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Microbubble Embolism as a Cause of Computed Tomographic Changes of the Brain after Cardiopulmonary Bypass

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Introduction

Since the brain is most susceptible to hypoxia and the arteries of the brain are endarteries, effects of hypoxia and microemboli during cardiopulmanary bypass(CPB) would reflexed in the brain more sensitively than any other organs.

Although occurrence of brain damage with clinical manifestation has greatly decreased with the modern techniques of cardiac surgery, subclinical or concealed changes of the brain might occur more frequently than has been expected. With the advent of computed tomography(CT), morphologic changes of the brain can be visualized easily in detail. In the present study, the effects of CPB on the brain morphology were clarified by means of CT scans of the brain. Moreover, the possible factors which may account for the CT changes of the brain after CPB were examined by the modern sophisticated apparatus (i.e. an ultrasonic microbubble detecting device and electron microscope) and the techniques and equipments of CPB which prevent these CT changes of the brain are presented.

I. CT Scans of the Brain after CPB

Patients and Methods

CT scans of the brain were performed in 70 patients with congenital heart diseases at Shizuoka Children's Hospital. To analyze the exact effects of CPB, 4 patients who had episodes of cardiac arrest or severe low cardiac output syndrome with sustained hypotension in the postoperative period were excluded from this study. Accordingly, detailed analysis of 66 patients comprises the basis of this study. There were 33 boys and 33 girls whose ages at operation ranged from 8 months to 10 years (mean 4.2+SD 2.6 years).

They were operated upon by means of conventional CPB with high flow (2.4 to 2.7 l/min/m^2 of body surface area) and mildly hypothermic perfusion (28° to 33° C). Defects repaired were

Key words: Computed tomography of the brain, Arterial line filter, Microbubble embolism, Ultrasonic microbubble measurement, Cardiopulmonary bypass.
索引語：脳CT，送血回路フィルター，微小気泡塞栓，超音波気泡計測，人工心肺.
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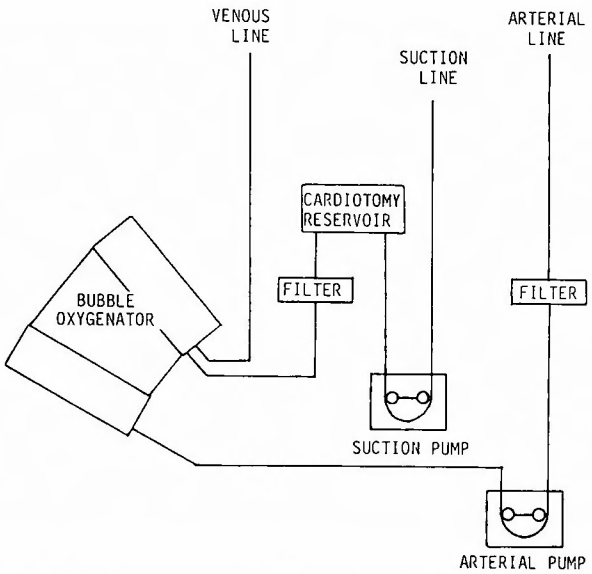


Fig. 1. Cardiopulmonary bypass circuit with a bubble oxygenator

ventricular septal defects in 27, atrial septal defects in 23, tetralogy of Fallot in 7, and miscellaneous lesions in 9. Bubble oxygenators (Temptrol Q-110 or Q-130, Bentley Laboratories Inc., Irvine, Calif.) were used in 38 patients and membrane oxygenators (Kolobow, SciMed Life

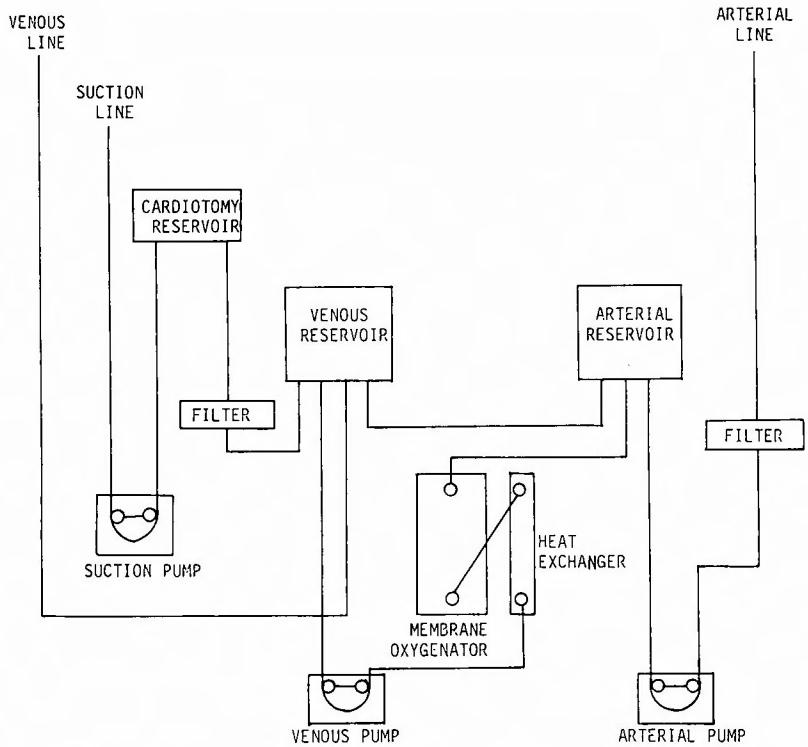


Fig. 2. Cardiopulmonary bypass circuit with a membrane oxygenator

Table 1. Priming Contents of Cardiopulmonary Bypass

acid-citrate-dextrose blood	1200 ml
3% Dextran in Lactate-Ringer(pH 8)	30 ml/kg
20% Mannitol	5 ml/kg
7% $NaHCO_3$	20 ml
aprotinin	10 ml
heparin	1000 unit/200 ml of ACD blood
8.5% calcium gluconate	5 ml/200 ml of ACD blood

System, Ins., Mineapolis, Minn.) in 28. The cardiopulmonary bypass circuit containing a bubble oxygenator is illustrated in Fig. 1, and that containing a membrane oxygenator is illustrated in Fig. 2. Priming contents of cardiopulmonary bypass circuit is listed in table 1. Polyester screen blood filters of 40 μ pore size were used during blood priming (Pall filter Model SQ40. Pall Corporation, Glen Cove, N. Y.) and in the suction line (Pall filter Model EC3840) in all patients. In the arterial line, woven fabric blood filters of 20 μ pore size (Intersept 1330, Johnson & Johnson Products, Inc., New Brunswick, N. J.) were inserted in 41 patients and polyester blood filters of 40 μ pore size (Pall filter Model EC3840) were inserted in 14; no filters were used in the remaining 11.

CT scans of the brain were performed on an EMI 1010s 160 matrix head scanner before and after operation. The first postoperative scans were obtained from 19 to 49 days (mean 29±SD 6 days) after operation when the patients had fully recovered from the operation and had neither restriction of fluid intake nor any medication. When abnormalities were noted at the first scans, serial scans were performed up to 11 months after the operation. CT scans of the brain and clinical neurologic findings including states of consciousness, seizures, choreo-athetosis, occular signs, and disturbances of refrexes were evaluated by a pediatric neurologist.

