

Cerebral protection during open-heart surgery¹

TORKEL ÅBERG AND MARGARETA KIHLGREN

From the Department of Thoracic Surgery, Uppsala University Hospital, and the Psychology Department, Uppsala University, Uppsala, Sweden

Åberg, T., and Kihlgren, Margareta (1977). *Thorax*, 32, 525-533. **Cerebral protection during open-heart surgery.** To reduce the incidence of cerebral damage after open-heart surgery measures were undertaken based on physiological principles and consideration of the possible injury caused by microemboli. Intellectual function was measured by psychometric tests before and after operation. The results were compared with those of an earlier series. There was a striking reduction in the incidence of neurological complications. There was also a considerable reduction in the degree of impairment of intellectual function previously shown to develop after open-heart surgery. However, there are still signs that cardiopulmonary bypass brings about subclinical cerebral injuries. The measures taken and their rationale are discussed. Psychometric testing is a useful method for evaluating the quality of cardiopulmonary bypass as it allows a quantitative assessment of postoperative cerebral function.

Of all the complications of open-heart surgery, derangement of cerebral function may nullify the benefit resulting from the operation. In the past, reports have been published describing large series of patients with a very high incidence of cerebral complications (Tufo *et al.*, 1970; Lee *et al.*, 1971; Branthwaite, 1972). It seems clear that many of these injuries are preventable and that the goal must be to eliminate all cerebral damage during cardiopulmonary bypass (Patrick *et al.*, 1958).

Between 1972 and 1974 the incidence of cerebral complications at the Thoracic Clinic in Uppsala after open-heart surgery was 14.5% (Åberg and Kihlgren, 1974). These patients (in this presentation called ECC group I) were investigated by psychometric methods. It was found that in patients who had no neurological symptoms or signs, intellectual impairment could be detected after the operation. This impairment was interpreted as indicative of cerebral damage. Thus what was clinically observed was but the tip of an iceberg. By analysing the psychometric results two major factors were identified among the cases with poor test results. The first factor was the perfusion time, and the second was the presence and degree of valvar calcification in those patients undergoing valve replacement. These findings suggest that microembolism was an important mechanism

underlying the intellectual impairment. The emboli seem to have two possible sources—the pump oxygenator and debris from the operating site.

With these findings as a background, we took several measures to try to eliminate the causes of the brain damage. This paper presents the results of these measures.

Patients

Between August 1974 and June 1976, 418 patients underwent open-heart surgery. Of these, 124 (ECC group II) were submitted to three selected psychometric tests a few days before, about one week after, and two months after the operation (Table 1).

The patients participating in the test programme were selected at random, with a few exceptions.

Table 1 Number of patients in different diagnostic groups

| Diagnosis | ECC group I | | ECC group II | |
|---------------------------|-------------|-----|--------------|-----|
| | No. | % | No. | % |
| Congenital heart disease | 15 | 15 | 9 | 8 |
| Coronary heart disease | 19 | 19 | 35 | 28 |
| Mitral valve disease | 22 | 22 | 28 | 23 |
| Aortic valve disease | 35 | 35 | 45 | 36 |
| Aortic and mitral disease | 7 | 7 | 7 | 6 |
| Total | 99 | 100 | 124 | 100 |

¹Supported by grants from the Swedish Medical Research Council and the Swedish National Association against Heart and Chest Diseases

Patients with a history of previous cerebral damage, especially hemiplegia, were not included as it had been shown that these patients are prone to show signs of intellectual damage after cardiopulmonary bypass (Åberg and Kihlgren, 1974). Only adults (>20 years) were included. A substantial proportion of the patients was excluded because they were undergoing emergency operations or had an insufficient knowledge of the Swedish language. Among the eligible patients, the workload of the tester (MK) decided which patients to include.

The timing of the first postoperative test varied according to the following criteria: the patient should be out of the intensive care unit, up and about, on oral nutrition, and having no stronger analgesic than aspirin. The mean interval between the operation and the first postoperative test was 6.5 (range 3–10) days.

Methods

For details of the investigation procedure see Åberg and Kihlgren (1974). Three psychometric tests were used: (1) test of verbal comprehension (Synonyms, Syn.) which had previously been shown to be fairly insensitive to the injuries occurring during bypass, and this was used as a holding test; (2) a test of visuospatial ability (Figure rotation test, F. rot.) which had been shown to be very sensitive to such injuries; and (3) a test of perceptual speed (Figure identification test, F. iden.) which had also proved to be sensitive. The combined series of tests was measured as the sum of the subtests (SS₃).

