UNIVERSITY OF CAMBRIDGE

NEUROLOGICAL DAMAGE FOLLOWING CARDIO-PULMONARY BYPASS:

the role of cerebral perfusion.

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INTRODUCTION

The advent of cardio-pulmonary bypass as an adjunct to surgery offered the hope of functional recovery to many patients who were either incapacitated by cardiac disease or whose life span was threatened by the natural progression of their disease. It is perhaps inevitable that a therapeutic advance of this magnitude and complexity should be accompanied by hazards of great importance. Nevertheless, it is a tragedy when the benefits of surgical correction are offset by the handicap of a serious, and perhaps irrecoverable, neurological lesion.

Cerebral damage has remained a common complication of open-heart surgery whereas many other early problems have been eliminated as skill and experience have developed. This may be due in part to the vulnerability of neural tissue and to its poor regenerative capacity, but the lack of a single, easily identifiable cause and the technical difficulties of quantitating cerebral and cerebro-vascular function have also hampered progress.

The present study was designed to investigate the nature of neurological damage occurring in a surgical centre which undertakes between four and six hundred open heart procedures annually. The findings suggest that the onset of cardio-pulmonary bypass is a time of particular hazard, and that micro-emboli from the extracorporeal apparatus and inadequate cerebral perfusion are both contributory factors. A significant reduction in the incidence of neurological damage has followed the introduction of prophyiactic measures designed to eliminate or minimise these risks.

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CHAPTER I

REVIEW

Techniques for extracorporeal maintenance of circulation and respiration were introduced into the clinical practice of cardiac surgery between 1950 and 1955 (Galletti and Brecher, 1962). Both mortality and morbidity were high at first, but the particular importance of brain damage was apparent from several early reports (Clowes, Neville, Hopkins, Anzoia and Simeone, 1954; Adelman and Jacobson, 1960; Paton, Pearcy and Swan, 1960; Ehrenhaft and Claman, 1961). Advances in operative and post-operative management have extended the scope of surgery and decreased overall mortality since then, but many experienced centres recognise that neurological and psychological abnormalities continue to feature as common complications which may lead to permanent disability in some cases.

The reported incidence varies considerably (Gilman, 1965; Javid, Tufo, Najafi, Dye, Hunter and Julian, 1969; Hill, Aguilar, Baranco, de Lanerolle and Gerbode, 1969). These discrepancies may depend in part upon the design of the study and the criteria chosen to define neurological and psychological abnormality, but variations in work load and technique are probably of importance as well. These features change with the passage of time within individual centres as well as between different centres, and it is quite possible that the causes of cerebral damage vary in their relative importance as a result.

Potential aetiological factors can be classified into three major categories - emboli, which may be particulate or gaseous, inadequate cerebral perfusion, and miscellaneous hazards such as hypothermia, or mechanical interference with the arterial supply or venous drainage of

the brain.

Psychological disturbances may be related to organic cerebral damage (Blachly and Kloster, 1966) or to biochemical disorders (Khan, Hodge and Bassett, 1973), but sometimes, the stress of facing life-threatening surgery or the effects of prolonged exposure to the abnormal environment of a post-operative intensive therapy unit are of greater importance (Kornfeld, Zimberg and Malm, 1965).

THE ROLE OF CEREBRAL EMBOLISM

The entry of particulate material into the systemic circulation is always associated with the risk of cerebral infarction, and the danger of dislodging blood clot or calcium from within the left heart during surgery has been recognised from the days of closed mitral or aortic valvotomy (Baglio and Hunter, 1959). Less frequently, emboli are derived from friable vegetations on the valves of patients suffering from bacterial endocarditis, and occasionally, tumour material (e.g. left atrial myxoma) may be fragmented during removal.

Silicone anti-foaming agents have been used extensively on extracorporeal apparatus but an excess of these substances can result in tissue damage (Cassie, Riddell and Yates, 1960; Thomassen, Howbert, Winn and Thompson, 1961), and cerebral embolism can also be caused by fat derived from the sternum, pericardial sac or blood lipids (Miller, Fonkalsrud, Latta and Maloney, 1962; Evans and Wellington, 1964; Arrants, Gadsden, Huggins and Lee, 1973).

Filters designed to eliminate debris are included routinely in the extracorporeal circuit and are situated on the suction

lines which return blood to the oxygenator, and also on the 'arterial line' from the oxygenator to the patient (Galletti and Brecher, 1962). Fears of excessive resistance to flow or undue damage to the blood resulted initially in the selection of a relatively coarse mesh (pore size 150-300μ), but recent studies on the role of micro-emboli have emphasised the need for filters of smaller pore size (Lee, Krumhaar, Fonkalsrud, Schjeide and Maloney, 1961; Allardyce, Yoshida and Ashmore, 1966; Sachdev, Carter, Swank and Blachly, 1967; Hill, 1973).

Damage caused by particulate material in stored blood and in other intravenous fluids is not restricted to cerebral dysfunction after open heart surgery. Garvan and Gunner (1964) reported that intravenous fluids stored in glass bottles with rubber bungs, contained particles of rubber, cellulose fibres, chemicals and fungi, and that granulomatous lesions could be found in the lungs of patients receiving intravenous therapy, and in the cerebral circulation following angiography. Similarly, it has been shown that aggregates of platelets, leucocytes, fibrin strands and protein precipitates accumulate in stored blood as it ages (Swank, 1961; Mosely and Doty, 1970a; Solis and Gibbs, 1972), and these aggregates can also develop in vivo during episodes of acute hypotension and shock (Blaisdell, Lim and Stallone, 1970); the importance of this particulate material in the pathogenesis of post-traumatic pulmonary insufficiency has been emphasised in a number of reports Jenevein and Weiss, 1964; Mosely and Doty, 1970b; McNamara, Burran, Larson, Omiya, Suehiro and Yamase, 1972).

Recently, small pore filters (25-40μ pore size) have been introduced which consist of either Dacron wool ('Swank') or polyester

mesh ('Pall'), and there is both clinical and laboratory evidence that they trap micro-emboli effectively (Goldiner, Howland and Ray, 1972; Reul, Greenberg, Lefrak, McCollum, Beall and Jordan, 1973).

The benefits derived from using these filters during cardio-pulmonary bypass have been demonstrated in both animals and man (Patterson and Kessler, 1969; Hill, Osborn, Swank, Aguilar, de Lanerolle and Gerbode, 1970; Osborn, Swank, Hill, Aguilar and Gerbode, 1970), even though they do not eliminate fat emboli (Arrants, Gadsden, Huggins and Lee, 1973). In the series reported by Hill et al (1970), the incidence of cerebral non-fat emboli in autopsy material fell from 31 to 4.1% following the introduction of the Dacron wool filter, although evidence of fat embolism was still apparent in 75-80% of cases. Maximum protection is obtained if the filters are situated on the arterial return, as well as on the coronary suction lines and the channel through which additional blood is introduced (Connel, Page, Birtley, Bigelow and Webb, 1973). An alternative arterial route, preferably filtered, is required in case the arterial filter becomes blocked, but haemorrhage caused by the filtration of excessive numbers of platelets does not occur (Egeblad, Osborn, Burns, Hill and Gerbode, 1972).

Giannelli, Foster, Patterson, Chusid, Ayres and Nealon (1972) attempted to eliminate cerebral and myocardial damage caused by micro-emboli during cardio-pulmonary bypass by perfusing the aortic arch with venous blood which had been filtered by the systemic capillary bed, but one of 25 surviving patients was aphasic post-operatively, and signs of minor neurological dysfunction were apparent in several other cases.

The choice of oxygenator may contribute to the elimination of micro-emboli, not only of particulate material, but also gaseous emboli; important differences in the results achieved with various oxygenators were reported by Clowes, Neville, Hopkins, Anzoia and Simeone in 1954, and by Owens, Adams, Dawson, Lance, Sawyers and Scott in 1958. The comparison of different systems has been encouraged by the development of ultrasonic techniques for identifying bubbles and other micro-emboli (Austen and Howry, 1965), and by the advent of membrane oxygenators (Selman, McAlpine and Ratan, 1967; Spencer, Lawrence, Thomas and Sauvage, 1969; Kessler and Patterson, 1970; Simmons, MaGuire, Lichti, Helvey and Almond, 1972; Gallagher and Pearson, 1973; Carlson, Lande, Landis, Rogoz, Baxter, Patterson, Stenzel and Lillehei, 1973), but gasous emboli can also be generated away from the oxygenator at points of excessive negative pressure in the perfusion circuit (Bass and Longmore, 1969).

A further source of emboli is air trapped in the heart during surgery and expelled when the left ventricle contracts effectively at the end of the procedure (Nichols, Morse and Hirose, 1958; Nicks, 1969; Fishman, Carlsson and Roe, 1969). A number of surgical techniques are employed to minimise this hazard (Senning, 1952; Miller, Gibbon, Greco, Cohn and Allbritten, 1953; Groves and Effler; Selman, McAlpine, Albregt and Ratan, 1967; Padula, Eisenstat, Bronstein and Camishion, 1971). but it is doubtful if these methods are uniformly effective (Lawrence, McKay and Sherensky, 1971). The importance of gaseous emboli is difficult to assess because it is evident that the number of patients who are exposed to risk as judged by ultrasonic

monitoring, greatly exceeds the number who show clinical or electro-encephalographic evidence of cerebral damage (Gallagher and Pearson, 1973).

THE ADEQUACY OF CEREBRAL PERFUSION DURING CARDIO-PULMONARY BYPASS

The brain is particularly susceptible to the effects of hypoxia, and irreversible cerebral damage occurs in a high proportion of adults following complete cessation of the circulation for three minutes (Weinberger, Gibbon and Gibbon, 1940).

The importance of an adequate cerebral blood supply during extracorporeal circulation was emphasised by several early reports (Matthews, Buckley and van Bergen, 1957; Lopez-Belio, Balagot, El Issa, Lima, Sanchez, Gomez, Tasaki and Julian, 1957; Clowes, 1960), and experimental studies suggested that flow rates of more than 35-40 ml/kg/min were required to ensure values for cerebral or cerebro-spinal fluid oxygen tension equal to or greater than those obtained during general anaesthesia (Kaplan, Matthews, Schwab and Clark, 1956; Schwatrz, Deweese, Niguadula, Gabel and Mahoney, 1959). However, Clowes, Neville, Hopkins, Anzola and Simeone (1954) noted that the arterial blood pressure did not correlate well with the pump flow rate and that arterial hypotension (60-80 mm Hg) was associated with disturbances of the electro-encephalogram in 7 out of 13 dogs, in spite of high flow rates (50-110 ml/kg/min).

More recently, a prospective study of one hundred adult patients which was analysed by Javid, Tufo, Najafi, Dye, Hunter and Julian (1969), and separately, by Tufo, Ostfeld and Shekelle (1970),

suggested that arterial hypotension resulting in cerebral ischaemia remains an important cause of neurological dysfunction after open-heart surgery. The incidence of cerebral damage rose progressively as the lowest recorded value for mean arterial blood pressure fell from 60 to 40 mm Hg, and also increased with increasing duration of hypotension. This was determined by measuring the arterial blood pressure every five minutes and attributing $2\frac{1}{2}$ minutes to the value recorded at the start and end of each five minute period. The results were statistically significant only within the age group 40 to 49 years, and the difficulty of recording a meaningful blood pressure over a prolonged period when rapid changes are common, together with the lack of information concerning the aetiology of the hypotension interfere with interpretation of this study.

Arterial hypotension is common at the onset of perfusion in spite of high flow rates (Moffitt, Tarhan and Lundborg, 1968). Vasodilatation is most marked when dextrose-saline solution rather than whole blood is used to prime the extracorporeal circuit, and the acute reduction in viscosity combined with dilution of endogenous vasopressor substances may contribute to the decrease in pressure (Clement, 1971). Hypotension is accentuated if the heart fails as soon as perfusion is started, or if aortic cross-clamping is required immediately, e.g. to control gross aortic incompetence, and occasionally, the pressure drop results from excessive flow through low-resistance broncho-pulmonary collateral vessels which develop in some forms of cyanotic congenital heart disease. There is a tendency for the systemic vascular resistance

to increase throughout the remainder of the perfusion accompanied by the development of lactic acidosis (Galletti and Brecher, 1962), and the use of anaesthetic agents with vasodilator properties has been advocated by some authors to counteract this (Clement, 1971; Lowenstein, 1971). There is therefore, a natural reluctance to use vasopressors to treat the short-lived hypotension which occurs initially, but it is possible that cerebral oxygenation is jeopardised if the mean perfusion pressure drops profoundly, especially if the fall is abrupt (Harper, 1965).

Hasbrouck and Rigor (1969) obtained further evidence supporting the view that cerebral hypoxia occurs during cardio-pulmonary bypass in man. They monitored the oxygen tension in cerebro-spinal fluid, and found a progressive and significant fall which was related to a reduction in arterial carbon dioxide tension at the beginning of perfusion, but which continued independently thereafter. In a brief account based on a study of four young adults undergoing cardiac surgery, Stone, Nusbaum, Donnelly, Blakemore and Zinsser (1967) reported a rise in jugular venous lactate concentration which was 10-20 times that seen in arterial blood; they suggested that this represented an increase in cerebral anaerobiosis which was occurring in spite of systemic flow rates of 60-80 ml/kg/minute.

Relatively few studies have included direct measurements of cerebral blood flow. Halley, Reemtsma and Creech (1958) reported that cerebral blood flow during experimental extracorporeal circulation was directly proportional to the mean systemic blood pressure, and was increased by the administration of nor-adrenaline, even though flow to other organs was reduced (Halley, Reemtsma and Creech, 1959); comparable findings were reported by Ankeney and Viles in 1961.

These studies were carried out in dogs, and in this animal, there are extensive anastomoses between the external and internal carotid arteries so that changes in blood flow from the common carotid to the internal carotid and vertebral arteries may not reflect changes in cerebral blood flow. In some of their studies, Halley, Reemtsma and Creech (1958) enucleated the eye and coagulated the orbit to eliminate the anastomoses, but extensive surgery can interfere with normal cerebrovascular responses (Harper, 1965) so that the significance of their results is questionable. Similarly, cerebral autoregulation may have been impaired by severe acidosis in the series reported by Ankeney and Viles (1961).

Wollman, Stephen, Clement and Danielson (1966) assessed changes in cerebral blood flow in six patients undergoing cardio-pulmonary bypass by measuring changes in arterio-jugular venous oxygen content differences. The influence of perfusion pressure and the effects of altering the arterial carbon dioxide tension were investigated, but changes in perfusion pressure were mediated by the change in arterial carbon dioxide tension in all but two cases in which the flow rate was increased from 2.2 L/square metre/minute to 2.4 and 2.6 L/square metre/minute respectively. Under these conditions, arterial carbon dioxide tension was the most important determinant of cerebral blood flow, and changes in mean cerebral perfusion pressure were unimportant.

Halley, Reemtsma and Creech (1958) noted a profound reduction in cerebral metabolic rate at the onset of perfusion which they attributed to a reduction in venous oxygen content, rather than recognising this as a consequence of the fall in metabolic rate.

Wollman, Stephen, Clement and Danielson (1966) suggested that this fall in metabolic rate was hypoxic in origin because some of the experiments carried out by Halley and his colleagues were undertaken at low flow rates (11-45 ml/kg/min), but similar findings were demonstrable when high flow rates were employed (50-73 ml/kg/min). Gianneili, Conklin, Patterson, Chusid, Ayres and Nealon (1972) noted a marked reduction in cerebral oxygen extraction in their studies on aortic arch perfusion with filtered venous blood, but they did not measure cerebral blood flow and were unable therefore, to relate the findings to a fall in cerebral metabolic rate.

Geha, Malt, Nara and Baue (1971) reported an experimental study in dogs in which changes in cerebro-spinal fluid oxygen tension, lactate and pyruvate concentrations were used to assess changes in cerebral metabolism during normothermic, non-pulsatile perfusion at high flow rates (80ml/kg/min) from a 'Temptrol' oxygenator primed with blood (20 ml/kg) and saline (10 ml/kg). Cerebro-spinal oxygen tension rose during perfusion, particularly when the arterial carbon dioxide tension was elevated, but neither cerebral blood flow or metabolic rate were measured directly, and the influence of a reduction in haematocrit was not discussed. The lactate/pyruvate ratio remained unaltered, but the concentrations of lactate and pyruvate increased in both arterial blood and cerebro-spinal fluid; these changes were greater in the presence of hypocapnia and also in a few preliminary studies in which the arterial blood pressure was low (30-40 mm Hg). The authors concluded that the finding of an increase in cerebro-spinal fluid oxygen tension

did not substantiate the hypothesis that cerebral hypoxia develops during perfusion. They suggested that the abnormal concentrations of lactate and pyruvate, which developed in spite of hypercapnia, were derived predominantl from the arterial blood and represented an increase in anaerobic metabolism of all organs, possibly associated with non-pulsatile perfusion.

The value of pulsatile rather than non-pulsatile perfusion during cardio-pulmonary bypass has been a topic of interest for some time (Mandelbaum and Burns, 1965; Shephard and Kirklin, 1969; Mukherjee, Beran, Hirai, Wakabayashi, Sperling, Taylor and Connolly (1973), and has been reiterated recently by Sanderson, Wright and Sims (1972) who described the elimination of diffuse nerve cell changes in the brains of dogs when two to three hour perfusions were undertaken with a pulsatile pump. In a subsequent paper, Wright and Sanderson (1972) confirmed their previous findings, but noted that both mortality, and the incidence of focal cerebral and pulmonary damage were unchanged following pulsatile perfusion.

It is apparent therefore, that there is conflicting evidence relating to cerebral haemodynamics and metabolism during cardio-pulmonary bypass. It is not clear whether cerebral hypoxia occurs or contributes to post-operative neurological dysfunction, nor is it apparent whether or not there is a change in cerebral metabolic rate. If these changes do occur, it is important to define which factors are responsible, and to examine in particular, the role of systemic hypotension.

MISCELLANEOUS HAZARDS

One of the earliest reports of cerebral damage associated with open-heart surgery drew attention to the risks of profound hypothermia in children (Björk and Hultquist, 1960), and this was confirmed by Drew (1961), who advocated gradual cooling in the presence

of vaso-dilatation to ensure that excessive temperature gradients were not established within the tissues.

Obstruction of the superior vena cava is another well-recognised hazard (Theye, Patrick and Kirklin, 1957; Paton, Pearcy and Swan, 1960), and Pampiglione and Waterston (1961) stressed the rapid onset and severity of electro-encephalographic changes which can occur as a result. Mechanical disturbances can also affect the cerebral arterial supply, especially when the aorta is cannulated to provide the site for arterial return from the oxygenator (Magner, 1971; Krous, Mansfield and Sauvage, 1973).

EVIDENCE DERIVED FROM AUTOPSY FINDINGS

Neuropathological studies have confirmed the high incidence of cerebral damage related to open-heart surgery. Brierley (1963 and 1967) reported evidence of cerebral damage in 80% of a group of 46 patients and a similar figure (85%) was quoted by Aguilar, Gerbode and Hill (1971) in a larger series of 206 cases.

Lesions consisting of acute neuronal necrosis, focal haemorrhages, and emboli composed of fibrin-platelet aggregates, neutral fat, or crystalline material which is visible under polarised light, have all been described and these findings add weight to the view that multiple factors contribute to cerebral dysfunction. The danger of assuming that the problem is of similar magnitude and origin in all centres is underlined by the variation in emphasis placed upon each factor in different series, in particular, the uncertainty surrounding the role of cerebral perfusion. It was this conclusion which prompted an appraisal of the incidence and aetiology of cerebral damage related to open-heart surgery at the Brompton Hospital.

CHAPTER II

CLINICAL SURVEY 1970

OUTLINE OF THE CASELOAD, CLINICAL ORGANISATION AND METHODS

Cardiac surgery at the Brompton Hospital is undertaken by four independent surgical teams. The caseload consists of patients of all ages, suffering from a wide variety of congenital and acquired cardiac lesions; some are operated on at an advanced stage in their disease when the risks of surgical intervention are high and a few require emergency surgery. Cardio-pulmonary bypass is established with the assistance of a single team of perfusion staff who are responsible for the selection, maintenance and running of the apparatus. An extra-corporeal oxygenator (rotating disc, disposable bubble or membrane) is used in all cases, and although moderate hypothermia ($30^{\circ}C$) is employed commonly, profound hypothermia with circulatory arrest is reserved for procedures undertaken on neonates and very small children, and for very occasional, complex repairs in adult patients. Haemodilution is achieved by priming the extracorporeal circuit with dextrose-saline, sodium bicarbonate solution or human plasma protein fraction as well as with whole blood, so that the haematocrit during perfusion lies between 20 and 30%.

A uniform technique of general anaesthesia is employed in most cases, consisting of premedication with papaveretum and hyoscine followed by a thiopentone-nitrous oxide-oxygen-relaxant sequence, supplemented with additional opiates when necessary. Further doses of relaxant and analgesic drugs are given just before the onset of cardio-pulmonary bypass but thereafter, the oxygenator is supplied only with 2.5% carbon dioxide in oxygen. The author has worked with only one

of the surgical teams and the disparity of the case distribution is such that this represents personal involvement in only about 20% of the total number of cases.

THE DEFINITION AND INCIDENCE OF NEUROLOGICAL DAMAGE IN 1970

The first clinical survey was undertaken retrospectively on all patients submitted to open heart surgery during 1970. Those who died in the operating theatre were excluded, as were patients who succumbed within the first few post-operative hours, before a neurological assessment could be made.

Neurological damage was defined as impairment of consciousness, voluntary movement or vision, separately or together, apparent and recorded within three days of operation. Impaired consciousness ranged from coma to confusion of a severity sufficient to interfere with response to simple commands. Confusion alone in patients who were hypoxic post-operatively (arterial oxygen tension less than 60 mm Hg) was discounted. These relatively crude criteria for the definition of neurological damage were chosen intentionally. Uncomplicated anaesthesia and non-cardiac surgery in elderly patients may sometimes be followed by transitory and minor signs of neurological or psychological dysfunction which are of doubtful aetiology (Bedford, 1955). Psychological manifestations alone may be related to aspects of the cardiac surgical procedure other than the operative period itself (Cohen, 1967), and clinically important sequelae are seen only in patients who show severe dysfunction in the immediate post-operative period. By restricting the study to gross and obvious disability, the hazard of

data loss through retrospective collection was minimised.

417 patients survived the operative procedure and signs of neurological damage fulfilling these criteria were recorded in 80 cases, an incidence of 19.2%. The nature of the abnormality is shown in Table I.

TABLE I

Nature of neurological damage detected post-operatively

Right hemiplegia	14
Left hemiplegia	22
Coma	20*
Confusion	22
Midbrain damage	2
Quadriplegia	1
Epilepsy	2

*Three patients in coma had localizing signs of a left hemiplegia.

21 of the 80 cases with neurological damage died in the post-operative period; 11 of these deaths were wholly or partly attributable to the neurological lesion. The remaining 59 patients survived, but 17 were left with some residual neurological disability at the time of discharge from hospital. The 22 patients with confusion as the sole index of neurological damage all recovered and left hospital with no grossly detectable disability. Routine post mortem examination was carried out on only 7 of the 21 patients who died, including 5 of the 11 in whom

neurological damage contributed to the fatal outcome. Details of the post mortem findings are given in Appendix B, table (i). Both diffuse and focal lesions were apparent and although emboli were not identified in any of the sections examined, a specific search for embolic material was not undertaken.

FACTORS ASSOCIATED WITH NEUROLOGICAL DAMAGE

Information on a number of a pre- and peri-operative features (which are listed in Table II) was collected at the same time as the details of neurological damage. In 52 instances, including one patient with cerebral damage, one or more items of information were not available and these cases were excluded from the statistical analysis.

TABLE II

Factors considered in relation to incidence of neurological damage

Age
Duration of perfusion
Mean flow rate
Pre-operative neurological status
Cardiac rhythm
Presence of calcification
Presence of clot or vegetations
Use of hypothermia
Nature of operation
Type of oxygenator
Nature of priming solution
Technique of arterial return.

Age was quoted in years. For patients less than 2 years, an approximation was used:- less than 3 months - 0 3 to 9 months - 0.5
10 to 18 months - 1 19 to 24 months - 2

Duration of Perfusion was recorded in minutes. No distinction was made between partial and complete bypass, or supportive perfusion. In thirteen instances where the technique of profound hypothermia and circulatory arrest was employed, the total time of perfusion including the arrest period was used.

Mean flow rate was calculated as ml/min/kg body weight. Flow rates of 60 to 80 ml/min/kg were used in adult patients whereas higher flows were preferred in children (100 to 300 ml/min/kg for infants, and up to 100 ml/min/kg for children under 12 years of age).

Pre-operative neurological status. The pre-operative evaluation included an account of current neurological symptoms, a history of previous neurological disorder, a note of mental status, particularly in patients with severe heart failure or those undergoing emergency surgery, and a record of abnormal neurological signs detected on examination. For statistical analysis, the pre-operative neurological status was recorded as normal or abnormal. A history of syncope associated with Fallot's tetralogy or aortic valve disease was not regarded as evidence of neurological abnormality. Four patients with severe acute pulmonary embolic disease who were operated on as emergencies and who were confused pre-operatively but had no abnormal neurological signs were considered to be neurologically normal, as were two patients with a history of previous trauma (one head injury and one peripheral nerve lesion). The aetiology of the pre-operative neurological abnormality in the remaining 35 cases is listed in Table III, p. 20. 15 of the 35 cases had residual neurological signs pre-operatively.

TABLE III

Aetiology of pre-operative neurological disorders

Cerebral embolism	27
Arteriosclerosis	2
Epilepsy	3
Congenital basal ganglia disease	1
Acute ischaemic spinal cord damage	1
Hemiplegia following previous bypass	1

Cardiac rhythm A number of arrhythmias were recorded and in some patients the rhythm was unstable. For statistical purposes, the rhythm was documented as sinus rhythm (283 cases) or "other than sinus" (130 cases).

Calcification, clot and vegetations Calcification in one or more sites was recorded as present or absent. Thrombus and vegetations were considered together, and one patient with a left atrial myxoma was included in this group. Patients with pulmonary emboli were excluded except one case with a patent foramen ovale who had sustained a paradoxical embolus simultaneously. Calcification was present in 129 cases and either clot or vegetations in 29.

Hypothermia Body temperature was recorded in the nasopharynx, and small variations (35 to 38°C) were common during "normothermic" perfusions. A decrease in body temperature below 35°C was employed electively in 220 cases, generally to a temperature between 30 and 33°C, but occasionally to much lower levels. In 13 instances, hypothermic circulatory arrest was employed at temperatures between 12 and 28°C. For the statistical analysis, hypothermia was defined as any reduction in nasopharyngeal temperature to less than 35°C.

Nature of operation Classification of the nature of the operative procedure was undertaken as outlined in Table IV. It was intended that this distinction should separate, as far as possible, those patients in whom embolism of air could occur easily from those in whom it was less likely.

TABLE IV

Operative Procedures

Mitral valve surgery	142	
Aorta and aortic valve surgery	115	
Multiple valve replacement	31	
Left to right shunts	56	
Right to left shunts	39	*
Relief of right heart obstruction	16	**
Ischaemic heart disease	10	***
Miscellaneous	8	****

* Right to left shunts included potential shunts

** Right heart obstruction included pulmonary embolectomy and relief of isolated pulmonary stenosis.

*** Surgery for ischaemic heart disease included resection of ventricular aneurysm and excision of acute infarct.

**** Miscellaneous conditions included: Ebstein's anomaly x2; isolated tricuspid valve replacement x2; excision of left atrial myxoma; coronary artery aneurysm with fistula to right ventricle; mitral valve replacement with closure of atrial septal defect.

Oxygenator The perfusion apparatus was either a rotating plastic disc oxygenator with a filter and bubble trap in the arterial line, or a disposable bubble oxygenator (Rygg or Temptrol). Filters for micro-emboli were not used at any point in the circuit during 1970.

The rotating disc oxygenator was employed for most elective procedures. A Rygg oxygenator was used for elective procedures which were expected to be of short duration (e.g. closure of atrial septal defect, relief of isolated pulmonary stenosis or open mitral valvotomy), and the Temptrol was largely reserved for emergency surgery. 326 perfusions were carried out with the rotating disc oxygenator, 56 with the Rygg and 30 with the Temptrol oxygenators.

Nature of priming solution Human plasma protein fraction was not available in 1970 and the oxygenator and circuit were primed with fresh citrated blood (less than 72 hours old), reconstituted with heparin and calcium chloride, together with 5% dextrose solution, 1.26% sodium bicarbonate, and Ringer's solution. The choice of priming solution was determined by the patient's age, weight and pre-operative haematocrit, and the volume of fluid required for a particular circuit. Whole blood was used for infants and children under 3 years of age; for patients between 3 and 60 years, up to 30 ml/kg of electrolyte solution were used provided the haematocrit was more than 40%. Smaller volumes of electrolyte solution were used for patients over 60 years, or if there was evidence of poor renal function, or considerable pre-operative fluid retention. The priming fluids were classified as blood only (59 cases), electrolyte solution alone (39 cases) or a mixture of the two (288 cases).

Technique of arterial return Three methods were employed. A straight metal cannula was used for the femoral artery, inserted most commonly on the left side. Alternatively, arterial return was to the aorta using either a flexible plastic end-hole Bardic cannula or a fenestrated metal cannula (Parker, 1969). The choice between these three techniques

was largely a reflection of the policies of different surgical teams, but all three methods were well represented (181 femoral; 106 Bardic aortic; 111 fenestrated aortic).

Statistical Analysis

The association between these factors and the incidence of neurological damage was analysed in two stages. Initially, each item was considered in isolation and several were found to be correlated to a significant degree with the appearance of neurological damage, whereas others were associated with a lower than average incidence. These findings are presented in Table V, p. 24.

