	266	482	
Hgb (g/100 mL)	DBT	7.3	0.72	7.2	3	.187
	Dummy	7.6	1.1	7.4	4.4	
Mean AP (mm Hg)	DBT	40.8	9.7	38	28	.372
	Dummy	43.4	10.9	42	42	
mFV re (cm/s)	DBT	28.4	6.2	28	22	.377
	Dummy	26.7	7.3	24	29	
mFV li (cm/s)	DBT	28.3	5.9	28	22	.756
	Dummy	29	8.2	27	32	

BSA, Body surface area; *Bodytemp*, mixed venous blood temperature after aortic crossclamping; *Hgb*, hemoglobin sampled in phase 2; *mean AP*, mean arterial pressure in phase 2; *mFV*, mean flow velocity in both middle cerebral arteries.

TABLE 2. Number of bubbles in arterial line of bypass circuit

Parameter	Group	Mean	SD	Median	Range	P value
Before trap	DBT	2825	3180	1921	16,442	.435
	Dummy	2042	1420	1587	6114	
After trap	DBT	520	419	418	1550	.001
	Dummy	1409	840	1921	3069	

After the blood of group 1 patients passed the DBT, it contained significantly fewer bubbles than the blood of group 2 patients after passing the placebo DBT. The results of bubble detection in the arterial line are shown in Table 2. Transcranial Doppler emboli detection showed 2 to 3 times more HITS in group 2 compared with those in group 1 as far as total bypass time and different phases of bypass are concerned. These differences were significant, except in phases 3 and 4 (Table 3). Serum S100 β values were increased in both groups at the end of the operation compared with preoperative values. A comparison between the groups at the 5 different time points showed higher S100 β values in group 2 (Table 4). This difference is significant 48 hours postoperatively ($P = .0133$) and has a strong tendency 6 hours postoperatively ($P = .11$; not significant but small

enough to suggest a tendency). Regression analysis between age and S100 β values showed a correlation in group 1 ($R = 0.42$, $P < .05$) but not in group 2.

Discussion

Doppler ultrasonography was used to detect cerebral emboli during coronary artery bypass surgery.¹⁷ The majority of emboli are detected after release of the aortic crossclamp and partial occlusion clamp. It has therefore been suggested that these signals mostly represent atheromatous debris rather than gaseous microbubbles. Reichenspurner and colleagues³⁰ showed that an intra-aortic filtration system could effectively catch these particles (fibrous atheroma, medial tissue, epiaortic debris, and thrombus material).

Many studies suggest that use of a 40- μ m arterial filter in the arterial line of the ECC might also reduce microemboli. Our study shows that gaseous microemboli detected after the arterial filter ranged from 415 to 16,442 bubbles in the DBT group and from 453 to 6,114 bubbles in the placebo group. We conclude that this situation necessitates supplemental measures to remove this air from the extracorporeal bypass circuit.

The DBT effectively eliminated a large percentage of these microbubbles. However, after the placebo, we also measured a minor reduction of microbubbles (2042 vs 1409,

$P > .001$). The explanation for this is that a DBT without a helix was used as the placebo. The shape of the separation chamber and the existence of the collection site and recirculation line resulted in a minor reduction of microbubbles. Even a simple tube (without a separation chamber but with a collection site and recirculation flow) would show a low efficacy. Transcranial Doppler ultrasonography in the middle cerebral arteries showed significant reductions of emboli in the DBT group compared with that seen in the placebo group, but the numbers in both groups are one decimal power lower than those in the arterial bypass line. Obviously a large number of bubbles have traveled to other parts of the body or to anterior and posterior cerebral regions.

The bubble-reducing effect of the DBT is most pronounced during phases 1 and 2. At the beginning of CPB, the number of microbubbles per minute measured in the arterial line is high because of remaining air in the venous line at the initiation of cardiopulmonary bypass. In phase 2 the manipulation at the ascending aorta after crossclamping is relatively rare, but air introduced by means of blood sampling and drug administration by the perfusionist or over leaking purse-string sutures of the venous cannula during heart manipulation does occur far more frequently. This air can be successfully removed by the DBT.

In phases 3 and 4 embolic signals are predominantly caused by solid particles originating from manipulations of the aorta, such as partial crossclamping and removal of the aortic vent.^{3,5,30} Therefore the DBT has no effect on this origin of cerebral HITS.

An increased level of serum S100 β in patients with uneventful clinical outcomes might provide evidence of subclinical injury, which could be due to diffuse microemboli and increased permeability of the blood-brain barrier, but not irreversible cerebral damage through neuronal ischemia and death.³¹ Lloyd and associates³² showed similar S100 β values in 30 on-pump patients for coronary artery bypass surgery without any finding of cerebral damage. The lower air embolic load in this group, which lays bare the negative effect of age on cerebral outcome, can explain the phenomenon of age dependency of S100 β levels in the DBT group. In the placebo group all age brackets are similarly affected by microemboli, so that the age dependency is hidden.

Conclusion

Cardiopulmonary perfusion-aided coronary artery bypass surgery allows particulate and gaseous microemboli to enter the cerebral perfusion of the patient. Gaseous microemboli can be effectively removed by the DBT. However, the DBT is not able to prevent emboli originating from the aorta itself, although it is a helpful adjunct to reduce the total embolic load to the cerebral perfusion. Subclinical cerebral injury detectable by mild increases of S100 β protein disappears earlier after the operation when using the DBT.

TABLE 3. Number of HITS during different phases of cardiopulmonary bypass in the right or left middle cerebral artery

Parameter	Group	Mean	SD	Median	Range	P value
Total CPB time (min)	DBT	28.3	19.6	23	79	<.001
	Dummy	63.1	47.6	49	230	
Phase 1	DBT	5.8	7.3	4	39	<.05
	Dummy	16	15.4	13	76	
Phase 2	DBT	6.9	8.2	4	44	<.05
	Dummy	24.2	27.3	15	143	
Phase 3	DBT	2	2.4	1	10	NS
	Dummy	5.8	5.9	3	20	
Phase 4	DBT	13.5	15.5	7	60	NS
	Dummy	16.7	14.6	13	74	

CPB, Cardiopulmonary bypass; phase 1, from beginning of cardiopulmonary bypass to aortic crossclamping; phase 2, from aortic crossclamping to beginning of rewarming; phase 3, from rewarming to aortic declamping; phase 4, from aortic declamping to end of cardiopulmonary bypass; NS, not significant.

TABLE 4. S100 serum values

Parameter	Group	Mean	SD	Median	Range	P value
Preoperative	DBT	0	0	0	0	NS
	Dummy	0.009	0.0438	0	0.21	
End of operation	DBT	0.479	0.25	0.438	1.06	NS
	Dummy	0.502	0.339	0.415	1.495	
6 h later	DBT	0.057	0.101	0	0.24	NS
	Dummy	0.151	0.167	0.2	0.575	
48 h later	DBT	0.026	0.0831	0	0.315	<.05
	Dummy	0.184	0.244	0.2	0.89	
At discharge	DBT	0.0362	0.093	0	0.315	NS
	Dummy	0.0591	0.103	0	0.265	

Serum probes were sampled preoperatively (a day before the operation), at the end of the operation, 6 and 48 hours postoperatively, and at discharge from the hospital (3–6 days postoperatively).

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