TECHNIQUE OF CARDIOPULMONARY BYPASS

Several radical changes were introduced during this period. They were all logical consequences of the suggestion that microemboli are responsible for much of the damage and are listed below:

- Inclusion of a micropore filter in the arterial line or within the oxygenator
- Inclusion of a micropore filter in the suction return line
- Change from disc oxygenator to bubble oxygenator
- Use of clear fluid prime
- Prolonged drainage of left ventricle before termination of bypass
- Decrease in length of perfusion time.

During the period of study of patients in ECC group II the following guide-lines were adopted in managing the period of cardiopulmonary bypass. The pump flow was maintained at 2.2–2.4 l m⁻² unless the perfusion pressure fell below 70 mmHg,

in which case flow was increased until perfusion pressure returned to around 70 mmHg. The ventilation of the oxygenator was adjusted to give a normal Po₂ and PCO₂. Improvements in surgical technique reduced the length of perfusion (Table 4). The requirement for donor blood was also reduced during this period (Table 4) and the priming of the heart-lung machine was carried out with clear fluids. Predominantly bubble oxygenators (Harvey or Galen) were used during the period of this study. These oxygenators include 100 µ micropore filters in their internal design. In 43 patients a 40 µ filter was included in the arterial line. A 40 µ filter was included in the suction return line. Pericardial and pleural blood was returned to the heart-lung circuit during perfusion, resulting in some of the reduction in blood requirements shown in Table 4. In both the original study of ECC group I and in this study (ECC group II) moderate hypothermia to 30°C was practised. For the original study (ECC group I) rewarming was carried out to 36°C but in the present study the patients were rewarmed to 38°C. During this longer rewarming period drainage of the left ventricle was continued with the heart beating in order to mobilise any intracardial debris or air and drain it into the heart-lung machine via the 40 µ filter in the suction return line.

Results

Compared with ECC group I a striking improvement occurred. Clinically detectable cerebral complications decreased from 14.5% to 5% during the first half of the period, and to 3% during the second half (Table 2). The number of patients who died with or from cerebral complications was 3 out of 114 (3%) in ECC group I and 1 out of 210 during the second half of the 1974–76 period.

Of the clinically recognised cerebral complications (Table 3), one was due to a large cerebral embolus from the left atrial appendage in a patient with atrial fibrillation who had a mitral valve replacement. One patient developed a Guillain-Barré syndrome two days after the opera-

Table 2 Percentage incidence of cerebral complications

| | EEC I | ECC II | |
|--|-------|----------|----------|
| | | 1st year | 2nd year |
| Cerebral complications | 14.5 | 5 | 3 |
| Dead with or from cerebral complications | 3 | | 0.5 |

Table 3 Diagnoses in cases with clinical cerebral complications

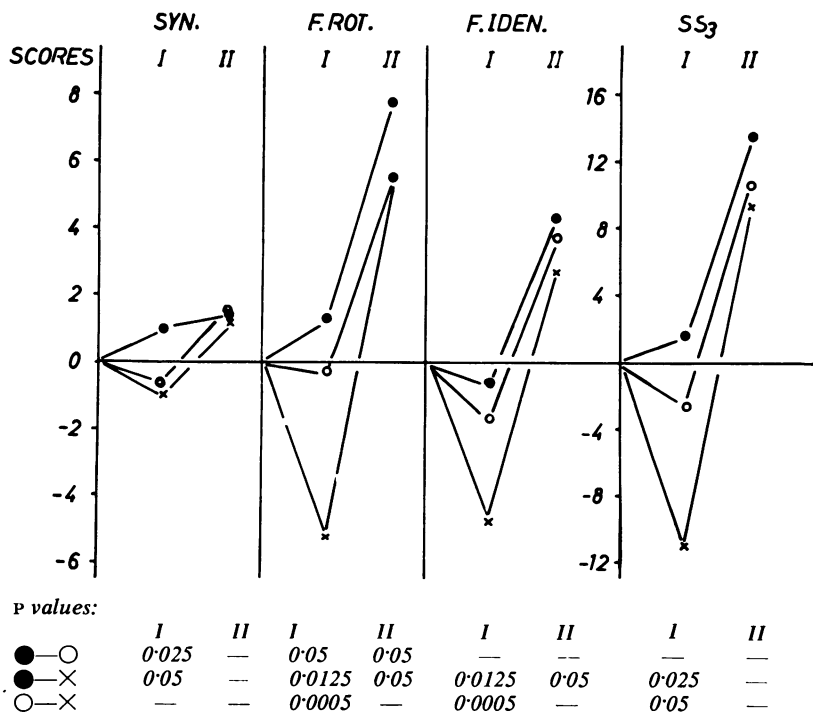
| |
|--|
| Aortic stenosis; confusion |
| Aortic stenosis; dizziness; no vestibular function |
| Aortic regurgitation; Guillain-Barré syndrome |
| Mitral stenosis; carotid embolus; died |
| Angina pectoris; delayed return of consciousness |

tion. Thus in only three patients were the causes of the cerebral complications possibly related to the perfusion and operation.