In view of the probable interrelationship of many of these factors, for example, calcification with advancing age, the findings were reconsidered by multiple regression analysis and the results are shown in Table VI, p. 25.

This analysis demonstrated that the only factors related to a higher incidence of neurological damage, independent of all other variables, were increasing age, longer duration of bypass, and a history of previous neurological deficit. The use of the Temptrol oxygenator was less likely to be associated with subsequent neurological injury ($p < 0.02$), but the significance of this findings was difficult to evaluate because the group was rather small (30 cases).

No age group was exempt from neurological damage although a marked increase in incidence was noted in patients aged over 50 years (Table VII, p. 25); similarly, even perfusions of short duration (less than 30 minutes) were sometimes associated with neurological injury (Table VIII, p. 26).

TABLE V.

Association of individual factors with neurological damage

	Correlation	Significance
Age	+	< 0.001
Duration of perfusion	+	< 0.001
Mean flow rate	-	< 0.01
Pre-operative neurological abnormality	+	< 0.001
Cardiac rhythm	+	> 0.05
Presence of calcification	+	< 0.01
Presence of clot or vegetation	+	> 0.05
Hypothermia	+	> 0.05
Mitral valve surgery	+	> 0.05
Aorta and aortic valve surgery	+	> 0.05
Multiple valves	+	< 0.05
Left to right shunts	-	< 0.01
Right to left shunts	-	> 0.05
Relief of right heart obstruction	-	> 0.05
Ischaemic heart disease	+	>0.05
Rygg oxygenator	-	< 0.01
Temptrol oxygenator	-	< 0.01
Disc oxygenator	+	< 0.001
Prime - electrolyte solution only	-	> 0.05
Prime - electrolyte and blood	+	< 0.001
Prime - blood only	-	< 0.05
Femoral arterial return	+	> 0.05
Aortic return - fenestrated	+	> 0.05
Aortic return - Bardic	-	< 0.05

A negative correlation indicates a lower than average incidence.

TABLE VI

Results of multiple regression analysis

	Correlation	Significance
Age	+	< 0.001
Duration of perfusion	+	< 0.01
Pre-operative neurological abnormality	+	< 0.01
Temptrol oxygenator	-	< 0.02

TABLE VII

Incidence of postoperative neurological damage related to age

Age (yr)	Total No.	No. with CNS damage	% CNS damage
< 1	9	1	11.1
1-10	58	2	3.5
11-20	43	6	14.0
21-30	42	8	19.1
31-40	58	4	6.9
41-50	78	15	19.2
51-60	89	29	32.6
61-70	39	15	38.5
> 70	1	0	0

TABLE VIII

Incidence of postoperative damage related to duration of perfusion

Duration (min)	Total No.	No. with CNS damage	% CNS damage
< 30	54	4	7.4
31-60	62	5	8.1
61-90	81	17	21.0
91-120	86	13	15.1
121-180	96	28	29.2
> 180	34	12	35.3

Information on the duration of perfusion was lacking in four instances, including one patient with neurological damage.

TABLE IX

Suspected aetiology of neurological damage in 32 patients

Hypotension, hypoxia or cardiac arrest	24
Suspected embolism of clot or air	5
SVC obstruction	2
Drug-withdrawal epilepsy	1

	32 Cases Aet. suspected	48 Cases Aet. unknown	Mean Diff. ±SEM	Significance
Age (yr)	42.8	49.4	6.6 ± 3.9	> 0.05
Duration of bypass (min)	129.7	124.1	-5.6 ± 12.6	> 0.1

The importance of a previous neurological lesion was demonstrated, even when there were no residual physical signs. In addition, there were two patients with acute pre-operative neurological lesions (one cerebral embolus and one with acute ischaemic spinal cord damage) who showed evidence of neurological deterioration in the post-operative period. These two cases were not included in the group of 80 patients who developed neurological damage, because the post-operative signs demonstrated only an accentuation of the lesion which had been present before operation.

INTERPRETATION OF THE RESULTS

Positive correlation between two variables does not prove aetiological association, but the importance of the duration of perfusion in the present study suggests that it is some feature of perfusion which is responsible for cerebral damage. However, episodes of circulatory embarrassment are inevitable when complex cardiac surgery is undertaken in critically sick patients and such episodes could be responsible for neurological deficits. It is possible that the most complex and hazardous surgery is undertaken in the older age groups and takes longer to carry out, and the case notes of the 80 patients with neurological damage were inspected therefore, to ascertain how often an episode of technical difficulty or cardio-respiratory embarrassment had been recorded. Potential aetiological factors were noted in 32 of the 80 cases and these are detailed in Table IX, p. 26. The mean age and duration of bypass in these 32 patients and the remaining 48 cases (in whom no untoward events had been recorded) were compared and no significant differences were found ($p \gtrsim 0.05$).

This analysis supports the hypothesis that post-operative neurological damage is related to the perfusion procedure, but whether it is embolic or ischaemic is less easy to define. The possibility of embolism occurring as an isolated event, for example, air trapped during closure of the heart and ejected with the return of a spontaneous circulation, seems unlikely in view of the positive correlation of neurological damage with advancing age and the duration of bypass, and the lack of correlation with those procedures in which air is more likely to be trapped in the left side of the heart.

The higher incidence with advancing years suggests the possibility that cerebral ischaemia, accentuated by co-existent arterial disease, may be important. The influence of pre-operative neurological damage, which in this series was largely embolic and therefore probably contributing to cerebrovascular pathology, could also be interpreted in the same way. Alternatively, it may be argued that the effects of repeated micro-embolism would be more apparent in patients with previous cerebral or cerebrovascular pathology or when cerebral circulatory adjustments to changes in blood pressure occur less readily, as is known to happen with advancing age (Shenkin, Cabieses, van den Noordt, Sayers and Copperman, 1951). The data collected in this survey provided no means of distinguishing between these two hypotheses but the findings emphasised the need to monitor cerebral function more intensively during the perfusion period.

CHAPTER III

THE CEREBRAL FUNCTION MONITOR

Continuous monitoring of the electroencephalogram (EEG) during cardiac surgery has been advocated for many years (Patrick, Theye and Moffitt, 1957; Fischer-Williams and Cooper, 1964; Witoszka, Tamura, Indeglia, Hopkins and Simeone, 1973), although some reports suggest that the changes observed are of limited prognostic value (Owens, Sawyers and Ward, 1955; Davenport, Arfel and Sanchez, 1959; Brazier, 1961; Arfel, Weiss and Du Bouchet, 1961). Routine use of the conventional EEG is limited in a busy surgical centre by the practical difficulty of collecting and interpreting lengthy records of complex waveforms which are derived from multiple sites, and which are liable to interference from artefacts (Sadove, Becka and Gibbs, 1967). This difficulty has been eliminated to a large extent by the development of a simplified EEG or Cerebral Function Monitor (CFM), which was designed for continuous assessment of patients undergoing intensive care (Maynard, Prior and Scott, 1969). It consists of an EEG signal derived from a single pair of parietal electrodes, filtered to pass frequencies between 2 and 15 Hz only, and recorded at slow speeds. Changes in cerebral electrical activity alter either the level or amplitude of the tracing and are easy to recognise by an untrained observer (Prior, Maynard, Sheaff, Simpson, Strunin, Weaver and Scott, 1971).

Relative freedom from interference, together with the ease of interpretation and slow speed of recording form a combination which is particularly suitable for monitoring cardiac surgery, and a prototype of the commercial version of the CFM* has been used in an attempt to identify the timing, and hence the presumptive nature, of neurological damage associated with the perfusion procedure.

* available from Devices Ltd.

USE OF THE CFM DURING CARDIAC SURGERY

200 unselected cases anaesthetised by the author have been monitored during a period of approximately three years (1970-1973). In spite of the simplicity of the system, electrical interference was a common problem at first, and only 33 satisfactory records were obtained in 1970.

The signal was recorded from two intradermal platinum needle electrodes* situated in the parietal region on either side of the midline, approximately 5 cm apart and a little behind the level of a line joining the external auditory meati. The impedance between the two electrodes was monitored continuously and was always well below 5K. At first, both the impedance and CFM signals were recorded on a Devices 2-channel pen recorder running at 6 mm/min; subsequently, an SE Laboratories multi-channel ultraviolet recorder was used at a speed of 10 mm/min. This enabled additional information to be recorded simultaneously, in particular, the arterial and superior vena caval pressures and the nasopharyngeal temperature.

The appearance of normal cerebral activity during anaesthesia is recorded in fig. 1; sudden interference with cerebral perfusion produces an abrupt change as shown in figs. 2 and 3. Surgical diathermy causes prohibitive interference if used frequently and, for this reason, the records could not be interpreted throughout the entire operation. The perfusion period and an interval of 15 minutes or more before and after perfusion could generally be recorded satisfactorily with only minimal

* Specialised Laboratory Equipment Ltd.



Fig. 1. Normal CFM record obtained during anaesthesia.

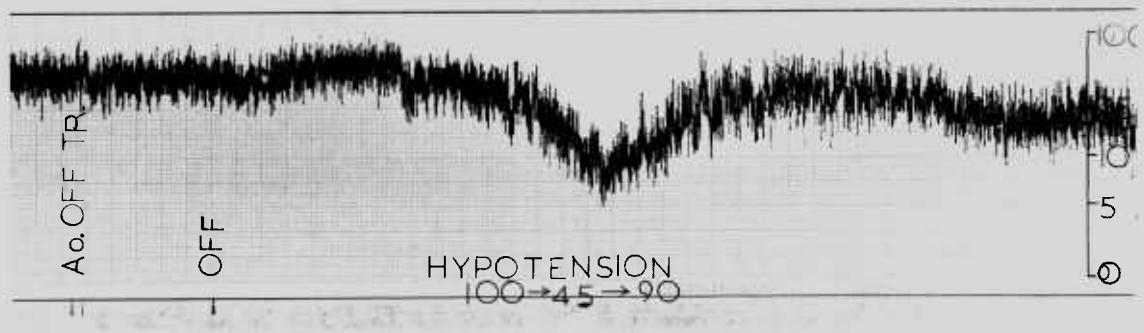


Fig. 2. Depression of cerebral activity associated with hypotension due to haemorrhage and the administration of protamine sulphate.

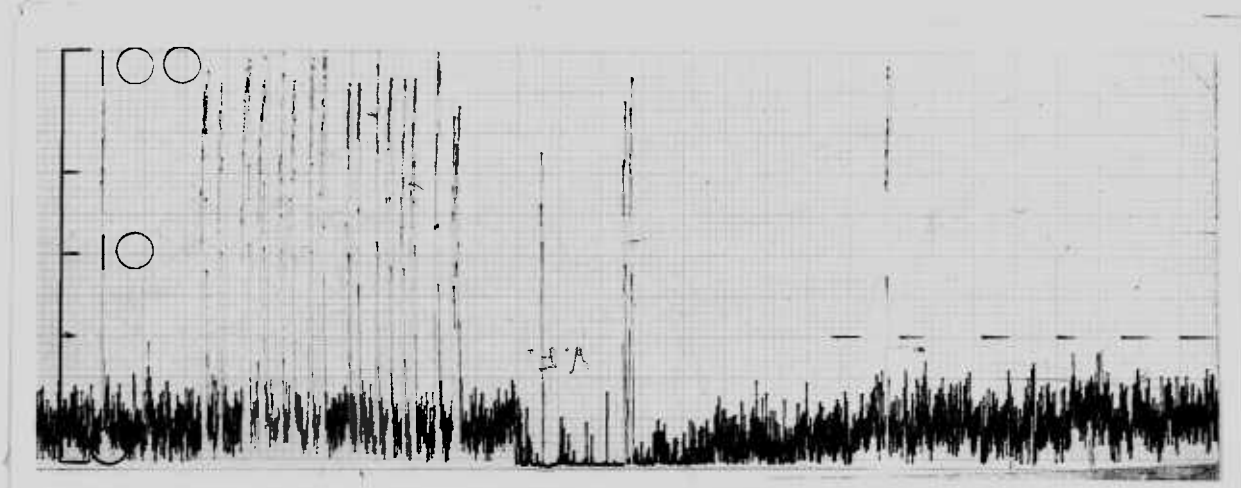


Fig. 3. Virtual abolition of cerebral activity during an episode of ventricular fibrillation (VF). The high voltage activity preceding this represents interference due to surgical diathermy.

interference .

IMPORTANCE OF THE ONSET OF CARDIO-PULMONARY BYPASS

It was apparent at an early stage in the study that abrupt changes in electrical activity are common at the onset of bypass, occurring in 88 of the first 140 cases. The patterns of alteration seen at the onset are illustrated in fig. 4 a-d, and consisted of either a sudden or gradual elevation of the record, a biphasic movement, or immediate depression. Although a slight decrease in the mean level of the record was seen occasionally at the end of perfusion, changes at other times were rare in the absence of profound hypothermia.

Several authors have commented upon the frequency with which changes occur in the conventional EEG at the onset of bypass (Theye, Patrick and Kirklin, 1957; Davenport, Arfel and Sanchez, 1959; Paton, Pearcy and Swan, 1960; Adelman and Jacobson, 1960.) Superior vena caval obstruction, arterial hypotension, acidosis and sudden hypothermia have all been suggested as possible causes, but differences in surgical, anaesthetic or perfusion technique may be responsible for variation in the importance of these factors in individual centres. A number of the features which are known to alter acutely at the onset of perfusion were examined individually therefore, in an attempt to determine which of them contribute to the changes observed with the CFM.

FACTORS INFLUENCING CEREBRAL FUNCTION AT THE ONSET OF CARDIO-PULMONARY BYPASS

Parenteral Drugs

The effects of thiopentone, pancuronium bromide, papaveretum

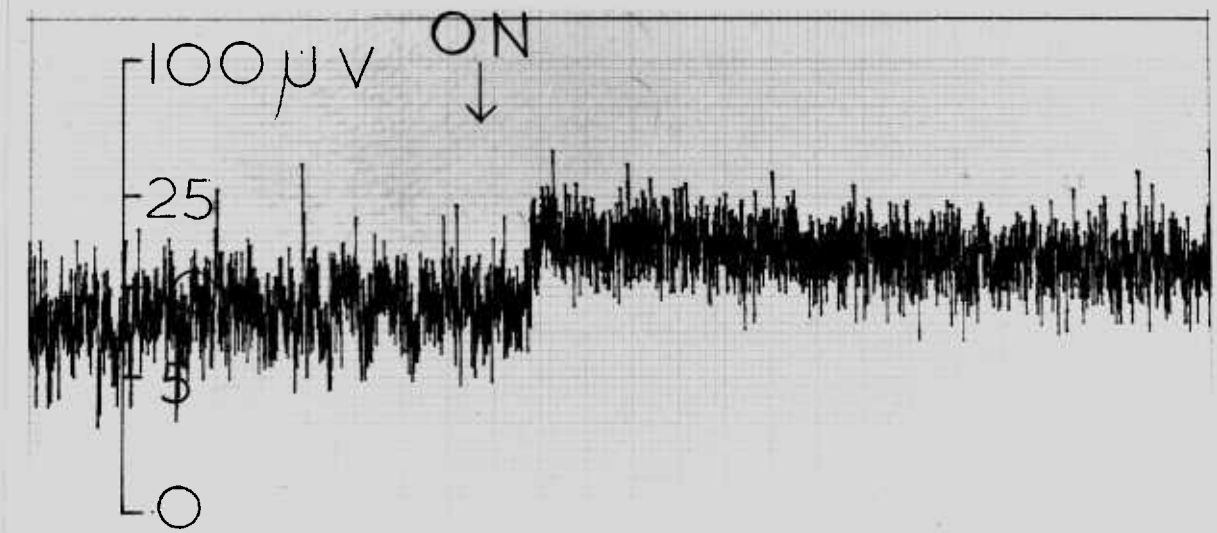


Fig. 4a. Acute elevation of CFM record at the onset of bypass.

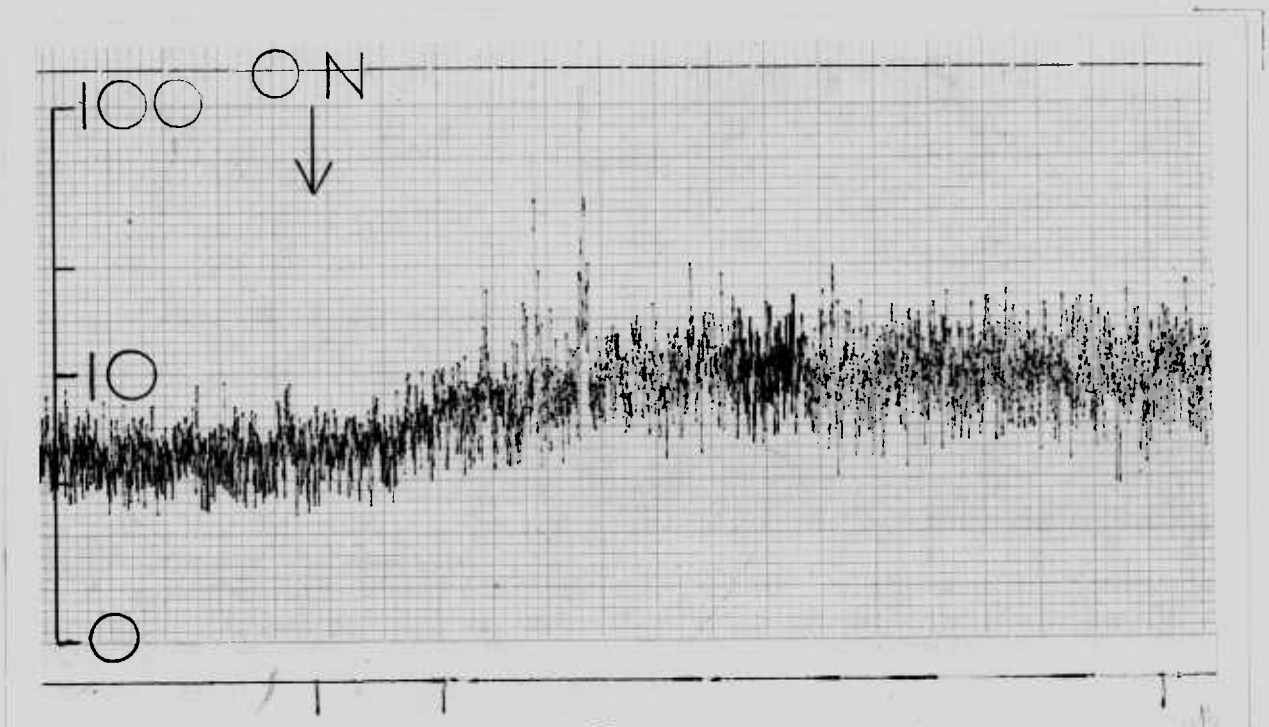


Fig. 4b. Gradual elevation of CFM record following the onset of bypass.

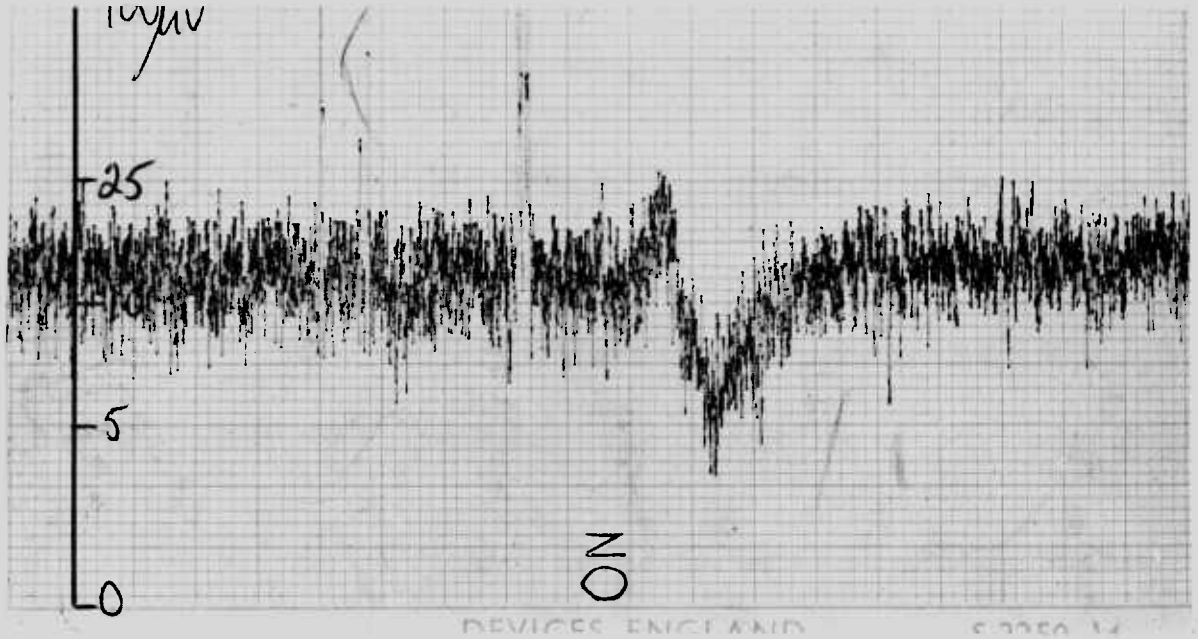


Fig. 4c. Biphasic change at the onset of bypass.

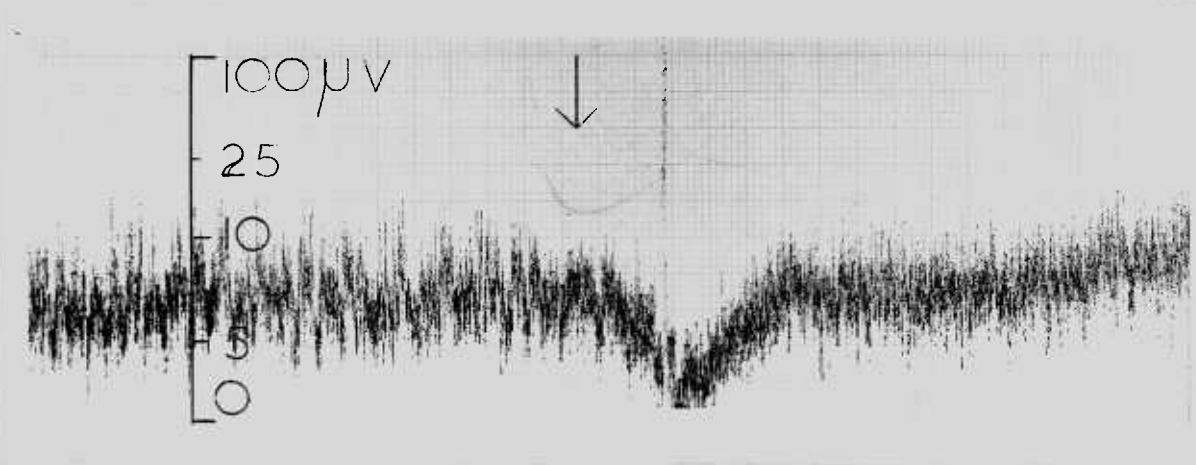


Fig. 4d. Immediate depression of the CFM record at the onset of bypass.

and heparin were documented by injecting each separately, in conventional dosage, with an interval of 5 minutes or more between each injection and the administration of any other agent. Each drug was studied in at least fifty cases and, whenever possible, was given during perfusion as well as before the perfusion period. No detectable alterations in cerebral electrical activity were observed on any occasion following the administration of papaveretum, pancuronium bromide or heparin, but the injection of thiopentone (3mg/kg) was followed by some change in 60 out of 66 instances. The pattern seen most commonly (48 instances) was a sharp, step-like elevation of the record (fig. 5), which varied in magnitude and was most marked in children. On 12 occasions, thiopentone caused a slight fall in the mean level of activity, and in 6 instances, no obvious alteration was seen in either direction

Inhalational Agents

Low concentrations of halothane (up to 1%) were used occasionally, and in fifteen cases, the addition or termination of halothane was documented while other factors remained constant. The effect of discontinuing nitrous oxide was studied in 12 patients during the application of dressings. The gas was discontinued for 5 minutes while alveolar ventilation at the same volume was continued with oxygen and air; nitrous oxide was then restarted for a further 5 minutes and finally, discontinued once again.

Variations in the concentration of halothane between 0 and 1% were never associated with any marked change, but discontinuing nitrous oxide was followed by a smooth, slow rise in the record which fell again

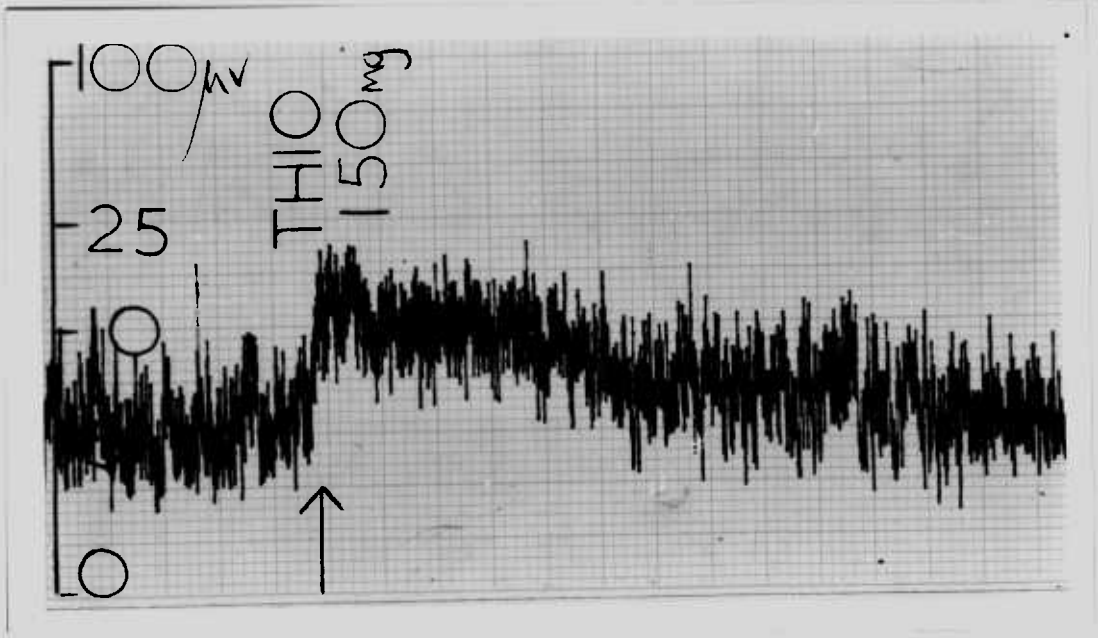


Fig. 5. Step-like elevation of CFM record following intravenous injection of thiopentone.

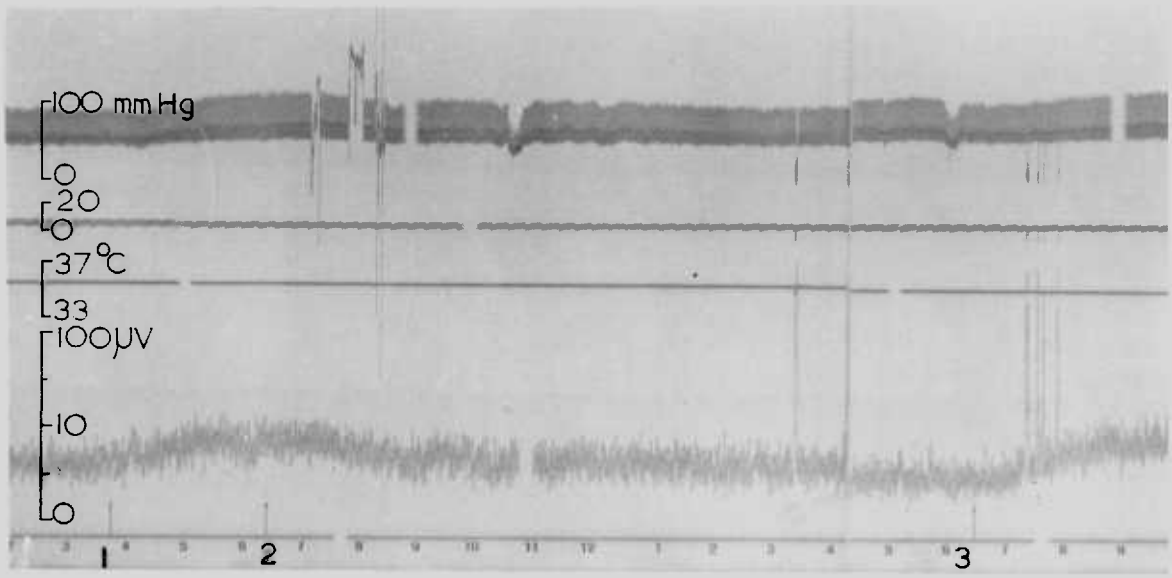


Fig. 6. Smooth elevation of CFM record occurring when nitrous oxide is discontinued (markers 1 and 3). Nitrous oxide was recommenced at marker 2. Tracings from above downwards are arterial blood pressure, superior vena caval pressure, nasopharyngeal temperature and the CFM signal. Duration of record displayed - 25 minutes.

when the gas was recommenced (fig. 6). The magnitude of this effect varied considerably and was barely detectable in some patients.

Arterial Carbon Dioxide Tension

The influence of arterial carbon dioxide tension (P_aCO_2) was evaluated in 10 patients, both during and outside the perfusion period. During perfusion, P_aCO_2 was raised by increasing the delivered carbon dioxide concentration from 2.5 to 5%, and lowered by supplying the oxygenator with carbon dioxide free oxygen. Outside the perfusion period, P_aCO_2 was increased by adding 3% carbon dioxide to the inspired gas mixture and decreased by raising the minute volume by 20%. Each alteration was maintained for 15 minutes and an arterial blood sample was collected at the end of this period for the determination of P_aCO_2.