Table 2. Computed tomographic (CT) scans of the brain after cardioupulmonary bypass

Filters in arterial lines	No. of cases	No. with CT changes	Duration of CPB (min)	
			Mean± SD	Range
Bubble oxygenator group				
No filters	5	1	47.4±20.5	(31- 81)
40 μ filters	8	3	67.8±19.5	(42- 96)
No filters+40 μ filters	13	4 (30.8%)*	60.2±21.4†	(31- 96)
20 μ filters	25	0 (0%)*	66.5±37.1†	(26-180)
Total	38	4 (10.5%)	64.3±32.4§	(26-180)
Membrane oxygenator group				
No filters	6	0	109.3±50.7	(60-189)
40 μ filters	6	0	80.3±19.9	(58-102)
20 μ filters	16	0	92.8±35.9	(44-176)
Total	28	0 (0%)	93.7±36.9§	(44-189)

* $p<0.01$
† Not significant
§ $p<0.01$

Results

(1) Bubble oxygenator group

Four of 38 patients (10.5%) operated upon with bubble oxygenators showed similar postoperative CT changes (Table 2), such as dilatation of the lateral ventricles, the third ventricle,

Table 3. Duration of hypotension, i.e., mean arterial pressure below 40 and 50 mmHg, during cardiopulmonary bypass

	No. of cases	Duration of hypotension (min) below 40 mmHg	Duration of hypotension (min) below 50 mmHg
Bubble oxygenator group			
Without CT changes	34	2.4±4.3*	11.3± 9.8†
With CT changes	4	5.3±7.3*	13.7±13.6†
Membrane oxygenator group			
Without CT changes	28	2.2±5.4*	8.9±12.9†
With CT changes	0	—	—

* Difference not significant
† Difference not significant

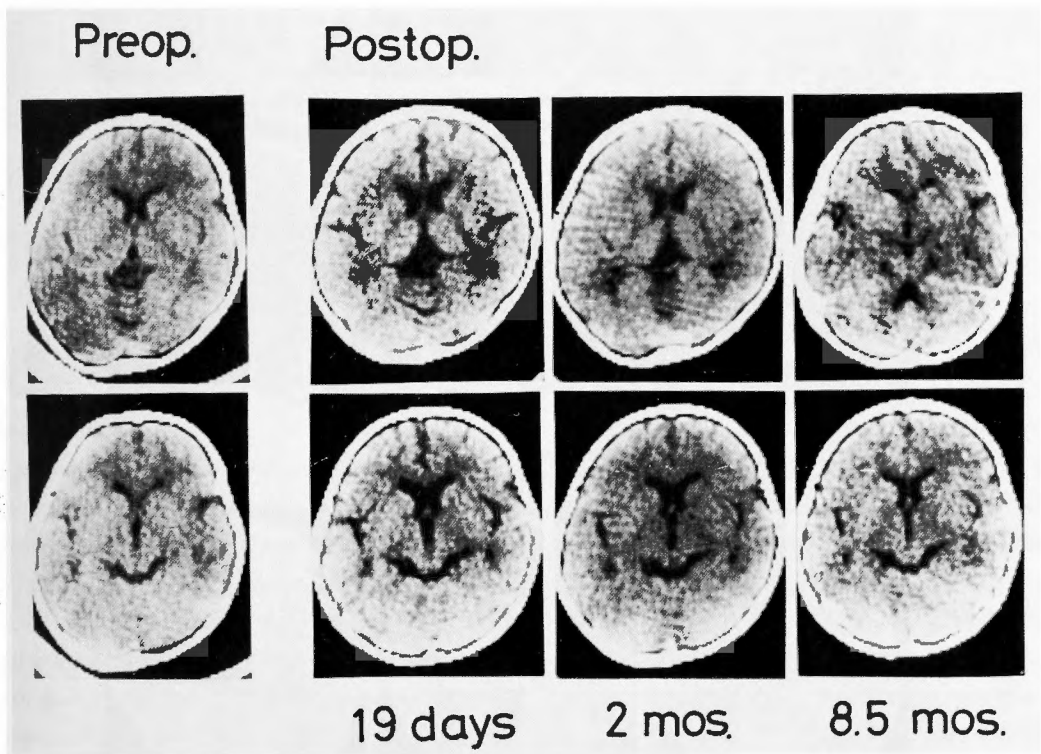


Fig. 3. CT scans of the brain of a 2.7-year-old girl with tetralogy of Fallot who underwent total correction during 96 minutes of cardiopulmonary bypass with a bubble oxygenator; a 40μ filter was in place in the arterial line. CT scans 19 days after operation showed mild-to-moderate enlargement of the internal and external cerebrospinal fluid space. CT scans 2 months after operation showed some improvements, and scans 8.5 months after operation showed recovery to the preoperative levels.

the fourth ventricle, the Sylvian fissures, the interhemispheric fissures, and the cortical sulci. They had no clinical symptoms and signs of neurologic disorders. The changes were seen in one of five patients without filters in the arterial line, in three of eight with 40μ filters, and in none of 25 with 20 μ filters in the arterial line. The incidence of CT changes was significant between the patients with 20 μ filters and the others including the patients with 40μ filters and those without filters ($p<0.05$). The duration of CPB was 66.5±37.1(SD) minutes in 25 patients with 20 μ filters and 60.2±21.4(SD) minutes in 13 patients with 40μ filters or without filters. The difference was not significant. All three patients who were perfused for more than 80 minutes and had 40 μ filters or no filters in the arterial lines showed postoperative changes, whereas none of the three with 20 μ filters who were perfused for more than 80 minutes were affected (Table 2). The duration of hypotensive periods in which mean arterial pressure was less than 40 and 50 mmHg during CPB was not significantly different in the affected patients as compaired with the unaffected patients (Table 3). In all four patients who showed CT changes at the first postoperative study, serial scans obtained 6 months to 8 months after operation revealed recovery to the preoperative levels. CT scans of affected and unaffected patients are shown in Figs. 3 and 4.

(2) Membrane oxygenator group

None of 28 patients operated upon with membrane oxygenators showed postoperative CT