The psychometric test data also showed considerably better results (Fig. 1). In all three subtests there was an improvement compared with ECC group I. This was small in the verbal test but statistically highly significant in the test of visuo-spatial ability and the test of perceptual speed one week after the operation. The improvement still persisted two months after operation, although not to the same degree.

However, when the results were compared with those of 46 patients who were operated on for non-cardiac thoracic surgical disease (mostly lung resections) (Åberg and Kihlgren, 1974), it is clear that although they were much improved, ECC group II still showed signs of cerebral damage. This was evident in all subtests both at one week and at two months.

A number of statistical analyses which were performed on ECC group I were repeated on group II. As a rule the findings were similar although the test scores were now on a higher level, indicating less cerebral damage. Thus the same variation in test scores that was found among different diagnoses in ECC group I still prevailed in group II. The congenital cases (mostly atrial septal defect) suffered the least impairment, followed by coronary artery bypass cases, single valve replacements, and multiple valve replacements in order of increasing impairment of intellectual function (Fig. 2).



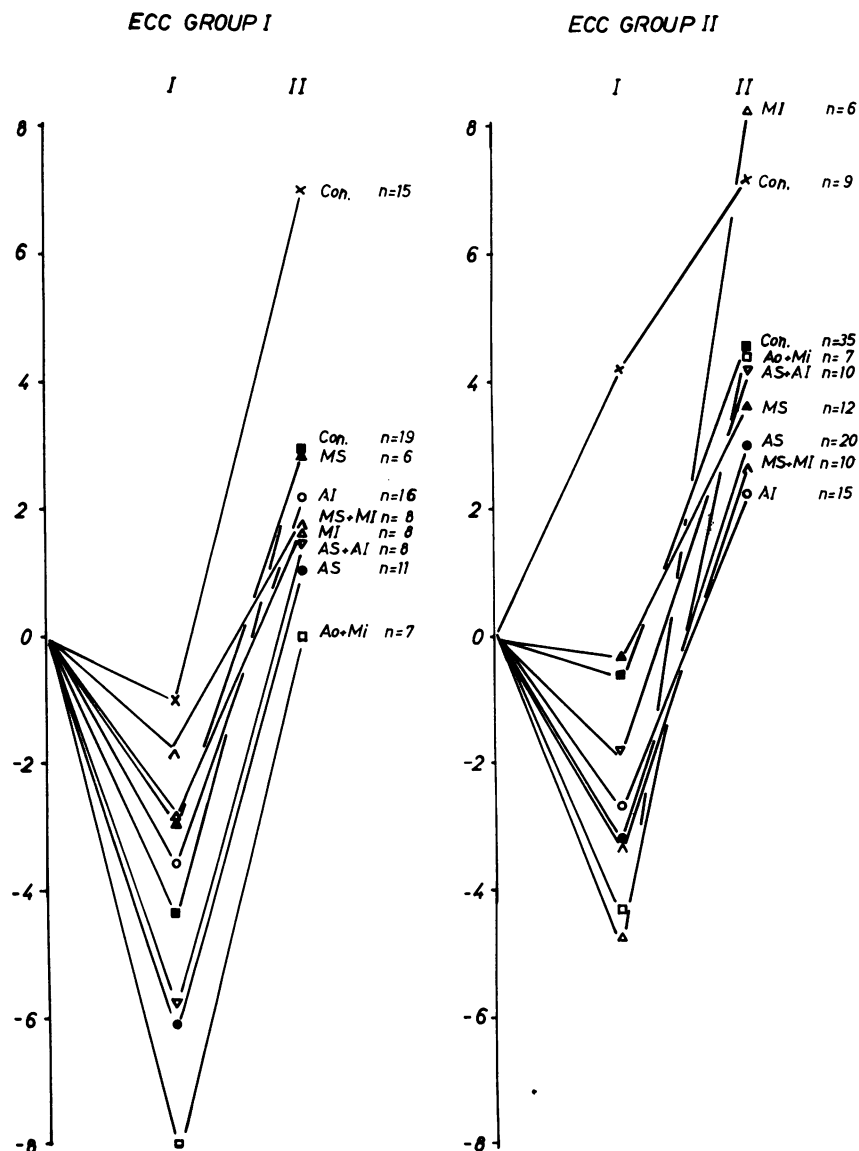


Fig. 2 Test results in different diagnostic groups in figure identification test. The general level in test scores has increased; several diagnoses show a marked improvement, whereas others show much less or no improvement.