These manoevres resulted in variation of P_aCO_2 between 28 and 65 mm Hg but no alterations were seen on the CFM record, either during or outside the perfusion period.

Temperature

Major changes in body temperature do not occur outside the perfusion period but during perfusion, body temperature is sometimes altered progressively when conditions are stable otherwise (flow rate, depth of anaesthesia, arterial gas tensions and pH). In 23 patients, changes in temperature of more than $5^{\circ}C$ occurred while these factors remained constant but reduction in nasopharyngeal temperature did not affect the CFM record until the temperature fell below about $30^{\circ}C$. Thereafter, a further fall in body temperature was associated with a more marked reduction in activity (fig. 7).

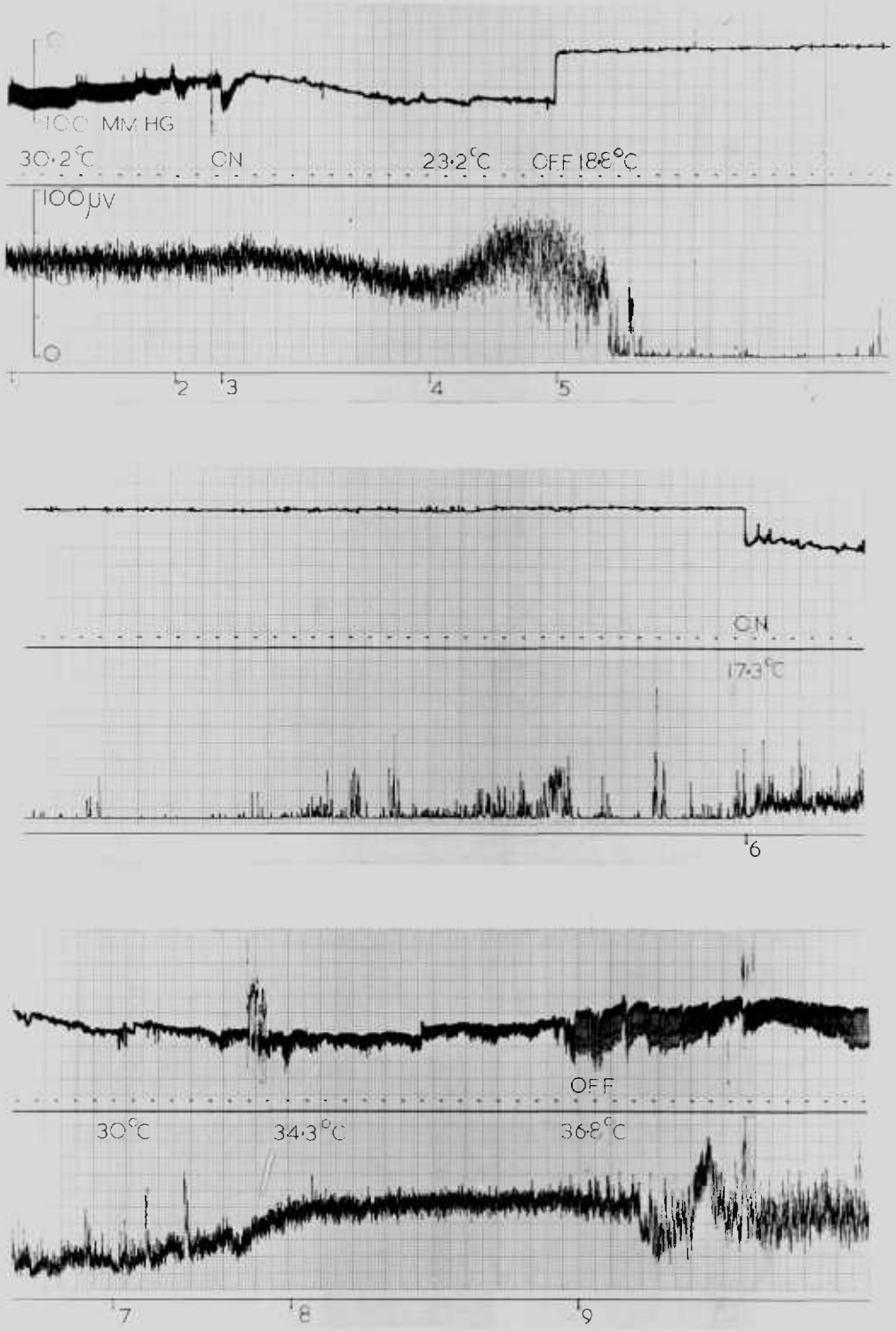


Fig. 7. Complete record of perfusion and hypothermic circulatory arrest in a 14 month old child subjected to bath cooling to a temperature of 30°C before the operation started. Each panel shows the arterial blood pressure and CFM record, but the arterial trace is inverted relative to the CFM record. The transitory abnormality on the CFM after bypass had been discontinued may have been due to air embolism, but there were no neurological sequelae.

Arterial Blood Pressure

In 80 patients, systemic arterial pressure and the CFM signal were recorded simultaneously, but no attempt was made to alter the pressure intentionally. In most instances, the blood pressure was lowest during the first 1-2 minutes of perfusion and then rose to reach 50 mm Hg or more by 5 minutes. The lowest value of arterial pressure reached during the first 5 minutes was correlated with the pattern of change seen on the CFM record at the same time, but no estimate of the duration of hypotension was included.

There was no change in cerebral electrical activity in 30 patients, but a further 30 cases showed elevation of the record, a biphasic response was seen in 6 instances and immediate depression occurred on 14 occasions. The lowest value of arterial blood pressure associated with a biphasic movement or immediate depression on the CFM (mean 36.8 mm Hg) was significantly less than the corresponding mean value (46.3 mm Hg) in patients in whom the CFM record either rose, or did not change (mean difference 9.5 mm; S.E. 3.9 mm; $p<0.02$), and the patients showing a biphasic change or immediate depression were also older (mean difference 12.2 years; SE 4.7;$p<0.02$

INTERPRETATION OF THE INFLUENCE OF INDIVIDUAL FACTORS

Few of the drugs evaluated produced noticeable alterations in the CFM record, but thiopentone and nitrous oxide were notable exceptions. The lack of definite change with some agents, for example halothane and carbon dioxide, does not accord with their known effect on the conventional EEG (Sadove, Becka and Gibbs, 1967), but is presumed to reflect the relative insensitivity of the CFM which only records marked trends in mean amplitude or frequency. Prior, Maynard, Sheaff, Simpson, Strunin, Weaver and Scott (1971) reported only minimal changes on the CFM

record when the concentration of halothane was varied during anaesthesia, unless this was combined with hypothermia.

The effect of nitrous oxide was consistent but often so slight that identification of a definite change was difficult. The smooth, relatively slow elevation produced by discontinuing nitrous oxide is very similar to the second pattern of change seen at the onset of perfusion (fig. 4b p. 34) and nitrous oxide elimination must occur at this time because the agent is never included in the fresh gas supply to the oxygenator. The absence of marked alteration in all cases can be attributed to the varying magnitude of the change in cerebral activity which follows a reduction in the depth of nitrous oxide anaesthesia.

The prominent effect of thiopentone was noted at an early stage in the study and the use of this agent prior to perfusion was restricted subsequently to the induction of anaesthesia in all but 11 cases. In these 11 patients, 2-3 mg/kg thiopentone was added to the priming solution in the oxygenator and may have been responsible for the sharp, step-like elevation of the CFM record which was seen in each case when perfusion commenced. A similar increase in cerebral activity was seen however in many other patients to whom thiopentone had not been given since induction of anaesthesia. An induction dose of 4 mg/kg was rarely exceeded and there was generally an interval of at least 1 hour between induction and the onset of perfusion. In these circumstances, changes in the concentration of thiopentone due to the circulation of barbiturate-free blood from the oxygenator would be small and an acute alteration in cerebral activity seems unlikely.

Heparin, papaveretum and pancuronium bromide are given to the majority of patients at, or just before, the onset of perfusion but none of these agents produced any detectable alteration in cerebral activity when studied individually. It seems unlikely therefore, that variations in the concentration of anaesthetic agents were often responsible for the changes seen at the onset of pertusion, with the exception of the nitrous oxide withdrawal effect and the 11 patients to whom thiopentone was given. It seems particularly unlikely that the biphasic pattern (fig. 4c) or immediate depression of cerebral activity (fig. 4d) were ever caused by a change in drug concentration. Even though thiopentone can cause depression of the CFM record occasionally, it was not given, other than for induction, to any patient in whom either a biphasic response or depression of cerebral activity occurred.

Acute changes in temperature, haematocrit or arterial carbon dioxide tension have been suggested as possible causes of altered cerebral activity at the onset of perfusion (Sadove, Becka and Gibbs, 1967). Temperature changes within the range 30 - 37°C , and variations in P_aCO_2 did not appear important in the present study, perhaps because of the limited sensitivity of the CFM. The haematocrit does not vary acutely at any time other than at the onset of bypass and it was impossible therefore, to separate any effect of this from other events occurring at the same time.

Similar difficulty prevented a detailed investigation of the effect of changes in superior vena caval pressure. Minor alterations in cerebral activity were noted in a few instances when cannulation of

the superior cava before bypass caused a transitory increase in caval pressure, but at the onset of perfusion, the superior vena caval pressure generally drops suddenly.

A significantly greater degree of hypotension during the first 5 minutes of perfusion was associated with either a biphasic change or immediate depression of the CFM record. These changes could represent cerebral ischaemia, the initial elevation of the biphasic response indicating the fast, high-voltage activity which is characteristic of the very early stages of cerebral anoxia (Sadove, Becka and Gibbs, 1967), and which precedes slowing and voltage reduction.

It is apparent from these findings that benign events such as variation in the depth of anaesthesia can contribute to changes in cerebral electrical activity at the onset of bypass, but cerebral ischaemia may be responsible in some cases, and unexplained alterations are common.

CHAPTER IV

DETECTION OF NEUROLOGICAL DAMAGE WITH THE CEREBRAL FUNCTION MONITOR

Twenty patients who showed signs post-operatively of neurological damage which fulfilled the criteria of this study, have been monitored with the CFM; 5 patients were anaesthetised by colleagues of the author. Clinical details are summarised in Appendix B Table (ii) and the changes observed on the CFM are described and illustrated below.

DEPRESSION AT THE ONSET OF CARDIO-PULMONARY BYPASS (8 patients)

Four adults aged 53-60 years were hemiplegic post-operatively and considerable disability has persisted since discharge in one case. In these four patients, the only abrupt change in the CFM record was at the onset of perfusion when there was a marked and sustained depression with slow, high-voltage activity persisting for 5-20 minutes. Fig. 8 p. 46 is a representative example and also illustrates the drop in systemic pressure which occurs frequently at the onset of perfusion. Three of these four patients were known to be suffering from either cerebral or coronary arterial disease.

A similar record, showing marked depression at the onset of perfusion with no other remarkable features, was obtained in a 6-year old child subjected to correction of Fallot's tetralogy. In spite of a high flow rate from the oxygenator, there was profound hypotension (mean arterial pressure 15 mm Hg) due to the run-off into bronchial collateral vessels; the administration of vasopressors resulted in a gradual rise in blood pressure to 50 mm Hg over a period of 13 minutes, and the CFM tracing rose in parallel. In the immediate post-operative period, this child was unduly restless and irritable and suffered a short episode of cardiac arrest within the first 12 hours. Subsequent

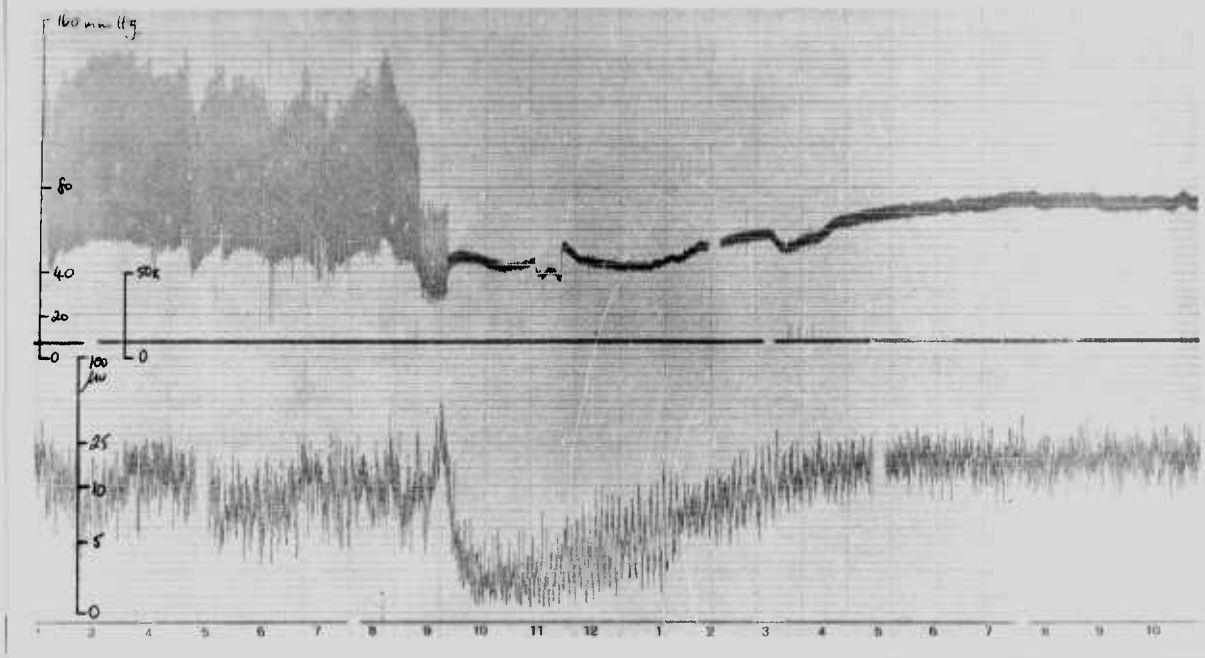


Fig. 8. Profound depression of CFM record at the onset of perfusion. The drop is followed by a period of high-voltage, slow activity, taking 10 minutes to recover. Tracings from above downwards are arterial blood pressure, impedance between the two CFM electrodes and the CFM record itself.

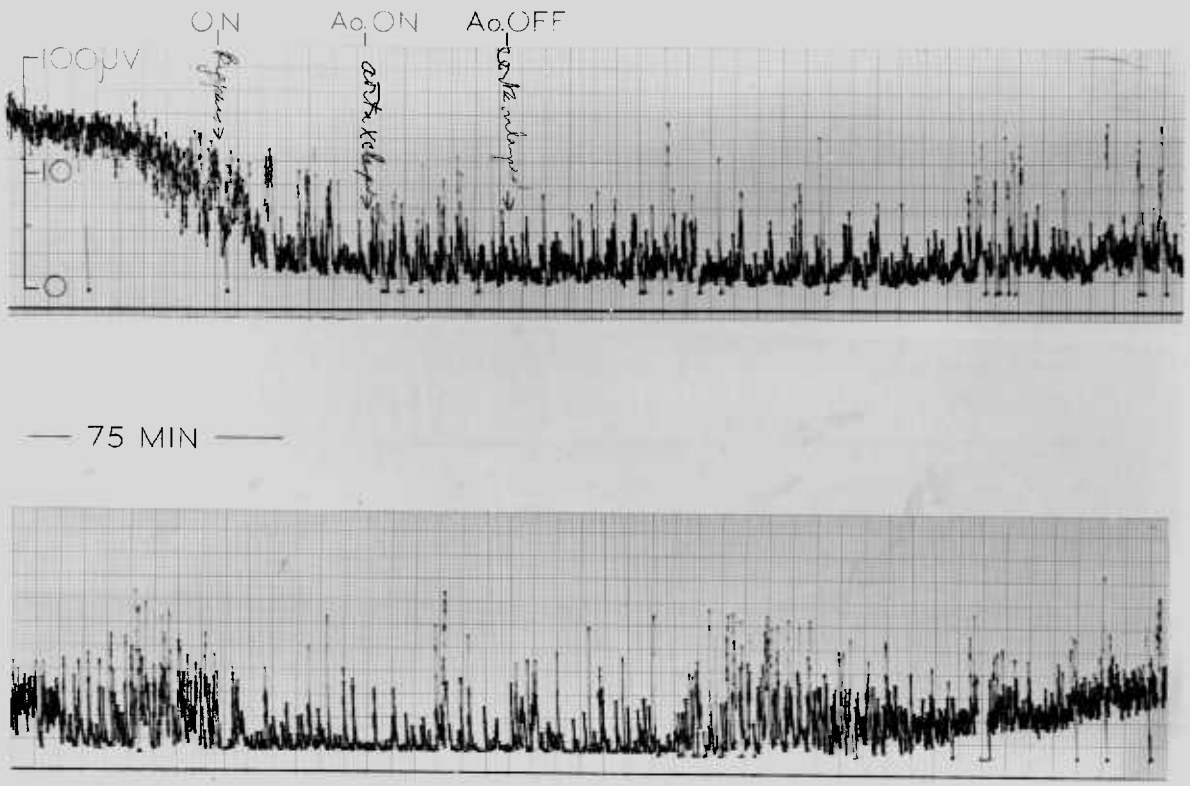


Fig. 9. Profound depression of CFM record at the onset of perfusion. 75 min. later, there is some slight recovery.

examination revealed evidence of gross cerebral damage and the child died several weeks later without regaining consciousness.

A 24-year old woman required an unusually prolonged bypass (405 minutes) for a technically difficult and complicated double valve replacement. Profound depression of the CFM record occurred almost immediately after the onset of perfusion and was associated with extreme hypotension (blood pressure 25 mm Hg). Therapy with vasopressors was ineffective and both the perfusion pressure and the mean level of activity on the CFM remained low for more than 90 minutes. Subsequently, there was some increase in the mean level of cerebral activity but repeated unsuccessful attempts to discontinue perfusion caused further episodes of cerebral depression. This patient never regained consciousness post-operatively, and died 8 days later; no post mortem examination was performed. Representative sections of the CFM record are shown in Fig.9, p64

A 60-year old man required emergency aortic and mitral valve replacement for intractable left ventricular failure, Four minutes after the onset of perfusion, the arterial blood pressure fell to 25 mm Hg in spite of a flow rate of 80 ml/kg/min, and this was associated with depression of the CFM record which lasted 11 minutes (Fig. 10, p.48). Post-operatively, the patient was confused and disorientated and died two months later of septicaemia following episodes of renal and hepatic failure and a cerebro-vascular accident on the 18th day, which was assumed to be embolic in origin. A lesion found at post mortem in the right postcentral gyrus and internal capsule was considered to be compatible with this embolic incident.

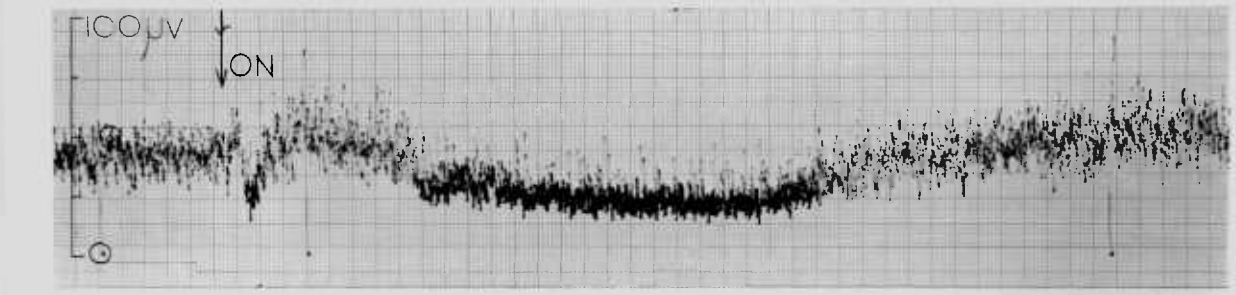


Fig. 10. Depression of the CFM record associated with systemic hypotension soon after the onset of perfusion.

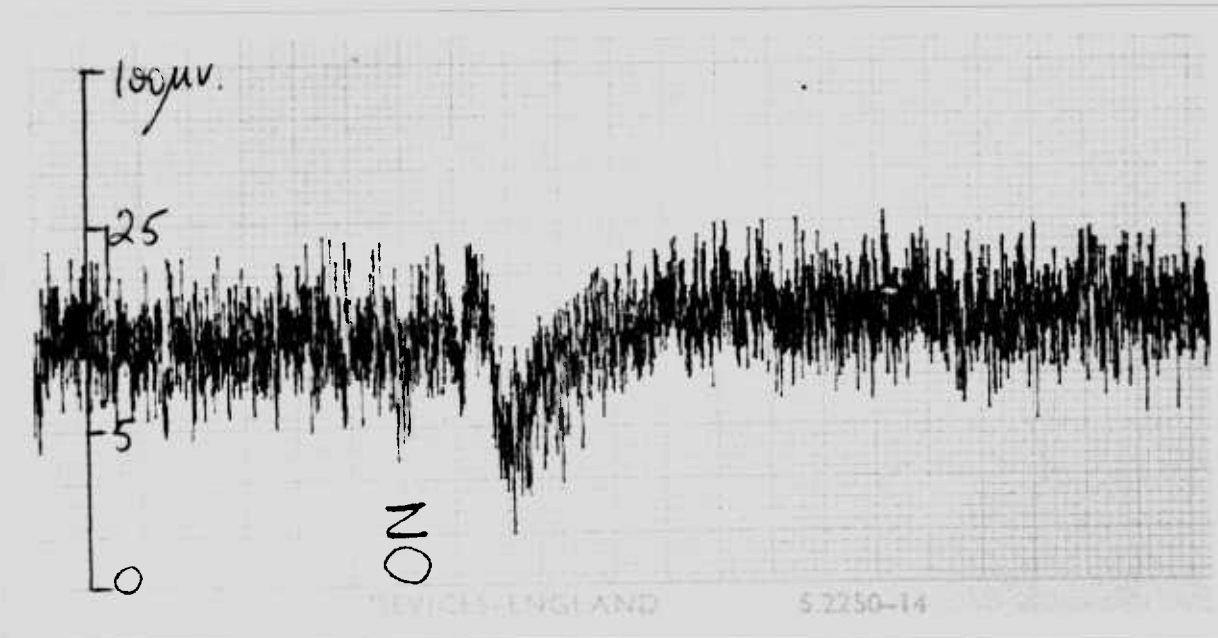


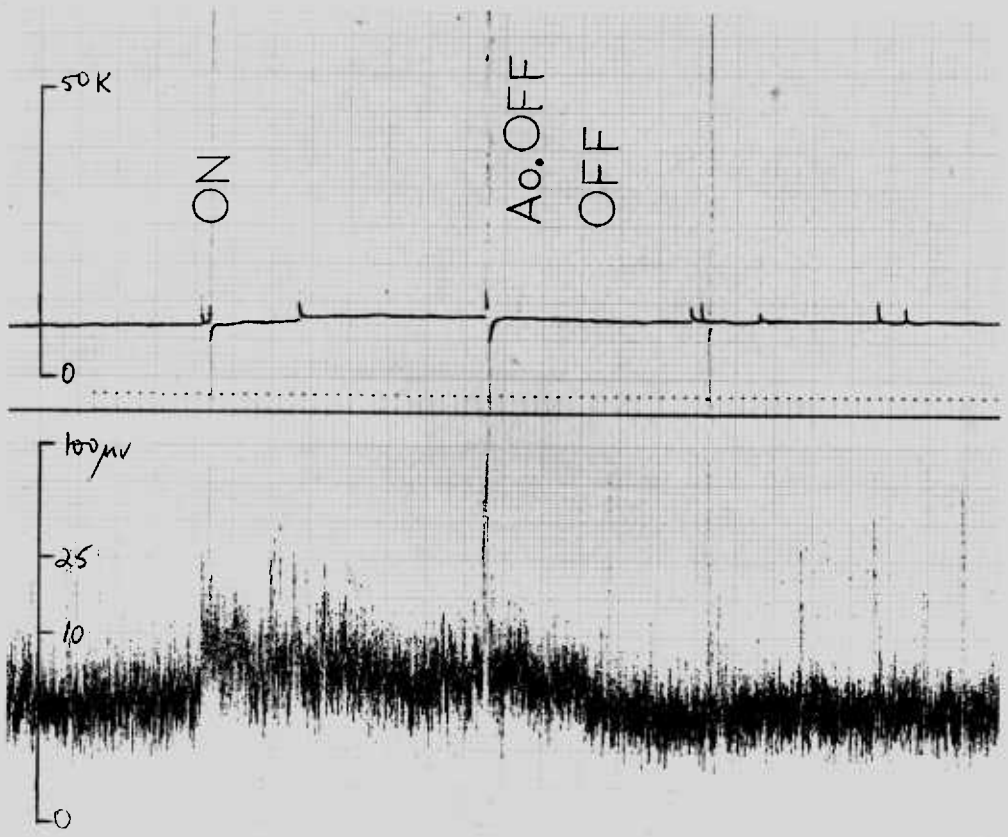
Fig. 11. Biphasic record at the onset of perfusion in an elderly diabetic who suffered an epileptic fit on the second post-operative day.

An elderly diabetic (aged 66 years) suffered an epileptic fit on the second post-operative day and thereafter, was confused, and showed signs of a right hemiparesis which recovered within 24-48 hours. Prior to this, her post-operative course had been satisfactory with no apparent neurological deficit, and the possibility of a transitory rhythm change preceding the convulsion could not be excluded. The record of this patient's cerebral function during surgery revealed a biphasic pattern at the onset of perfusion (Fig. 11), but the rest of the record was uneventful.

ABRUPT INCREASE IN ACTIVITY AT THE ONSET OF BYPASS (2 patients).

A severe mid-brain lesion was apparent post-operatively in a 36-year old woman. The CFM tracing (Fig. 12) was recorded at an unusually slow speed (1.5 mm/min) and lacks detail, but apart from the abrupt elevation at the onset of perfusion, which persisted throughout the procedure, there were no other major changes. Studies of the oxygen content of jugular venous blood (see Chapter V) suggested that the lesion occurred at the onset of perfusion and details of these findings are appended to the figure (p. 50).

A 73-year old woman was confused and showed signs of a mild left hemiparesis for a few days following mitral valve replacement. The CFM record showed abrupt elevation at the onset of perfusion but no other abnormality throughout the remainder of the 70 minute procedure. The arterial blood pressure fell during the first five minutes of perfusion from a mean of 90 mm Hg to 40 mm Hg.



	Before	30	60	90	120	150	180	240	300 sec
C_vO_2 vols %	7.3	6.3	6.6	10.4	9.4	4.2	3.5	4.2	4.6
C_aO_2 vols %	15.7					10.4			10.7
P_aO_2 mm Hg	84								77.5
P_aCO_2 mm Hg	36.5								38.5
PCV %	38	36	34	32	29.5	28	28	28.5	28

Fig. 12. Complete record of a 35 minute perfusion in a patient who sustained a severe mid-brain lesion. Paper speed 1.5 mm/min.
Upper panel - impedance between CFM electrodes
Lower panel - CFM record.

Changes in jugular venous oxygen content and related variables for this patient are shown in the Table. Samples were collected at 30 second intervals during the first 5 minutes of perfusion and sudden arterialisation of the jugular blood occurred in the second minute.

DEPRESSION ASSOCIATED WITH REMOVAL OF AORTIC CLAMP OR END OF PERFUSION

(3 patients)

Two patients (aged 50 and 64 years) showed signs of a hemiplegia and monoplegia respectively in the post-operative period. In both these patients, the onset of perfusion produced little change in the CFM record but a marked depression of activity occurred when the aortic clamp was removed, even though the left ventricle was not ejecting at this time in either case. Fig. 13 is representative of these two records.

An apparently uneventful record of the entire perfusion period was obtained in a 53-year old man undergoing aortic valve replacement (Fig. 14). The slow rise in the mean level of cerebral activity following the onset of bypass was attributed to the elimination of nitrous oxide, with the converse occurring when intermittent positive pressure ventilation (IPPV) was restarted. Recording was discontinued soon after the termination of perfusion (when surgical diathermy is used frequently) and the tracing was not inspected again until it was apparent that this patient had sustained mild cerebral damage. He was confused for several days and there was slight left-sided weakness, predominantly affecting the upper limb, but neurological recovery was complete by the time of his discharge from hospital.

Detailed inspection of this tracing shows that there are several short periods of cerebral depression in the immediate post-perfusion period, each lasting less than 1 minute. Large volumes of air had been seen escaping from the aorta during the final stages of the operation, and both cerebral damage, and the slight post-perfusion abnormality of the CFM record may, perhaps, be attributed to air embolism occurring at this time.

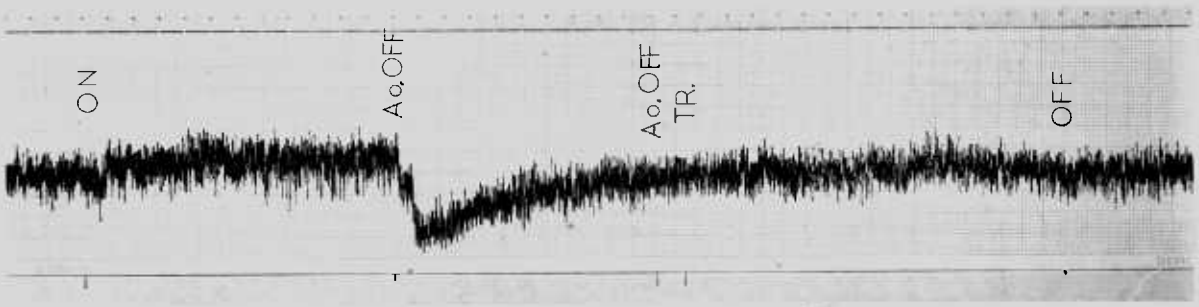


Fig. 13. Acute depression of CFM record following release of the aortic clamp during perfusion.

