THE ROLE OF PER-OPERATIVE MONITORING IN THE

PREVENTION OF NEUROLOGICAL DEFICIT FOLLOWING

CORONARY ARTERY BYPASS SURGERY

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ABSTRACT

Post-operative neuropsychometric deficit is now a well accepted complication of coronary artery bypass surgery. Little is known of the aetiology of this deficit , although both cerebral hypoperfusion and cerebral microembolisation have been cited as likely causes, despite a lack of hard confirmatory evidence. This study sets out, by means of intensive monitoring to investigate per-operative factors that may be contributing to this deficit and to identify areas requiring future improvement.

65 patients undergoing isolated coronary artery surgery and 15 patients undergoing peripheral vascular surgery underwent detailed neuropsychometric and ophthalmological assessments pre-operatively and again twice in the first post-operative week.

Per-operatively arterial and jugular bulb venous pressures, arterio-venous(jugular) oxygen content differences and blood gas tensions were monitored frequently but the surgeon and anaesthetist were not informed of the results.

In 35 patients (Group A), ventilatory perameters were at the discretion of the anaesthetist, who referred to his own intermittent blood gas samples according to accepted practice.

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In the remaining 30 cardiac patients (Group B), end-tidal CO_2 monitoring was utilised pre-bypass and an arterial "in-line" CO_2 electrode per-bypass, to maintain a state of normocapnia throughout the operation. The patients were otherwise subjected to identical surgical and anaesthetic protocol as Group A.

15 patients undergoing peripheral vascular surgery (Group C) were subjected to a similar per-operative management as Group A with ventilatory parameters at the discretion of the anaesthetist.

Post-operatively a significant neuropsychometric deficit was detected in 71% of Group A patients but only 40% of Group B. and 27% of Group C.

Ophthalmological changes, consistent with ocular hypoperfusion, were found in 20% of Group A. Neither Groups B nor C demonstrated any evidence of new ophthalmological signs post-operatively.

Statistical analysis of the data from the two cardiac groups revealed that Group A members demonstrated a significantly greater incidence of post-operative neurological deficit associated with ;

1. lower mean $PaCO_2$ value, and a higher mean cerebral arterio- venous oxygen content difference immediately prior to the onset of perfusion.

2. significantly greater increases in cerebral venous pressure (consequent upon excessive fluctuations in measured CO_2 tensions), following the onset of the perfusion period.

3. significantly lower cerebral perfusion pressures in the first ten minutes following the onset of bypass; a period not maximally covered by the protective benefits of hypothermia.

Examination of the results from the non-cardiac patients (Group C) showed a strong correlation between a combination of mean per-operative $PaCO_2$ values / per-operative blood loss and the incidence of post-operative deficit.

Group A and Group C results suggest that inadequate per-operative monitoring often results in extreme degrees of unrecognised hypocapnia; while crude attempts at correcting this can often compound the problem by inducing a hypercapnic state in which cerebral autoregulation is lost.

Group B showed a significant reduction in post-operative deficit as a result of "on-line" manipulation of per-operative parameters.

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I take this opportunity to thank my parents for their unfailing support over many years and for providing me with the skills and desire to perform this task.

I dedicate this Thesis to my wife, Christine and to my two sons Joseph and George; my closest allies in times of hardship, and my greatest friends in moments of happiness.

The work described in this thesis was performed in conjunction with clinical and scientific colleagues. The author was responsible for both the design and also the performance of all administrative aspects of the study. All per-operative monitoring together with post-operative analysis were also performed by the author. Both Neuropsychometric and Ophthalmological patient assessments were by design performed by other members of the research group, so maintaining an absence of bias from assessment parameters. The author did however play a major role in the original formulation of the various assessment protocols.

Some of the results presented in this thesis have already been published in modified or preliminary form. The publications are listed below.

