

Transitory cerebral microvascular blockade after cardiopulmonary bypass¹

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Patterson, R. H., Jr., Rosenfeld, Lynda, and Porro, R. S. (1976). *Thorax*, 31, 736–741. **Transitory cerebral microvascular blockade after cardiopulmonary bypass.** Dogs were submitted to cardiopulmonary bypass (CPB) carried out under conditions calculated to generate large numbers of microbubbles and microemboli. On the day following the procedure the dogs showed evidence of neurological damage including impaired consciousness and ataxia. These abnormalities largely cleared within a week. When the animals were sacrificed at intervals after the procedure, the cerebral microvasculature was demonstrated by injecting a suspension of lamp black into the carotid artery. This revealed that multiple filling defects were present in the microcirculation of the brain immediately after CPB and for two days thereafter. However, by seven days the microvascular blockade had disappeared, and the vascular pattern of the brain had returned to normal. Neuropathological findings were sparse and restricted to the cerebellum.

This study suggests that the transient neurological syndromes that sometimes follow cardiopulmonary bypass for heart surgery may be due to a transient microvascular blockade, perhaps by microbubbles and microparticles.

A substantial body of laboratory and clinical evidence has shown that microemboli can be formed in the blood during cardiopulmonary bypass (CPB). Microbubbles and microparticles have been counted with an ultrasonic device by Kessler and Patterson (1970) and Lubbers *et al.* (1974). Williams (1971) has observed the small particles in the retinal arteries during open-heart surgery. Solis *et al.* (1975) have characterized the particles further using an electronic particle-size analyser, and Dutton *et al.* (1974) have provided evidence that many of the particles are platelet aggregates. These microemboli have been linked to the brain damage that sometimes is observed as an unwanted consequence of heart surgery. How frequently brain damage occurs appears to vary, but in one prospective study, abnormal neurological signs were elicited in 50% of patients during the postoperative period (Tufo, Ostfeld, and Shekelle, 1970). The evidence that microemboli are responsible for much of the trouble rests largely on the observation that the use of

small-pore filters in either the arterial line or the coronary suction apparatus reduces the extent of the injury. In a study in dogs, Brennan, Patterson, and Kessler (1971) showed that the consumption of oxygen and of glucose by the brain was reduced 45% and 60% respectively under certain conditions of CPB but that the use of a fine-mesh filter in the arterial line prevented these changes and preserved normal parameters of cerebral metabolism.

Åberg (1974), who used a battery of psychometric tests to study 113 patients before and after heart surgery, found that the use of a micropore filter reduced the intellectual impairment that he otherwise observed. Branthwaite (1975) likewise noted a reduction in the incidence of cerebral damage after heart surgery when a fine-pore filter was introduced into the bypass circuit.

Although cerebral damage after heart surgery can be permanent, the evidence is that it is often transient (Tufo *et al.*, 1970; Åberg, 1974; Branthwaite, 1975). We wondered if the clinical evidence of transient cerebral dysfunction might be associated with a transient morphological

¹Support for this work was received from the Coleman Foundation, The Pall Corporation, and the US Public Health Service

alteration in the brain microvasculature. Ames *et al.* (1968) originally suggested that the microvasculature could be outlined by perfusing the brain with a suspension of lamp black, and we previously found the technique useful in identifying microvasculature blockade after CPB (Patterson, Wasser, and Porro, 1974). Based on this experience, a study was planned using lamp black to stain the brain microvasculature in dogs sacrificed at intervals after CPB. CPB was to be implemented by a technique calculated to deliver large quantities of microemboli to the brain (Patterson and Kessler, 1969). These measures included directing a portion of the arterial return from the bypass circuit towards the cerebral hemispheres, keeping the ratio of oxygen flow to blood flow high, and permitting the level of blood in the reservoir of the oxygenator to be low. Dogs were sacrificed at various intervals after CPB, and the brain microvasculature was stained with carbon black. In this way we planned to answer the question whether the previously observed obstruction of the cerebral microvasculature was permanent and long-lasting or, as clinical experience suggests, transitory and reversible.