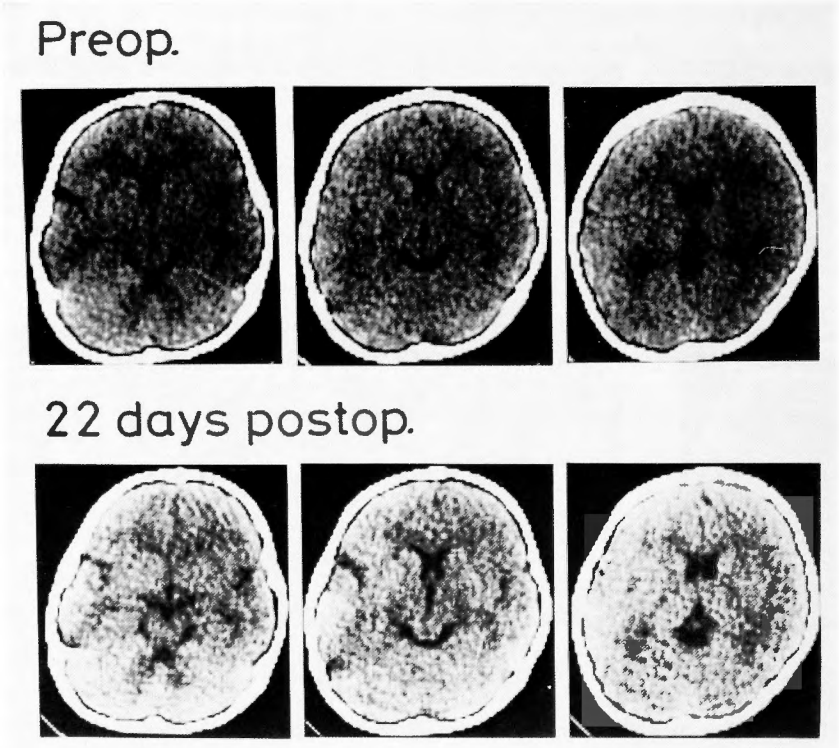


Fig. 4. Preoperative and postopeative CT scans of the brain of a 4.3-year-old girl with congenital mitral regurgitation who underwent annuloplasty during 116 minutes of cardiopulmonary bypass with a bubble oxygenator; a 20 μ filter was in place in the arterial line. No postoperative changes were noted.

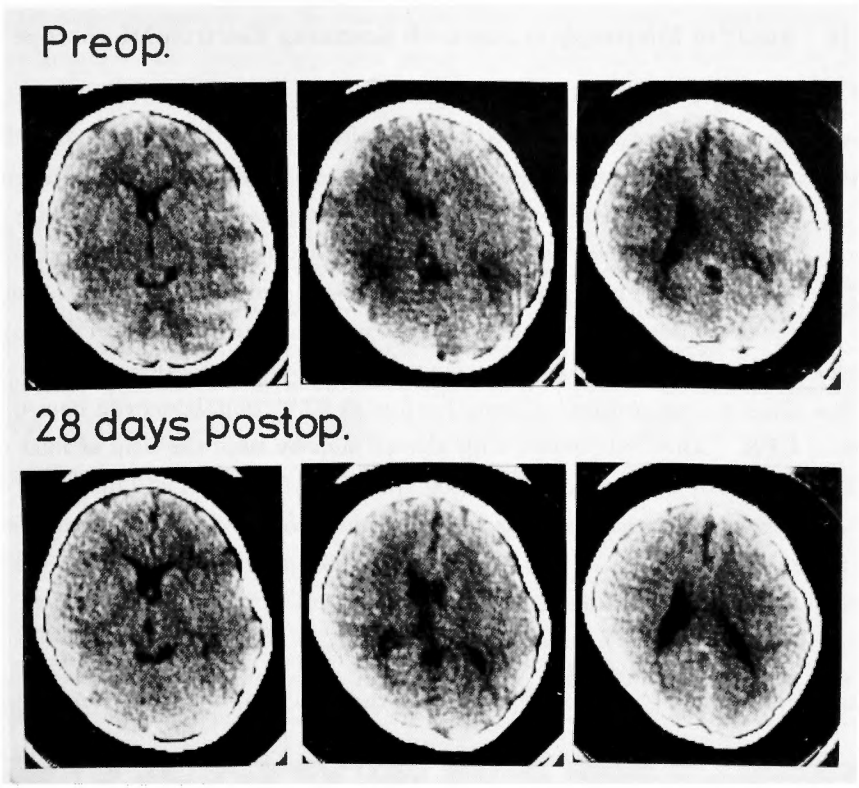


Fig. 5. Preoperative and postoperative CT scans of the brain of a 7-year-old girl with tetralogy of Fallot. She had total corredtion combined with closure of a Waterstone shunt and pulmonary valve replacement. Cardiopulmonary bypass with a membrane oxygenator lasted 189 minutes. There was no filter in the arterial line. No postoperative changes were noted.

changes or clinical symptoms and signs of neurologic disorders. Six patients were perfused without the use of filters, six with 40 μ filters, and 16 with 20 μ filters in the arterial line (Table 2). The presence of filters in the arterial line and the kind of filters had no relation to postoperative CT changes. The duration of CPB was 93.7 ± 36.9 (SD) minutes and was significantly longer than in the bubble oxygenator group ($p < 0.01$). The duration of hypotensive periods in which mean arterial pressure was less than 40 and 50 mmHg during CPB was not significantly different from that in the bubble oxygenator group (Table 2). Fig. 5 shows an example of this group.

In brief a 20 μ filter in the arterial line prevented CT changes of the brain after CPB with bubble oxygenators, while absence of filter or a 40 μ filter failed. In the membrane oxygenator group no CT changes occurred regardless of the presence or the kind of filters in the arterial line. Consequently embolism of microaggregates or microbubbles which were generated in the bubble oxygenator and were trapped by a 20 μ filter but not by a 40 μ filter were suspected as the cause of CT changes of the brain after CPB.

II. Study of Microaggregates with Scanning Electron Microscope

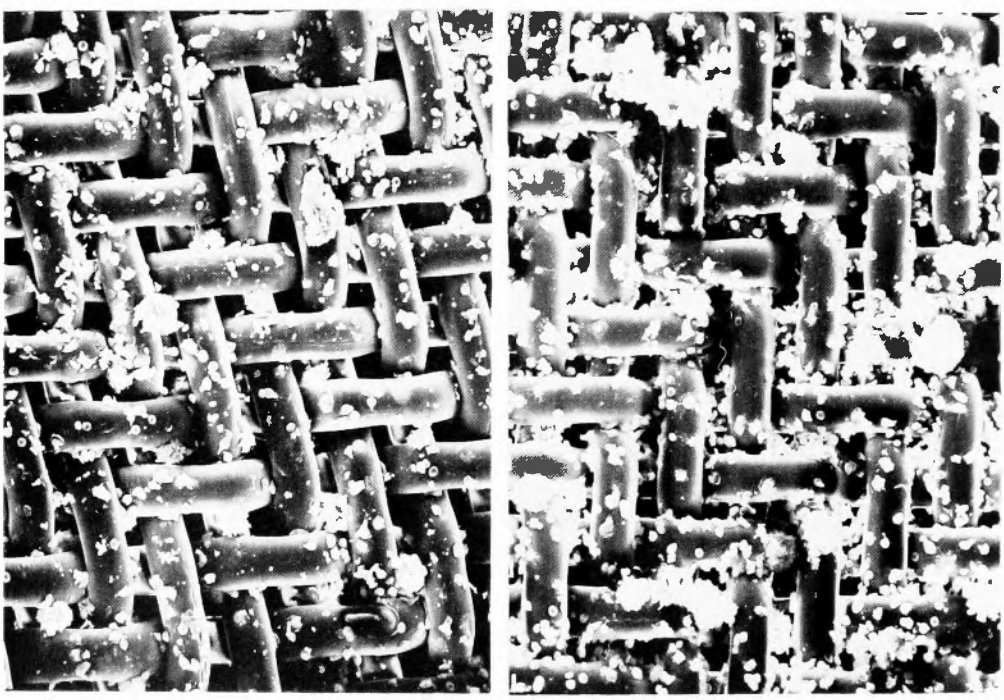
Materials and Methods

To detect the microaggregates trapped by 20 μ filters, the surface of the 20 μ filters in the arterial line were surveyed with scanning electron microscope (JSM-T200, Japan Electron Optics Laboratory CO., LTD) in nine cases with bubble oxygenators, and in nine cases with membrane oxygenators. The total blood volume which had passed through the filter during CPB was averaged 116.2±56.8(SD) liters in the bubble oxygenator group and 99.3±29.8 liters in the membrane oxygenator group and no significant difference was present between these two groups. The priming contents and methods of CPB were same as those forementioned.