Nevin M., Colchester ACF, Adams S, Pepper JR.
Evidence for the involvement of hypocapnia and hypoperfusion in the aetiology of neurological deficit after cardiopulmonary bypass.
Lancet: 1987: ii: 1493-95

Nevin M., Colchester ACF, Adams S, Pepper JR.
Prediction of Neurological damage after Cardiopulmonary Bypass surgery - Use of the Cerebral Function Analysing Monitor.
Anaesthesia 1989; (In Press)

3. INTRODUCTION

The question of neurological deficit following cardiopulmonary bypass surgery remains a controversial issue despite almost 15 years of intensive investigation . The number of coronary operations performed each year in the UK is rising steadily, reaching nearly 10,000 in 1984.(1) This figure falls short however of the ideal rate suggested by the DHSS of 300 operations /million population.(2,3) This figure remains well below the numbers of similar operations in both the USA (900 / million of population) and Australia (600 / million of population).

It is likely therefore that there will be a continued expansion of the population exposed to this type of surgery over the coming years; many of whom will probably either have a lesser degree of disease or be of significantly greater age than those to whom the operation is offered at the present time. The implications of this, especially with regard to the effect of coronary artery surgery in patients over the age of 75 years have only recently been fully documented (4,5). With this knowledge in mind, it is paramount that there is an ongoing appraisal of patient risk factors both with regard to the mortality and morbidity associated with this type of surgery. Improvements in both surgical and anaesthetic technique together with considerable technicological advances in equipment have resulted in a steady fall in peri-operative mortality associated with cardiopulmonary bypass surgery.

Almost all cardiac surgical units in the UK have recorded mortality rates of less than 3% overall(1); - a figure less than twice that quoted for major general surgery in a British teaching unit(6).

When considering patient morbidity however, the matter becomes considerably more controversial. Stroke and encephalopathy are probably the two major causes of morbidity complicating cardiopulmonary bypass surgery. Patients undergoing this particular type of surgery are often unavoidably exposed to a variety of haemodynamic, embolic, and metabolic threats to the brain, yet the true cause of the neurological damage often remains uncertain in the individual patient.

This may merely reflect our basic lack of understanding of the complex interrelating factors which might bring about a common outcome; and which may lead to an overemphasis on factors, which while being more visible, are often less clinically significant. Prior to the 1980's research was mainly devoted to examination of the incidence of major focal neurological deficit.In the majority of these cases the measured deficit was associated with major irreparable cellular damage in the brain. The aetiology of this per-operative cerebral infarction was often embolic and related to a variety of individual per-operative conditions; such as the occurrence of dysrhythmias, mural thrombus, aortic atheroma, air in the coronary arteries or the perfusion circuit, microaggregate formation or cerebrovascular disease.(7-14)

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In the majority of the cases described above the cerebral damage only became evident by a delay in the return of full consciousness in the immediate post-operative period and the appearance of hemiplegia, associated dysphasia and often visual disturbances. While many of these cases improved considerably over ensuing days or weeks, especially the true visual field defects (15,16), the cases where massive embolic damage had occurred often showed incomplete recovery with residual major deficit.(17,18)

Over the last 15 years dramatic improvements in regard to patient safety have undoubtedly been made. Greater awareness of the importance of air introduced into the bypass circuit, and measures to exclude it, together with further improvements in blood oxygenation and the greater appreciation of the physiological changes associated with the perfusion period were responsible for the consistent reduction in the incidence of focal deficit which has fallen from around 10-15% in the mid-1970's to the presently agreed level of less than 4%.(19,20,21)

Attention has therefore switched to the more subtle, diffuse deficit that while apparently less severe, appears to affect a much higher percentage of patients undergoing cardiac surgery (22-26). Although many carefully constructed studies, both in this country and also in the USA have served to highlight this problem, until recently few could agree upon its true incidence.

In the early 1970's the problem was estimated by various authors to affect between 15 - 44% of patients.(27,28,29) There were however several major criticisms of these studies.

Firstly, the majority were retrospective in nature, resulting in neither the methods of clinical practice nor the patient assessment protocols being standardised. In addition the recording of recognisable post-operative deficit, based almost exclusively on the recognition of new clinical neurology, was always dependent upon the accuracy of the clinical records.

This approach to the interpretation of clinical data lays itself open to justifiable criticism from a methodological point of view.

It was probably no great surprise therefore to discover that many of the published findings were contradictory and that no uniform approach to the problem could be agreed upon.In the last seven years, however, several new studies have rekindled the fires of interest in a subject that had begun to smoulder in contradiction at the end of the previous decade. These prospective studies, while varying in size and the fine detail of testing, have utilised standardised methodology and timing of patient assessments. They have also gained further credibility in that they have involved many differing medical disciplines, all supplying their individual expertise while allowing the "blind" assessment of patient variables.