MATERIAL AND METHODS

Two hours of CPB were carried out in mongrel dogs weighing about 20 kg. Anaesthesia was induced with sodium thiopental and maintained with methoxyflurane delivered from a ventilator after tracheal intubation. Cannulae were placed in the right atrium through the jugular vein and in the inferior vena cava through the femoral vein. Blood drained to a bubble oxygenator that was primed with approximately 1500 ml of fresh, heparinized blood and about 500 ml of isotonic sodium chloride. The rate of blood flow varied between 1500 and 2000 ml/min, and the rate of oxygen flow was maintained at 12 l/min. These conditions were known from previous experience to generate microemboli in large quantities. Arterialized blood was returned to the dog through two cannulae, each in the right common carotid artery, one pointing towards the brain and the other pointing proximally towards the aortic arch.

Partial bypass was continued for two hours. The mean arterial pressure was kept above 80 mmHg by the periodic administration of saline, dextrose in water, or low molecular weight dextran. During bypass, small amounts of sodium pentobarbital were given to supplement the methoxy-

flurane anaesthesia. The concentration of microemboli being returned to the dog was estimated by a device employing ultrasound (Patterson and Kessler, 1969). At the end of the perfusion some of the perfusate was returned to dogs that were intended to survive, their cannulae were removed, and penicillin, intravenous fluids, and other supportive care were administered as necessary. The neurological status of each dog was estimated regularly after operation and graded on the following scale:

Grade	Neurological Status
0	normal
1	feeds, walks unsteadily
2	cannot stand but attempts to eat and does drink adequately
3	cannot stand, does not eat, may attempt to drink, appears quite sick

Five groups of dogs of five each were perfused. The first group was sacrificed immediately after the perfusions, and the other four groups were sacrificed on the first, second, fourth, and seventh postoperative days. The dogs were anaesthetized with a barbiturate and given 5000 units of heparin. Both common carotid arteries were cannulated in order to perfuse the brain, and a cannula was placed in the proximal carotid artery in order to exsanguinate the dog. The process of exsanguination was begun, and in 3–5 minutes, after approximately 1000 ml of blood had been removed, the head was perfused with 500 ml of isotonic sodium chloride at a temperature of 37°C and a gravity pressure of 145 cm. After the saline, the head was perfused with 200 ml of a suspension of lamp black that had been filtered twice at a temperature of 37°C. The body was then refrigerated for 24 hours to allow the gelatin in the lamp black suspension to solidify, and the brain was removed on the following day. Further fixation was achieved by immersing the brain in 10% formalin.

After thorough fixation the cerebral hemispheres were sliced into 8–10 coronal sections. The extent of cerebral microvascular blockade was estimated on a grading scale as follows:

0	normal, or single, small equivocal defect
1	0–24
2	25–49
3	50–74
4	75–100

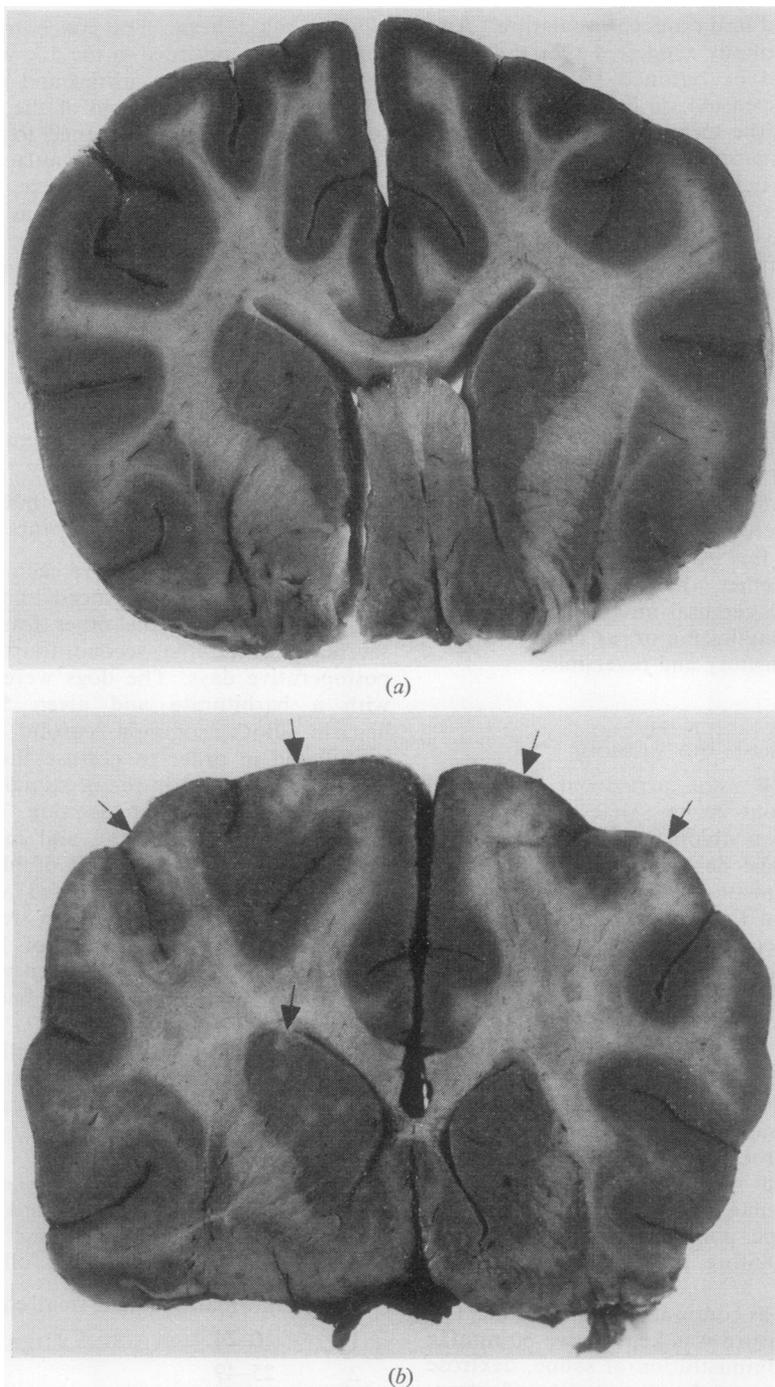


FIG. 1. (a) A brain slice made after an intracarotid injection of lamp black. This is an example of complete filling, grade 0. (b) Filling defects are present in the cortex near the midline and in the right basal ganglia, grade 2.

Examples of grades 0 and 2 are given in Figure 1. All the brain sections were graded in a random order on the same day by an observer who had no knowledge from which experimental group the slices had originated. Representative sections of the brain were embedded in paraffin and stained for microscopic examination with haematoxylin and eosin and with Luxol fast blue.

RESULTS

PARTICLE COUNTS WITH ULTRASOUND Microparticles were counted in the efflux from the oxygenator at a mean rate of 42 968 echoes/min shortly after the start of CPB. As CPB continued, particle counts rose slowly to a mean of 90 481 echoes/min after two hours, which is evidence that a two-fold increase in the concentration of microparticles or microbubbles had occurred (Patterson and Kessler, 1969).

MORTALITY Five dogs failed to survive the planned number of days and were excluded from the series. Three of them died on the day of CPB; two of these proved to be infested with heart worms. Two other dogs died one day and two days after CPB.

NEUROLOGICAL STATUS The neurological status of the dogs after CPB is shown in Figure 2. A typical dog in the first postoperative day was unable to stand but attempted to eat and drink. During the next two or three days it would regain appetite and begin to stand and walk unsteadily. By six or seven days most dogs appeared to have made a good recovery, though some were perhaps a bit unsteady.