The correlation with perfusion time found in ECC group I was found in group II, although weaker. Figure 3 shows the test results in the coronary bypass cases. In the short perfusions the results are indistinguishable from those of the comparison group. There is a significant difference in the results of the figure identification and synonym tests between those patients perfused

for less than 140 minutes and those perfused for more than 140 minutes in both groups I and II postoperatively. However, there was no longer a correlation between test scores and perfusion time in the valve replacement cases. This is probably due to a restriction of range, as most valve replacements now take about 90 (mean 89 ± 25) minutes on bypass.

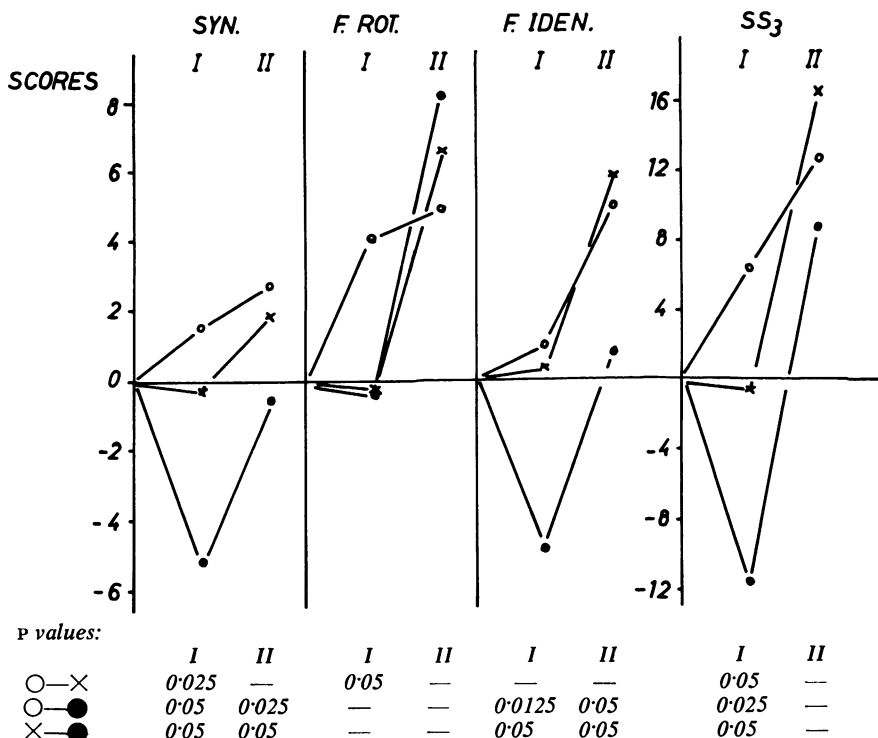


Fig. 3 Test results in coronary bypass patients divided into perfusion time: ○ <90 min perfusion (n=10); × 90–140 min perfusion (n=15); ● >140 min perfusion (n=6).

The correlation between test scores and presence and degree of valvar calcification in the removed valves found in ECC group I was not found in group II.

POSTOPERATIVE COURSE

During this period we also followed some other parameters (Table 4). Although the mean age of the patients has increased, there is a gratifying decrease in the length of time spent in the intensive care unit. The need for blood has also decreased. The patients are more alert, are routinely extubated on the morning after operation, require less special supervision, and are not as prone to get other complications (eg, pulmonary) as previously.

Table 4 Some clinical parameters (mean)

| | ECC I | ECC II |
|---------------------------------|-------|--------|
| Age (years) | 50 | 55 |
| Perfusion time (min) | 128 | 94 |
| Blood given (units) | 24 | 15 |
| Intensive care unit time (days) | 6.5 | 3.8 |

Discussion

The importance of cerebral protection during

cardiopulmonary bypass is now widely recognised. After an initial period when heart surgeons were mainly interested in patient survival, the incidence of neurological or psychiatric complications started to attract interest. During the mid-sixties considerable attention was devoted to psychiatric complications (Hazán, 1966; Kornfeld *et al.*, 1965). During the last few years several investigations have been published dealing with the presence or absence of cerebral complications. Mean arterial pressure during perfusion (Javid *et al.*, 1969), the patient's age, duration of perfusion, and a history of previous neurological damage (Branthwaite, 1972) have all been related to the occurrence of postoperative neurological dysfunction.

The need for more refined methods to evaluate cerebral function after cardiopulmonary bypass has been recognised by several workers. Lee *et al.* (1971) reported findings in 71 patients undergoing open-heart surgery. Included in the protocol were neurological, psychiatric, psychometric, and other clinical parameters. Among the clinical parameters tested, the following showed a statistically significant correlation with brain damage: duration of perfusion, hypotension, volume of blood

transfused, and insertion of a valve prosthesis. Frank *et al.* (1972) used a broad psychometric test battery on 49 patients. They found that patients who were very anxious before the operation showed significantly more improvement in the intelligence test afterwards. There was also suggestive, although not statistically significant, evidence that a longer time on cardiopulmonary bypass was associated with an increased inability to learn a test.