The limited scope of the early studies with regard to patient assessment has been greatly expanded, now involving intricate psychometric assessment in addition to the previously accepted standard of the clinical neurological examination.

Three studies in particular, have been responsible for putting into context the exact nature of this problem. Two of these studies were carried under carefully controlled circumstances here in Britain(21,25) while the third was conducted in the USA (19).

Interestingly perhaps, in view of the findings reported here, the study from the USA , where intensive per-operative monitoring is extremely well established, found a significantly lower incidence of post-operative deficit (20). All three studies, while confirming the acceptably low incidence of major focal neurological deficit, have conclusively proven the presence of this new syndrome of diffuse cerebral impairment, demonstrable post-operatively in the vast majority of patients undergoing cardiopulmonary bypass surgery.In this syndrome the degree of cerebral damage appears superficially to be much more subtle and less severe. While impairment of level of consciousness in the immediate post-operative period does occur, it is usually transitory with persistent cerebral dysfunction evident as either a diffuse reduction in intellectual function or as a more localised decline in cognitive function associated with loss of memory and personality change.

These last features, while being a source of immense psychological unrest, both for the patient and also their friends and relatives, may often go unnoticed in a busy clinical setting; and as such may be responsible in part, for the syndrome going unrecognised for so many years.

Of the three studies mentioned above The Cleveland Clinic study (19) was a prospective trial conducted in 1980, and included 421 patients undergoing coronary artery bypass grafting as a sole procedure. Stroke occurred in only 2% of the patients although prolonged encephalopathy was detected in 11.6% . This study was able to provide little new information as to the aetiology of the measured deficit, although the peri-operative use of an intra-aortic balloon pump was found to be associated with a higher incidence of neurological deficit than would otherwise be expected. The Newcastle study (21), was also a prospective study, concentrating on patients undergoing coronary artery bypass graft surgery; and included 312 patients, with an incidence of new clinical neurology in 61% of participants, and psychometric deficit evident in 79%. This study also included a control group of patients undergoing non-cardiac surgery (a mixture of thoracic and vascular cases); who while demonstrating an appropriate degree of cardiovascular disease for their age, showed a significantly lower incidence of post-operative neuropsychometric deficit than the cardiac surgical patients. These anaesthetics were in the main however, of significantly shorter duration (22).

The Middlesex group (25), prospectively examined 55 coronary artery patients and a control group of 20 patients undergoing thoracic or vascular surgery. Although only one patient showed evidence of major focal neurological deficit post-operatively, 60% of the cardiac group had clinically detectable neurological abnormalities, including poor coordination, depressed reflexes, drowsiness and nystagmus. They also however, in contrast to the Newcastle group found a similar pattern of post-operative neurological dysfunction in their control group..." and yet, to clinical eyes, they were recovering as well as expected"(1). Long term follow-up assessments in the Middlesex study would suggest that while the majority of the patients with an original deficit improve completely there was still a sizeable group (35%) in whom a deficit was still recognisable at 12 months (26). In members of both the cardiac and control groups demonstrating post-operative deficit a significant fall in mean post-operative cerebral blood flow was found, although pre-existing cerebrovascular disease (even when identified by pre-operative digital subtraction angiography) played little part in post-operative outcome (25). These points highlight the need for an extensive appraisal of peri-operative management during both cardiac and, perhaps just as importantly, major non-cardiac surgery.

In accepting in principle the presence of this syndrome of diffuse cerebral deficit following cardiopulmonary bypass surgery it is essential to investigate in detail the most likely causes in an attempt to improve the situation for the future.

Authors have implicated multiple factors in the aetiology of the behavioural changes described above. These include pre-operative neurological and psychiatric status, age, duration and complications of the operative procedure, post-operative cardiac status and general medical condition, especially fluid and electrolyte balance and liver and kidney function (30,31,32). The extent to which each of these various parameters contributes to the individual case is ,of course, extremely variable and as such possibly accounts for the variation in emphasis placed on contributory factors by different studies.