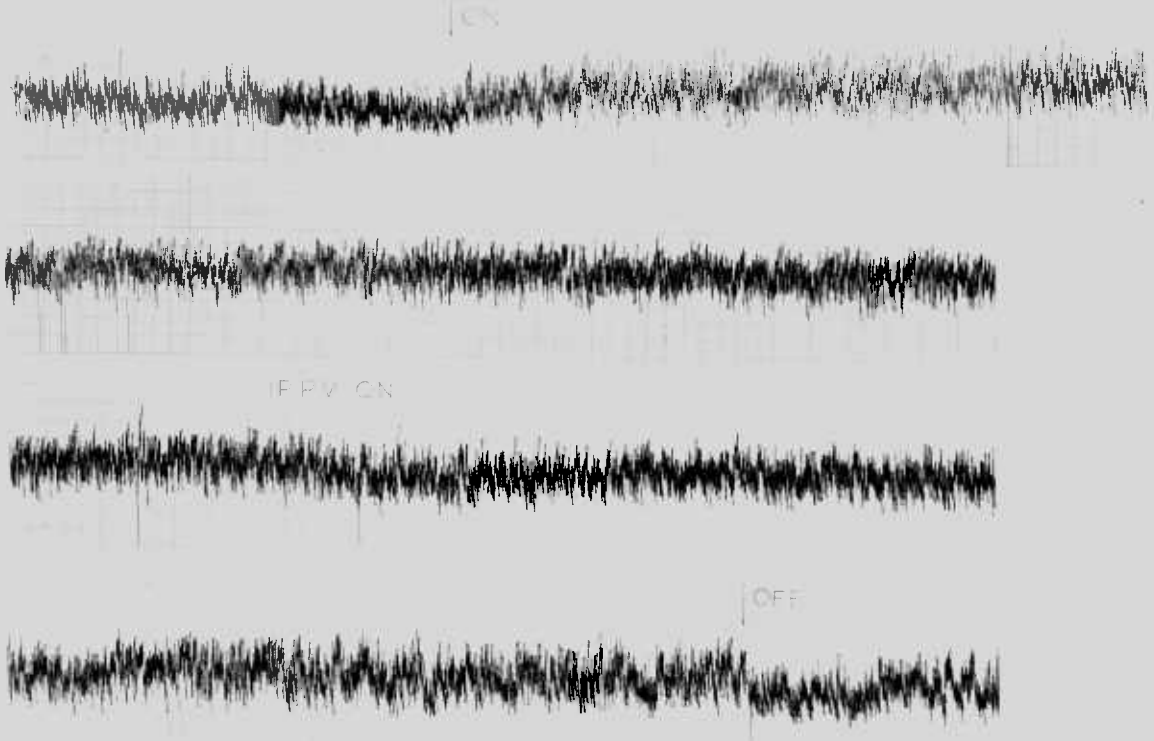


Fig. 14. Transitory, saw-tooth appearance of CFM record at the very end of the lowest panel, detected after perfusion had been discontinued.

DEPRESSION RELATED TO HYPOTHERMIC CIRCULATORY ARREST (3 patients)

A 1-year old child suffered from convulsions and a left hemiparesis following circulatory arrest for 14½ minutes at a naso-pharyngeal temperature of 27°C. The only notable feature on the CFM record was a sudden change at the start of the arrest period, from an apparently normal trace to very low voltage activity which tended to diminish even further until the circulation was restarted, when cerebral activity recovered fairly quickly (Fig. 15, p.54).

Similar traces, showing abrupt cerebral depression with the onset of circulatory arrest at a nasopharyngeal temperature of 20°C were obtained in two infants aged 4 and 5 months. In one of these children, circulatory arrest lasted for 52 minutes and cerebral activity was very slow to reappear when the circulation was restarted and the patient rewarmed (Fig. 16). Both these infants suffered the first of several episodes of cardiac arrest within 12 hours of operation and in both, there was evidence of gross neurological damage, manifest as convulsions, blindness or coma. One child survived to leave hospital but is thought to show residual neurological abnormality. In both cases, the importance of damage sustained during the operative procedure cannot be assessed.

MISCELLANEOUS EVENTS ASSOCIATED WITH CEREBRAL DEPRESSION (4 patients)

A 74-year old man was suffering from hypotension and severe heart failure caused by ventricular septal rupture following myocardial infarction. In the pre-perfusion period, the CFM record in this patient was low in mean level and amplitude but rose considerably at the onset

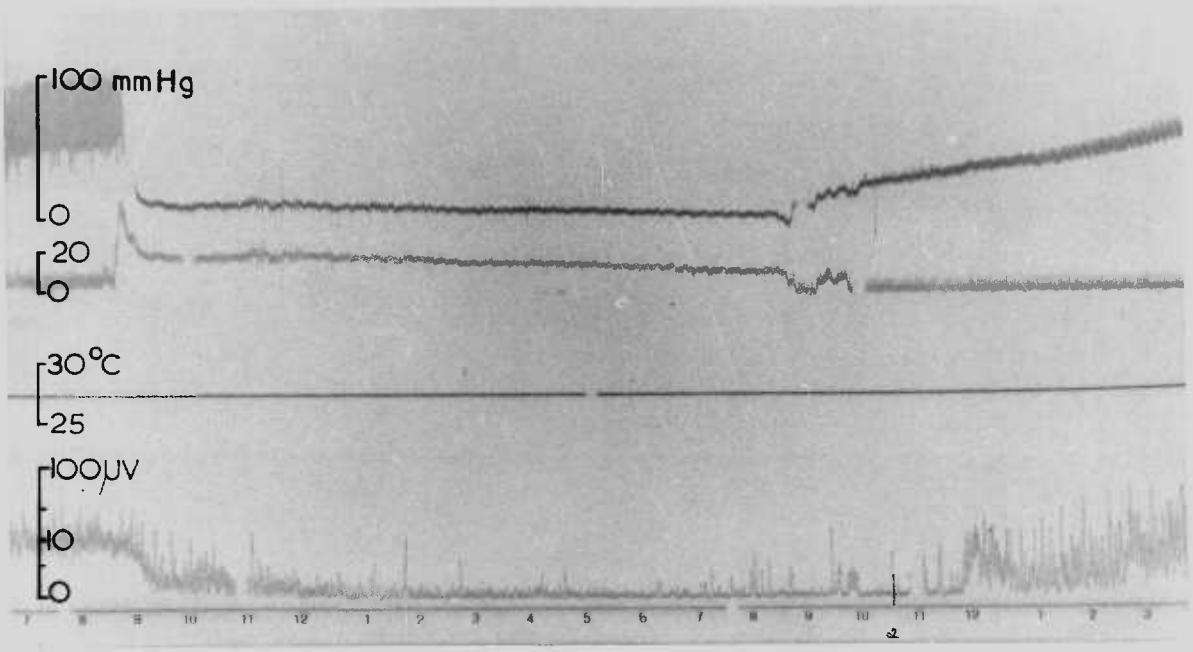


Fig. 15. Depression of CFM record associated with circulatory arrest at a nasopharyngeal temperature of 27°C in a 1 year old child. Records from above downwards are arterial blood pressure, superior vena caval pressure, nasopharyngeal temperature and the CFM record. The duration of circulatory arrest was 14½ minutes.

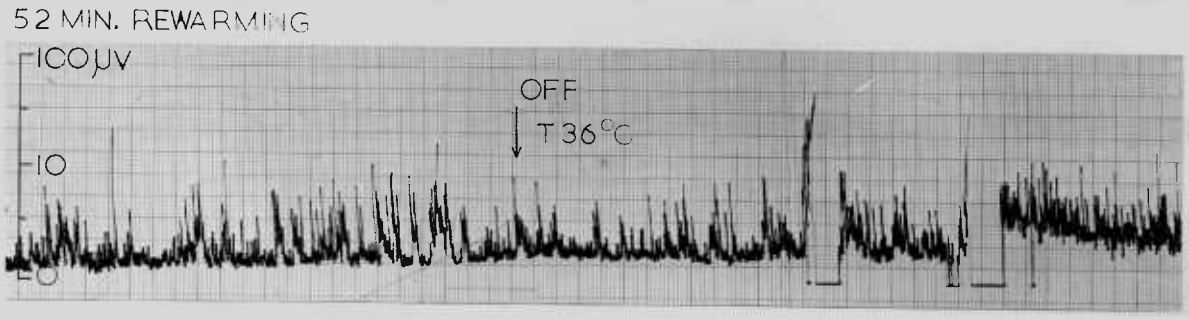


Fig. 16. Delayed recovery of CFM record after hypothermic circulatory arrest. The level and amplitude are low after 52 minutes of rewarming and a normal tracing is not seen until several minutes after perfusion has been discontinued, when artefacts due to diathermy are disturbing the record.

of bypass when the arterial blood pressure increased also (Fig. 17, p.56). This man was confused and aggressive for a few days post-operatively but thereafter, made a complete recovery.

Technical difficulty with perfusion occurred soon after the onset of bypass at normothermia in a 60-year old man undergoing coronary arterial surgery. During the insertion of a left ventricular vent, venous drainage to the oxygenator became impeded and the caval pressures rose. Extracorporeal circulation was discontinued for about a minute while this difficulty was being corrected and as a result, cerebral activity fell abruptly. Return of the circulation with normal arterial and caval pressures did not restore the CFM record which remained severely depressed for 7 minutes before rising slightly, but never regaining the original amplitude (Fig. 18, p.56). Further depression occurred during several subsequent episodes of circulatory failure which were precipitated by rhythm disturbances and by the end of the operation, the mean level and amplitude of the CFM record were very low. This patient never regained consciousness and suffered from right sided convulsions before death occurred on the fifth post-operative day.

A 56-year old man required prolonged perfusion (203 minutes) for aortic valve replacement. After a transitory, biphasic movement of the CFM record at the onset of perfusion, the mean level of activity fell slowly and then, in the post-perfusion period, there was a sudden episode of ventricular fibrillation which resulted in a 2 minute period of effective electrical silence (Fig. 3, Chapter III, p.32). This man was confused for a few days post-operatively before making an excellent recovery.

A 63-year old woman was confused transitorily following

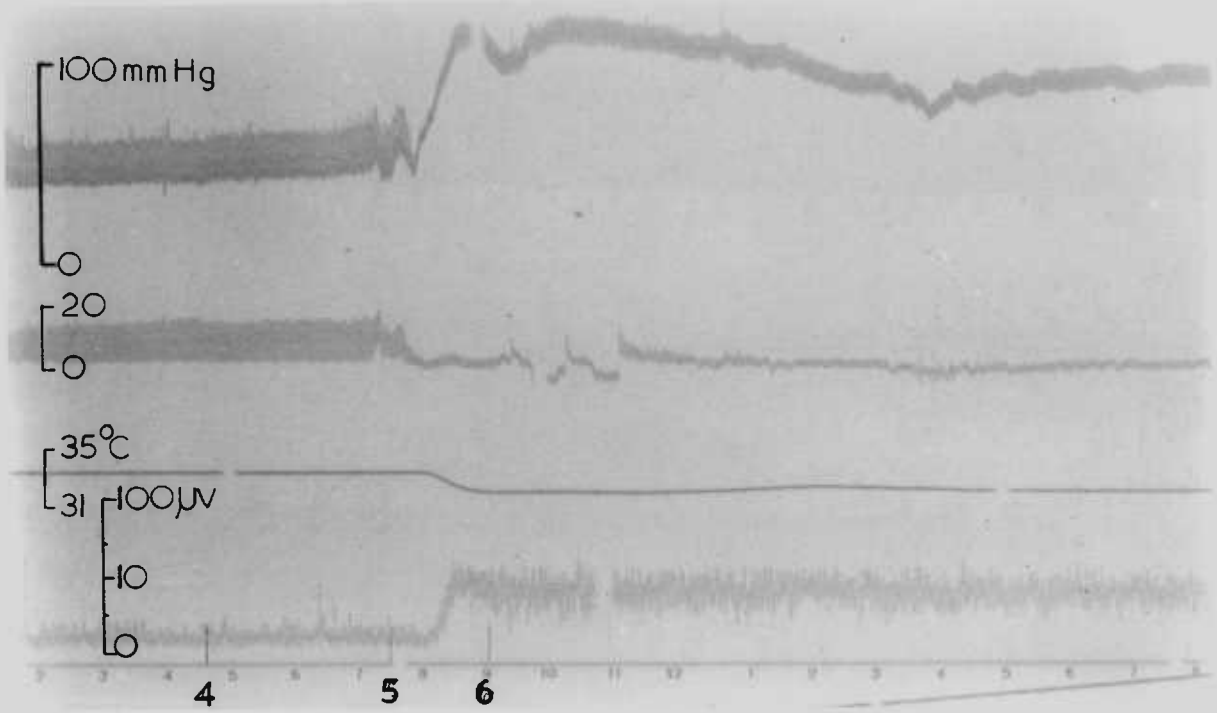


Fig. 17. Elevation of CFM record at the onset of perfusion (marker 5) associated with an increase in arterial blood pressure in a 74 year old man suffering from severe heart failure. Tracings are as in Fig. 15.

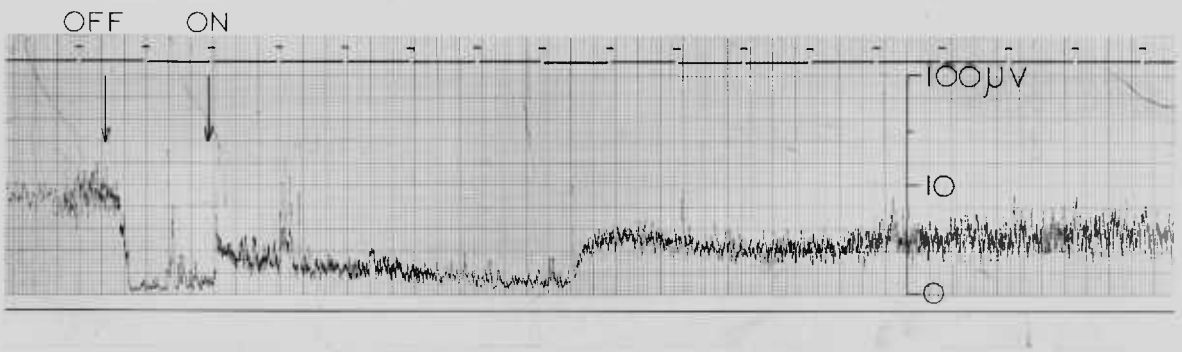


Fig. 18. Abrupt depression of the CFM record associated with cessation of perfusion for about one minute. Severe depression persisted for a further 7 minutes, and the record never regained its original characteristics.

mitral valve replacement. The CFM record throughout a 58 minute perfusion was entirely unremarkable apart from a slight increase in the mean level of activity at the onset which was associated in this case with the administration of an increment of thiopentone (Fig. 19, p. 58).

INTERPRETATION OF CFM RECORDS IN PATIENTS WITH NEUROLOGICAL DAMAGE

It is apparent from the findings in the 20 patients described here that episodes of cerebral depression cannot be identified with the CFM in all cases who show signs of neurological damage post-operatively, and the value of this monitoring technique is discussed in detail in Chapter VIII.

However, in 14 of the present series, unequivocal evidence of cerebral depression was seen at some stage during the perfusion procedure (Cases 1-8; 11; 12; 14-16 and 18 in Appendix B, Table ii). In three instances, this was related to hypothermic circulatory arrest, but in eight of the remaining eleven cases, the change was related soleiy to the onset of perfusion and was associated with extreme hypotension on several occasions.

A drop in arterial blood pressure, accompanied by loss of the pulsatile component of the waveform, is common at the onset of bypass and occurs in spite of high flow rates from the perfusion apparatus. Although the cerebral circulation has the capacity to autoregulate so that cerebral blood flow is maintained in the face of wide changes in arterial pressure (Lassen, 1959), there is a limit below which cerebral blood flow falls. The adjustments cannot compensate for very rapid changes in pressure (Harper, 1965), and the degree to which

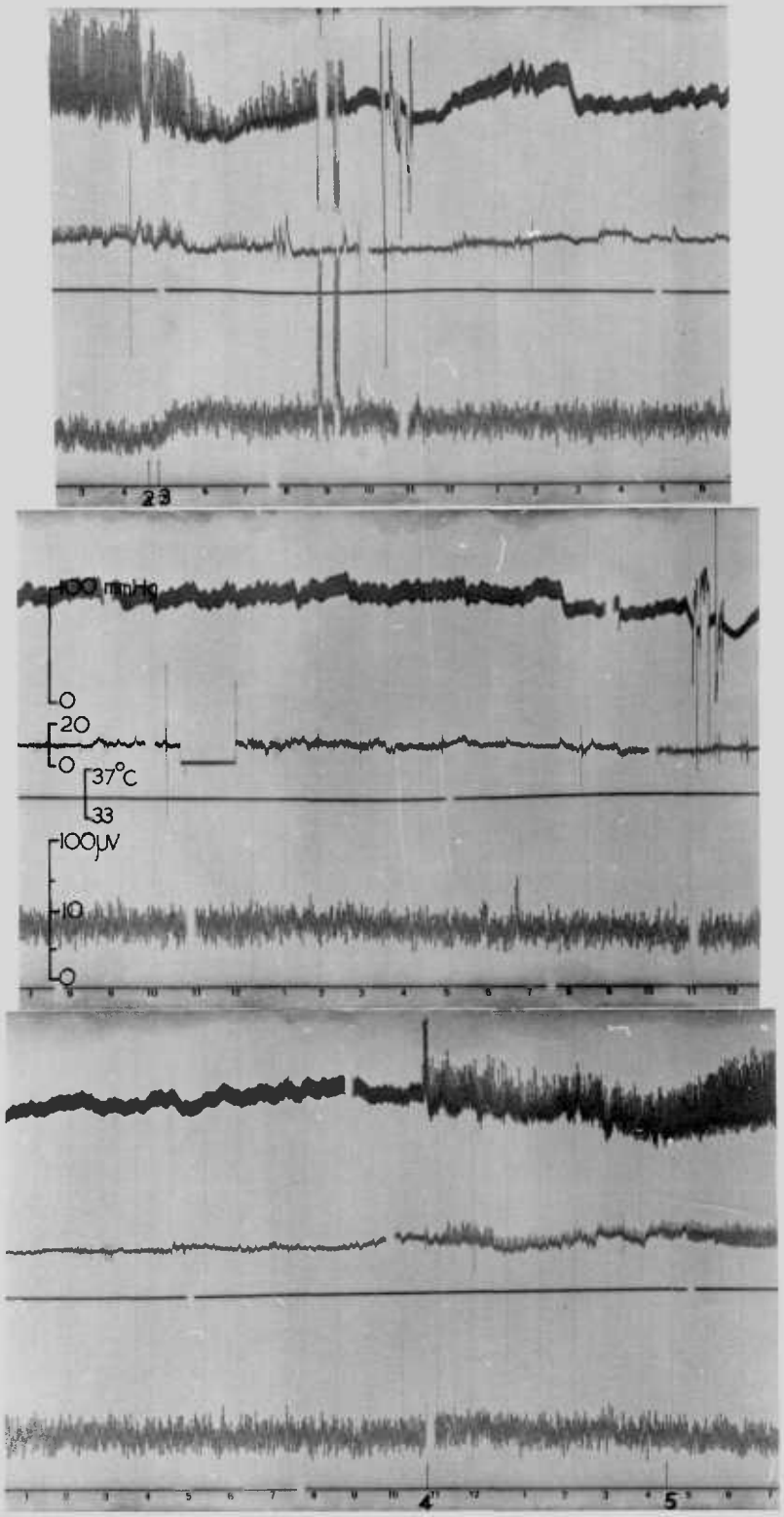


Fig. 19. Uneventful record of perfusion in which an increment of thiopentone was given (marker 4) immediately before the onset of bypass (5). The aortic clamp was released at marker 4 and perfusion discontinued at marker 5. Tracings as in Fig. 15.

the cerebral vessles can dilate is probably reduced in the elderly, especially in those with cerebro-vascular disease (Bromage, 1953). Six of the eight patients in whom cerebral depression occurred at the onset of bypass were aged more than 50 years and at least three were known to be suffering from arterial disease. Although other factors such as micro-emboli from the perfusion apparatus may have been involved as well, the findings detailed here support the view that cerebral ischaemia does contribute to neurological dysfunction associated with open-heart surgery.

CHAPTER V

STUDIES OF JUGULAR VENOUS OXYGENATION

A number of authors have advocated monitoring jugular venous oxygen saturation as a means of detecting cerebral ischaemia during carotid endarterectomy (Lyons, Clark, McDowell and McArthur, 1964; Clauss, Hass and Ransohoff, 1965; Viancos, Sechzer, Keats and De Bakey, 1966), and Lyons et al suggested that a saturation of more than 50% ensured adequate cerebral oxygenation. The method depends upon a number of assumptions, in particular, that the cerebral metabolic rate remains constant, that the sample is truly representative of mixed cerebral venous blood, and that it is uncontaminated by extra-cerebral blood. Even if these assumptions are valid, regional differences in the cerebral circulation are easily obscured and the influence of focal areas of ischaemia or over-perfusion may be inapparent. Larson, Ehrenfeld, Wade and Wylie (1967) could not find any reliable relationship between jugular venous oxygen saturation and cerebral function during trial occlusion of the carotid artery under local anaesthesia.

During carotid endarterectomy, the crucial factor is the adequacy of cerebral blood flow during occlusion of a single vessel, whereas the haemodynamic effects of cardiopulmonary bypass exert a global influence upon the brain and regional differences of flow may be less important. This fact prompted a study of changes in jugular venous oxygenation during the first few minutes of bypass, which, from the evidence obtained with the CFM, appears to be a time of particular hazard.

PRELIMINARY STUDY OF CHANGES IN JUGULAR VENOUS OXYGEN TENSION

Cannulation of both the radial artery and internal jugular vein are routine procedures during open heart surgery in this unit and consent for the insertion of a second jugular catheter was obtained

at the time of the pre-operative visit.

The vessels were cannulated immediately after the induction of anaesthesia, when the second jugular catheter was introduced percutaneously and threaded in a retrograde direction towards the base of the skull until its passage was arrested, generally after approximately 15 cm had been inserted from the level of the upper border of the larynx. The catheter was then withdrawn by 1 cm to ensure easy sampling and secured in position. In most patients, this second jugular catheter was withdrawn at the end of the operation, but, in the first few studies, it was left in place until a post-operative X-ray confirmed that its tip lay just below the base of the skull.

Samples of arterial and jugular venous blood were collected into heparinised, all-glass syringes before and 5 minutes after the onset of bypass. All samples were stored in ice until analysed for oxygen and carbon dioxide tensions using a Radiometer BMS 3 electrode system. The electrodes were calibrated with chemically analysed mixtures of carbon dioxide in white spot nitrogen and the results were corrected for temperature when necessary.

There was no change in arterial carbon dioxide tension following the onset of bypass but the jugular venous oxygen tension tended to rise (Table X). None of these patients sustained neurological injury but there was depression on the CFM record at the onset of bypass in one case (Fig. 20, p. 63).

	Before	5 min.	Mean Diff.	Significance
P_vO_2 mm Hg	33.8 ± 2.5	41.4 ± 4.5	7.6 ± 4.7	$0.2 > p > 0.1$
P_aCO_2 mm Hg	30.0 ± 1.6	31.0 ± 1.8	1.0 ± 2.0	> 0.1

Table X Changes in jugular venous oxygen tension and arterial carbon dioxide tension five minutes after the onset of bypass. Values quoted are mean and standard error of the mean.

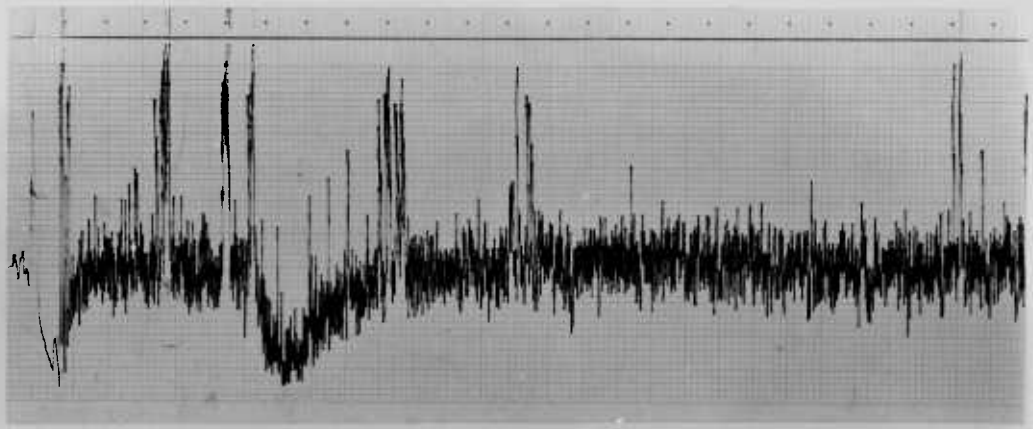


Fig. 20. Depression of the CFM record at the onset of bypass which was associated with an increase in jugular venous oxygen tension, in spite of a fall in arterial carbon dioxide tension.

CHANGES IN JUGULAR VENOUS OXYGEN CONTENT

The results of the preliminary study did not support the hypothesis that cerebral ischaemia at the onset of cardio-pulmonary bypass can be detected by progressive desaturation of jugular venous blood. However, the onset of bypass is associated with sudden, major alterations in a number of physiological variables and interpretation of changes in jugular venous oxygen tension is particularly difficult because of the concomitant change in haematocrit.

A further study was undertaken therefore on a group of 30 patients whose ages ranged from 20 to 73 years. Samples of both arterial and jugular venous blood were collected immediately before and at one minute intervals for five minutes after the onset of perfusion; these were used for the determination of oxygen content, either by the method of Linden, Ledsome and Norman (1965), or with a Lexington Oxygen Content Analyser* which had been validated by comparison with the electrode method. The haematocrit was measured on each arterial sample using a Hawkesley microhaematocrit centrifuge.

Two separate arterial samples were collected before and five minutes after the onset of bypass for the determination of blood gas tensions. The same blood sample cannot be used for the measurement of both oxygen content and tension because complete mixing is necessary for content determinations, and agitation of blood with a small bead of mercury which ensures this, causes disruption of red cells so leading to erroneous values for oxygen tension. Conversely, the measurement of oxygen

* Lex-O_2-Con; Albury Instruments Ltd.

tension before shaking with mercury, invalidates subsequent determinations of oxygen content because division of the sample alters the haematocrit.

In all cases, the arterial and superior vena caval pressures, nasopharyngeal temperature and the CFM signal were recorded on the ultraviolet recorder, running at 10 mm/min; in 12 patients, changes in jugular venous blood flow were assessed using a modified thermo-velocity technique which is described in detail in subsequent chapters.

Changes in arterial and jugular venous oxygen content were expressed as the Cerebral Blood Flow Equivalent (CBFE) which is the ratio of cerebral blood flow (CBF) to cerebral oxygen consumption ($CMRO_2$), or, more simply, blood flow per unit oxygen consumption. It is derived as the reciprocal of the arterio-venous oxygen content difference $(A-V)O_2$ (Cotev, Lee and Severinghaus, 1968). Five minutes after the onset of bypass, the CBFE had increased from 15.2 to 23.4 ml blood/ml oxygen uptake and, at the same time, the mean arterial blood pressure, superior vena caval pressure and haematocrit decreased. There was a small but significant increase in the arterial carbon dioxide tension together with a small, but highly significant fall in nasopharyngeal temperature. Detailed figures are given in Table XI, p. 66.

Four patients were found post-operatively to have sustained neurological damage which was a hemiplegia of varying severity in three cases and a mid-brain lesion in one. The changes in CBFE and related variables in these four patients were compared with those in 24 undamaged patients who survived operation (Table XII); two patients died on the table and were excluded from this comparison. Although none of the

	Before	5 min.	Mean Diff.	Significance
C_vO_2 vols %	8.9 ± 0.6	5.2 ± 0.5	-3.66 ± 0.56	< 0.001
$(A-V)O_2$ vols %	7.3 ± 0.4	5.1 ± 0.4	-2.27 ± 0.54	< 0.001
CBFE ml blood/ml O_2	15.2 ± 1.0	23.4 ± 2.2	8.3 ± 2.0	< 0.001
* BP mm Hg	79.0 ± 2.1	44.0 ± 2.3	-35.7 ± 3.17	< 0.001
SVC mm Hg	11.4 ± 0.9	1.9 ± 0.7	-9.5 ± 0.9	< 0.001
Temperature °C	36.3 ± 0.1	35.8 ± 0.2	-0.5 ± 0.15	< 0.01
PCV %	41.3 ± 0.9	28.1 ± 0.9	-13.1 ± 0.6	< 0.001
P_aCO_2 mm Hg	33.0 ± 1.1	35.2 ± 1.1	2.2 ± 0.8	< 0.05
P_aO_2 mm Hg	104.4 ± 4.4	100.0 ± 6.9	-4.4 ± 6.92	> 0.1

* Pulsatile pressures were adjusted to a calculated mean by taking diastolic pressure + (1/3 x pulse pressure.)

TABLE XI

Mean and standard error of mean for jugular venous oxygen content and related variables in 30 patients before and 5 minutes after the onset of cardio-pulmonary bypass.

	4 patients c CNS damage	24 undamaged survivors	Mean Diff. ± S.E.M.	Significance
Age in years	53.8	42.3	11.5 ± 7.4	N.S.
Δ (A-V)O_2 vols %	-3.83	-2.18	-1.65 ± 1.63	N.S.
Δ CBFE ml blood/mlO_2	18.2	7.3	10.9 ± 5.74	$0.1 > p > 0.05$
Δ BP mm Hg	-32.5	-36.2	3.7 ± 9.4	N.S.
ΔP_aCO_2	2.4	1.8	0.6 ± 2.2	N.S.
$\Delta T\ ^oC$	-0.25	-0.62	0.37 ± 0.42	N.S.