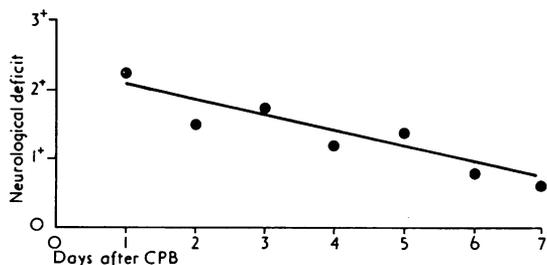


FIG. 2. The neurological deficit of dogs from one to seven days after cardiopulmonary bypass on a scale of 0-3+. The bypass procedure was performed in a way calculated to generate microbubbles and microparticles in large numbers.

MICROVASCULAR BLOCKADE The extent of the microvascular blockade, as revealed by the perfusion of carbon black, is shown in Figure 3. On the grading scale of 0-4+, the mean damage in the group sacrificed immediately on termination of CPB was 2.2+, which implies that more than 50% of the vascular bed was abnormal. The same extent of microcirculatory damage was observed at one day, and a slight fall to 2+ was observed in the group sacrificed at two days. By four days after CPB the mean damage was just 1+, and by a week the cerebral microvasculature had been totally reconstituted. No difference between the two cerebral hemispheres in the nature and extent of the microvascular blockade was observed.

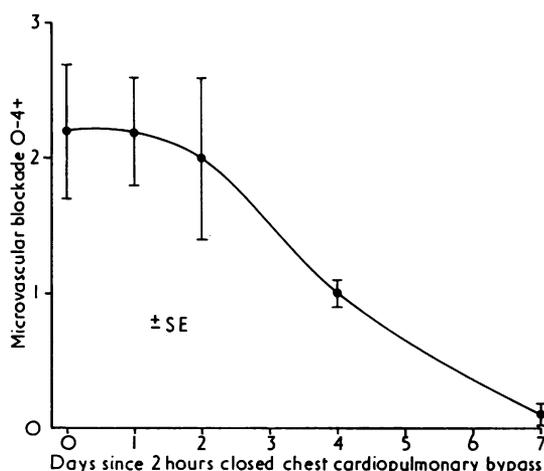


FIG. 3. The extent of cerebral microvascular blockade in dogs sacrificed at intervals after cardiopulmonary bypass.

HISTOPATHOLOGY No histopathological changes were noted in the brain of the dogs sacrificed at one, two or four days after CPB. However, changes were observed in the group sacrificed at the end of seven days. These were restricted to the cerebellum and included some thinning of the granular layer and some focal, mild loss of Purkinje cells.

DISCUSSION

The dogs sacrificed immediately after CPB showed impaired filling of more than 50% of the brain microvasculature. What could account for

this? One possibility is that a soluble toxin or unrecognized metabolic abnormality produced cerebral oedema, and the resulting increased intracranial pressure was sufficient to compress small arterioles and capillaries. However, our past experience leaves little doubt that microemboli are the principal cause of microvascular blockade. In experiments quite comparable to these, dogs were submitted to total CPB for three hours, but a fine-mesh filter to remove microemboli was inserted in the arterial line by which blood was returned from the oxygenator to the dogs, except for a control group in which no filter was used. The filters were from 93–99.4% effective in removing the microemboli from the blood, as judged by the ultrasonic particle counter. The extent of microvascular blockade in the dogs receiving filtered blood ranged between 1+ and 2.5+, depending on which filter was used, whereas it was 3.6+ in the dogs that were perfused with unfiltered blood (Patterson *et al.*, 1974). The dogs in the present study that were sacrificed immediately after CPB had a lesser degree of cerebrovascular blockade than in the experiments cited above, 2.2+ in comparison with 3.6+. Probably the fact that CPB lasted for only two hours in the present study rather than the three hours employed in the early work accounts for this difference. In any case, mechanical filtration of the blood offered effective protection to the brain microvasculature, which is strong evidence that microemboli are the major cause of the blockade in these circumstances.