While it is true that at the present time, there is no clear evidence in the literature regarding the definition of pre-operative predisposing conditions, two per-operative factors are heavily implicated by most authors; namely microemboli and cerebral hypoperfusion (33).

The occurrence of particulate microembolism was not fully appreciated in the early days of cardiac surgery until the suggestion in 1961 that it was a possible cause of cerebral injury (34).

Two years later it was demonstrated that particulate matter could be filtered from banked blood with a Dacron wool filter (35). This began the move towards the routine use of filters in a variety of positions in the circuit during cardiopulmonary bypass,in an attempt to trap particulate matter.

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The particles may result from air (36,37,38), fat(39,40), silicone(41), polyvinyl chloride fragments(42), aggregates of platelets, white cells or fibrin (43,44,45). Attempts at quantifying both the location and size of microemboli have resulted in both the routine use of filters in the cardiotomy suction line and in some centers to the placement of additional filters in the arterial line from the oxygenator (46,47). While it is true that microemboli have been shown to be reduced in number and associated with an improved outcome in animal models (48,49,50,51), there is still little evidence that the routine use of filters is associated with a reduction in morbidity in clinical practice (52,53,54).

There is now some evidence that the overzealous use of filters may well be an additional cause of blood cell fragmentation above and beyond that already caused by the pump itself and that they may in themselves be contributing to the very problem that they are designed to be preventing (55).

Where blood cell aggregates are liberated as microemboli, cell injury additional to that caused by the obstruction of small arterioles may occur. Electron-microscopy studies have shown that mast cells retained in such aggregates extrude their secretory granules from the cell surface, liberating histamine, kinins, serotonin and other potentially harmful substances (56).
Attention however, is still focused on the prevention and also the mechanisms of generation of microembolic debris.

Recent evidence from several centres including both The Hammersmith Hospital (57) and also the Freeeman Hospital, Newcastle, (58,59) would suggest that there is a need for a radical rethink in both filtering policy and also methods of oxygenation; together, possibly, with the routine use of membrane oxygenators and platelet activation inhibitors such as prostacyclin (60-64). At the present time only the routine use of retinal photography will allow the accurate detection of cerebrovascular microembolism in vivo (57) . This type of investigation is both expensive, cumbersome and most importantly, not without risk to the patient. Although there is now reasonable evidence that microemboli can be demonstrated in the retinal vessels of the majority of patients undergoing coronary artery surgery per-operatively(57), the clinical implications of these emboli remain uncertain. In addition the relative inaccessibility of reliable data makes interventional trials involving per-operative manipulation difficult to construct and their results impossible to interpret.

Conclusive evidence incriminating cerebral hypoperfusion as a major aetiological factor has also remained elusive. This is due, partly to the fact that our basic knowledge of cerebral pathophysiological events during and after these operations is extremely scanty (64); and that the implications of changes in per-operative parameters on cerebral perfusion pressure are as yet unexplored.

We neither know the ideal mean blood pressure needed to ensure cerebral protection during cardiopulmonary bypass (65); nor how these limits might be affected by pre-existing disease in the individual patient (although available evidence from The Middlesex group would suggest that the presence of unilateral carotid arterial disease does not increase the risk of post-operative deficit (25)).

What seems likely, is that irreversible hypoxic brain damage may occur when the perfusion of certain areas of brain falls below critical ischaemic thresholds and that this damage will in most cases be concentrated along the boundary zones between the arterial territories of the cerebrum and cerebellum -the so called "watershed" areas (66)

Various authors have suggested that cerebral deficit is more likely if mean arterial pressures, at 37 deg.C., are maintained below 50mm Hg (67,68); and, while this rule is often strictly enforced, there is no irrefutable evidence to suggest that this premise is true. The suggestion that the most vital parameter is the mean arterial pressure, is in fact, extremely misleading, and possibly dangerous. From a basic physiological viewpoint any computation of the pressure difference across the brain, i.e. "cerebral perfusion pressure", must pay regard to both the cerebral arterial, venous, and intracranial pressures.

It has been shown on several occasions that the primary elevation of cerebral venous pressure can have a dramatic effect on cerebral perfusion, and hence viability(69-72).

The concept of auto-regulation with regard to blood flow is fundamental to the understanding of cerebral physiology. This term has been defined as "the continuous local adjustment of blood flow in proportion to the requirements of the tissues for nutrients"(73).