TABLE XII

Comparison of changes occurring during the first five minutes of cardio-pulmonary bypass in 4 patients with neurological damage and 24 undamaged survivors.

differences reached statistical significance, there was a tendency for the increase in CBFE during the first five minutes to be greater in patients who suffered neurological injury. The CFM record was unsatisfactory for technical reasons in one of these patients but in the other three, there was a sudden change at the onset of bypass which could not be attributed to any other variable known to influence this signal. These three patients appear as numbers 2, 9 and 10 in Appendix B, Table ii. Apart from the changes at the onset of bypass, the remainder of these three CFM records was unremarkable and there were no unusual technical difficulties with the operation in any case.

INTERPRETATION OF CHANGES IN JUGULAR VENOUS OXYGEN CONTENT

A number of the physiological variables which change acutely at the onset of bypass could influence either cerebral blood flow or metabolic rate and so lead to the increase in CBFE wich was observed. These factors are represented schematically in Fig. 21, p. 69.

The influence of changes in arterial blood gas tensions

Under normal circumstances, the arterial carbon dioxide tension (P_aCO_2) is the most important determinant of cerebral blood flow which rises approximately 1 ml/100gm/min for each increment of 1 mm Hg in P_aCO_2 (Smith and Wollman, 1972). The behaviour of the cerebral vessels when subjected to an alteration in P_aCO_2 during perfusion is a matter of dispute (Halley, Reemtsma and Creech, 1958; Wollman, Stephen, Clement and Danielson, 1966), but even if the response is normal, the predicted increase in CBFE due to the increase in P_aCO_2 in the present series would only be of the order of 6%. (see Table XV, p.103).

$$\frac{CBF}{CMRO_2} = CBFE = \frac{1}{(A\text{-}V)O_2}$$

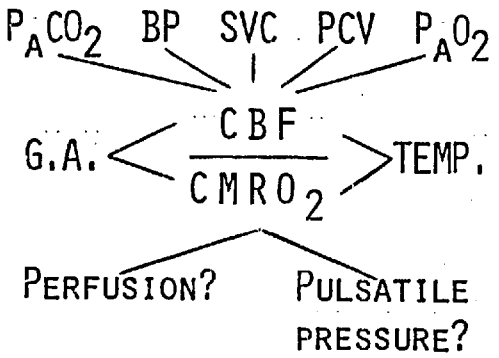


Fig. 21. Factors which might influence the cerebral blood flow equivalent at the onset of cardio-pulmonary bypass.

The mean arterial oxygen tension did not change during the first five minutes of perfusion and no values below 70 mm Hg were recorded in any patient throughout this period. Hypoxia does not influence cerebral blood flow until the arterial oxygen tension falls to less than 50 mm, whereas hyperoxia causes cerebral vasoconstriction(Harper, 1965), and it is most unlikely therefore, that individual variations in arterial oxygenation contributed to the changes observed in the CBFE.

Measurements of arterial pH were not included in the study because, as a result of the slow entry of hydrogen and bicarbonate ions into cerebral extracellular fluid, acute changes in arterial pH, other than those mediated by changes in P_aCO_2, have little effect on cerebral blood flow (Smith and Wollman, 1972). Routine clinical monitoring did not reveal serious derangements of pH in any patient, either before or soon after the onset of bypass, and the priming fluid in the oxygenator and extracorporeal circuit was always adjusted to a physiological pH before bypass commenced.

The influence of changes in haematocrit

Acute fluctuations in whole body haematocrit (PCV) alter the oxygen carrying capacity so that sensible comparison of cerebral $(A\text{-}V)O_2$ is only possible when the arterial sample, which was collected from the radial artery in the present series, is representative of carotid arterial blood. Full flow (80 ml/kg/min or more) from the oxygenator was reached in less than five minutes in all cases and the arterial PCV remained constant to within 1% from three minutes onwards. Satisfactory mixing of the priming solution with the patient's blood was

assumed therefore, to be complete by five minutes, and comparison of $(A\text{-}V)O_2$ and hence of CBFE, was restricted to the two pairs of samples which were collected before perfusion and five minutes after the onset.

The effects of dilutional anaemia on cerebral blood flow and metabolism were studied in dogs by Michenfelder and Theye (1969). They found that a fall in haemoglobin concentration from 12.4 to 7.8 gm/100 ml (a decrease of 37.1%) did not alter cerebral metabolic rate, but was associated with an increase in cerebral blood flow so that the CBFE rose from 16.1 to 19.4 ml blood/ml oxygen uptake (+20.5%). In the present study, a fall in PCV from 41.3 to 28.1 (a reduction by 32% of the initial value) was associated with an increase in CBFE from 15.2 to 23.4 ml blood/ml oxygen uptake (+54%). Even if similar mechanisms apply in man during cardio-pulmonary bypass, the increase in CBFE is more than twice that recorded by Michenfelder and Theye (1969) for a comparable degree of haemodilution in dogs and is out of proportion to the reduction in haematocrit.

The influence of changes in body temperature

Cerebral blood flow and metabolic rate can be influenced by changes in temperature in dogs (Rosomoff and Holaday, 1954; Kleinerman and Hopkins, 1955; Michenfelder and Theye, 1968), and in man (Stone, Donnelly and Frobese, 1956; Cohen, Wollman, Alexander, Chase and Behan, 1964). Although it is generally considered that the two variables are decreased in proportion so that the CBFE remains unchanged (Smith and Wollman, 1972), Michenfelder and Theye (1968) and Kleinerman and Hopkins (1955) noted disparity between the depression of blood flow and metabolism in some circumstances. A

selective decrease in cerebral metabolic rate must result in an increase in CBFE but, assuming a Q_{10} value for the human brain of 2.5 (Smith and Wollman, 1972), this being the factor by which a metabolic rate is altered when the temperature changes by 10°C, the rise in CBFE caused by a reduction in body temperature of only 0.5°C would be trivial (approximately 3%).

The effect of changes in the depth of general anaesthesia

The value for CBFE before the onset of bypass in the present series (15.2 ml blood/ml oxygen uptake) is compatible with the nett effect of light anaesthesia with thiopentone and nitrous oxide (Wollman,Alexander, Cohen, Smith, Chase, van der Molen, 1965; McDowall, 1965), moderate hypocapnia and, in some patients, reduction in cerebral blood flow due to a poor cardiac output (Donald, 1959). The depth of anaesthesia falls at the onset of bypass, largely because of the elimination of nitrous oxide, and this would tend to lower rather than increase the CBFE (Smith and Wollman, 1972).

The importance of changes in systemic arterial and superior caval pressure

The abrupt reduction in both arterial and superior vena caval pressures at the onset of perfusion reduced the cerebral perfusion pressure (mean arterial minus mean superior caval pressure) from 68 mm Hg before bypass to 42 mm Hg five minutes later, with even lower values occurring sometimes between one and three minutes. Although autoregulation can preserve the cerebral blood flow in spite of wide changes in perfusion pressure, the mechanism may take several minutes to occur (Kogure, Scheinberg, Fujishima, Busto and Reinmuth, 1970), starts to fail when the mean

arterial pressure falls below approximately 60 mm Hg (Lassen, 1959), and may be impaired by deep anaesthesia or extensive surgery (Harper, 1965).

An increase in CBFE at the onset of perfusion could represent an increase in cerebral blood flow consequent upon an increased systemic flow rate when the extracorporeal circuit takes over from a failing heart, but in view of the limitations of the autoregulatory mechanism detailed above, it is difficult to believe that this can occur when the cerebral perfusion pressure falls so profoundly. This analysis emphasised the need to make some direct assessment of changes in cerebral blood flow at the onset of bypass and a limited study has been undertaken using a modified thermo-velocity technique.

CHAPTER VI

THERMO-VELOCITY SYSTEM FOR MONITORING JUGULAR VENOUS BLOOD FLOW

The methods employed most commonly to measure cerebral blood flow in clinical studies are the insert gas uptake (Kety-Schmidt) and tissue clearance techniques (Ingvar and Lassen, 1965), but neither is entirely suitable for use during cardiac surgery. At the onset of bypass, a number of biochemical and haemodynamic factors change acutely, the lungs are excluded from the circulation, the head vessels are not exposed and the patient is fully heparinised so that intra-arterial injection or cannulation is more hazardous than usual. In a review of techniques for monitoring cerebral blood flow and metabolism in patients with cerebro-vascular disease, Meyer,Gotoh, Tomito and Akiyama (1966) state that the thermo-velocity method (Meyer,Gotoh, Naran and Handa, 1964) proved the most practical for detecting small, rapid changes in cerebral venous flow, although other methods were preferable for accurate, quantitative studies. The method suffers from a number of disadvantages, largely because it measures velocity rather than volume flow in a vessel of unknown diameter, and because of the inequality of blood flow between the two internal jugular veins (Munck and Lassen, 1957). The advantages for the present study were that only a single intravenous cannula is placed in the patient, bulky apparatus is not required, and the measurement is infinitely repeatable at short intervals. Unexpected difficulties were encountered initially, but with a modification of Meyer's technique, it has proved possible to make a qualitative assessment of changes in cerebral blood flow at the onset of cardio-pulmonary bypass in man.

CONSTRUCTION OF THERMO-VELOCITY PROBE

Two thermistors (Standard Telephones and Cables, type U23US) are soldered to strands of 'Lewmex' 42 gauge enamelled copper wire which are coiled into separate pairs (Fig. 22 p. 77). The soldered junctions are insulated with PTFE spray ('Hiflon') and buttressed with 'Araldite' to prevent mechanical distortion. The two mounted thermistors are then drawn into the lumen of a 'Portex' nylon intravenous cannula (ID 1.2 mm; length 30 cm), so that they are close together, but not touching, near the tip of the cannula. After confirming that there is no electrical contact between the pairs of wires, even in the presence of saline, silicone rubber adhesive sealant ('Silcoset') is injected into the tip of the cannula until it reaches the distal edge of a side-hole which has been made previously in the wall of the cannula, about 2 cm from the tip. The terminal plug of 'Silcoset' immobilises the thermistors in position and prevents the accumulation of blood inside the lumen of the cannula, distal to the side-hole, where it is difficult to remove. The pairs of wires are brought out through the side of the Luer hub and soldered separately to twincore, screened cable. These junctions are insulated with 'Araldite' which is also used to seal the holes in the Luer hub.

Before use, the entire assembly is sterilised using ethylene oxide. It can then be introduced percutaneously into the internal jugular vein through a 14 gauge needle, and threaded in a retrograde direction as described previously, until the tip lies at the level of the base of the skull.

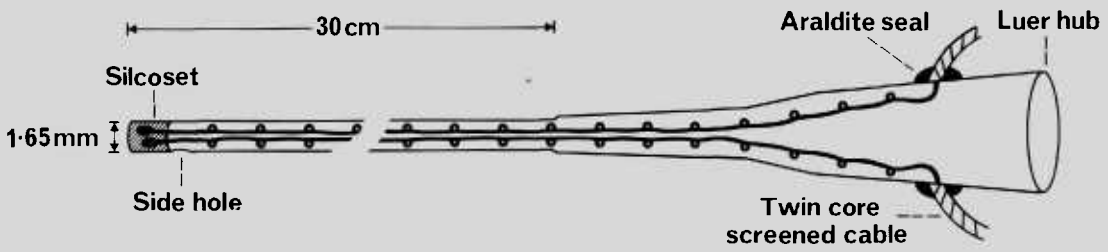


Fig. 22. Detail of the thermo-velocity probe.

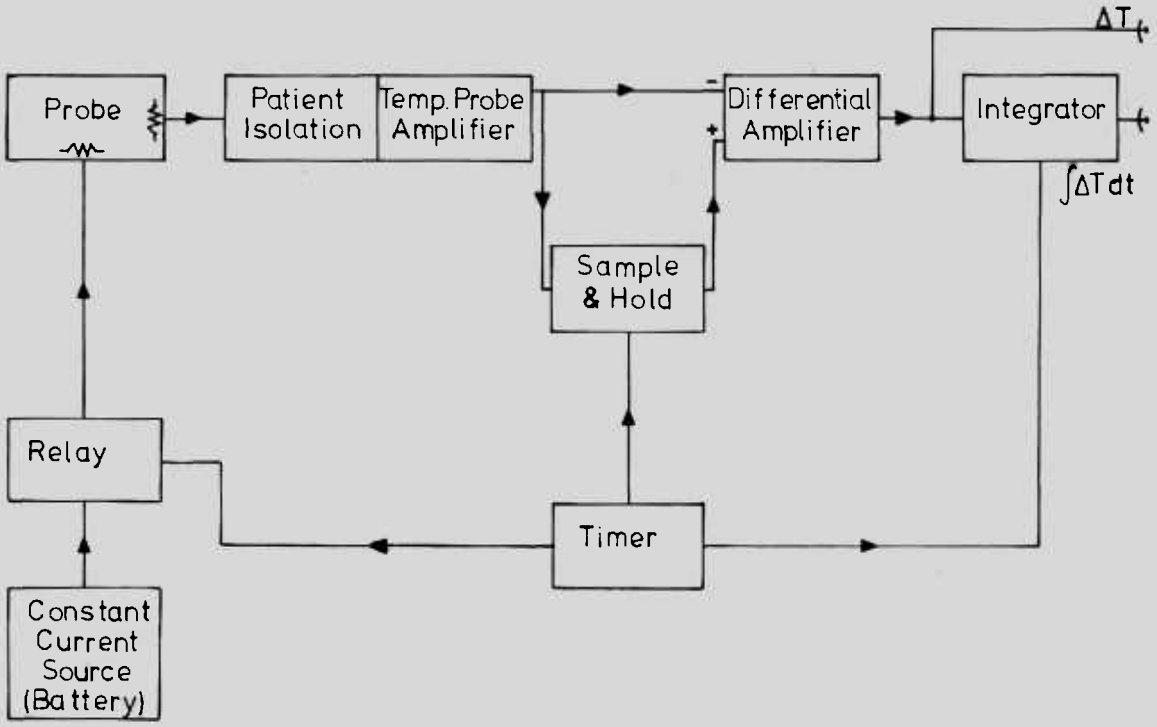


Fig. 23. Circuit diagram for thermo-velocity system.

THERMO-VELOCITY CIRCUIT

The distal thermistor is heated intermittently by a battery-operated constant current source, while the change of temperature sensed by the proximal thermistor is amplified and recorded using the temperature detecting circuit of a thermo-dilution cardiac output monitor* (Fig. 23 p. 77).

The heating circuit is controlled by the timer, operating via a glass encapsulated reed relay (Alma Relay Ltd.) which has both an operating and a release time of less than 5 msec. The duration of each heating pulse is 5 sec and the current required to produce a peak change of 0.5 - 1.0°C in the detecting thermistor varies between 2 and 5 mA, depending on the proximity and thermal insulation of the pair of thermistors. The timer and its associated logic also control the function of a circuit which samples the temperature of the detecting thermistor during the 5 sec preceding each heating pulse, and holds the value registered at the end of this 5 sec period, so providing a 'baseline' value for one input to a differential amplifier. The other input is the subsequent change in temperature induced by the heating pulse.

The output of the differential amplifier is fed to an integrator, and this too, is controlled by the timer and relay circuits so that integration starts when the heating pulse is initiated, and continues for a total of 15 sec. The integrator is reset automatically at the end of this time, and remains in this condition for 5 sec until integration restarts with the onset of the next heating pulse. The duration of the entire cycle is therefore, 20 seconds.

The height of the integrated signal is inversely proportional

* Devices Ltd.

to the velocity of blood flow past the tip of the cannula and is recorded three times each minute.

EVALUATION OF THERMO-VELOCITY SYSTEM IN VITRO

The performance of the system was investigated by inserting the probe through one limb of a Y-connector into a circuit of 1.27 cm diameter tubing which was immersed in a constant temperature water bath (Fig. 24, p. 80). The tip of the probe was supported in the centre of the tubing and pointed against the direction of flow. Volume flow through the circuit was controlled by a roller pump* which had been calibrated at different settings by pumping saline from the reservoir through the circuit and into a graduated cylinder.

Calibration curves for the thermo-velocity probe were constructed by plotting the height of the integrated signal against volume flow under varying circumstances. Most studies were carried out at 37°C in 1.27 cm diameter tubing which is comparable to the diameter of the normal internal jugular vein. The performance of the system was also evaluated in 2.54 and 0.635 cm diameter tubing, at different temperatures ranging from 30 to 38°C, and with blood rather than saline in the circuit. The ability of the system to adjust to variations in background temperature was studied by allowing the stirred water bath to cool slowly towards room temperature while the thermo-velocity system continued to record with saline circulating at a constant flow rate.

* Watson-Marlow MHRE 200.

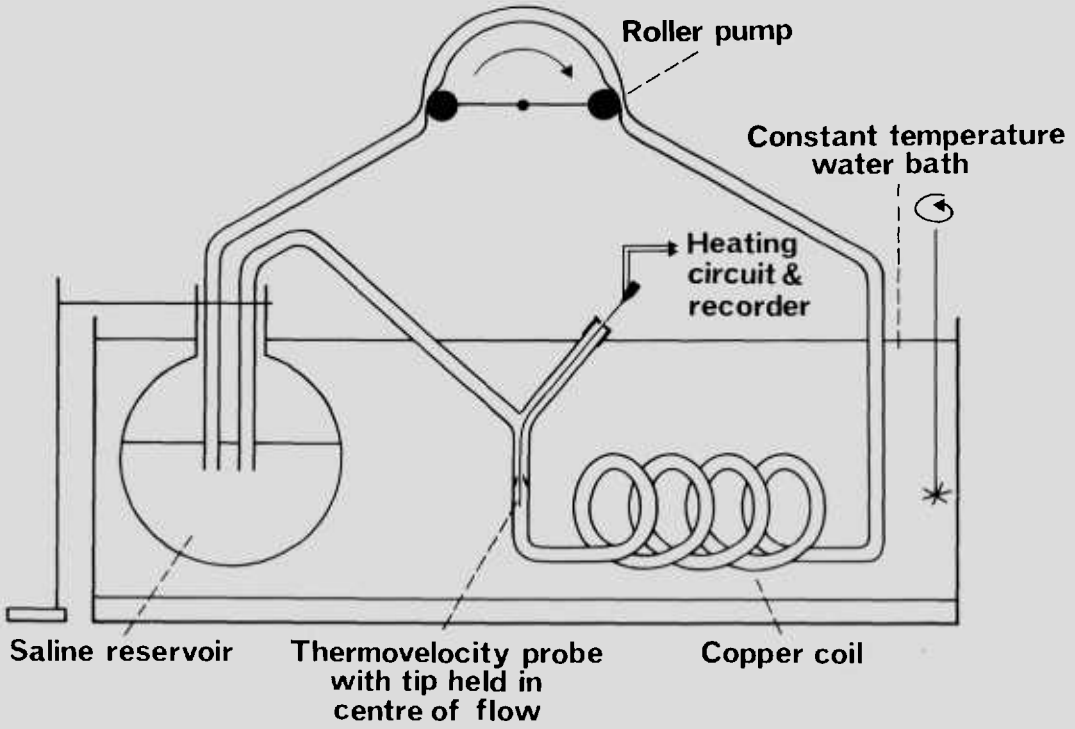


Fig. 24. Calibrating circuit for thermo-velocity system.

The influence of tubing diameter

A typical calibration curve is shown in Fig. 25, p 82. The absolute height of the integral varied from one probe to another but their performance was similar in other respects. In particular, adequate resolution could only be achieved up to flows of 200-250 ml/min in tubing of 1.27 cm diameter. Attempts to improve this by varying the geometry of the thermistors at the tip of the probe were unsuccessful, and although some increase in resolution resulted from the use of higher heating currents, this was considered prohibitive for clinical application because of the risk of tissue damage which might lead to thrombosis.

At constant volume flow rate, velocity is inversely proportional to the square of the radius of the tubing. As a result, the integral height was greater in larger diameter tubing and adequate resolution could be obtained over a slightly larger range of volume flow rates (Fig. 26, p 82).

The effect of differences in thermal conductivity

Use of blood rather than saline in the circuit resulted in an increase in integral height, representing less effective heat clearance (Fig. 27, p 83). This finding is in keeping with values quoted* for thermal conductivity of blood and 0.9% saline solution:-

thermal conductivity of saline 625 mWatts m^{-1} K^{-1}

thermal conductivity of blood 506 mWatts m^{-1} K^{-1}

The effect of changes in background temperature

The resistance (R) of a thermistor is inversely proportional

* Personal communication; National Engineering Laboratory, East Kilbride.

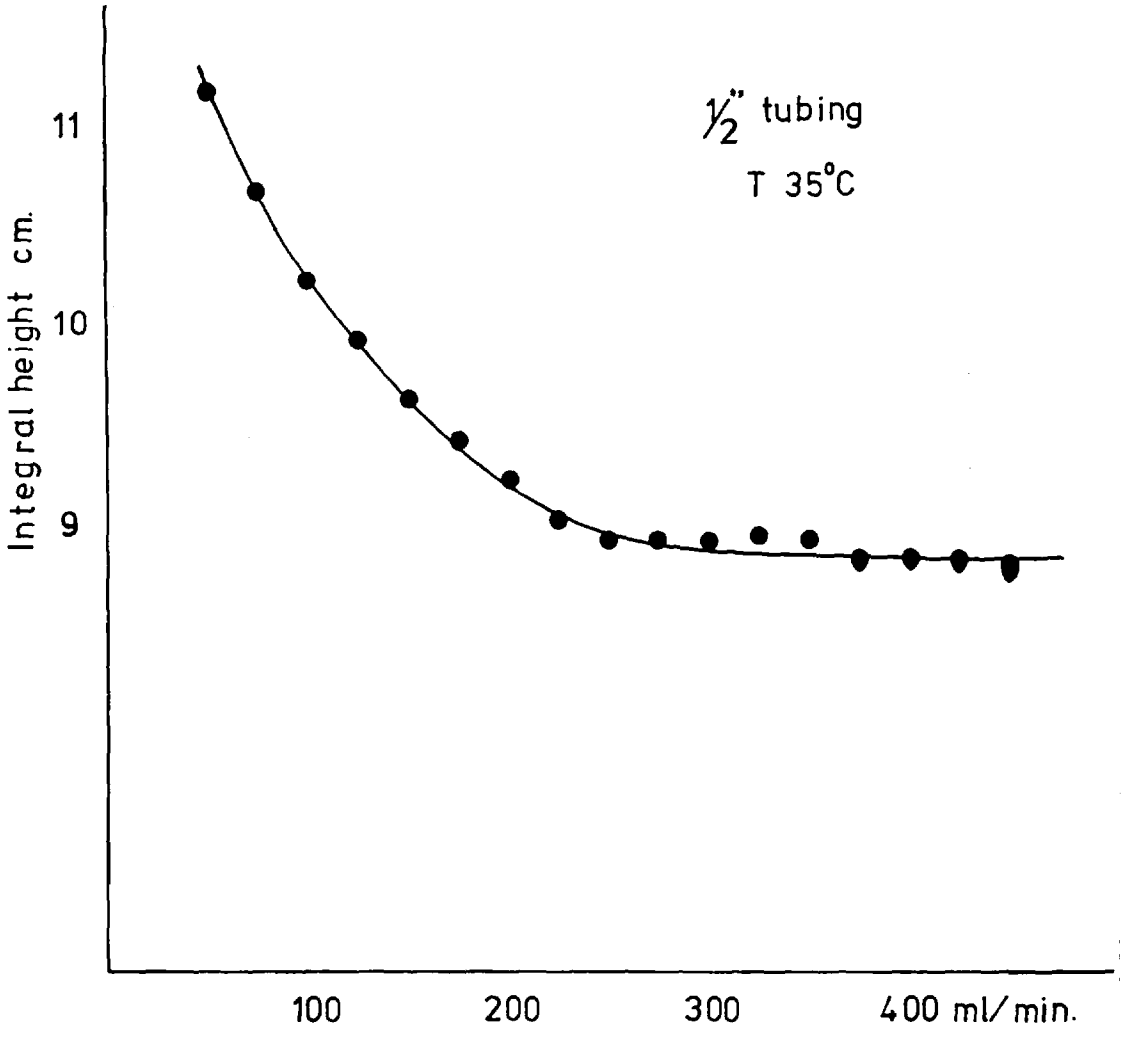


Fig. 25. Typical calibration curve of thermo-velocity system.

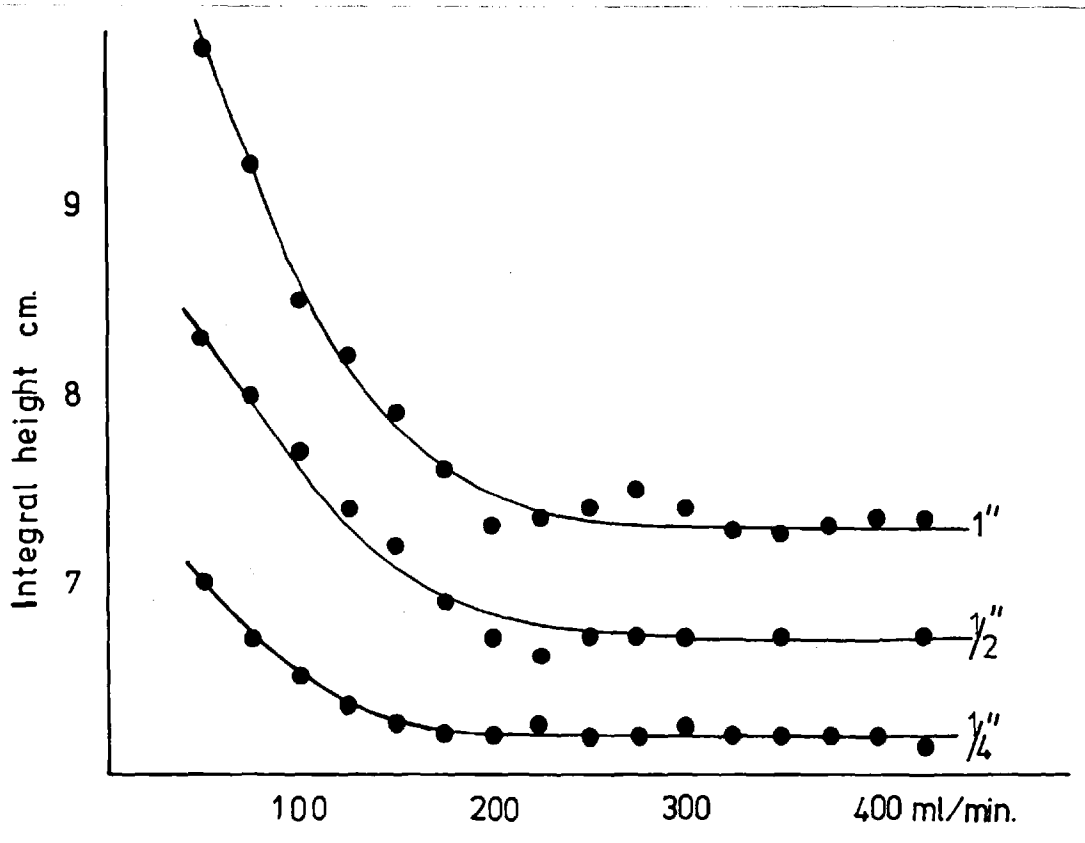


Fig. 26. Effect of tubing diameter on thermo-velocity system.

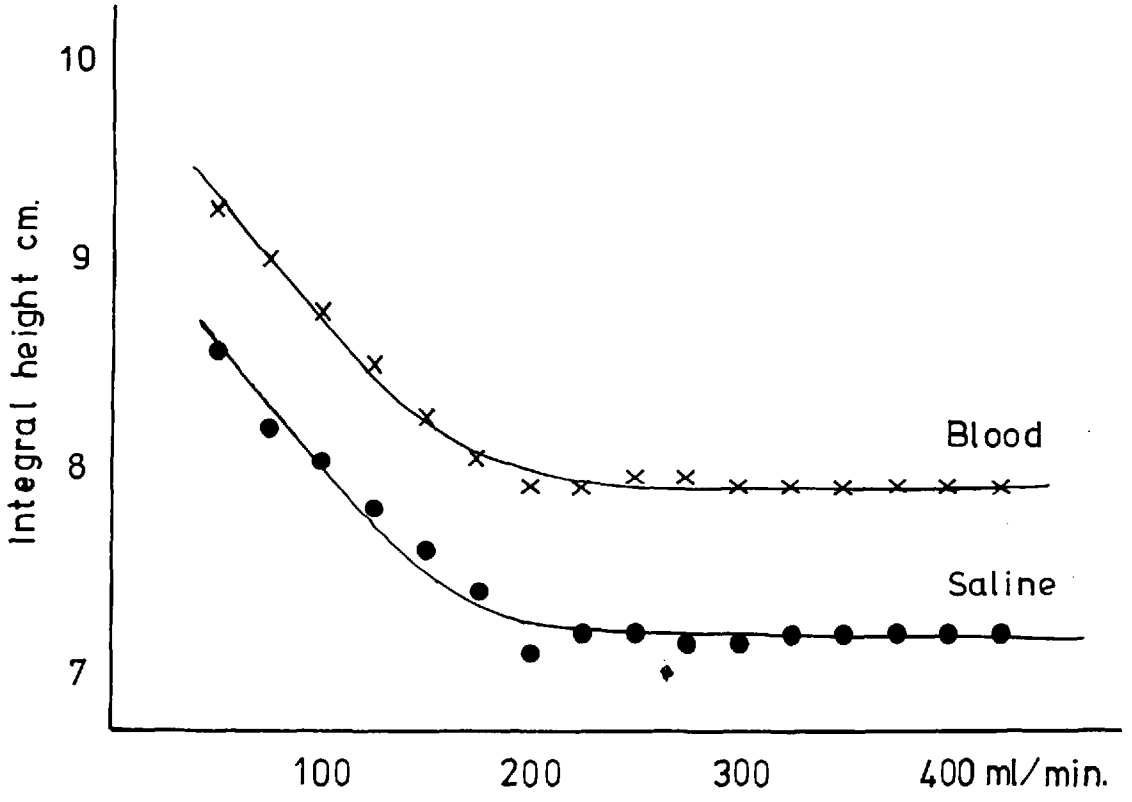


Fig. 27. Comparison of the performance of a thermo-velocity probe when calibrated in saline and in blood.