The 20 μ filters in the arterial line were fixed with 0.5% glutalaldehyde immediately after termination of CPB. After dehydrated with alcohol step by step, the strip of filter (5×5 mm) was coated with gold by ion sputter (JFC-1000, Japan Electron Optics Laboratory Co., Ltd), and then was surveyed by the scanning electron microscope. With 200 magnification, the number of microaggregates deposited in random 10 fields of the strip was counted and compaired between these two groups.

Results

The number of microaggregates depositted on the 20 μ filter was averaged 9.6±2.9 pieces/



(a) (b)

Fig. 6. No significant difference was recognized in the number of microaggregates deposited in the 20 μ filters between the bubble oxygenator group (a) and the membrane oxygenator group (b).

fileld of 200 magnification in the bubble oxygenator group, and 12.1±3.9 pieces/filed of 200 magnification in the membrane oxygenator group. Microaggregates deposited on the filter were revealed to be platelets, some of which contained RBC and/or WBC (Fig. 6).

III. Study of Microbubbles with Ultrasonic Microbubble Detecting Device

With the ultrasonic microbubble detecting device ("Microbubble Activity Monitor TM 8", Technique Laboratories Ltd.), the number and the size of microbubbles in the arterial line of the CPB circuit were measured in the clinical cases. This equipment consists of a compact electronic unit and a small light-weight detecting head which clamps on to the external surface of the polyvinyl chloride or silicon rubber tubing (Fig. 7). The detectable bubble size range is 10–1000 μ.

1. Test of Reliability of Microbubble Activity Monitor

Before employing Microbubble Activity Monitor in the clinical study, the reliability of this monitor was tested in the following three points.

First, it was tested whether Microbubble Activity Monitor indicates 0 counts when blood contains no bubbles. Carbondioxide, which is easily soluble in the water or blood, may produce scanty numbers of microbubbles when introduced into the bubble oxygenator. It was tested whether the microbubble counts measured by Microbubble Activity Monitor reduced to 0 level when carbon dioxide was introduced into the bubble oxygenator. Using the test circuit composed

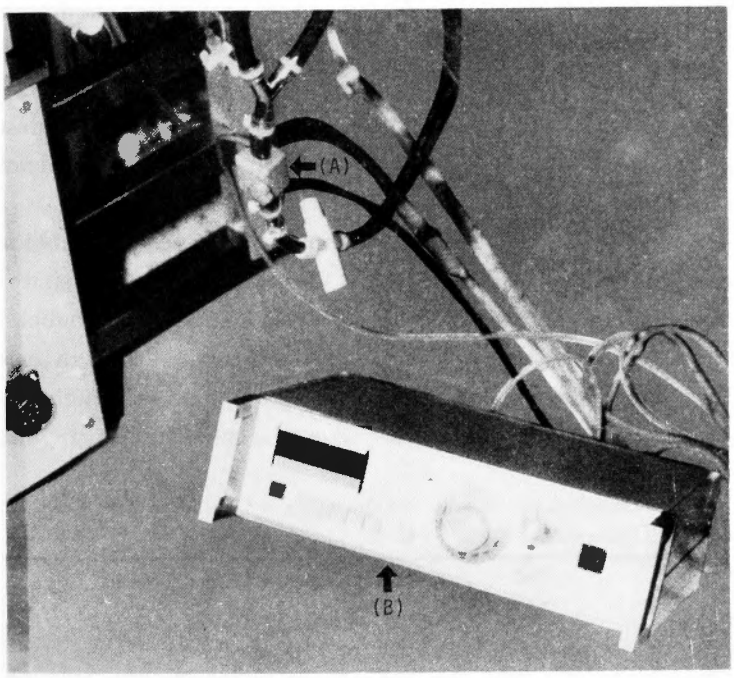


Fig. 7. "Microbubble Activity Monitor TM 8"
This equipment consists of a small detecting head (A) and a compact electronic unit (B).

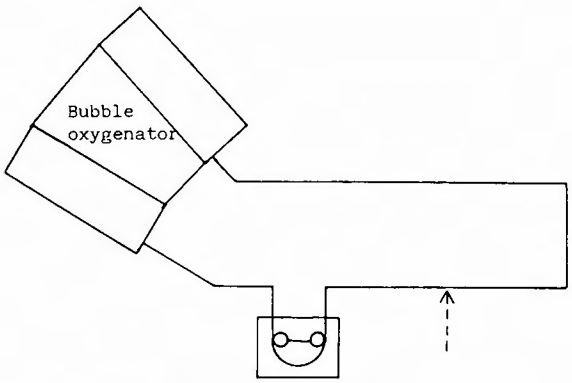


Fig. 8. Test circuit for zero calibration
- -- indicates the microbubble counted opint.

of a bubble oxygenator and a closed loop of tubing (Fig. 8), oxygen was first introducde into the oxygenator with oxygen flow of 1 l/min and blood flow of 2 l/min and microbubble counts and sizes were measured by Microbubble Activity Monitor. Then oxygen was replaced by carbon dioxide with the flow of 1 l/min and microbubble counts and sizes were measured. As listed in Table 4, a considerable number of microbubbles up to 400 μ in size were measured when oxygen was introduced into the bubble oxygenator. While when carbon dioxide was introduced into the same oxygenator, the microbubble counts and sizes soon reduced to nearly 0 level.

Second, the accuracy of microbubble sizes measured by Microbubble Activity Monitor was tested. The test circuit was composed of a bubble oxygenator, closed circuit of tubing and 40 μ filter (Fig. 9). The microbubble counts and sizes were measured at two points: upstream and downstream sites of a filter. The results are diagrammed on Fig. 10. With relatively low blood flow and oxygen flow, microbubbles of various sizes up to 200 μ were detected upstream of a filter, while the majority of microbubbles detected downstream of a filter by Microbubble Activity Monitor was under 40 μ in size.