It would appear from available data that this ideal is maintained even during periods of non-pulsatile cardiopulmonary bypass provided there is careful control of oxygenation and hypercarbia, and an avoidance of both carotid artery occlusion and cerebral oedema(74,75).

Therfore if hypoperfusion is a major cause of postoperative deficit the actual cause of the reduced flow will probably be multifactorial.

Is it however advantageous to have "on-line" information regarding cerebral perfusion, and does the patient do better if we act upon that information? There is now extensive evidence to suggest that if the decrease in cerebral blood flow is progressive, threshold values can be defined for alterations in cerebral activity, electrical silence and cerebral membrane failure(76,77,78).

Careful experimentation has allowed identification of these very thresholds and has also suggested that ischaemic damage may also be accentuated by the rapid reinstitution of adequate perfusion (79). The available data would suggest that non-functioning, but viable neurones may be rescued by prompt intervention before permanent cell loss occurs (80).

The recognition of these classical thresholds, will however require both continuing per-operative vigilance on the part of the anaesthetist and also both the availability of the appropriate monitoring equipment and the expertise to use it.
As in many cases the events likely to bring about sudden changes in cerebral perfusion may be of an unpredictable nature, only the continuous use of a wide range of monitoring equipment on every patient is likely to be associated with improved outcome.

This being the case, the accepted level of per-operative monitoring in this country would seem to be inadequate.

Mean arterial pressure alone may be a poor indicator of the pressure difference across the brain, and the infrequent measurement of oxygen tensions in radial arterial samples is unlikely to accurately reflect dynamic cerebral requirements.

At the present time intensive investigation is being undertaken into the cerebral protective properties of a wide range of drugs.

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The use of high dose per-operative barbiturates has now been shown by one group to provide a degree of cerebral protection (provided that a continuous state of cerebral electrical silence is maintained) (81,82); but the necessity for extremely high dose regimens may have far reaching effects with regard to both peri-operative cardiovascular stability and also post-operative sedation.

Prophylactic calcium antagonists, with their potential for both selective blood-brain transmission , and the preservation of adequate cerebral blood flow to the ischaemic penumbra may yet prove a major advance (83-87), although extensive further investigation is still required.

In conclusion, although pharmacological measures may well provide a degree of security, if applied in all cases, the most logical step is for the institution of a system of per-operative monitoring that takes regard of both the "on-line" assessment of cerebral activity and also the monitoring of parameters that most accurately reflect cerebral tissue characteristics.

Such a system of continuous monitoring is readily available today; requires little in the way of training to gain an acceptable level of proficiency; and remains relatively inexpensive. This study sets out to see if this level of investment in intensive per-operative montoring is really necessary.

4. PLAN OF STUDY

It would appear, from careful examination of the facts available at the present time, that it is unrealistic to expect a small prospective study, carried out over the course of only 12 months, to be able to clarify the role of microemboli in the production of post-operative neurological deficit. This is mainly due to the relative unavailability of any standardised method for either accurate detection or prevention, and also because of the lack of any recognised "end-point" against which any interventional trial could be measured.

Cerebral hypoperfusion however, is a concept which is eminently more tenable, as its origins are based on the basic physiological principle concerning the supply and demand of oxygen to an end-organ. This therefore lends itself more readily to a system of intensive monitoring, especially as the best indicators of adequacy of oxygen supply are familiar, and the measurements are often both straightforward and reproducible , involving equipment that is well tested and reliable. In addition all the important parameters have an "on-line" capability that allows for frequent per-operative manipulation.

This ,in itself approaches one of the ideals of any monitoring system, in that it hopefully allows for correction, prior to the reaching of ischaemic thresholds, so minimising any cerebral insult.

The aims of this study therefore, were;

1.- to document the incidence of post-operative
neurological deficit, in a group of patients
undergoing routine coronary artery bypass surgery.
This assessment involved the use of a clinical
neurological examination, a battery of 10
psychometric tests and an extensive
ophthalmological examination. Assessments were
performed pre-operatively and then repeated at
pre-determined intervals in the first post-
operative week. All assessments were "blind" and
carried out by independent qualified
practitioners.