A visual motor test was used by Carlson *et al.* (1973) to judge the postoperative progress of patients after perfusions using membrane and bubble oxygenators. Although their results were not statistically significant, fewer patients in the membrane group showed impairment of postoperative function than those in the bubble oxygenator group.

In 1974, the findings in the present ECC group I were published (Åberg and Kihlgren, 1974). It was concluded that cardiopulmonary bypass as practised at that time brought about impairment in intellectual function, that this intellectual impairment probably reflected cerebral injury, and that most of the injuries were reversible but that permanent injuries do occur. A further detailed analysis showed that along with some minor factors there were two major factors associated with intellectual impairment, namely, time on perfusion and the presence and degree of valvar calcification. These findings suggested microembolism as a major mechanism underlying the intellectual impairment and that these emboli had two sources, the pump oxygenator and debris from the operation site.

Cardiopulmonary bypass is a multifactorial method of treatment. What is evident as a complication after the operation may be the result of several interacting factors. It seems important to try to divide cardiopulmonary bypass into its various components and to scrutinise these with special regard to the consequences of effects of microemboli. Furthermore, general physiological principles must be taken into consideration with respect to brain protection during cardiopulmonary bypass. The results of the present study in conjunction with the previous study allow us to consider some of the factors which may be involved.

FLOW

It is generally agreed that an adequate flow is essential during cardiopulmonary bypass in order to maintain organ viability. Inadequate flow has not been incriminated as a cause of cerebral damage because of the general acceptance of the

policy of maintaining a pump flow of 2.2–2.4 l m⁻² of body surface area. It is probable that the flow may be safely reduced during hypothermia, although precise data on this question are lacking.

BLOOD GASES

The role of the gas exchange device is to maintain the normal level of the blood gases. There seems to be a general opinion that both Po₂ and Pco₂ should be kept at physiological levels. The importance of not having the Po₂ too high is evident from the fact that a high oxygen/blood flow ratio in a bubble device has been reported to give a higher microembolus count and possibly to increase the oxygen toxicity (Kessler and Paterson, 1970).

PERFUSION PRESSURE

There is no general agreement about a safe level of arterial blood pressure during bypass. However, several studies have clearly shown that in patients with low arterial pressures there has been an increased incidence of cerebral complications (Javid *et al.*, 1969; Branthwaite, 1973), especially when the period of hypotension has been prolonged (Stockard *et al.*, 1973). Theoretical considerations lead to the supposition that an adequate arterial pressure is needed to overcome subclinical arteriosclerotic obstructions to cerebral flow. Increased age was found to be associated with an increased incidence of neurological complications in the patients studied by Branthwaite (1972). These patients may be assumed to have a greater degree of arteriosclerosis in their cerebral vessels. Previous cerebral damage, at least sometimes indicative of cerebrovascular disease, also carried a higher incidence of neurological complications (Branthwaite, 1972) and impairment in intellectual function (Åberg and Kihlgren, 1974). Raised preoperative systolic and diastolic arterial blood pressure was related to postoperative intellectual impairment (Åberg and Kihlgren, 1974). In our patients there is no correlation between the test results and the lowest arterial blood pressure during cardiopulmonary bypass, probably because of the policy already followed in the period of ECC group I of not allowing the arterial blood pressure to fall below 70 mmHg for any length of time.

Many centres regard cardiopulmonary bypass as a state of controlled shock and accept low arterial pressures with apparently good results. This question cannot be said to have been definitely settled. Most of the published data, however, point to the necessity of maintaining an adequate blood pressure, especially in old, hypertensive patients with known arteriosclerosis.

DURATION OF PERFUSION

The time factor is important in considering the physiological requirements. A normal patient will tolerate short periods of inadequate flow, pressure, and oxygenation. An extremely quick surgeon will be able to take short cuts across the physiological requirements that a slow surgeon may not permit himself. This element of time is probably one of the reasons for the discrepancies in policy, for instance, towards blood pressure, in different centres. As a general rule it must be stated that cardiopulmonary bypass is a hazardous procedure with many inherent risks and that its duration should be kept as short as possible.