Third, to estimate the linearity between the actual number of microbubbles and the microbubble counts measured by Microbubble Activity Monitor, the following study was performed. The equally bifurcated tubes were settled in the test circuit composed of a bubble oxygenator and a closed circuit (Fig. 11). In this test circuit, microbubbles may pass through the equally bifurcated tubes in half and half. Consequently microbubbles which pass through the one side of the bifurcated tubes may arise to twice in number when the other side of the bifurcated tubes is

Table 4. Microbubble counts with introducing O_2 or CO_2 into a bubble oxygenator.
Blood flow: 2 liter/min

	Microbubble counts per second					
	10-30 μ	30-50 μ	50-100 μ	100-200 μ	200-300 μ	300-400 μ
O_2 1 liter/min	2.3±2.9	20±6.2	78±13	69±18	29±7.1	8.4±4.9
CO_2 1 liter/min	1.6±1.9	0.4±0.5	0	0	0	0

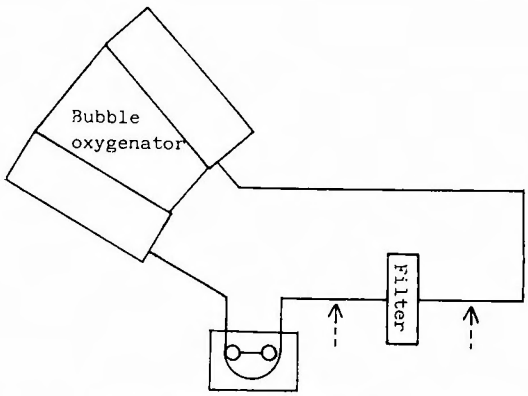


Fig. 9. Test circuit for size calibration
←– indicates the microbubble counted points.

clamped. First, microbubble counts and sizes were measured at the one side of the bifurcated tubes with the other side opened. Then with clamping the other side of the bifurcated tubes, microbubble counts and sizes were measured at the one side of the bifurcated tubes. The results were diagrammed in Fig. 12. It was revealed that microbubbles of each size measured at one side of the bifurcated tubes arose nearly twice in number with clamping the other side of the bifurcated tubes. These measurements were performed by changing the blood or oxygen flow,

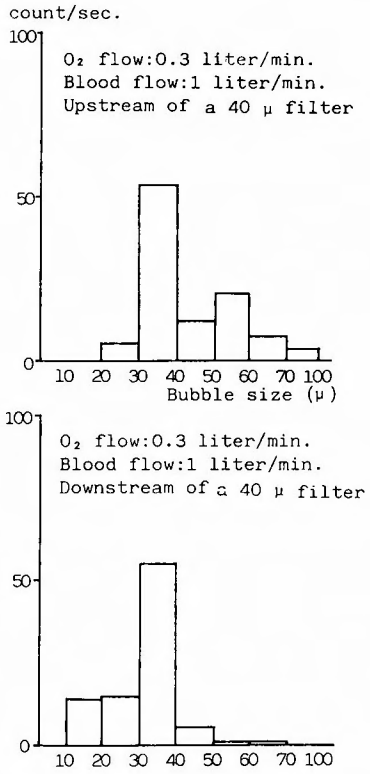


Fig. 10. Results of size calibration

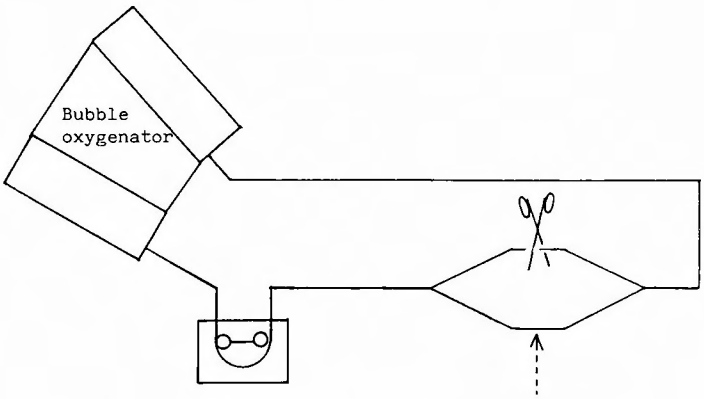


Fig. 11. Test circuit for count calibration
←— indicates the microbubble counted point.

and the similar results were obtained.

From the above mentioned tests, this Microbubble Activity Monitor proved to be accurate in the measurements of the numbers and sizes of microbubbles.

2. Clinical Study of Microbubble Measurement by the Ultrasonic Microbubble Detecting Device in the Extracorporeal Circulation

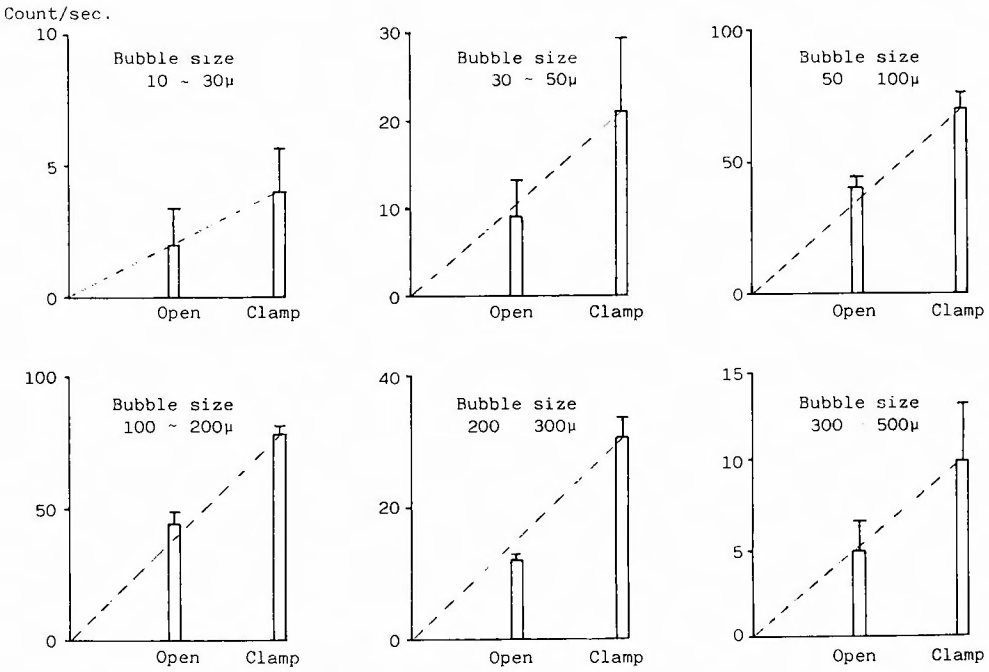


Fig. 12. Results of microbubble count calibration
O_2 flow: 1 liter/min Blood flow: 2 liter/min
Microbubbles of each size (10～30 μ, 30～50 μ, 50～100 μ, 100～200 μ, 200～300 μ, 300～500μ) mesaured at one side of the bifurcated tubes of the test circuit (Fig. 11) arose nearly twice in number with clamping the other side of the bifurcated tubes.

Materials and Methods

The clinical study of microbubble measurement by Microbubble Activity Monitor TM 8 was performed in 34 patients. Twenty-four patients, from 18 months to 79 months of age (medium 43), weighing from 7.1 to 16.9 kg (medium 11.9), were perfused with a bubble oxygenator. Ten patients, from 34 to 91 months (medium 72), weighing from 8.1 to 24.4 kg (medium 16.9), were perfused with a membrane oxygenator. The priming contents and methods of perfusion were the same as forementioned.