2.- to accurately record per-operative parameters
that closely reflected the relative adequacy of
cerebral perfusion, and by means of careful
statistical analysis of these results, to
correlate the incidence of post-operative
neuropsychometric deficit with both individual,
and group, per-operative trends. The per-operative
monitoring was designed to examine a variety of
variables all indicative of the state of cerebral
well-being.

The per-operative monitoring parameters chosen were;

a)- a continuous measure of cerebral perfusion
pressure (the mean arterial - cerebral venous
pressure)

b)- an accurate estimation of cerebral oxygen
extraction at tissue level (the cerebral arterio-
venous oxygen content difference and the cerebral
venous oxygen saturation).

c)- a continuous recording of cerebral electrical
activity(the Cerebral Function Analysing
Monitor).

d)- an assessment of cerebral and whole body acid-
base status.(both intermittent and continuous "in-
line" monitoring of arterial and venous pH and CO_2
tensions).

The provisional findings of a pilot study strongly suggested that
per-operative fluctuations in arterial CO_2 tensions could play a
possible role in the production of post-operative neurological
deficit. To test this hypothesis the study population was divided
into three groups.

The first group, (Group A) received the routine management protocol for patients undergoing routine coronary artery surgery at this institution. The per-operative ventilatory parameters were determined by the anaesthetist who referred to his own intermittent acid-base analysis as he felt necessary. All three groups were additionally monitored using the parameters described above; but those results were not made available to either the surgeon or anaesthetist.

The second group, (Group B) were exposed to exactly the same protocol as the first except that attempts were made to maintain a state of normocapnia(PaCO2 35-45mm.Hg) throughout the per-operative course.

The third group, (Group C) was constructed of patients undergoing peripheral vascular operations of over two hours duration. They were exposed to an identical management protocol as the first group; no additional attempts being made to control per-operative CO2 tensions.

Patients were randomly selected from the waiting lists of the respective surgical teams for entrance to the trial groups. Groups A and B while were constucted with sequential groups of patients. Group C was constructed of patients selected at random from the waiting list for peripheral vascular surgery.

Only patients undergoing routine elective coronary artery surgery, for the first time, were accepted into study Groups A and B.

There were no other exclusions on the basis of medical disease.

Informed consent was obtained from all participants.

5. METHODS

5.1 : Sample population Characteristics

The patients in this study were all taken from the routine catchment area for this hospital. For the cardiac surgery patients this covered an extremely large area, with patients being referred, from regions as far apart as Oxford and the Channel Islands. While this has undoubtedly helped to minimise personalised bias towards the selection of patients being offered for surgery, it has also raised problems, with regard to patient compliance with long term follow up appointments. Group C was chosen directly from the Wandsworth Health Authority and as such formed a very homogenous population.

All of the cardiac surgical patients had their pre-operative cardiac assessment conducted at St.Georges by one of two cardiac surgical teams. This consisted of routine biochemical and haematological screening together with both electrocardiographic (standard resting, and exercise ECG's) and angiographic interpretation of the extent of coronary disease.
The results of these investigations were not available to the research team until after daily patient selection had taken place and in no way played any influence on the allocation of patients to their respective groups.

The daily operating lists were printed out at the begining of each week. All patients who were scheduled to undergo elective coronary artery bypass surgery during the course of that week were listed, together with the name of their respective surgeon.

From the list, three patients were randomly chosen, by means of a random number generator and the patients birthdate, and allocated to one of the two cardiac groups. One operation was performed on the Tuesday, another on Wednesday and the third on Thursday.

This schedule ensured that firstly, the same operating team (including anaesthetists, surgeons and non-medical staff) remained constant throughout the study, and secondly it allowed the application of a standardised protocol with regard to the timing of both the pre-, and post-operative assessments.

Following surgery all patients were taken to a cardiac surgical intensive care unit where they remained, on average, for approximately 24 hours. During the course of this stay, decisions were made with regard to anaesthetic, surgical and medical matters by the on-call staff; participation in this trial in no way influenced any daily management decisions.

At the end of the standard 24 hour stay, and provided they had made satisfactory progress, patients were transferred back to the routine cardiac ward, where they remained until their discharge home, routinely on the seventh post-operative day.