USE OF STORED BLOOD

Donated blood always contains microemboli (Moseley and Doty, 1970; Wright, 1976). These are mostly platelet and leucocyte aggregates but fibrin is also present. Recent studies on the influence of donated blood upon the lung in massive blood transfusions have shown that the lungs have a good, though limited ability to act as a filter for these emboli (Goldiner *et al.*, 1972). Donated blood in the prime or added during bypass is not filtered in the lungs but enters the systemic arterial system directly. There is good evidence (Hill *et al.*, 1969; Patterson *et al.*, 1974) that particulate emboli harm the brain.

In addition, current cross-match techniques only take account of the donor and the recipient and do not consider any incompatibilities occurring between donors. It is not inconceivable that blood added to the heart-lung machine during the procedure may react with any other donated blood and set up microemboli. This situation would be more common in cases of massive blood transfusion or a large blood prime.

After consideration of these points we now prime the extracorporeal circuit with clear fluid in order to use as little blood as possible and, if blood has to be given, to filter it through a micro-pore filter.

THE OXYGENATOR

The oxygenator is known to be an important source of emboli. Silicone particles (Valentin and Vilhelmsen, 1976), cotton fibres and plastic chips (Reed *et al.*, 1974), platelet and other blood-formed particles (Solis *et al.*, 1975), and gaseous microbubbles (Gallagher and Pearson, 1973; Loop *et al.*, 1976) have all been shown to be delivered to the perfused patient. Improvements in the design of bubble oxygenators leading to decreased oxygen/blood ratios have already diminished gaseous emboli in bubble oxygenators (Simmons

et al., 1972). Investigations on the amount of particulate and gaseous emboli originating from several different types of oxygenators have given conflicting and confusing results (Kessler and Patterson, 1970; Simmons *et al.*, 1972; Solis *et al.*, 1975), partly because of difficult or unreliable methods. The membrane oxygenator is claimed to produce less particulate emboli than the bubble oxygenator (Solis *et al.*, 1975).

Our investigations (Åberg and Kihlgren, 1977) have shown that a disc oxygenator primed with blood and saline results in greater intellectual impairment than either of two different bubble oxygenators used with a clear fluid prime. Our present practice is to use bubble oxygenators primed with a clear fluid.

FILTRATION OF ARTERIAL BLOOD

Because oxygenators produce particulate emboli it is logical to try to eliminate the emboli by filtration. The inclusion of an arterial blood filter of a pore-size in the region of 40 μ has become popular (Osborn *et al.*, 1970; Skagseth *et al.*, 1974; Guidoin *et al.*, 1976). A filter has also been incorporated within several oxygenators. Carlson *et al.* (1973) showed in a small series that psychometric scores were improved when a filter was introduced into the arterial line. In our original study of patients in ECC group I (Åberg and Kihlgren, 1974), we demonstrated a reduction in the impairment of intellectual function when an arterial filter was used. This difference was only weakly significant ($P=0.05$).

Our present policy is to rely on the 100 μ filter incorporated in the oxygenator and not to add an additional filter in the arterial line (Heimbecker *et al.*, 1976). The use of filters is not the best way to circumvent the problem of microemboli from the heart-lung machine, and future developments must be directed to preventing the occurrence of emboli. Only by eliminating the source of microemboli can a high quality of cardiopulmonary bypass be provided.

SUCTION RETURN TO HEART-LUNG MACHINE

Several authors have identified the suction return as the source of most particulate emboli (Solis *et al.*, 1975; Clark *et al.*, 1976). These emboli include fibrin, fat, calcium, arteriosclerotic debris, and tissue as well as foreign material introduced by the operative equipment (talc, thread, dust, cloth particles, and even hair). Even if these emboli could be eliminated at the source by improved methods, a completely clean operative field will probably never be achieved. Effective filtration of the suc-

tion return blood is therefore essential at present and will probably remain so in the future.

The volume of suction return and thus the number of microemboli can be reduced by ischaemic cardiac arrest.

EMBOLI FROM OPERATIVE SITE

In ECC group I the presence and degree of valvar calcification proved to have a very marked influence on intellectual function. This correlation was no longer found in ECC group II. It must be concluded that the measures taken have been effective. Elimination of calcific emboli and of arteriosclerotic debris may be achieved by a high level of awareness and care by the use of proper operative equipment, especially suckers. It is essential to incorporate a mechanism for removing all the debris that has moved outside the visible field and indeed for all particles below the resolution power of the eye.

In our opinion, prolonged drainage of the left ventricle with the heart beating will considerably help in removing debris and air that might have lodged in the heart. The debris will be trapped in the suction return filters.