A 40 μ filter and a 20 μ filter were settled in the arterial line parellel to the original arterial line (Fig. 13). The detecting head of Microbubble Activity Monitor was placed in the arterial line downstream of these filters. The number of microbubbles downstream of each line which contained a 40 μ filter or 20 μ filter or no filter were counted, by clamping the other two lines. Each number of microbubbles of 10–30 μ, 30–40 μ, 40–50 μ, 50–70 μ, 70–100 μ, 100–200 μ, 200–300 μ in diameter was counted for 10 seconds with each line which contained a 40μ filter or 20μ filter or no filter. Counts per 10 seconds were converted to counts per liter of perfusate by multiplying by flow rate to compare with other cases.

Results

(1) Correlation between PaO_2 and volume of microbubbles

It is probable that PaO_2 may affect the volume of microbubbles; the product of microbubble sizes and counts. To confirm correlation between PaO_2 and the volume of microbubbles, statistical analysis was performed.

The volume of microbubbles of each case was calculated by the following way. A collection of 10–30 μ microbubbles was regarded as a collection of 20 μ microbubbles, and the volume of a collection of 10–30 μ microbubbles was calculated by the following formula; (number of 10–

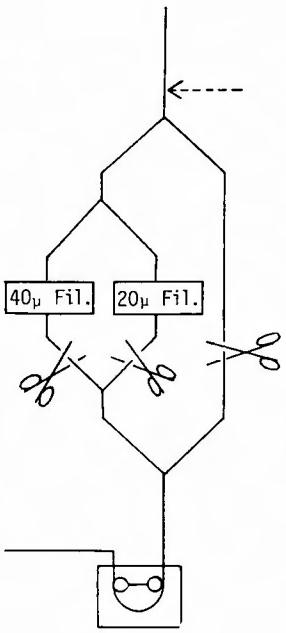


Fig. 13. Arterial line for clinical study of microbubble measurenemt.
←— indicates the microbubble counted point.

30 μ microbubbles) $\times 4/3 \times \pi \times (20/2)^3 \mu^3$. Similarly the volume of a collection of the other size microbubbles was calculated and totalized in each case.

There proved to be a positive correlation between PaO_2 and the volume of microbubbles in the bubble oxygenator group, that is the higher the PaO_2, the more and larger microbubbles are detected in the arterial line. This relationship was presented by the following formula and diagrammed in Fig. 14-1; $y=0.0316\times10^{0.00274x}$, $r=0.692$, $p<0.001$, (y: the volume of microbubbles (mm^3/liter), x; PaO_2 (mmHg))

In the membrane oxygenator group, the volume of microbubbles was not correlated with PaO_2 ($r=0.003$) (Fig. 14-2).

(2) Comparison of microbubble counts and sizes among three groups

It was revealed that the volume of microbubbles which was generated in a bubble oxygenator was greatly influenced by PaO_2. Hence the bubble oxygenator group was divided into two groups; the group with PaO_2 under 250 mmHg, and the other group with PaO_2 over 250 mmHg. There was no correlation between PaO_2 and the volume of microbubbles in the membrane oxygenator group, the membrane oxygenator group was regarded as one group regardless of PaO_2. Consequently the results of microbubble measurement were analyzed in three groups; group 1 (bubble oxygenator with PaO_2 under 250 mmHg), group 2 (bubble oxygenator with PaO_2 over 250 mmHg), group 3 (membrane oxygenator), and compared among these groups (Table 5).

a) Microbubble counts and sizes with no filter

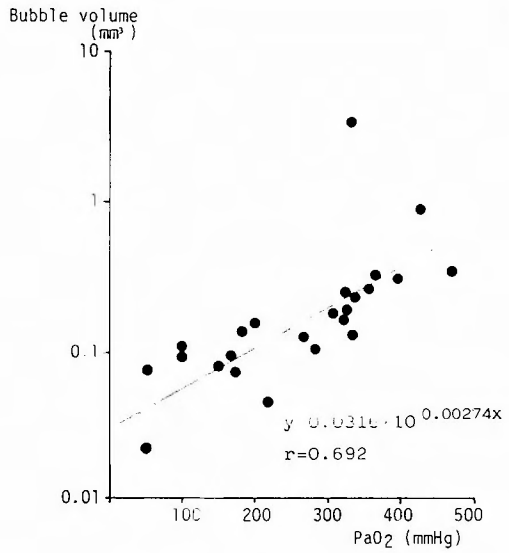


Fig. 14-1.

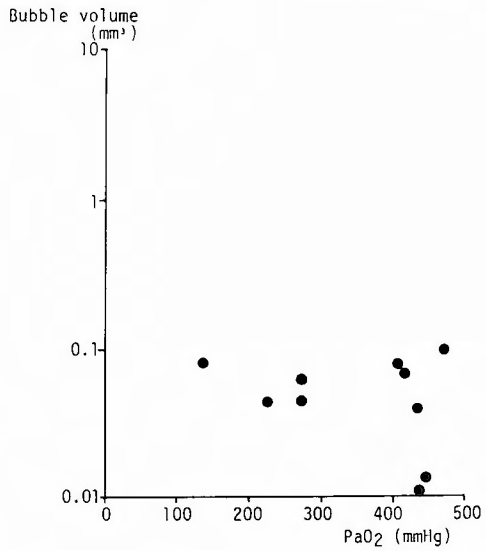


Fig. 14-2.

Fig. 14-1. The relationship of microbubble volume to PaO_2 in the clinical cases of cardiopulmonary bypass with a bubble oxygenator. There proved to be a positive correlation between the volume of microbubbles and PaO_2 in the bubble oxygenator group.

Fig. 14-2. The relationship of microbubble volume to PaO_2 in the clinical cases of cardiopulmonary bypass with a membrane oxygenator. In the membrane oxygenator group the volume of microbubbles was not correlated with PaO_2 ($r=0.003$).

Table 5. Results of microbubble measurement in the clinical study

Group 1 (Bubble oxygenator with PaO_2 under 250 mmHg, $PaO_2=140\pm61$ mmHg, n=10)

	10~30 μ	30~40 μ	40~50 μ	50~70 μ	70~100 μ	100~200 μ	200~300 μ
No filters	1185±1131	2672±1628	384±424	60.5±73.9	4.6±10.8	0	0
40 μ filters	665±600	1808±1887	127±301	0.4± 1.3	0	0	0
20 μ filters	838±793	1763±2111	50±100	1.4± 4.3	0	0	0

Group 2 (Bubble oxygenator with PaO_2 over 250 mmHg, $PaO_2=348\pm55$ mmHg, n=14)

	10~30 μ	30~40 μ	40~50 μ	50~70 μ	70~100 μ	100~200 μ	200~300 μ
No filters	1065±1454	3182±2406	1417±1068†	546±576††	147±292†††	110±359	7.1±27.4
40 μ filters	848±1110	3742±2614*	898±1104**	96.5±130***	7.0±25.7	0.7±2.6	0
20 μ filters	895±1425	3631±3157	408±946§	7.2±24.5§§	0	0	0

Group 3 (Membrane oxygenator, $PaO_2=395\pm139$ mmHg, n=10)

	10~30 μ	30~40 μ	40~50 μ	50~70 μ	70~100 μ	100~200 μ	200~300 μ
No filters	2456±2931	2026±1320*	108±100†**	10.9±24.7††***	0†††	0	0
40 μ filters	629±1287	2223±1865	300±789§	31.9±53.8§§	0	0	0
20 μ filters	741±645	2199±2568	495±870	12.7±26.0	0	0	0

† $p>0.001$, †† $p>0.005$, ††† $p>0.01$
* $p>0.05$, ** $p>0.025$, *** $p>0.05$
§,§§ Not significant

In group 1 a total of approximately 4,300 counts of microbubbles per liter of perfusate was detected. The largest microbubbles detected were 70–100 μ in size, and 30–40 μ microbubbles were detected most frequently.