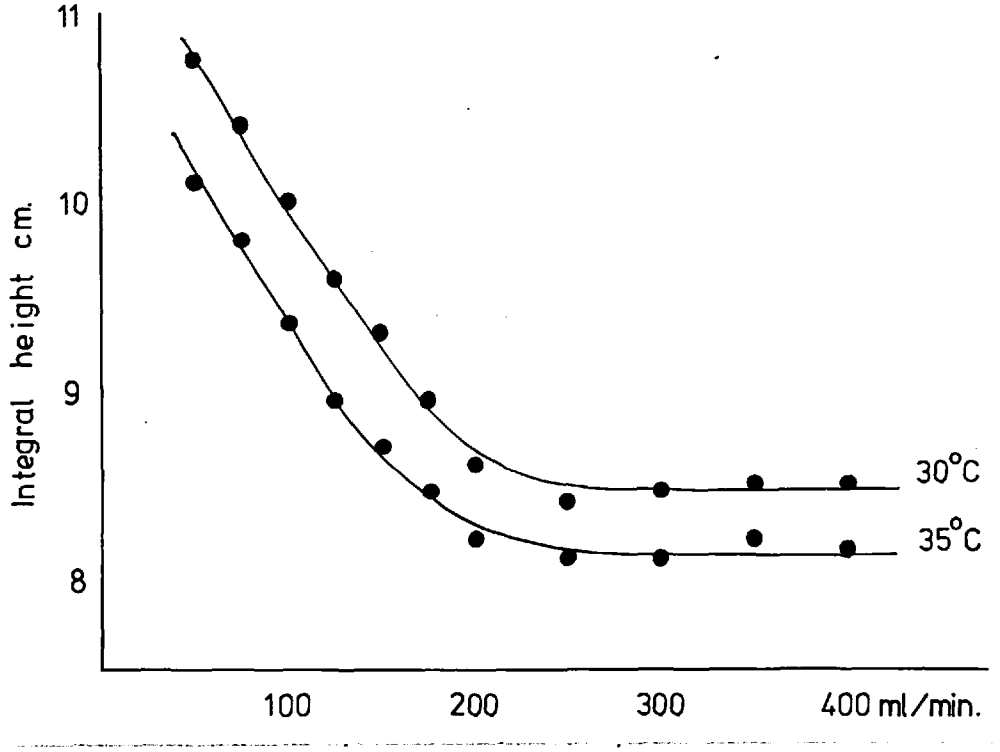


Fig. 28. The effect of a change in background temperature on the performance of the thermo-velocity system.

to temperature and therefore, at constant current flow (I), the magnitude of each heating pulse (I^2R) will also be inversely proportional to temperature. In the system described, this resulted in an increase in the height of the integral of less than 1% for each degree C decrease in temperature (Fig. 28, p 83). A rapid change in background temperature caused gross distortion of the integral height because of the increment or decrement of heat which summated with each pulsed signal, but the effects of slow changes in temperature were only slight (Fig. 29, p 85) because of the compensating effects of the temperature 'sense and hold' circuit which was coupled to the differential amplifier.

These in vitro findings with the thermo-velocity system led to the prediction that it might prove ineffective as a means of identifying changes in cerebral blood flow at the onset of bypass, but, because of the simplicity and safety of the method, and the possibility that the changes in cerebral flow might be gross at this time, it was decided to proceed with the clinical study.

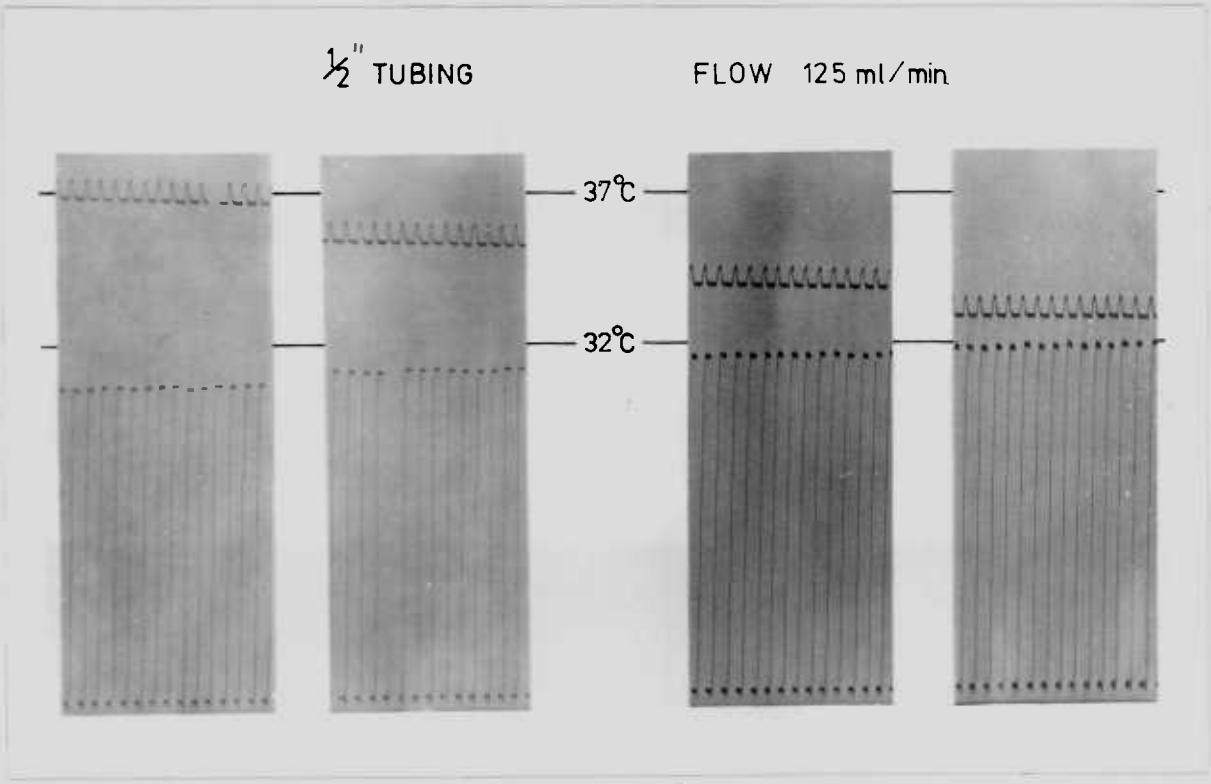
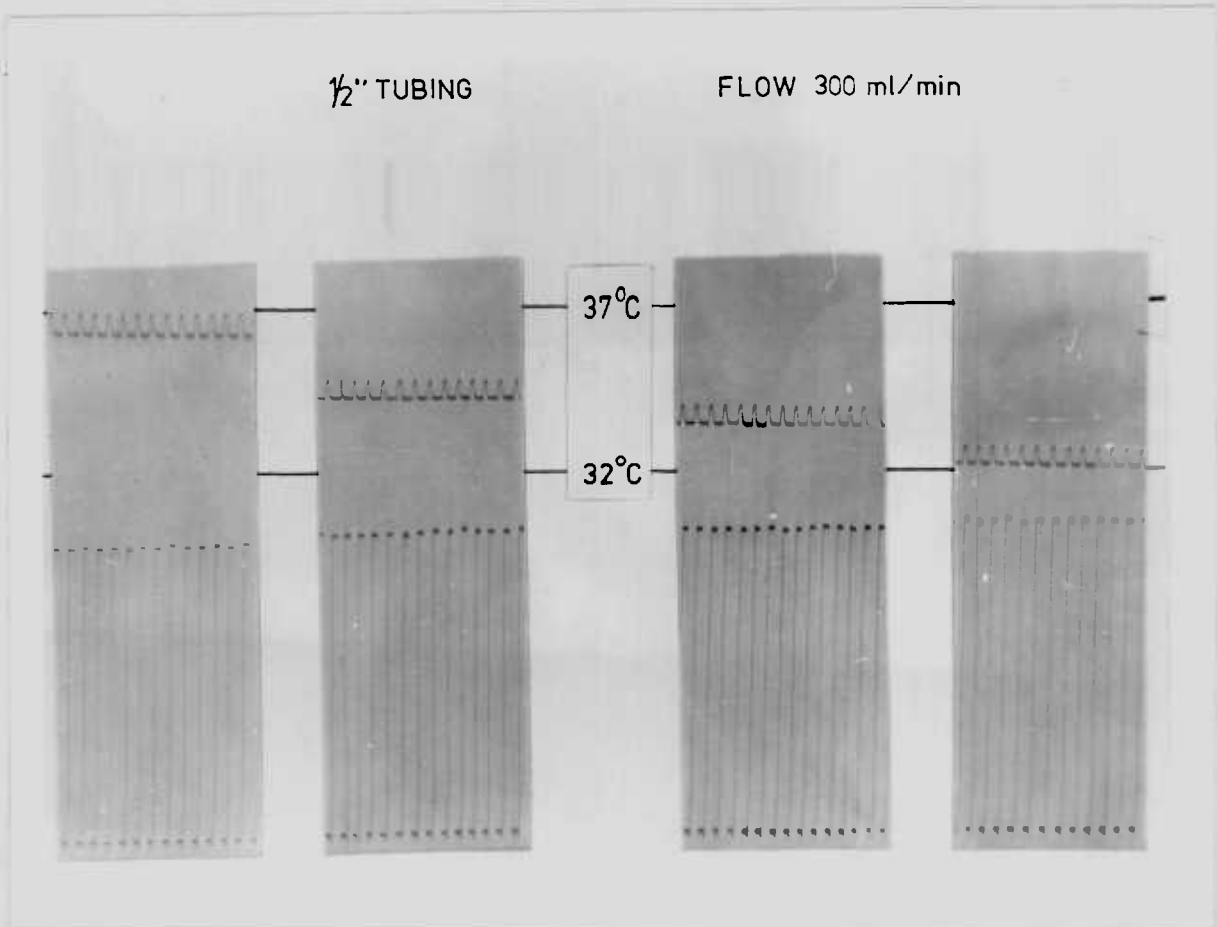


Fig. 29. The effect of a slow change in background temperature at different flow rates.



CHAPTER VII

CLINICAL STUDIES WITH THE THERMO-VELOCITY SYSTEM

The thermo-velocity system was used in 12 unselected adult patients aged from 20 to 64 years who formed part of the larger group of 30 patients in whom changes in jugular venous oxygen content were investigated during the first five minutes of perfusion (Chapter V).

The probe was introduced into the right internal jugular vein after the induction of anaesthesia, but the circuit remained switched off until the chest had been opened and surgical diathermy was only being used infrequently. Then, the integrator was balanced while there was no current flowing in the heating circuit and finally, the heating circuit was switched on a few minutes before the heart was cannulated.

The height of the integrated signal was recorded by superimposing this trace over those derived from the other variables which were being monitored on the ultraviolet recorder - arterial and superior vena caval pressures, CFM signal and body temperature. Instead of naso-pharyngeal temperature, the temperature of the detecting thermistor was recorded at low amplification to show changes in body temperature, and consequently, the pulsed thermo-velocity signal gave a saw-tooth appearance to this trace. Recording was continued until decannulation of the heart at the end of bypass when the thermo-velocity probe was removed, after the effects of heparin had been reversed with protamine sulphate. One patient died on the table very soon after bypass had been discontinued, and in this patient, recording was continued until the time of death.

CHANGES IN INTEGRAL HEIGHT AT THE ONSET OF PERFUSION

The integral height was measured in every patient for the first 15 cycles (5 minutes) following the onset of perfusion and compared with the last 6 cycles (2 minutes) preceding the onset. Although every effort was made to hold the body temperature constant, there was often a transitory, sudden change during the first few minutes representing the circulation of fluid which had been lying in the extracorporeal circuit, beyond the heat exchanger, while the heart was being cannulated and the various connections made. The thermo-velocity system cannot compensate for very rapid changes in temperature (Chapter VI) and 26 obviously artefactual values were eliminated (see Figs. 30-32, p.89 & 90 This decreased the number of integral heights which were included in the analysis of the first five minutes of perfusion from 180 to 154.

For the group as a whole, there was no significant change in integral height following the onset of perfusion, but there was considerable variation between patients, in 5 of whom there was a significant fall, whereas in 7, there was either no change or an increase.

Inspection of the traces (Figs. 30-32) suggested that the direction and magnitude of the change in integral height at the onset of perfusion was related to the degree of arterial hypotension which occurred simultaneously, and comparison of several variables (Table XIII, p.91) showed that in the 5 patients in whom the integral height fell, there was a greater increase in P_aCO_2 and a tendency towards a smaller fall in mean arterial blood pressure than in the 7 patients in whom the integral height increased or remained unchanged.

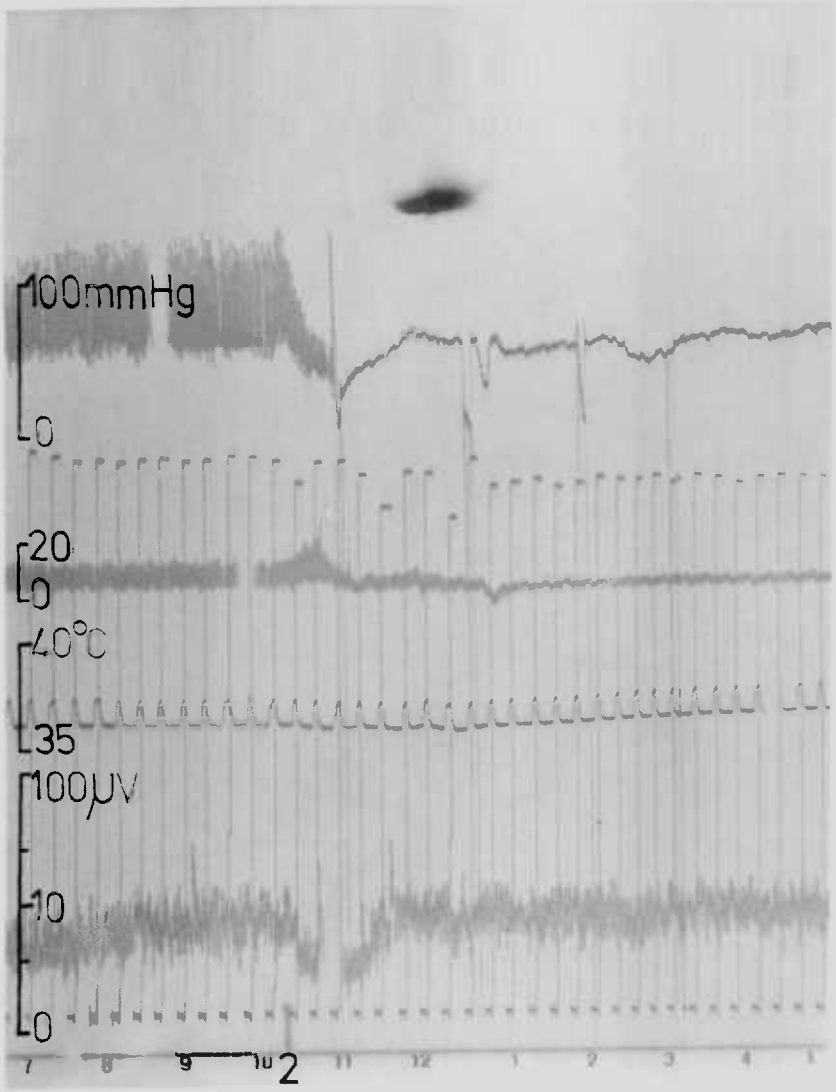


Fig. 30. Change in the height of the integrated thermo-velocity signal at the onset of bypass (marker 2) in a patient in whom there was only minimal hypotension. This should be compared with Figs. 31 and 32, p. 90, in which the onset of bypass (markers 4 and 3 respectively) is followed by mild (Fig. 31) or severe (Fig. 32) hypotension.

Tracings in this and subsequent figures are, from above downwards, arterial blood pressure, superior vena caval pressure, temperature of the detecting thermistor in the jugular bulb, with the thermo-velocity pulse giving a saw-tooth appearance, and finally, the CFM record. The integrated thermo-velocity signal appears as an uncalibrated, tall, step-like signal, superimposed across the other records.

One or two obviously artefactual integral heights are visible in each figure, associated with a sudden alteration in body temperature, but the lack of change with a gradual alteration of temperature is apparent in Fig. 30, after the onset of bypass.

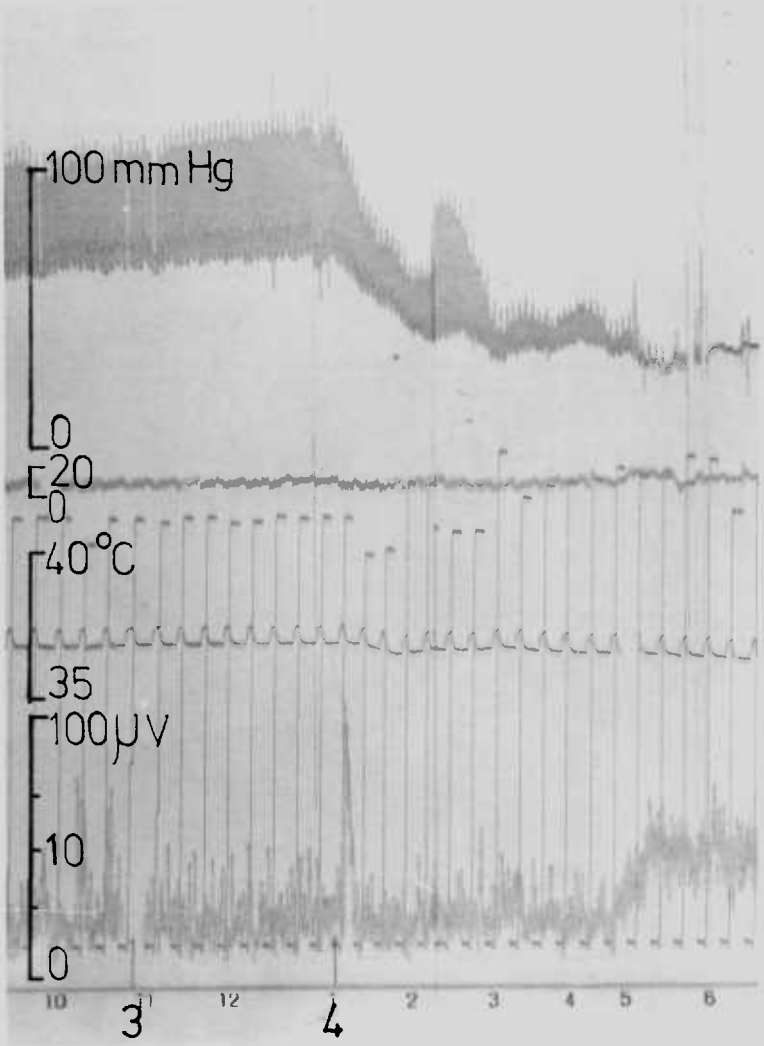
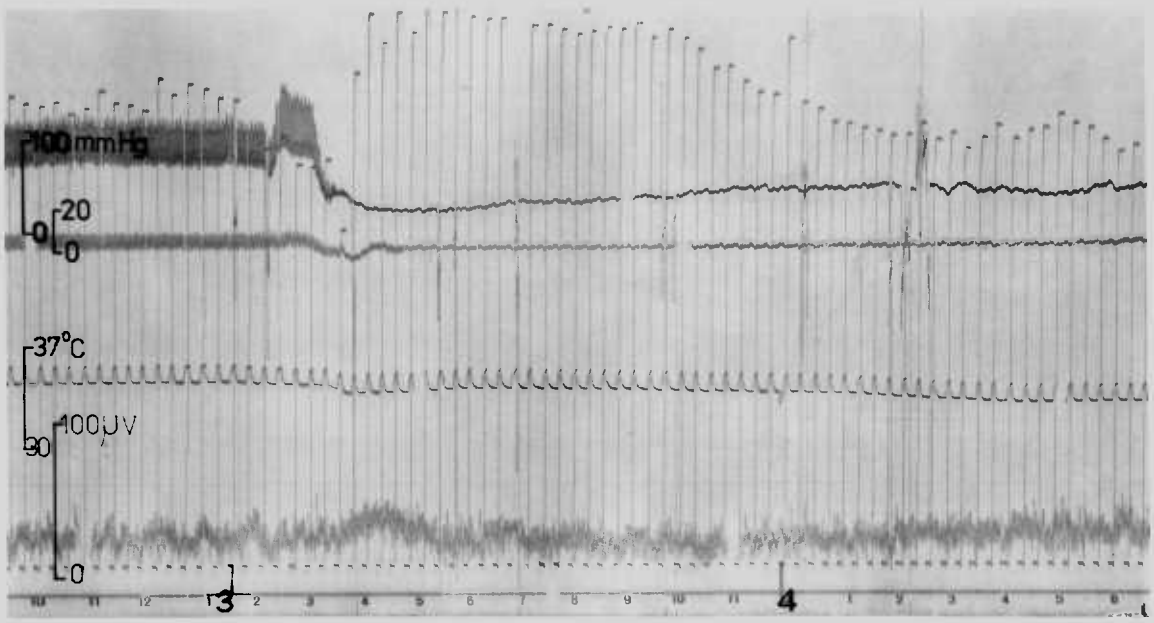

100 mm Hg
0
20
0
40°C
35
100µV
10
0
10
11
12
1
2
3
4
5
6
3
4

Fig. 31.

Fig. 32.


100 mm Hg
0
20
0
37°C
90
100µV
0
3
4

	Group A	Group B	Mean Diff/SEM	Significance
Δ C_vO_2 vols %	-4.22	-5.07	-0.85 $\pm$ 2.28	> 0.1
Δ $(A-V)O_2$ vols %	-2.36	-1.77	0.59 $\pm$ 2.33	> 0.1
Δ CBFE ml blood/ml O_2	6.34	8.50	2.16 $\pm$ 6.96	> 0.1
Δ BP mm Hg	-28.8	-49.0	-20.2 $\pm$ 9.79	$0.1 > p > 0.05$
BP at 5 minutes mm Hg	45.0	33.3	-11.7 $\pm$ 5.7	$0.1 > p > 0.05$
Δ P_aCO_2 mm Hg	5.8	1.53	-4.27 $\pm$ 1.76	< 0.05
Δ T^oC	-0.04	-0.64	-0.60 $\pm$ 0.44	> 0.1

Table XIII. Comparison of changes during the first 5 minutes of perfusion in Group A (patients in whom height of integrated thermo-velocity signal fell) with Group B, (patients in whom height of integrated thermo-velocity signal increased or remained unchanged).

INTERPRETATION OF CHANGES IN INTEGRAL HEIGHT AT THE ONSET OF PERFUSION

Volume flow and velocity are related consistently only if the diameter of the vessel remains constant, the flow characteristics are unaltered, and the probe is positioned centrally (Hill, 1970). Additional factors such as thermal conductivity and temperature influence the relationship between integral height, velocity and volume flow in the thermo-velocity system (Chapter VI) and it is apparent therefore, that several variables other than changes in volume flow might be expected to contribute to the alterations in integral height which were observed at the onset of perfusion.

Although the internal jugular vein is surrounded by the dense fascia of the carotid sheath and is more firmly tethered at the base of the skull than lower in the neck (Jamieson, 1945), the abrupt reduction in superior vena caval pressure associated with the onset of perfusion may cause a decrease in the diameter of the vessel. At constant volume flow, this would increase the velocity of flow and so tend to decrease the height of the integrated thermo-velocity signal (Fig. 26, p 82). Haemodilution also facilitates thermal dissipation and should accentuate the reduction in integral height (Fig. 27, p 83). Only a very marked reduction in body temperature would offset this change (Fig. 28, p 83) and small variations such as occurred in the present series (mean reduction 0.5°C) are unlikely to have a significant influence.

No attempt was made to ensure that the probe was positioned centrally in the vein during clinical studies because the method was only used to make a qualitative assessment of change, but if

irregularity in the integral height was noted before the onset of perfusion when haemodynamic conditions were stable, this was assumed to represent artefact caused by the probe touching the side of the vessel (Meyer, Gotoh, Naran and Handa, 1964). This irregularity could be eliminated easily by minor adjustment to the position of the probe which was not moved again throughout the course of the study. Occasionally, random irregularities were noted after this adjustment had been made; these lasted for only a few seconds (one or two thermo-velocity 'pulses') and were thought to be related to transitory alterations in jugular flow during manipulations of the superior vena cava which were too short-lived to be detected as changes in mean caval pressure.

This analysis leads to the prediction that, unless there is a concomitant change in cerebral blood flow, the height of the integrated thermo-velocity signal should decrease at the onset of perfusion because of the effects of haemodilution and the reduction in vessel diameter. An increase in cerebral blood flow would accentuate this reduction in integral height, whereas a fall in cerebral blood flow would tend to offset it. If the fall in cerebral blood flow was profound, it would be sufficient ultimately, to obliterate the influence of haemodilution and a change in vessel diameter, and therefore, the integral height would remain unchanged or even increase. In 5 of the 12 patients studied, a significant fall in integral height was recorded during the first five minutes of perfusion, but in the remaining 7 instances, the integral height either rose or remained unchanged. This implies that the cerebral blood flow had fallen in these 7 patients, and the association between this finding and the tendency towards a greater fall in systemic arterial pressure has been noted already (Table XIII, p. 91).

THE INFLUENCE OF CHANGES IN P_aCO_2: RESOLUTION OF THERMO-VELOCITY SYSTEM

The increase in arterial carbon dioxide tension during the first five minutes of perfusion was less in the 7 patients in whom the integral height rose or remained unchanged than in the remaining 5 patients. Although the variations in P_aCO_2 were small (1.5 - 6 mm Hg), it is possible that they contributed to changes in cerebral blood flow occurring at this time.

The division of opinion on the ability of the cerebral vessels to respond normally to changes in P_aCO_2 during extracorporeal circulation has been referred to in Chapter V, and a subsidiary study was undertaken therefore, to establish whether a normal cerebro-vascular response to changes in carbon dioxide was preserved under the conditions of the present study.

P_aCO_2 was altered during perfusion on 10 occasions, either by doubling the flow rate of carbon dioxide delivered to the oxygenator, or by eliminating it entirely for periods of 10-15 minutes. Samples of arterial and jugular venous blood were collected for the determination of gas tensions and oxygen content at the beginning and end of each of these periods, and were analysed by the methods described previously.

Accurate interpretation of the findings was hampered in several instances by simultaneous variations in mean arterial blood pressure or body temperature. On 8 occasions, there was a reciprocal relationship between P_aCO_2 and $(A\text{-}V)O_2$ (Fig. 33, p95), but in 2 patients, both $(A\text{-}V)O_2$ and P_aCO_2 decreased together. In these 2 patients, there was an increase in mean arterial blood pressure of 20 and 25 mm Hg

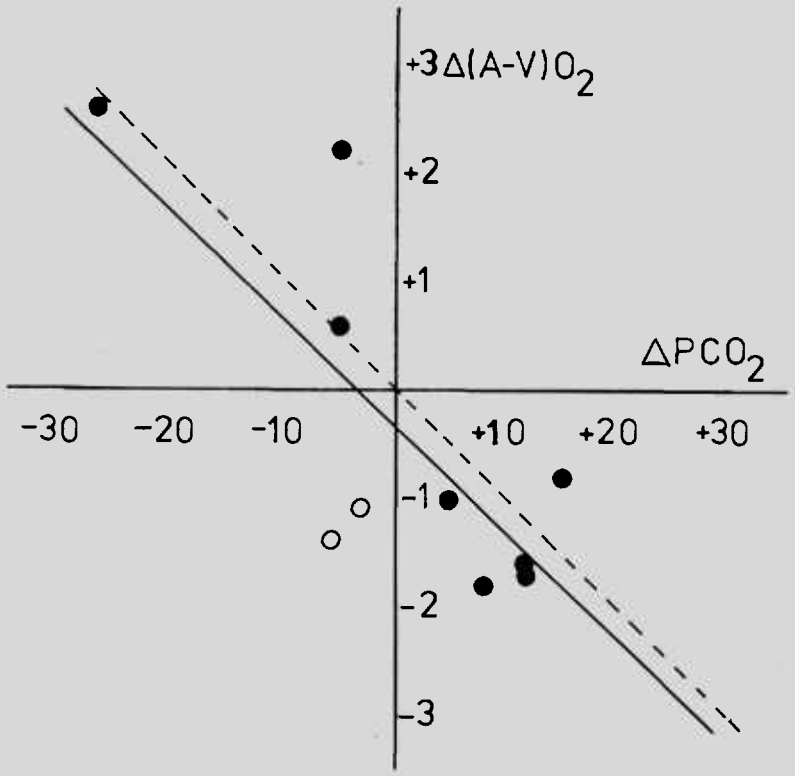


Fig. 33. The solid line is the regression equation between changes in $(A-V)O_2$ and arterial carbon dioxide tension for 10 cases.

The two open circles represent values obtained in two patients in whom a decrease in P_aCO_2 was associated with an increase in arterial blood pressure of 20 and 25 mm Hg respectively from an initial figure of less than 40 mm Hg.

The dotted line is the regression equation between changes in $(A-V)O_2$ for 8 values (i.e. excluding the 2 open circles).