AIR EMBOLI FROM THE HEART

Gallagher and Pearson (1973) have shown that it is common to detect air emboli in the carotid artery when the ventricle begins to eject, but further studies to assess the relative importance of air embolism in the development of postoperative cerebral complications are needed. It may be safely stated that a small amount of air did not seem to have a deleterious effect on brain function. Using our psychometric tests the patients who had operations for congenital heart disease were indistinguishable from the comparison group. It may be equally safely stated that large volumes of air going to the brain may result in death or coma with long-term sequelae (Vanetti *et al.*, 1975). Air embolism from the opened heart cannot, however, be the only major cause of cerebral complications. If this did constitute the major cause, it should happen equally in all diagnostic groups where the heart is opened. This is not the case. There is furthermore a correlation between intellectual impairment and perfusion time. Our studies have not been able to pinpoint air emboli as a major source of intellectual impairment. One of the possible conclusions is that our air removal at the end of bypass has been effective, and it may be that our practice of prolonged drainage of the left ventricle with a beating heart significantly reduces the volume of cerebral air embolism.

The theory of microembolism as a major cause

of cerebral damage is mainly a mechanical theory which postulates blocked arterioles. There are findings which suggest a much more intricate and dynamic mechanism. Rådegran (1971) showed that vasoconstriction rather than intravascular obstruction was the cause of a raised pulmonary arterial pressure when platelet aggregation was induced. He suggested that microscopic demonstration of microemboli did not justify a conclusion that these emboli were the direct cause of simultaneously observed macrocirculatory changes. He postulated a biochemical substance with a smooth muscle contracting action, possibly delivered by the platelets themselves. Williams *et al.*, (1975), in a study on the fine structure of nervous tissues subjected to microembolism, concluded that the changes were due primarily to products of thrombosis and not to impaired nutrition consequent upon blockage of small vessels by microaggregates.

Our investigations show that it is possible to reach a low level of clinical cerebral complications and that measures based on physiological principles and directed at eliminating microemboli will yield good results. There is still, however, a definite incidence of debilitating cerebral complications and of subclinical degrees of brain damage. These must be abolished and, as Branthwaite (1975) puts it, 'there can be no room for complacency until this ideal has been achieved'.

References

- Åberg, T., and Kihlgren, M. (1974). Effect of open heart surgery on intellectual function. *Scandinavian Journal of Thoracic and Cardiovascular Surgery*, Supplement 15.
- Åberg, T., and Kihlgren, M. (1977). Cerebral protection during open heart surgery. A comparison between a disc oxygenator and two bubble oxygenators. *Journal of Cardiovascular Surgery*, in press.
- Branthwaite, M. A. (1972). Neurological damage related to open-heart surgery. *Thorax*, 27, 748-753.
- Branthwaite, M. A. (1973). Detection of neurological damage during open-heart surgery. *Thorax*, 28, 464-472.
- Branthwaite, M. A. (1975). Prevention of neurological damage during open-heart surgery. *Thorax*, 30, 258-261.
- Carlson, R. G., Landé, A. J., Landis, B., Rogoz, B., Baxter, J., Patterson, R. H., Jr., Stenzel, K., and Lillehei, C. W. (1973). The Landé-Edwards membrane oxygenator during heart surgery. *Journal of Thoracic and Cardiovascular Surgery*, 66, 894-905.
- Clark, R. E., Dietz, D. R., and Miller, J. G. (1976). Continuous detection of microemboli during cardiopulmonary bypass in animals and man. *Circulation*, 54, Supplement III, 74-78.
- Frank, K. A., Heller, S. S., Kornfeld, D. S., and