In group 2 the microbubbles were much larger in size and in number than in group 1 and 3. A total of approximately 6,500 counts of microbubbles per liter of perfusate was detected. The largest microbubbles were 200–300 μ in size and the most frequently detected microbubbles were 30–40 μ in size. There proved to be significant differences in microbubble counts of 40–50 μ, 50–70 μ, 70–100 μ in size between group 2 and group 3.

In group 3 a total of approximately 4,600 counts of microbubbles per liter of perfusate was detected. The largest microbubbles detected were 50–70 μ in size and the most frequently detected microbubbles were 0–30 μ in size. Although fewer microbubbles over 50 μ in size were detected in group 3 than in group 1, no significant defference was present between these two groups.

b) Effect of blood filter on the microbubble counts and sizes

In group 1, both 40 and 20 μ filters recuced the microbubble counts of all sizes. With no filter the largest microbubbles detected were 70–100 μ in size, while with 40 or 20 μ filters the largest microbubbles detected were 50–70 μ in size. With the 40 μ filter only 50–70 μ microbubble counts were reduced significantly compared with no filter. With the 20 μ filter 40–50 μ and 50–70 μ microbubble counts were reduced significantly compared with no filter.

In group 2, 40 and 20 μ filters reduced the microbubble counts of all sizes except for 30–40 μ

microbubbles. The 20 μ filter reduced the microbubble counts more effectively than the 40 μ filter. With the 40 μ filter only 50–70 μ microbubbles were significantly smaller in number than with no filter, and 30–40 μ, 40–50 μ and 50–70 μ microbubbles downstream of the 40 μ filter were still significantly larger in number than those with no filter in group 3. With the 20 μ filter 40–50 μ and 50–70 μ microbubble counts significantly reduced than those with no filter, and this time the microbubble counts of all sizes were not significantly larger in number than those without filter in group 3.

In group 3, neither 40 or 20 μ filters reduced the microbubble counts significantly.

Discussion

With the modern technique and devices of CPB, the incidence of clinically detectable neurologic disorders following open cardiac surgery in children has become rare, but subclinical or concealed changes of the brain may occur.

In this report I performed CT scans of the brain in 66 patients before and after open heart surgery with cardiopulmonary bypass, and found that four of 66 patients showed decreases in brain mass on CT scans while no clinical symptoms or signs were manifested. These CT changes were manifested by dilatation of the lateral ventricles, the third ventricle, the fourth ventricle, the Sylvian fissures, the interhemispheric fissures, and the cortical sulci. It has been reported that cerebral atrophy occurs following cerebral anoxia[21], severe hypoglycemia[11], reduced cerebral blood flow[15] and prolonged steroid theraphy[3]. In the present study, the incidence of enlarged cerebrospinal fluid space was significantly higher in patients who had perfusion for more than 80 minutes with bubble oxygenators combined with 40 μ filters or no filters in their arterial lines. All patients perfused with membrane oxygenators and the patients with combined use of bubble oxygenators and 20 μ filters in the arterial line had no CT changes even with perfusion of more than 80 minutes. Although the actual pathological changes of the brain is unknown, the results of CT scans of the brain after CPB suggest that microbubbles and/or microaggregates which are arising in the bubble oxygenators and could be trapped by 20 μ filters but not by 40 μ filters may be responsible for these CT changes.

Arterial hypotension during perfusion may be an important factor in brain damage. WITOSZKA and his associates[22] reported that a fall in the mean arterial pressure to less than 45 mmHg for at least 5 minutes brought about postoperative neurologic abnormalities in adults. In the present study, arterial hypotension during perfusion and CT scans had no significant correlation, probably owing to high flow and mildly hypothermic perfusion used in the children.

Solid microembol;[5,8,10,14,16,17,20,23] platelet aggregates, fat emboli, fibrin debris and denatured protein, have been proved to be arising in the disc or bubble oxygenators and blamed as the cause of brain damage. However, the superiority of membrane oxygenators in solid microemboli formation (i.e. less solid microemboli formation with membrane oxygenators) is still controversial. HAYASHI[7] reported less microemboli formation in the membrane oxygenators compaired with the bubble oxygenators by Screen Filtration Pressure method, but this method does not clarify the type of microemboli; microbubbles or microaggregates. Ashmore and his

associates[1,2] showed that microaggregates form more readily in the disc oxygenators than in the membrane oxygenators by Screen Filtration Pressur method and by microscopic examination of the perfused lung. HILL and his associates[9] examined the incidence of fat and nonfat particulate microemboli in the brains of autopsy cases of patients who had died after cardiopulmonary bypass, and revealed no difference between the disc and membrane oxygenator group. DUTTON[6] and his associates studied the number of platelet aggregate emboli by counting and sizing platelets aggregate emboli trapped in the screen filter and reported that although a membrane oxygenator produced fewer emboli than a bubble oxygenator, the venous reservoir used with the membrane oxygenator produced more emboli than that used with the bubble oxygenator and the total number of platelet aggregate emboli produced in these two systems did not differ. The present survey of the 20 μ filters with a scanning electron microscope revealed no significant differences in the number of microaggregates trapped on the 20 μ filters between the bubble oxygenator group and the membrane oxygenator group. If microaggregates are responsible for the CT changes of the brain after CPB, the 20 μ filters used with a bubble oxygenator should trap more microaggregates than that used with a membrane oxygenator. Consequently, judging from previous reports and our present study, microaggregates arising in the bubble oxygenators could not be defined as the major cause of CT changes of the brain after CPB. Although those microaggregates might affect CT changes of the brain to some degree.

In the present study we measured the number and size of microbubbles in the arterial line of CPB with the ultrasonic microbubble detecting device (Microbubble Activity Monitor TM 8). Before clinical application, we tested this ultrasonic microbubble detecting device and it was proved that the number and size of microbubbles measured by this device are reliable. Introduction of carbon dioxide into the bubble oxygenator revealed that almost all of the paticles detected by this device are microbubbles. The results of measurement of microbubble counts and sizes in the clinical cases were consistent with the results obtained by CT scans of the brain after CPB. The study of CT chranges of the brain after CPB suggested that microbubbles and/or microaggregates which are arising in the bubble oxygenators and could be trapped by 20 μ filters but not by 40 μ filters may be responsible for these CT changes of the brain. The measurement of microbubble counts and sizes in the clinical cases revealed that a bubble oxygenator produced significantly more and larger microbubbles than a membrane oxygenator. A 20 μ filter reduced the numbers and sizes of the microbubbles to the level of those with the membrane oxygenators, but a 40 μ filter failed. Consequently the sufficient number of microbubbles arising in the bubble oxygenator was considered as the major cause of the CT changes of the brain after CPB.