For all values:-

$$\Delta (A-V)O_2 = -0.1\Delta P_aCO_2 - 0.34 \qquad r = 0.77, \; p < 0.01$$

For 8 values:-

$$\Delta (A-V)O_2 = -0.11\Delta P_aCO_2 + 0.02 \qquad r = 0.88, \; p < 0.01$$

respectively from initial values of 40 mm Hg or less, whereas in the remaining 8 instances, the mean arterial blood pressure was 50 mm Hg or more throughout the interval concerned. Alterations in integral height associated with changes in P_aCO_2 were always small, but supported the conclusion that the cerebral vessels responded normally (Fig. 34, p.97).

These small changes in integral height which were seen when P_aCO_2 was changed during perfusion reinforced the belief that major increases in cerebral blood flow could not be detected with this system because of poor resolution at high flow rates. However, the observations recorded during the final stages of surgery in the patient who died on the table (Fig. 35, p.97) support the view that important decreases in flow rate can be detected in clinical practice with this method. The apparent consistency of integral height in spite of marked fluctuations in arterial blood pressure during the pre-terminal period in Fig. 35, p.97 could signify inability of the system to detect small changes in cerebral blood flow, or, alternatively, could be attributed to lack of change in cerebral blood flow because autoregulation compensated for changes in arterial blood pressure until hypotension was extreme.

EVALUATION OF CLINICAL OBSERVATIONS WITH THERMO-VELOCITY SYSTEM

The clinical study confirmed the importance of many of the limitations which were anticipated as a result of the in vitro evaluation of the system. However, the evidence suggests that the method is capable of detecting marked reductions in cerebral blood flow.

Unequivocal conclusions cannot be drawn from the

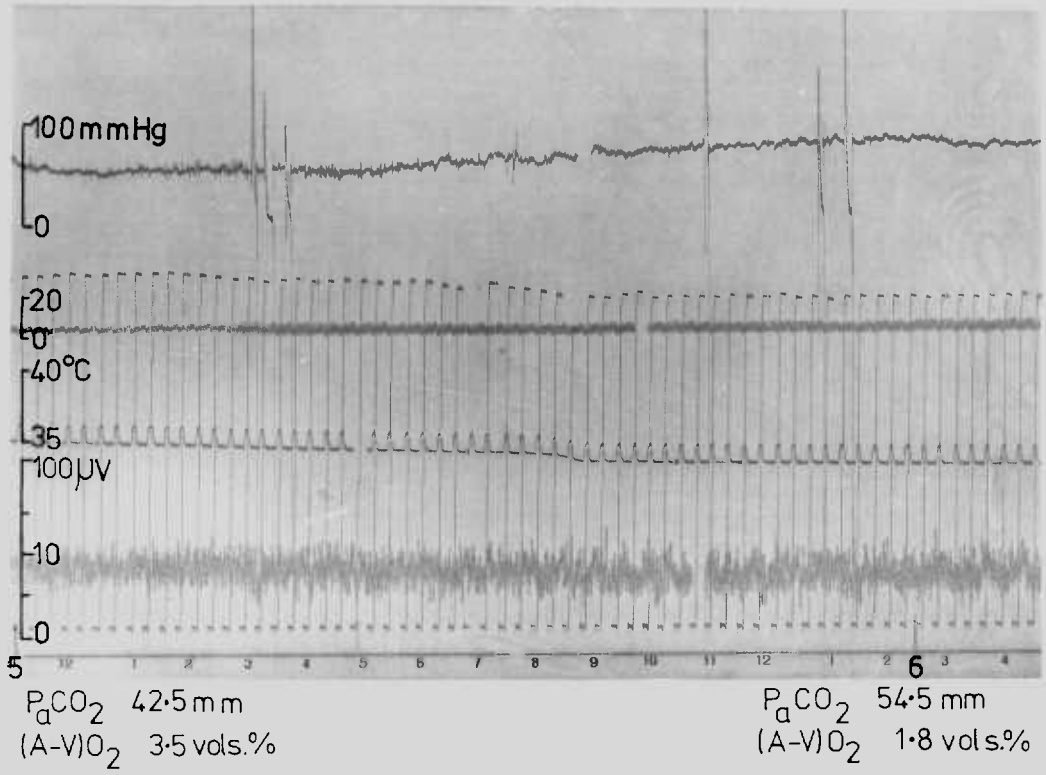


Fig. 34. Slight reduction in integral height, suggesting an increase in CBF when P_aCO_2 is increased during perfusion. The change in $(A-V)O_2$ in consistent with an increase in CBF.

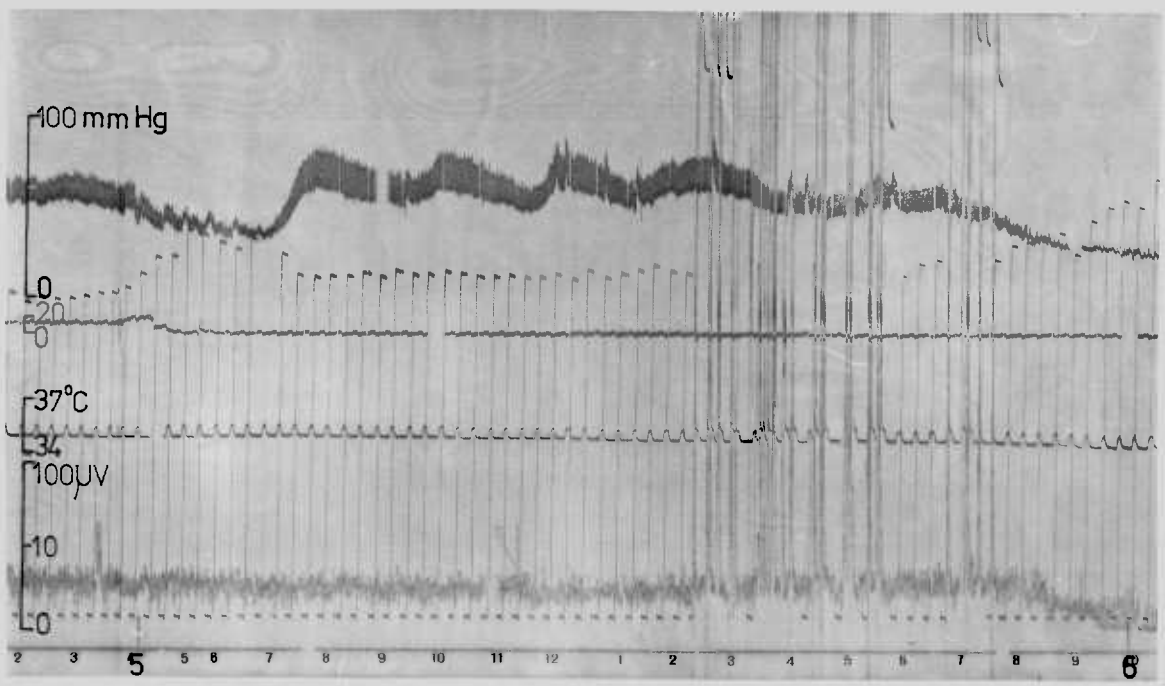


Fig. 35. Terminal circulatory failure (death at marker 6) following the end of bypass (marker 5). Therapy with inotropic agents (isoprenaline followed by adrenaline) resulted in only transitory elevation of the blood pressure.

observations presented because of the limitations enumerated, but the findings favour the hypothesis that in at least 50% of patients, cerebral blood flow falls at the onset of cardio-pulmonary bypass in association with sudden systemic hypotension. This fall occurs in spite of high overall flow rates, but may be offset to some extent by an increase in arterial carbon dioxide tension.

SIGNIFICANCE OF CHANGES IN CBFE: THE ROLE OF CEREBRAL METABOLIC RATE

The combination of hypotension and a fall in cerebral blood flow, together with a reduction in haematocrit due to haemodilution, must seriously impair oxygen availability at tissue level (Nunn and Freeman, 1964), and it is of particular interest therefore, that the cerebral blood flow equivalent rose. This must indicate a very considerable fall in cerebral metabolic rate ($CMRO_2$).

A decrease in $CMRO_2$ during extracorporeal circulation in dogs was reported by Halley, Reemtsma and Creech (1958), who measured cerebral blood flow directly using a magnetic rotameter, and calculated $CMRO_2$ as the product of $(A\text{-}V)O_2$ and the measured value for cerebral blood flow. Judging from the values quoted for arterial oxygen content, haemodilution was not employed, and although the authors were unable to exclude the effects of either hypothermia or hyperoxia, they noted that the decrease in $CMRO_2$ occurred as soon as perfusion started. The fall was consistent, but the consequent increase in jugular venous oxygen content was obscured when there was a simultaneous, marked reduction in cerebral blood flow. Halley et al (1958) were unable to show any correlation between the fall in $CMRO_2$ and the concentration of

lactic and pyruvic acids, or the lactate/pyruvate ratio in vertebral venous blood, but unfortunately, these are questionable indices of tissue hypoxia during general anaesthesia (Chamberlain and Lis, 1968).

Wollman, Stephen, Clement and Danielson (1966) attributed the reduction in $CMRO_2$, which had been reported by Halley et al (1958), to cerebral hypoxia. They make no comment on $CMRO_2$ in their own study, but inspection of the data shows that more than 50% of their values for $(A-V)O_2$ were less than 5.0 vols%, which is below the normal range (5.9-6.9 vols%; Sokoloff, 1960; or 6.7-7.1 vols%; Smith and Wollman, 1972), and compatible therefore, with a reduction in $CMRO_2$. Hypothermia and halothane anaesthesia would influence both cerebral blood flow and metabolic rate under the conditions of their study (Smith and Wollman, 1972) so that firm conclusions cannot be drawn from these figures.

The findings in the present study were comparable with those of Halley et al (1958). The mean value for the cerebral blood flow equivalent rose to a very highly significant degree following the onset of perfusion, but there were four patients in whom this index fell during the first five minutes. In these four young subjects, the associated reduction in arterial blood pressure was very marked (Table XIV, p.100), and in one patient in whom the thermo-velocity probe was used, the apparent reduction in cerebral blood flow was very striking (Fig. 32, p.90). In this patient, the jugular venous oxygen content five minutes after the onset of perfusion was only 0.9 vols%, which represents a saturation of approximately 7% (arterial content 13.5 vols%), and a venous oxygen tension of less than 10 mm Hg. In spite of this, there was no change

	Group X	Group Y	Mean Diff. ± SEM	Significance
Age in years	29.3	47.1	-17.8 ± 6.8	<0.02
Δ (A-V)O_2 vols%	+2.7	-3.0	5.7 ± 1.2	< 0.001
Δ CBFE ml blood/ml O_2	-5.0	+10.4	-15.4 ± 5.2	< 0.01
Δ BP mm Hg	-56.0	-34.5	-21.5 ± 9.7	< 0.05
BP at 5 minutes mm Hg	34.0	44.6	-10.6 ± 7.3	> 0.1

TABLE XIV Comparison of changes during the first five minutes of perfusion in Group X (4 patients in whom the CBFE fell) with Group Y, (26 patients in whom the CBFE rose).

in the CFM signal and the patient regained consciousness immediately after the operation.

The results are therefore, consistent with the hypothesis that the cerebral metabolic rate falls at the onset of perfusion and that this metabolic depression is responsible for elevation of the cerebral blood flow equivalent, although the effect is obscured by an unusually extreme reduction in cerebral blood flow in a few patients. The hypothesis is also compatible with the widely recognised clinical observation that only negligible quantities of anaesthetic agents are required to maintain unconsciousness during the procedure (see p. 15).

The aetiology of the reduction in cerebral metabolic rate remains uncertain. It could be related to a decrease in oxygen availability caused by the combination of hypotension, haemodilution, and, in some cases, a reduction in cerebral blood flow. Unequivocal proof of the presence or absence of cerebral hypoxia is not available, and the conflicting results obtained from studies which attempted to identify cerebral hypoxia during perfusion by measurements of cerebrospinal fluid oxygen tension, or lactate and pyruvate levels in jugular venous blood, have been noted already (Chapter I, p. 9-12).

An apparent reduction in overall cerebral metabolic rate could result from redistribution of cerebral blood flow away from areas of high metabolic rate. This occurs during thiopentone anaesthesia, but is thought to follow the greater metabolic depression caused by the higher concentrations of thiopentone which accumulate in areas where the initial blood flow is also high (McDowall, 1965). Redistribution of

cerebral blood flow occurring as the primary event could lead to local hypoxia in areas of high metabolic activity and this would be difficult to detect by methods which only examine overall oxygen availability. The change from pulsatile to non-pulsatile perfusion may perhaps influence the distribution of cerebral blood flow; alternatively, non-pulsatile perfusion may depress aerobic tissue metabolism in general (Geha, Malt, Naha and Baue, 1971), while McDowall (1970) suggested that lack of arterial pulsation decreases cerebral pulsation, so preventing the normal movement of interstitial fluid and promoting the accumulation of metabolites. These various possibilities warrant further study.

Comparison between the values for cerebral blood flow equivalent in the present series and those obtained in other clinical situations (Table XV, p.103), suggests that cerebral metabolic depression during perfusion is of considerable magnitude. The significance of this change is difficult to evaluate because of its uncertain aetiology, but it may be noted that it occurs suddenly, is uncontrolled, and tends to be greater in patients who sustain neurological damage (Table XII, p.67). It could be argued, by analogy with the effects of hypothermia, that a reduction in cerebral metabolic rate may act protectively and render a possible reduction in cerebral blood flow less hazardous. However, until it can be shown that cerebral hypoxia is not responsible, it is probably wiser to ignore this interpretation for practical purposes.

	CBFE ML BLOOD/ML O_2	PRINCIPAL MECHANISM OF CHANGE	SOURCE
Normal	14 - 15		(i)
Thiopentone/Nitrous oxide	15 - 17	↓ $CMRO_2$	(i)
P_aCO_2 30 mm Hg	11 . 3	↓ CBF	(i)
50 mm Hg	18 . 0	↑ CBF	(i)
Hypothermia	unaltered	↓ CBF; ↓ $CMRO_2$	(i)
Anaemia (7.8 gm%) - dogs	19 . 4	↑ CBF	(ii)
Deep ether or cyclopropane	30 - 34	↓ $CMRO_2$ ++; ↑ CBF	(i)
Cardio-pulmonary bypass	23 . 4	Probable ↓ $CMRO_2$	(iii)
Irreversible cerebral death (isoelectric EEG)	variable gen. high	$CMRO_2$ < 1/3rd normal	(iv)

TABLE XV Changes in cerebral blood flow equivalent in common clinical situations.

(i) Smith and Wollman, 1972 (Values reproduced or derived from figures quoted).
(ii) Michenfelder and Theye, 1969.
(iii) Present Study
(iv) Shalit, Beller, Feinsod, Drapkin and Cotev, 1970.

CHAPTER VIII

EVALUATION OF THE PROJECT AND IMPLICATIONS FOR CLINICAL PRACTICE

The stimulus which initiated this study in 1970 was the frequency and severity of cerebral damage following open heart surgery in an experienced centre with an annual caseload of several hundred patients. The accuracy of the estimate of the magnitude of the problem was limited by retrospective data collection, but it was hoped that data loss caused by failure to record minor degrees of dysfunction would be avoided by choosing crude criteria to define nerulogical damage. The inclusion of patients who were confused may have resulted in an over-estimate because other factors, such as drug therapy and biochemical abnormalities, can contribute to confusion, but the exclusion of patients with confusion as the sole index of neurological damage reduces the incidence by only 5.3% (from 19.2 to 13.9%).

The use of standardised case sheets and perfusion record cards facilitated the collection of data concerning the other variables which were studied, but some records were incomplete or missing and information on at least one of the twelve variables was missing in 52 cases. Even when these patients had been excluded, there were still 365 complete records available for the final statistical analysis.

Three potentially important factors were not considered in the survey - haematocrit, carbon dioxide tension and the level of arterial blood pressure. Haematocrit and arterial carbon dioxide tension are recorded intermittently so that an estimate of the duration at any particular value is impossible, and the arterial blood pressure is so variable that a reliable reading for statistical analysis could not be included, even in a prospective study.

VALUE OF THE CEREBRAL FUNCTION MONITOR

The design of the CFM prohibits detailed analysis of the electroencephalogram but it has the advantage of generating a short, simple record with only minimal interference, and it is now used routinely to monitor all patients subjected to open heart surgery in this hospital.

The chief factors which have limited its value in the present study are that it only records from a single pair of bi-parietal electrodes and so may not detect small focal lesions, and the lack of electrical detail prevents any attempt to distinguish between different types of neurological injury.

Precise identification of the timing of neurological damage was impossible in 6 of the 20 cases discussed in Chapter IV (Appendix B, table ii, numbers 9,10, 13, 17, 19 and 20). In three of these patients (nos. 9, 10 and 13), there was evidence of focal damage which was severe in one (case 9) and mild and transitory in the other two. Case 9 showed signs of a mid-brain lesion and therefore a change in the EEG, and consequently in the CFM, would not occur inevitably. In the other two patients with signs of focal neurological damage, the CFM record in one (no. 10) did show an abrupt elevation at the onset of perfusion which could not be attributed to the administration of thiopentone, but this is such a common pattern in patients who have an entirely normal post-operative course that it cannot be used to identify those who have suffered a cerebral injury. The third patient with signs of a mild focal injury may have suffered from cerebral air embolism, but the abnormality on the CFM (Fig. 14, p.52) was minimal and easily missed, and lethal

cerebral air embolism can occur following the injection of air experimentally, without any alteration of the EEG (Gomes, Pereira, Castagna, Bittencourt, Amarel and Zerbini, 1973).

There were various minor abnormalities on the CFM record in one of the three patients who were confused post-operatively (no. 19), but in case 17, the only finding was low voltage activity throughout the pre-perfusion period in a man with severe circulatory failure, and in case 20, there were no inexplicable features on the CFM record at all.

These cases can be regarded as 'false negatives' because the CFM did not permit accurate prediction of the neurological lesions. There were also a number of 'false positives'- records showing episodes of severe cerebral depression in patients who recovered without any detectable evidence of neurological damage, even when it was sought specifically. Two representative examples are shown in Figs. 36 and 37, on p.108, and their similarity to records obtained from patients who sustained cerebral damage is obvious (c.f. Figs, 8, 10 and 13, P. 46, 48 & 52). These abnormalities probably represent episodes of considerable cerebral depression, but by analogy with syncope and concussion, it is evident that sequelae which can be detected by clinical examination will not be apparent in all cases.

These conclusions are at variance with those of Schwartz, Colvin, Prior, Strunin, Simpson, Weaver and Scott, 1973. They classified changes recorded with the CFM during cardiac surgery into four types, and claimed a prognostic accuracy of 83% overall. However, the

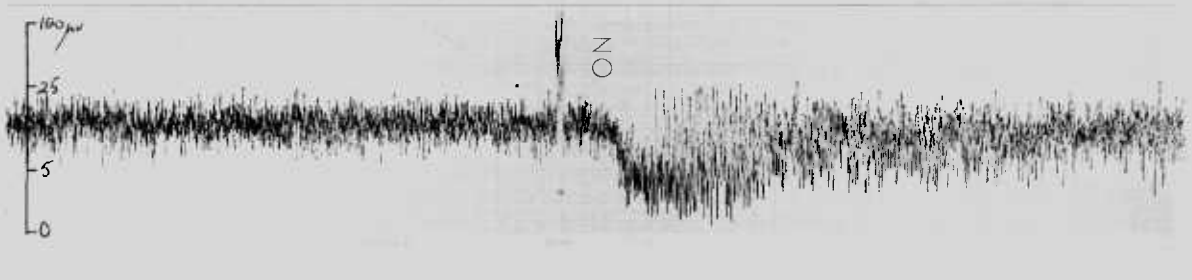


Fig. 36. Depression of CFM record at the onset of perfusion, followed by slow, high-voltage activity lasting for 8 minutes. The patient recovered consciousness without evidence of neurological damage.

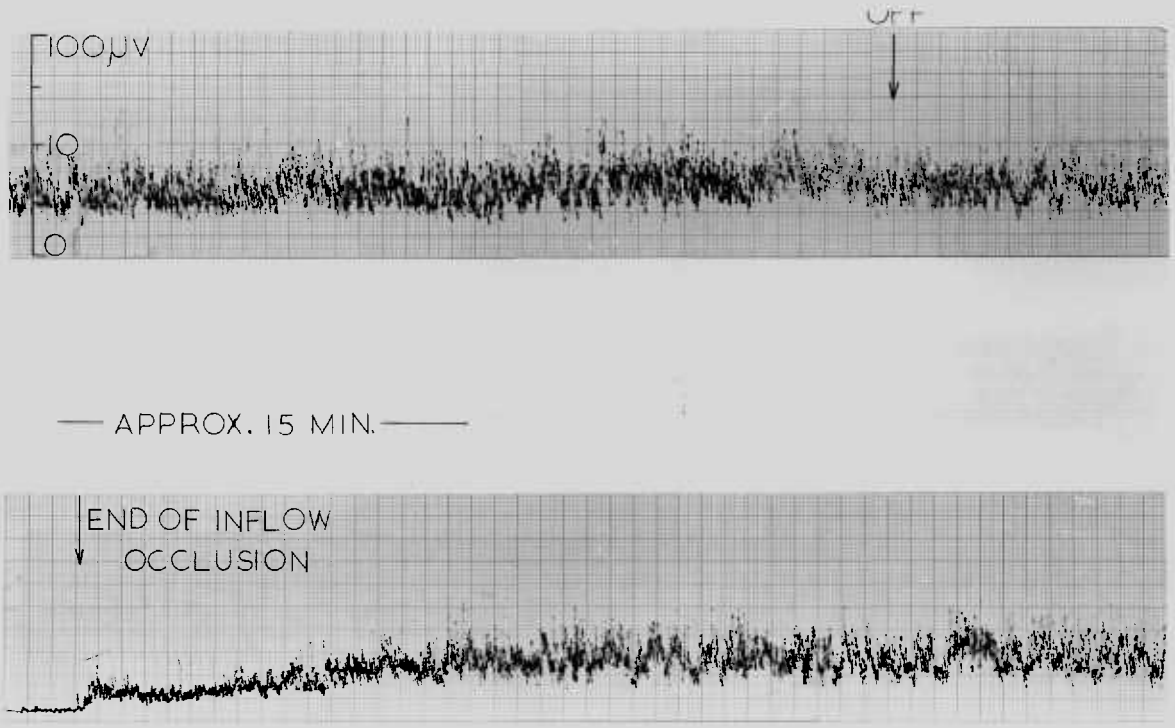


Fig. 37. The upper panel shows the CFM record at the end of an entirely uneventful perfusion. About 15 minutes later, a period of inflow occlusion lasting 2 minutes 20 seconds was required to control torrential haemorrhage. The CFM recorder was switched on again towards the end of this period (lower panel) and the episode of electrical silence is followed by a prolonged recovery phase lasting about 9 minutes. This patient had no neurological deficit in the post-operative period.

neurological outcome in cases with a 'Type II' record (a single, sudden abnormality lasting from three to ten minutes, or one or two abrupt but short-lived episodes, or constant, low-level recording) was more difficult to predict, and nine errors occurred in 24 instances (39% inaccuracy). Thus, it seems wise to conclude that the CFM identifies the majority of cortical disturbances occurring during cardio-pulmonary bypass, but that it provides little guide to the severity of the disturbance and the clinical sequelae.

One other application of particular importance is the control of hypothermia. Cerebral damage caused by circulatory arrest before adequate depression has been achieved by whole body cooling has been described in Chapter IV. The onset of slow, high-voltage activity on the CFM is now regarded as a prerequisite before the circulation is arrested, rather than determining this time by measurements of naso-pharyngeal temperature. In cases where this has been done, recirculation is associated with either an immediate return of cerebral electrical activity (Fig. 38, p.110), or with the elimination of 'burst suppression' which is seen sometimes throughout the arrest period in very young children (Fig. 39, p.111).

In addition to its value as a clinical monitor, studies with the CFM have identified the onset of perfusion as a time when important cerebral damage can occur and this emphasised the need to examine the changes which occur at that time in greater detail.

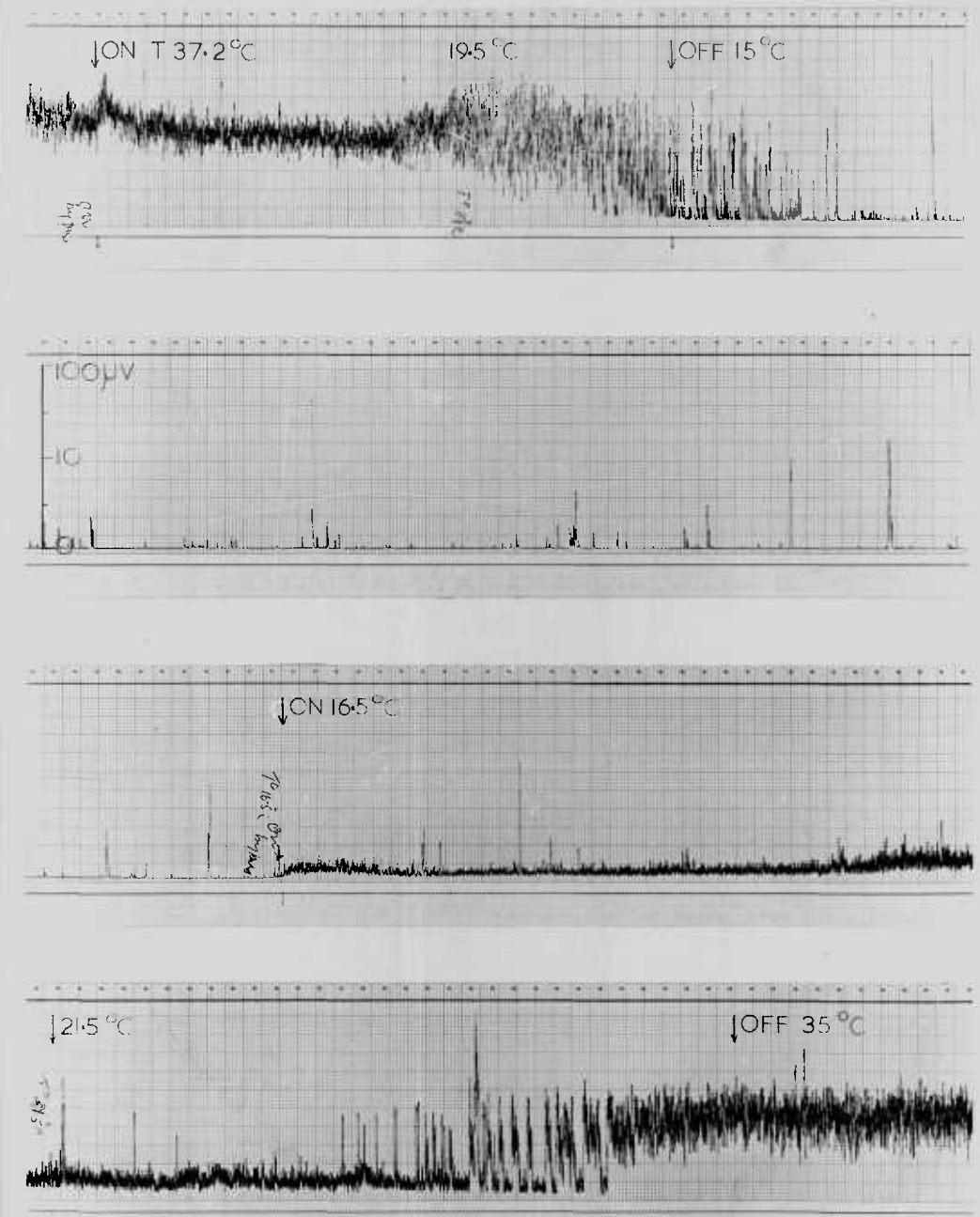


Fig. 38. Complete record of perfusion in a 3-year old child subjected to 69 minutes of circulatory arrest. The CFM record shows considerable depression of cerebral activity before the arrest, and there is prompt recovery when the circulation is restarted. A normal level has been reached before perfusion is finally discontinued at a temperature of 35 degrees C.

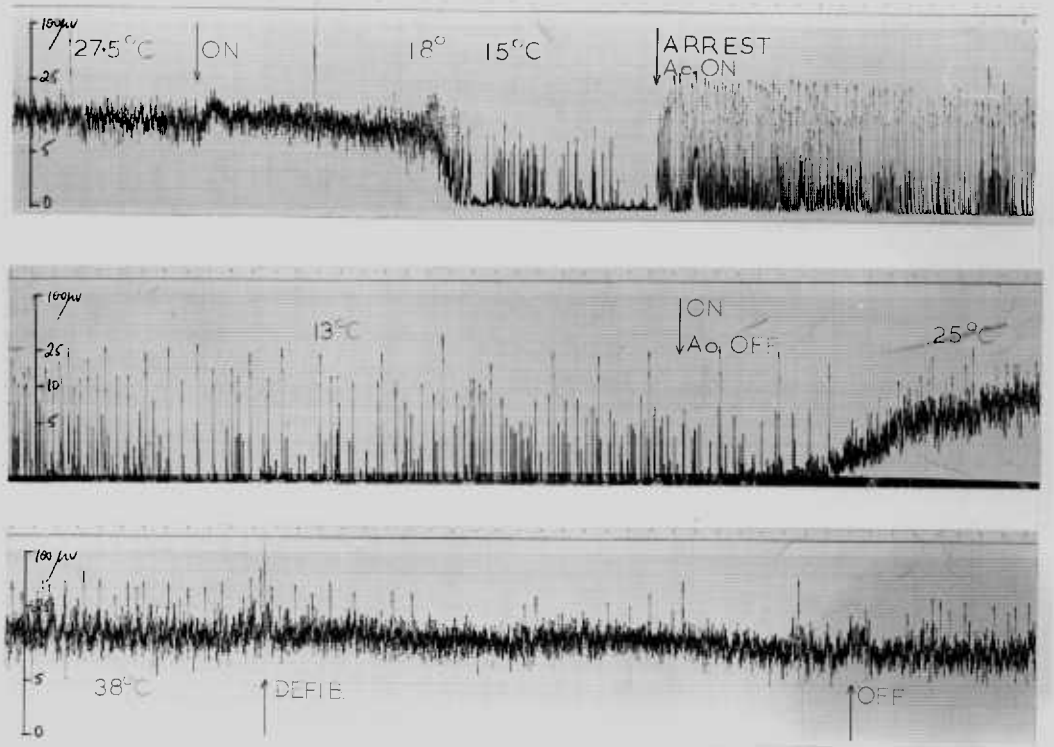


Fig. 39. Burst suppression was seen on the CFM record throughout the 49 minute period of circulatory arrest in this 18-month old child. Cerebral activity returned rapidly as soon as the circulation was restarted, and was normal by the time the nasopharyngeal temperature had reached 25°C.