Probably this microvascular blockade is the anatomical substrate for our earlier work that showed an impairment in cerebral metabolism after CPB in dogs unless the arterial return from the oxygenator was passed through a fine mesh filter. Use of a filter markedly reduced the concentration of microemboli, as judged by the sonar particle counter, and preserved normal parameters of cerebral metabolism (Brennan *et al.*, 1971). The act of exsanguination and perfusion of the brain with colloidal carbon appears not to contribute to the changes since the microvasculature was intact in the dogs in this experiment that were sacrificed after one week, and the method of sacrifice was identical in all groups.

Although the arterial blood from the oxygenator was returned only to the right carotid artery, the microvasculature of the two cerebral hemispheres showed an equal degree of non-filling with colloidal carbon. This seeming paradox probably has two explanations. In the first

place, a substantial proportion of the arterial blood was directed retrograde in the carotid artery and brachiocephalic trunk towards the heart and no doubt reached the opposite cerebral hemisphere through the left carotid artery, which, like the right carotid artery, is also a branch of the brachiocephalic trunk. Probably some of the arterial blood directed towards the right cerebral hemisphere also reached the left hemisphere. The dog has excellent collateral circulation between the two carotid systems which Moss (1967) has exploited to perfuse the entire dog brain through one carotid artery by the expedient of keeping pressure in that artery 20 mmHg higher than systemic blood pressure. Others have used this particle to attain selective cerebral hypothermia (Lourie *et al.*, 1960; Misko, 1965). Either one of these two mechanisms could account for the effects of CPB appearing equally in the two cerebral hemispheres.

The present experiments and ample evidence in the literature confirm that CPB sometimes causes cerebral damage in both patients and dogs (Tufo *et al.*, 1970; Brennan *et al.*, 1971; Åberg, 1974; Branthwaite, 1975). The extent of the damage may be limited by proper regulation of the perfusion and through the use of filters (Patterson and Kessler, 1969; Hill *et al.*, 1970; Kessler and Patterson, 1970; Hissen *et al.*, 1974; Solis *et al.*, 1975). In this study no filter was used, and the perfusion was managed in such a way that an extensive microembolic encephalopathy could be anticipated. This was done in order to produce in dogs an exaggerated example of the post-perfusion state that has been shown to occur sometimes in patients undergoing heart surgery. The dogs in these experiments displayed clinical evidence of an extensive encephalopathy after CPB characterized by a depressed state of consciousness and inability to carry out motor activity, such as standing, walking, and feeding. During the course of a week, clinical evidence of brain dysfunction resolved completely, or nearly so. Those who have recorded cerebral damage in patients after CPB have likewise reported that the condition in most cases is self-correcting (Tufo *et al.*, 1970; Åberg, 1974).

Changes in the brain microvasculature correlated well with the clinical picture. Extensive areas of poor filling were observed immediately after CPB and persisted for approximately two days. Then the patency of the vessels began to return and was restored after one week, the time when the dogs appeared to have recovered from

the effects of the perfusion. The microvascular blockade and the neurological abnormalities are probably the pathological and clinical correlates of the impaired cerebral metabolism after CPB that has been documented previously (Brennan *et al.*, 1971).

Histopathological abnormalities in the cerebral hemispheres in our dogs were sparse. This, together with the observation that the vascular bed re-opens as time passes, raises the question whether or not the neurones survived the period of temporary obstruction of the microcirculation. Some work by others suggests that the brain in some circumstances is more resistant to ischaemia than has previously been recognized. Miller and Myers (1970) have shown that some juvenile monkeys are able to recover from 12–14 minutes of crossclamping of the aorta. Hossman and Sato (1970) were able to report recovery of enzymatic function in the cat brain after one hour of cerebral ischaemia. Since our pathological studies have not revealed any striking abnormalities of the brain, we must presume that most of the neuronal and glial population were able to withstand the ischaemic insult inflicted by CPB in the experiments. That and the compensatory potential of the brain appear to be sufficient to allow the animal to regain normal function. A number of questions remain to be answered. These concern the exact pathogenesis of the transient blockade, the energy state of the brain distal to the obstructed arterioles, and how the microvasculature is able to reconstitute itself.

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