A follow up appointment was given for 6 weeks after the operation, at which time a further assessment of any neuropsychometric deficit could be performed. This also provided an excellent opportunity to discuss, with the friends and relatives who accompanied the patient to the hospital, the real effect of any measured deficit on the lifestyle of the patient.

5.2 - Principles of patient assessments

In the context of clinical research, the use of the word assessment refers to both a diagnostic process - the initial identification of lost functions and new signs - and also to a measuring process that defines the extent of any losses.

The majority of assessment protocols used for routine clinical practice are also ideal for use as research tools. However, it should be remembered, that while clinical practice can continue in the . absence of good clinical assessments, proper and accurate assessments are vital in research related to subjects such as stroke because, whatever the study design or the statistical procedures used, there is no way to improve upon poor original data.

It is essential to measure accurately the pre-operative state of all participants, and the assessment protocol should include parameters that are known or suspected to be related to the expected outcome.

Post-operative assessments are necessary to measure the changes brought about during the peri-operative period.

The more sensitive and reliable the outcome measure used, the more likely it is that any change, beneficial or detrimental, will be detected.

It is unfortunately true, that many of the recent investigations into this problem (excepting Cleveland, Newcastle and the Middlesex) have used widely varying methods of pre-, and post-operative assessment. This has resulted in a situation where objective observers find it difficult to extrapolate from one study to another, resulting in the unnecessary repetition of research merely to examine an alternative method of assessment.
In this study, attempts to combine the two classical methods used in the assessment on neurological problems, namely the "checklist" and "representational" approaches are made; in the hope that this compromise will allow other groups to identify with, and to extrapolate from our results.

The use of a checklist assessment, containing all the possible defects, is one way of ensuring that some vital disability is not overlooked. The patient is subjected to a wide range of tests in order to identify (and measure) every single possible disability and problem. This in turn, leads to the formulation of an individual "profile", giving a detailed description of the precise ability and disability of that patient which if accurately and diligently recorded, lends itself easily to retrospective analysis at any future date.

There are however some basic problems with this form of asessment. One major characteristic is that at the end of the examination no summary/score is arrived upon, other than by simply abbreviating the description.

The other major disadvantage lies in its thoroughness, which inevitably means that it is both long to complete and to describe to somebody else. This type of assessment is therefore very limited when it comes to following the progress of a group of patients over a peri-operative period.

In contrast, the measurement approach gives a score, usually numerical, which reflects the extent of the deficit being measured. It is necessary however, to use the same tests on each and every patient. Normally the assessment would be constructed of relatively few tests, so making it representive rather that fully descriptive. The great advantage of this method of assessment is its speed and simplicity. It offers both reproducibility, and an ability to communicate the results easily and quickly to others.

There are however several major disadvantages with his technique when it is used as the sole method of assessment.

Firstly, it may not actually represent what it actually claims to: - it may give false information.

Secondly, even if it is a reasonably accurate representation, an occasional patient may not fit the model, and major problems may be missed.

Lastly, retrospective analysis, reveals a series of scores; the true value of which are known only to the original investigator. A combination of the two methods of assessment was therefore made to examine what we felt were the important areas related to post-operative deficit. In constructing the assessment protocols attempts were made to combine the essentials of clinical relevance, validity and reliability with the desirable ingredients of sensitivity, simplicity, communicability and scalability.

The three categories of assessment; neurology, psychometry and ophthalmology each had their own experienced operator who performed all of the pre-, and post-operative assessments in that specialty.

The incorporation of a pilot study prior to the commencement of the study proper, avoided the unnecessary bias associated with any operator "learning-curve" and allowed for the fine tuning of the assessment protocol. In addition to the trained assessors, mentioned above, we also obtained the assistance of senior members (senior registrar/consultant) of the specialties concerned, to provide expert opinion on the discovery of unexplained abnormalities.

The multi-disciplinary approach to assessment ensured that it was possible to fully examine the eight classsical components of stroke assessment. These are Medical problems, Cognition, Communication, Motor and Sensory function, Daily activities, Housing, Social function and Emotional state.

a) Neurological assessment

All patients involved in the trial had neurological assessments performed on the day prior to their operation, and then again on several occasions in the first post-operative week.

The exact form, that each assessment took is shown in Table 1.