VALUE OF STUDIES OF CEREBRAL BLOOD FLOW AND METABOLISM AT THE ONSET OF BYPASS

The measurement and interpretation of changes which occur at the onset of bypass have proved difficult because of the complexity of the procedure, the critical condition of many of the patients and the simultaneous changes in a number of factors which can influence both cerebral blood flow and metabolism.

The effect of altering individual factors may be studied later in the procedure when conditions are more stable, but the period of risk may be passed and there is more variation then between patients, whereas the changes at the onset are common to all. Many variables can be controlled with greater accuracy during studies in experimental animals and more precise measurement techniques can be employed (Ingvar and Lassen, 1965). However, the surgical preparation required with these methods may influence the results, there are important differences in the anatomy of the cranial vessels in some species, especially dogs (Capon, Cleempoel, Lenaers and Martin, 1968), and no animal preparation is comparable with the clinical situation in which patients with varying degrees of cerebro-vascular and cardiac disease are submitted to major surgery.

This reasoning lay behind the decision to pursue the changes which occur during routine clinical surgery, even though this automatically imposed a number of limitations in both design and methodology.

The inability to equate changes in jugular venous oxygen content with alterations of cerebral blood flow was confirmed at an early stage in the study, but it was apparent that there were major changes in either cerebral metabolism or blood flow which occurred consistently, unless the samples were contaminated with extra-cerebral blood.

The position of the catheter through which the jugular venous samples were collected was not confirmed radiologically in more than two or three early cases because of the risk of thrombosis, caused by the presence of the second catheter. The vessel was punctured above the normal entry point of the common facial vein which is the highest tributary of the internal jugular vein (Jamieson, 1945), and the catheter was directed for several inches towards the base of the skull with no difficulty in any case. There is therefore, no reason to suspect that the samples were contaminated with blood from any extra-cranial source.

The most serious limitations of the study surrounded the attempts to measure cerebral blood flow. The reasons for selecting the thermo-velocity method, and the problems which were encountered, have been discussed in detail in Chapters VI and VII. Particular emphasis must be placed on the poor resolution at high flow rates, susceptibility to extraneous factors such as thermal conductivity and temperature, and the inconsistent relationship between volume flow and velocity.

The normal value for cerebral blood flow in conscious man is approximately 44 ml/100 gm/min (Smith and Wollman, 1972), and with 1430 gm as the average weight of an adult male brain (Documenta Geigy, 1970), total cerebral blood flow is of the order of 630 ml/min, of which 315 ml/min

may be assumed to flow through each jugular vein. Some reduction in cerebral blood flow before the onset of perfusion was probable in the present series, resulting from light anaesthesia with thiopentone and nitrous oxide, moderate hypocapnia, and depression of the cardiac output (Chapter V, p.72); in addition, the diameter of the internal jugular vein may have been much greater than normal in many of the patients because of chronic, congestive cardiac failure with elevation of the jugular venous pressure. All these factors would favour improved resolution in the system (Chapter VI), so permitting identification of changes in jugular blood flow at the onset of bypass in spite of the limited range of the method.

The argument in favour of interpreting either no change, or an increase, in integral height at the onset of bypass as evidence of a reduction in cerebral blood flow, has been outlined in Chapter VII, p.92-93. The conclusion that the cerebral blood flow fell in more than 50% of the cases studied is based largely upon this argument. It is supported by the observation that the systemic arterial pressure fell, in the larger group of 30 cases, to a mean value below that at which autoregulation can preserve cerebral blood flow in the face of hypotension in conscious man (Table XI, p.66), and by the finding that the reduction in pressure tended to be greater in patients in whom recordings with the thermo-velocity system suggested that cerebral blood flow had fallen (Table XIII, p.91).

The important derivation from this conclusion, namely that the increase in cerebral blood flow equivalent is due to a decrease in cerebral metabolic rate, is based therefore on evidence which is open to dispute. Even if this interpretation of the data is correct, the cause of the

reduction in metabolic rate is not apparent, although cerebral hypoxia remains an obvious possibility. Many conditions responsible for both reversible and irreversible cerebral depression can lead to a decrease in cerebral metabolic rate, and arterialisation of jugular venous blood occurs unless the cerebral blood flow is decreased proportionately (Sokoloff, 1960; Lassen, 1966; Alexander and Lassen, 1970; Table XV, p.103).

Complete understanding of the nature and aetiology of the changes in cerebral haemodynamics and metabolism at the onset of bypass may reveal that there is no danger in the decrease in metabolic rate which appears to occur, but the conclusion that it represents the result of some type of cerebral injury is favoured by the findings in the present study.

IMPLICATIONS FOR CLINICAL PRACTICE

The onset of cardio-pulmonary bypass has been identified as a period of particular hazard when a low haematocrit, a reduction in cerebral blood flow and a low, non-pulsatile pressure may combine to impair oxygen availability. The extent to which individual patients can tolerate these conditions cannot be predicted, but a sudden change in cerebral electrical activity is a valuable warning sign which can be detected frequently with the Cerebral Function Monitor. Prompt treatment of hypotension and the avoidance of hypocapnia are useful prophylactic measures (Fig. 40, p.116).

The importance of sudden hypotension and the probability that cerebral hypoxia occurs at the onset of bypass does not exclude the possibility of particulate or gaseous embolism occurring at the same time.

The evidence favouring micro-embolism as an important cause of cerebral damage associated with open heart surgery has been discussed in Chapter I, and the use of small-pore filters must now be regarded as essential.

Finally, the Cerebral Function Monitor may be used to control the timing of circulatory arrest during profound hypothermia as outlined earlier in this Chapter.

Prophylactic measures based on these conclusions have been introduced at the Brompton Hospital during 1971 and 1972, and a final clinical survey of cerebral damage has been undertaken during 1973 to evaluate their success.

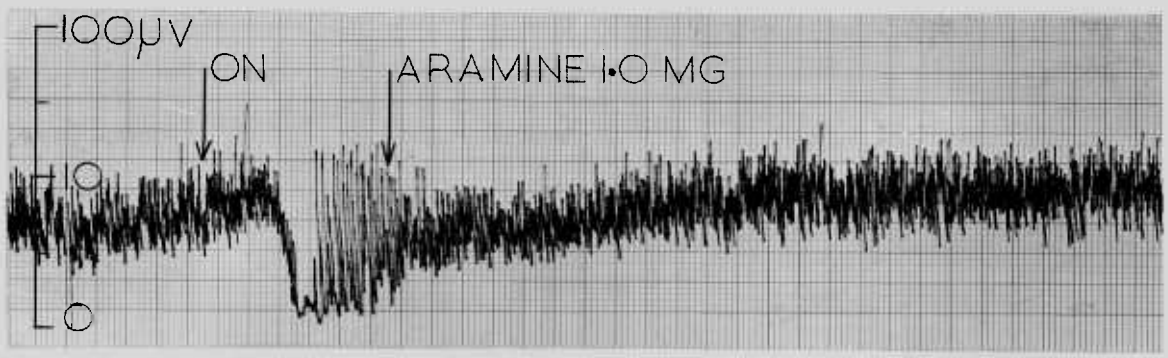


Fig. 40. CFM record at the onset of bypass in a 43-year old woman with mild mitral stenosis and hypertension (160/100). The arterial blood pressure fell to between 30 and 40 mm Hg when the aorta was cross-clamped, in spite of a flow of 80 ml/kg/min from the oxygenator. The resulting cerebral depression was reversed rapidly by the administration of metaraminol, and the patient regained consciousness after the operation without any evidence of neurological deficit.

CHAPTER IX

THE RESULTS OF PROPHYLAXIS: CLINICAL SURVEY 1973

The final clinical survey included all patients submitted to open-heart surgery during 1973. The data was collected retrospectively in order to preserve comparability with the methods used in 1970, and the same criteria were used to define neurological damage. A prospective study, requiring personal involvement in every case, would have been impractical.

Neurological damage was sustained by 40 of the 538 patients who survived the operative procedure (Table XVI); the incidence of 7.4% compares with a corresponding figure of 19.2% in 1970.

TABLE XVI

Nature of neurological damage sustained in 1973

Hemi- or mono-plegia or paresis	14
Coma	16*
Confusion	10
Quadriplegia	1
Epilepsy	1

*Two patients in coma had signs of a hemiplegia.

Nineteen of these 40 patients died in the post-operative period, and the neurological lesion was wholly or partly responsible in 10 cases. Twenty-one of the 40 patients survived to leave hospital, but 12 were left with residual disability of varying severity at the time of their discharge.

FACTORS ASSOCIATED WITH NEUROLOGICAL DAMAGE

The selection of other items of information which were to be recorded in 1973 was determined by the results of the 1970 survey. This had revealed the importance of increasing age, greater duration of perfusion, and the presence of a neurological lesion pre-opratively, and there was some evidence that the choice of oxygenator also influenced the outcome. Neither the nature of the operation, nor the composition of the fluid used to prime the extracorporeal circuit appeared important in the 1970 analysis, but these factors were included again in 1973 because of an awareness of a tendency towards change in the workload and perfusion technique.

One new factor was included in the final survey - whether or not the operation was being undertaken on a patient who had had previous intracardiac surgery, open or closed. There are two reasons why a higher than average incidence of neurological damage might be expected in this group, and both depend upon the presence of pericardial adhesions. These interfere with the dissection and mobilisation of the heart, and considerable haemorrhage is common when they are disturbed. The risks of micro-embolic damage are increased if large volumes of blood are returned to the oxygenator from the heart and pericardial cavity (Osborn, Swank, Hill, Aguilar and Gerbode, 1970), and failure to mobilise the ventricle impedes the evacuation of air at the end of the procedure, so enhancing the possibility of subsequent air embolism.

The list of factors considered in relation to neurological damage in 1973 is given in Table XVII, p. 120. Information on one or more

of these factors was unavailable in 23 instances and these patients were excluded from the statistical analysis. The collection of data was complete for the 40 patients who suffered neurological damage.

TABLE XVII

Factors considered in relation to incidence of neurological damage

Age
Duration of perfusion
Pre-operative neurological status
Nature of operation
History of previous intra-cardiac surgery
Type of oxygenator
Nature of priming solution

The conventions used to code the information for statistical analysis were the same as those employed in 1970. Table XVIII (p. 121) lists the nature of the pre-operative neurological disorders in 1973, and Table XIX (p. 121) enumerates the operative procedures which were carried out.

Nature of operation There were a number of significant differences in the caseload in 1973. Fewer patients were subjected to single valve replacement, but there were more who required multiple valve replacements or surgery for ischaemic heart disease. Fewer patients were operated on for the relief of right heart obstruction, largely because the majority of cases of pulmonary embolism were treated with thrombolytic therapy. All these differences were significant, at least at the 5% level. There has

TABLE XVIII

Aetiology of pre-operative neurological disorders

Cerebral embolism	13	
Epilepsy	4	*
Neurosyphilis	2	
Semi-coma due to heart failure	2	**
Congenital defects	2	
Arteriosclerosis	1	
Undiagnosed cerebral abscess	1	
Undiagnosed optic atrophy	1	
Previous poliomyelitis	1	
Previous leucotomy	1	
Hemiplegia following angiography	1	

* One patient with aortic and mitral valve disease had been operated on in 1970 and had suffered from a hemiplegia and epilepsy post-operatively. In 1973, there were no residual signs of hemiplegia and the epilepsy was controlled completely with drug therapy. Re-operation in 1973 was uneventful

** Both these patients were moribund and the plantar responses were extensor.

TABLE XIX

Operative Procedures

Mitral valve surgery	140	
Aorta and aortic valve surgery	111	
Multiple valve replacement	94	
Left to right shunts	84	
Right to left shunts	37	
Relief of right heart obstruction	9	
Ischaemic heart disease	44	
Miscellaneous	19	*

* Miscellaneous procedures included Mustard operation x 10; valve replacement + repair of septal defect x 3; coronary vein graft + repair of septal defect x 2; Fontaine procedure x 1; mitral valve replacement + resection of left ventricular aneurysm x 1; isolated tricuspid valve replacement x 1; excision of right ventricular tumour x 1.

also been a trend towards more operations designed to repair complex, congenital defects. These have been clasified as 'miscellaneous', but the difference between the numbers in this category did not reach statistical significance.

Oxygenator The proportion of patients perfused from the rotating disc and Rygg oxygenators in 1973 (79.7 and 15.3% respectively) did not differ significantly from the comparable figures for 1970 (79.1 and 13.6%), and similar indications governed the selection of these machines. The Temptrol oxygenator has been used very infrequently in 1973, even for emergency work, and only 4 perfusions (0.75%) were carried out with the Temptrol, compared with 30 (7.3%) in 1970.

Membrane oxygenators are now available for clinical use and have been introduced gradually throughout 1973. Their use is restricted at present to operations on children weighing less than 10 kg; twenty perfusions (3.7%) were undertaken in 1973 with a membrane oxygenator.

Filters for micro-emboli have been included routinely at various sites in the extracorporeal circuit since 1971. In 1973, a Pall filter* was used on the arterial line from the oxygenator to the patient in all cases, and a locally-designed filter and defoaming chamber was incorporated into the circuit between the intra-cardiac suction channels and the oxygenator.

Nature of priming solution The percentage of patients for whom the circuit was primed without blood has increased from 10.1 to 66.3%, while the frequency with which either whole blood, or a mixture of blood and electrolyte solution was used, has decreased from 15.3 and 74.6% to 3.9 and 29.9% respectively ($p < 0.001$ for all differences).

* 'Barrier' filter - Johnson & Johnson.

Human plasma protein fraction is now used as part of the priming solution.

Statistical Analysis

The association between the factors listed in Table XVII (p.120) and the incidence of neurological damage in 1973 has been analysed in two stages, as before. Initially, each item was considered in isolation (Table XX) and then, multiple regression analysis was used to eliminate the influence of interrelationship between some of the variables (Table XXI, p. 124).

TABLE XX

Association of individual factors with neurological damage

(a) Significant at 1%

Age *
Duration of perfusion
Pre-operative neurological abnormality
Operation classified as 'miscellaneous'
Use of membrane oxygenator
Use of an all-blood prime

(b) Not significantly associated at 5%

Each of the 7 specific operative categories
History of previous intracardiac surgery
All oxygenators other than the membrane
Priming solutions other than whole blood.

* The association with age was quadratic rather than linear, reflecting a higher incidence of neurological damage in the very young as well as in patients in the older age groups (see Table XXII, p. 124). The reasons for this are discussed subsequently.

TABLE XXI

Factors associated with neurological damage

Results of multiple regression analysis

	Variance Ratio	Significance
Duration of perfusion	27.3	<0.01
Pre-operative neurological abnormality	10.0	<0.01
Use of an all-blood prime	9.4	<0.01
Age *	4.7	<0.05

*The quadratic relationship with age is discussed on p. 125.

TABLE XXII

Incidence of post-operative neurological damage related to age

Age (yr)	Total No.	No. with CNS damage	% CNS damage
<1	8	2	25.0
1-10	93	7	7.5
11-20	65	2	3.1
21-30	48	2	4.2
31-40	71	2	2.8
41-50	93	6	6.5
51-60	101	9	8.9
61-70	55	9	16.4
>70	4	1	25.0

The factors which were found to be positively associated with an increased incidence of neurological damage in 1970 continued to feature in 1973; use of an all-blood prime appeared as an additional contributory factor.

The quadratic association with age has been noted already (Tables XX and XXI, pp. 123 and 124) and the emphasis on neurological damage at the extremes of age is apparent in Table XXII (p. 124). The definition of neurological damage included all abnormalities apparent within three days of operation (Chapter II, p.16), and the high incidence of damage in infants and young children is explained in part by the frequency with which clearly recognisable complications occur at this age, whereas unexplained dysfunction is common in the older age groups (Table XXIII, p. 126).

Inspection of Table XXI (p. 124) reveals that the length of perfusion remains the most important single factor related to subsequent neurological dysfunction, and this is particularly noticeable in perfusions which last more than two hours (Table XXIV, p. 126).

The nature of the operation, and whether or not the patient had been subjected to previous intra-cardiac surgery were factors which did not affect the subsequent neurological status. The more extensive use of haemodilution in 1973 was also unimportant, whereas perfusion with an all-blood prime was followed by a higher incidence of neurological damage which was independent of the influence of all other variables.

Potential aetiological factors were suspected in 22 of the 40 cases who sustained neurological damage in 1973 (Table XXIII, p. 126), compared with 32 out of 80 cases in 1970 (Table IX, p. 26). The outcome in patients with neurological damage of uncertain aetiology was unfavourable.

TABLE XXIII

Suspected aetiology of neurological damage in 22 patients

Hypotension, hypoxia or cardiac arrest	15
Suspected embolism of clot or air	2
Hypernatraemia *	2
'Vertebral steal' syndrome **	1
Uraemia	1
Cerebral abscess	1

* Complicating inadequate removal of salt crystals from the membrane oxygenato

** During resection of a thoracic aortic aneurysm.

	22 Cases Aet. suspected	18 Cases Aet. unknown	Mean Diff. ± SE of mean	Significance
Age (yr)	30.0	53.1	23.1 ± 7.0	< 0.01
Duration of bypass (min)	134.3	116.6	17.7 ± 25.1	> 0.1

TABLE XXIV

Incidence of post-operative damage related to duration of perfusion

Duration (min)	Total No.	No. with CNS damage	% CNS damage
< 30	55	0	0.0
31-60	131	10	7.6
61-90	131	7	5.3
91-120	106	5	4.7
121-180	86	11	12.8
> 180	26	7	26.9

Information on the duration of perfusion was missing in 3 instances.

Eight of these patients died, and the neurological lesions contributed to the fatal outcome on five occasions. Ten patients recovered, but five were left with residual neurological disability at the time of their discharge from hospital.

VALIDITY OF COMPARISON BETWEEN RESULTS IN 1970 AND 1973

There have been a number of changes in the nature of the workload and the techniques of perfusion between 1970 and 1973, but it is doubtful if these were responsible for the very highly significant decrease in the incidence of neurological damage, from 19.2 to 7.4% ($p < 0.001$).

The type of operative procedure was unrelated to the occurrence of neurological damage in either series, and the choice of oxygenator was also unimportant, apart from the apparently favourable influence of perfusion with the Temptrol in 1970. The virtual exclusion of this oxygenator during 1973 would be expected to enhance, rather than diminish the incidence of neurological damage, and is regarded therefore as an unimportant difference between the two years.

Use of an all-blood prime was an unfavourable feature in 1973, although the nature of the priming solution did not influence the neurological outcome in 1970. More patients in 1970 were subjected to perfusion from apparatus which had been primed with whole blood, but the number involved (59) was relatively small. It is highly unlikely therefore, that any inapparent, adverse effect derived from an all-blood prime could be responsible for more than a very small proportion of the excessive incidence of neurological damage in 1970.

Much greater uncertainty surrounds the accuracy of the data collection. The information was derived retrospectively from the case-notes and these had been completed by different staff. It is quite possible that greater awareness of the problem of neurological damage in 1970 favoured more accurate and detailed assessment, and comments on the neurological status appeared more commonly in the notes in 1970.

It is particularly likely that minor degress of dysfunction were not recorded in 1973, although the similarity in the recorded incidence of confusion in patients with neurological damage (27.5% in 1970; 25% in 1973), does not support this possiblity. The other lesions all represent major post-operative complications and it is unlikely that these would not be recorded. Furthermore, even if patients with confusion as the sole index of neurological dysfunction are excluded from the comparison, there is still a highly significant decrease in the incidence of damage, from 13.9% in 1970 to 5.6% in 1973 ($p < 0.001$).

THE ROLE OF PROPHYLACTIC MEASURES

Analysis of the results obtained in 1970 emphasised the importance of perfusion in the aetiology of neurological damage. Since that time, three prophylactic measures have been introduced:-

(1) Filters for micro-emboli have been incorporated into the extracorporeal circuit, both on the arterial line and on the coronary suction lines.

(2) The hazards of abrupt hypotension, particularly at the onset of bypass, have been recognised, and although opinion is divided on the indications for vasopressor therapy, these drugs are used if hypotension is associated with either depression on the Cerebral Function Monitor or dilatation of the pupils (see Fig. 40, p. 116). There is less

agreement on what constitutes 'abrupt' or 'profound' hypotension in the absence of these signs, and although vasopressor therapy is used more frequently than in 1970, hypotension to a mean systemic arterial pressure of less than 50 mm Hg is still regarded with equanimity by some staff.

(3) The danger of premature circulatory arrest during profound hypothermia has been accepted, and the Cerebral Function Monitor has been used to control the timing of this manoevre during procedures carried out in the latter half of 1973 (see Figs. 38 and 39, pp. 110 and 111).

The introduction of these measures has been associated with a significant reduction in the incidence of neurological damage, and, on the basis of the evidence presented in this study, it is suggested that these two events are causally related. There is however, no means of confirming this conclusion, nor is it possible to evaluate the relative importance of the prophylactic measures.

The incidence of neurological damage which could not be attributed, on clinical grounds, to any specific feature of the operative period has also fallen, from 11.5% (48 of 417 cases) in 1970 to 3.4% (18 of 538 cases) in 1973 ($p<0.001$). Four of the eighteen patients in this category in 1973 were anaesthetised by the author, and satisfactory Cerebral Function Monitor records were obtained on three occasions. These patients appear as numbers 7, 10 and 13 (Appendix B, table ii), and the three records are described and illustrated in Chapter IV, pp. 47, 49 and 51. It was suggested that the neurological injury may have been related to air embolism in case no. 13, but in cases 7 and 10, the only abnormality was

a change on the CFM record at the onset of perfusion which was associated, in both these elderly patients, with arterial hypotension to 25 and 40 mm Hg respectively.

The results presented in Chapter VII suggest that systemic hypotension results in a reduction in cerebral blood flow during perfusion, in spite of a high overall flow rate, and it is difficult to avoid the conclusion that cerebral ischaemia continues to contribute to the incidence of neurological damage. More frequent use of vasopressor drugs may eliminate this risk in some cases.

The evidence for a reduction in cerebral metabolic rate during extracorporeal circulation was presented in Chapters V and VII, although unequivocal proof of the existence, aetiology and importance of this finding has not resulted from the present study. Cerebral metabolic depression may be responsible for some proportion of the neurological damage associated with perfusion or it may summate with the other factors which have been identified. Alternatively, it may represent the effect, rather than the cause of neurological damage.

There is no room for complacency until these uncertainties have been resolved, and the occurrence of unexplained neurological damage after cardio-pulmonary bypass has been eliminated entirely.

CHAPTER X

CONCLUSIONS

(1) A number of factors continue to contribute to unexpected neurological damage following open-heart surgery.

(2) Most of these factors are related to the period of extracorporeal circulation.

(3) The occurrence of cortical damage can be identified with the Cerebral Function Monitor in many cases.

(4) Unexplained alterations in cerebral electrical activity are common at the onset of cardio-pulmonary bypass.

(5) Systemic arterial hypotension is more profound at the onset of bypass when the pattern of change on the Cerebral Function Monitor suggests cerebral depression.

(6) There is evidence, but not unequivocal proof, that cerebral metabolism is depressed at the onset of bypass.

(7) The cerebral blood vessels respond in a qualitatively normal way during bypass to changes in systemic arterial blood pressure and arterial carbon dioxide tension.

(8) Cerebral blood flow falls during bypass when systemic hypotension is prominent, in spite of high overall flow rates from the extracorporeal apparatus.

(9) The incidence of neurological damage has been reduced by the introduction of prophylactic measures designed to eliminate micro-emboli and minimise the risks of hypotension and hypothermic circulatory arrest.

(10) Changes in cerebral blood flow and metabolism during cardio-pulmonary bypass in man require further study.

APPENDIX

The work has been carried out at the Brompton Hospital during the author's appointment as Consultant Anaesthetist. One of the duties of the appointment was to establish a laboratory where studies related to anaesthesia could be undertaken, and the work presented in this dissertation represents the first of several studies which have been organised and supervised by the author.

The Medical Research Council supported the project with a grant for the salary of a technician over a period of three years. The author has been responsible for the training of the technician, and during the later stages of the study, he carried out some of the practical procedures. He also assisted Mr. R.B. Logan-Sinclair, H.N.C. of the Department of Medical Electronics, Brompton Hospital, with the design and construction of the circuit used for the thermo-velocity system. The remainder of the practical work was carried out by the author.

Statistical analysis of the clinical survey data was kindly carried out in both 1970 and 1973, by Miss C.M. Devine, B.Sc., of the Medical Research Council Tuberculosis and Chest Diseases Unit. The other statistical analyses have been undertaken by the author, using standard methods and a Hewlett-Packard calculator, programmed by the author.

The work was undertaken without supervision, but the author is indebted to the surgical and perfusion staff of the Brompton Hospital for their willing co-operation; in particular, thanks are due to
Mr. S.C. Lennox FRCS Consultant Surgeon and to
Mr. P.E. Ghadiali FRCS Consultant Clinical Physiologist.

Publications which have resulted from this study are listed below, and copies of the three which are in print are enclosed.

Neurological damage related to open-heart surgery. Thorax 27, 748-753.

Detection of neurological damage during open-heart surgery. Thorax 28, 464-472.

Factors affecting cerebral activity during open-heart surgery. Anaesthesia 28, 619-625.

Cerebral blood flow and metabolism during open-heart surgery. Submitted to Thorax.

APPENDIX B: table i.

Post mortem findings in 7 fatal cases in 1970.

Age (yr)	Clinical condition	Interval op.-death	PM Report
57	Coma	1 month	Brain normal macroscopically. No histology.
47	Coma + L hemiplegia	2 days	Agglomeration of small punctate haemorrhages, about 2 cm in diameter, in superior part of right precentral gyrus. Microscopy - haemorrhage and oedema. Cause of death given as cerebral embolism.
64	Coma	17 days	Brain congested and soft but no focal lesions. No histology.
31	Coma	6 days	Brain congested and soft throughout. Punctate haemorrhagic lesions were present in the right basal nuclei and left cerebral cortex. Cerebral embolism given as the cause of death.
60	L hemiplegia	10 days	The brain showed evidence of superficial vascular congestion and raised intracranial pressure. No histology.
68	Coma	5 days	The brain was soft and the samll vessels were congested, but there were no petechial haemorrhages and no spicules of calcium were felt. Histology showed areas of intracerebral haemorrhage but no emboli were seen within the area of section.
20	Coma	36 hours	The brain was swollen with areas of infarction in the right frontal lobes, right and left parietal areas, left internal capsule, right temporal lobe and the cerebellum. The basal vessels were normal. Histology showed cortical congestion with perivascular oedema and some small areas of haemorrhage. Cerebral embolism given as the cause of death.

APPENDIX B: table ii

Clinical details of 20 patients with neurological damage

(CFM records described and illustrated in Chapter IV)

No.	Age	Operation	Nature of damage	Outcome at discharge or death	CFM Record
1	57	Aortic valve replacement	Right hemiplegia	Considerably improved.	Fig. 8, p. 46.
2	53	Aortic valve replacement	Left hemiplegia	Complete recovery.	p. 45
3	55	Mitral valve replacement	Left hemiplegia + diplopia	Complete recovery	p. 45
4	60	Coronary vein graft	Right hemiplegia + dysphasia	Minimal recovery	p. 45
5	6	Repair of Fallot's tetralogy	Confusion progressing- Coma	Death; CNS lesion contributory.	p. 45
6	24	Double valve replacement	Coma	Death; CNS lesion contributory.	Fig. 9, p. 46
7	60	Double valve replacement	Confused and disorientated	Death	Fig.10, p. 48
8	66	Aortic valve replacement	Epileptic fit on 2nd. day	Complete recovery	Fig.11, p. 48
9	36	Open mitral valvotomy	Mid-brain lesion	Incomplete recovery	Fig.12, p..50
10	73	Mitral valve replacement	Confusion + left hemiparesis	Complete recovery	p. 49
11	50	Mitral valve replacement	Coma + left hemiplegia	Incomplete recovery	p. 51
12	64	Mitral valve repair	Left monoplegia	Complete recovery	Fig.13, p. 52
13	53	Aortic valve replacement	Confusion + left hemiparesis	Complete recovery	Fig.14, p. 52
14	1	Pulmonary valvotomy	Convulsions + L hemiparesis	Incomplete recovery	Fig.15, p..54
15	0.5	Closure, vent. septal defect	Coma	Death	p. 53
16	0.5	Closure, vent. septal defect	Convulsions	Probably blind	Fig.16, p. 54
17	74	Closure acquired ischaemic VSD	Confused & aggressive	Complete recovery	Fig.17, p. 56
18	60	Coronary vein graft	Coma	Death; CNS lesion contributory	Fig.18, p. 55
19	56	Aortic valve replacement	Confused	Complete recovery	pp.32&55;(fig.3)
20	63	Mitral valve replacement	Confused	Complete recovery	Fig.19, p.58.

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