PATTERSON and his associates[13,18,19] had been studied about microemboli during CPB with the use of ultrasound, and suggested that the brain damage was caused by microemboli arising in the bubble oxygenators. They speculated that most part of the emboli arising in the bubble oxygenators was microbubbles. CARLSON[4] and his associates reported the superiority of a membrane oxygenator over a bubble oxygenator in microbubble formation assessed by ultrasound and by Bender-Gestalt visual motor test. KARLSON[12] and his associates discriminated gas emboli and solid emboli in the CPB system by ultrasound. They reported that much more

gas emboli were produced in bubble oxygenators than in membrane oxygenators, and that there was a relatively small difference in the number of solid emboli between bubble and membrane oxygenators.

The present study of microbubble measurement showed that the volume of microbubbles; the product of microbubble counts and sizes, increased exponentially with PaO_2 in the bubble oxygenator group, and that microbubbles were much larger in size and number when PaO_2 during CPB with a bubble oxygenator was maintained more than 250 mmHg compared with those of a membrane oxygenator. Therefore, it is suggested that PaO_2 during CPB with a bubble oxygenator should be maintained under 250 mmHg, although it is not easy to maintain PaO_2 at an adequate level under 250 mmHg. Therefore, a 20 μ filter should be inserted in the arterial line of a bypass system when bubble oxygenators are used.

When a bubble oxygenator was used, a considerable number of microbubbles were detected even with the use of a 20 μ filter. When a membrane oxygenator was used in the clinical setting, a significant number of microbubbles were detected in some cases due to the microbubbles arising at the junction between the venous cannulas and the atrium or with injection into the bypass system or the patients[12]. However, in our preliminary study using a test circuit composed of a membrane oxygenator and a recirculation circuit, nearly zero count of microbubbles was recorded. Therefore, we now prefer to use a membrane oxygenator combined with a 20 μ filter rather than to use a bubble oxygenator combined with a 20 μ filter for open heart surgery which requires CPB of more than 80 minutes.

Conclusion

Effects of cardiopulmonary bypass (CPB) on the brain morphology were evaluated by computed tomography (CT). Of 66 children, 38 were perfused with bubble oxygenators and 28 with membrane oxygenators. In the bubble oxygenator group, all 25 children with a 20 μ filter in the arterial line showed no postoperative CT changes, whereas four of 13 patients (31%) with a 40 μ filter or without a filter showed decreases in brain mass on CT scans. In the membrane oxygenator group, none of 28 patients showed CT changes of the brain after CPB regardless of the presence or the kind of filters in the arterial line.

To clarify the cause of these CT changes of the brain after CPB, micro-solid emboli were surveyed by the scanning electron microscope and microbubbles by ultrasonic method. No significant difference was recognized in the number of microaggregates deposited in the 20 μ filters between the bubble and membrane oxygenator groups. Measurement of sizes and counts of the microbubbles by ultrasonic microbubble detecting device (Microbubble Activity Monitor TM 8) revealed that a bubble oxygenator generated microbubbles much lager in size and number than a membrane oxygenator, and that these microbubbles could be reduced to the level of those with a membrane oxygenator by a 20 μ filter inserted in the arterial line of the CPB system but not by a 40 μ filter. These facts are consistent with the results led from the study of CT changes of the brain after CPB. Consequently microbubbles arising in the bubble oxygenators were regarded as the major cause of CT changes of the brain after CPB.

When using a bubble oxygenator, a 20 μ filter should be inserted in the arterial line of the CPB system to prevent the CT changes of the brain, otherwise a membrane oxygenator should be employed.

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和文抄録

体外循環後の脳CT変化とその原因および予防法に関する研究

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臨床的に確認できるような開心術後の脳障害は減少して来ているが非顕性の軽微な脳障害発生の可能性は否定できない．また脳は低酸素に対して最も弱く，体外循環中の hypoxia や微小塞栓の影響が最も鋭敏に反映される臓器と考えられる．そこで体外循環による開心術前後の脳CT所見を比較し，体外循環が中枢神経系に及ぼす形態学的変化の有無及びその原因と予防法について検討した．

体外循環による開心術前後に脳CT検査を行った70例の内，術後に心停止や低血圧が長期間持続した重症低心拍出量症候群を示す4例を除く66例を対象とした．気泡型人工肺で送血回路に 20μ フィルターを併用した25例では術前後の脳CT所見に差を認めなかったが，気泡型人工肺で送血回路にフィルターを使用しなかったかあるいは 40μ フィルターを使用した13例ではそのうち4例に術後脳CT所見上びまん性の軽度の脳実質の縮小を認めた．これら4例中3例は体外循環時間が80分以上であった．膜型人工肺使用の28例では送血回路のフィルターの有無及び種類に関係なく術前後の脳CT所見に差を認めなかった．以上の結果より気泡型人工肺で生じる固形あるいは気泡による塞栓でかつ 40μ フィルターで捕捉できず 20μ フィルターで捕捉されるものが術後脳CT所見の悪化をもたらす主要な原因と推定され以下の検討を行った．

体外循環条件のほぼ等しい気泡型人工肺9例と膜型人工肺9例の送血回路に挿入した 20μ フィルターを走査電顕により比較した．200倍1視野中の血小板その他の凝集塊は気泡型人工肺使用群で9.6±2.9個，膜型人工肺使用群で12.1±3.9個であり両者間に有意差を認めなかった．

気泡型人工肺使用の24例及び膜型人工肺使用の10例において体外循環中の送血回路における微小気泡の数及び大きさを超音波微小気泡検出器 Technique-Laboratories 社の “Microbubble Activity Monitor TM 8” により計測した．臨床使用に先立ち予備実験により本計測器の信頼性を確認した．気泡型人工肺使用群では気泡数とその大きさは PaO_2 と正の相関を示し，PaO_2 の上昇に伴い気泡数とその体積の積である気泡量は指数関数的に増加し次式で表わされた．$y=0.0316\times10^{0.00274x}$，y：気泡量＝気泡数×気泡の体積 ($mm^3/l$)，x：$PaO_2$ (mmHg)，$r=0.692$，$p<0.001$．膜型人工肺使用群では気泡量と PaO_2 の間に相関を認めなかった ($r=0.003$)．気泡型人工肺で PaO_2 が 250 mmHg 以下の群では送血回路にフィルターを使用せずとも気泡の最も少なかった膜型人工肺使用群とほぼ同程度の気泡数及び大きさを保つことが可能であった．しかし気泡型人工肺で PaO_2 が 250 mmHg 以上の群では膜型人工肺群に比し 40～50μ，50～70μ．及び 70～100μ の気泡が有意に多量に認められ，40μ のフィルターの下流でも 30～40μ，40～50μ 及び 50～70μ の気泡は有意に多く，20μ フィルターによりはじめて膜型人工肺との間に有意差を認めなくなった．

以上より気泡型人工肺より発生する微小気泡が体外循環後脳CT悪化の主要な原因と考えられ，これを予防するには膜型人工肺を使用するかあるいは気泡型人工肺では送血回路に 20μ フィルターを挿入することが必要である．