- Malm, J. R. (1972). Long-term effects of open-heart surgery on intellectual functioning. *Journal of Thoracic and Cardiovascular Surgery*, **64**, 811–815.
- Gallagher, E. G., and Pearson, D. T. (1973). Ultrasonic identification of sources of gaseous microemboli during open heart surgery. *Thorax*, **28**, 295–305.
- Goldiner, P. L., Howland, W. S., and Ray, C. (1972). Filter for prevention of microembolism during massive transfusions. *Anesthesia and Analgesia*, **51**, 717–725.
- Guidoin, R., Laperche, Y., Martin, L., and Awad, J. (1976). Disposable filters for microaggregate removal from extracorporeal circulation. *Journal of Thoracic and Cardiovascular Surgery*, **71**, 502–516.
- Hazán, S. J. (1966). Psychiatric complications following cardiac surgery. *Journal of Thoracic and Cardiovascular Surgery*, **51**, 307–325.
- Heimbecker, R., Robert, A., and McKenzie, F. N. (1976). The extra-corporeal pump filter—saint or sinner? *Annals of Thoracic Surgery*, **21**, 55–58.
- Hill, J. D., Aguilar, M. J., Baranco, A., de Lanerolle, P., and Gerbode, F. (1969). Neuropathological manifestations of cardiac surgery. *Annals of Thoracic Surgery*, **7**, 409–419.
- Javid, H., Tufo, H. M., Najafi, H., Dye, W. S., Hunter, J. A., and Julian, O. C. (1969). Neurological abnormalities following open-heart surgery. *Journal of Thoracic and Cardiovascular Surgery*, **58**, 502–509.
- Kessler, J., and Patterson, R. H., Jr. (1970). The production of microemboli by various blood oxygenators. *Annals of Thoracic Surgery*, **9**, 221–228.
- Kornfeld, D. S., Zimberg, S., and Malm, J. R. (1965). Psychiatric complications of open-heart surgery. *New England Journal of Medicine*, **273**, 287–292.
- Lee, W. H., Jr., Brady, M. P., Rowe, J. M., and Miller, W. C., Jr. (1971). Effects of extracorporeal circulation upon behaviour, personality and brain function. 2. Hemodynamic, metabolic, and psychometric correlations. *Annals of Surgery*, **173**, 1013–1023.
- Loop, F. D., Szabo, J., Rowlinson, R. D., and Urbanek, K. (1976). Events related to microembolism during extracorporeal perfusion in man: effectiveness of in-line filtration recorded by ultrasound. *Annals of Thoracic Surgery*, **21**, 412–420.
- Moseley, R. V., and Doty, D. B. (1970). Changes in the filtration characteristics of stored blood. *Annals of Surgery*, **171**, 329–335.
- Osborn, J. J., Swank, R. L., Hill, J. D., Aguilar, M. J., and Gerbode, F. (1970). Clinical use of a Dacron wool filter during perfusion for open-heart surgery. *Journal of Thoracic and Cardiovascular Surgery*, **60**, 575–581.
- Patrick, R. T., Kirklin, J. W., and Theye, R. A. (1958). The effects of extracorporeal circulation on the brain. *Extracorporeal Circulation*, edited by J. G. Allen, pp. 272–278. Charles G. Thomas, Springfield, Illinois.
- Patterson, R. H., Jr., Wasser, J. S., and Porro, R. S. (1974). The effect of various filters on microembolic cerebrovascular blockade following cardiopulmonary bypass. *Annals of Thoracic Surgery*, **17**, 464–473.
- Rådegran, K. (1971). Circulatory and respiratory effects on induced platelet aggregation. An experimental study in dogs. *Acta Chirurgica Scandinavica*, Supplement **420**.
- Reed, C. C., Romagnoli, A., Taylor, D. E., and Clark, D. K. (1974). Particulate matter in bubble oxygenators. *Journal of Thoracic and Cardiovascular Surgery*, **68**, 971–974.
- Simmons, E., McGuire, C., Lichti, E., Helvey, W., and Almond, C. (1972). A comparison of the micro-particles produced when two disposable-bag oxygenators and a disc oxygenator are used for cardiopulmonary bypass. *Journal of Thoracic and Cardiovascular Surgery*, **63**, 613–621.
- Skagseth, E., Frøysaker, T., and Refsum, S. B. (1974). Disposable filter for microemboli in cardiopulmonary bypass. *Journal of Cardiovascular Surgery*, **15**, 318–322.
- Solis, R. T., Kennedy, P. S., Beall, A. C., Jr., Noon, G. P., and DeBakey M. E. (1975). Cardiopulmonary bypass. Microembolization and platelet aggregation. *Circulation*, **52**, 103–108.
- Stockard, J. J., Bickford, R. G., and Schauble, J. F. (1973). Pressure-dependent cerebral ischemia during cardiopulmonary bypass. *Neurology*, **23**, 521–529.
- Tufo, H. M., Ostfeld, A. M., and Shekelle, R. (1970). Central nervous system dysfunction following open-heart surgery. *Journal of the American Medical Association*, **212**, 1333–1340.
- Valentin, N., and Vilhelmsen, R. (1976). Blood and tissue silicone in extracorporeal circulation. *Journal of Cardiovascular Surgery*, **17**, 20–26.
- Vanetti, A., Fructus, X., Sauvage, Y., Pasquier, P., and Daumet, P. (1975). Traitement des embolies gazeuses cérébrales survenant lors des interventions à coeur ouvert. *Annales de Chirurgie Thoracique et Cardio-Vasculaire*, **14**, 285–287.
- Williams, I. M., Merrillees, N. C. R., and Robinson, P. M. (1975). Microembolism and the visual system. Part II. The consequence of emboli in the micro-circulation of nervous tissue, especially that comprising the visual system. *Proceedings of the Australian Association of Neurologists*, **12**, 179–184.
- Wright, G., and Sanderson, J. M. (1976). Cellular aggregation and destruction during blood circulation and oxygenation. *Thorax*, **31**, 405–409.

Requests for reprints to: Dr. T. Åberg, Department of Thoracic Surgery, Uppsala University Hospital, Uppsala, Sweden.