As stated above, each of the assessment modalities had a separate assessor who performed all examinations "blindly".

The results of all of the assessments were not analysed until the end of the study, so as to minimise any bias due to inter-operator discussion.

In addition to the history and clinical neurological examination we adopted a representive method of assessment of motor power.

The system that we used was first devised by the Medical Research Council (1976) for use in the study of war injuries to peripheral nerves. The scale classifies the motor power into 6 grades. While this rather simplistic approach was useful in its original purpose, it proved difficult at first to transpose its use to the stroke patient. This was mainly because stroke, in contrast to a pure peripheral nerve injury, specifically affects the central control of muscle groups, and loss of strength is only a small part of the resultant motor disability.

The MRC scale has therefore been adapted for use in the stroke patient (88). The new modified scale is called the "Motricity Index" and is based upon the fact that the strength of any one movement about a joint is similar to the strength of of all other movements around the joint, and so one only needs to measure the strength of one movement at each joint (89).

The scale also gives regard to the proportion of total recovery that it takes to change from one grade to the next (e.g. a change from grade 2 to grade 3 at the elbow was equivalent to progressing from 42% to 56% of total motor recovery).The use of these weighted scores, which are shown in Table 2., enabled the calculation of a score that represented the total both for that limb and also that side.

The complete protocol for the neurological assessment is shown in Table 3.

A final neurological assessment was performed at six weeks post-operatively when the patients returned to the unit for their first out-paients follow-up.

Table 1.

CLASSIFICATION OF THE CLINICAL NEUROLOGICAL EXAMINATION

		"CHECKLIST"	"REPRESENTATIONAL"
PRE-OP.	:	*	*
DAY 1.	:	/	*
DAY 2.	:	*	/
DAY 3.	:	/	*
DAY 4.	:	*	/
DAY 5.	:	/	*
DAY 6.	:	*	/
DAY 7.	:	*	*
6 WEEKS	:	*	*

An * represents the day on which this assessment was performed.

"checklist"= written assess: "representational"= motricity index

Table 2. :   ASSESSMENT OF MOTOR POWER - THE MOTRICITY INDEX

Arm :

(1) Pinch grip - 1 inch cube between thumb and index finger

(2) Elbow flexion

(3) Shoulder abduction

Leg :

(4) Ankle dorsiflexion

(5) Knee extension

(6) Hip flexion

Test	Score and criterion		
(1)	00	=	no movement
	33	=	beginings of prehension
	56	=	grips cube, without gravity
	65	=	holds cube against gravity
	77	=	grip against pull,weaker than other side
	100	=	normal
(2) - (6)	00	=	no movement
	28	=	palpable contraction, but no movement
	42	=	movement without gravity
	56	=	movement against gravity
	74	=	movement against resistance, but weaker than normal
	100	=	normal

Table 2. : Motricity Index   (cont)

--------   ----------------

Computation of final score

All totals have a range from 0 - 100

Arm score = (scores of (1) + (2) + (3)) / 3

Leg score = (scores of (4) + (5) + (6)) / 3

TOTAL MOTOR SCORE = (Arm + Leg) / 2

Table 3.

PROTOCOL OF NEUROLOGICAL EXAMINATION :

A. Direct Questioning :

For the following, if a positive result is obtained note the duration of the longest and shortest episodes, whether the syptoms are sill present or have resolved.

For any episode note the : DATE OF ONSET

DURATION OF WORSENING

DURATION OF THE RECOVERY PHASE

FREQUENCY OF RECURRENT EPISODES

1. History of C.V.A.	:	YES = 1, NO = 2.	[ ]
if yes, specify	:	number........................	
		probable site................	
		last episode.................	
		residual disability..........	

Describe below the original event and the subsequent recovery : _____

_____

2 Migraine	:		[ ]

_____

_____

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3. Severe headache   :   [ ]

4. Loss of consciousness :   [ ]

5. Visual disturbances   :   [ ]

            loss of vision :

            blurred vision :

            double vision   :

6. Speech disturbances   :   [ ]

            slurred speech :

    difficulty finding words :

7. Weakness or loss of feeling in :   arm   [ ]

                                        leg   [ ]

8. Hearing impairment   :   [ ]

9. Clumsiness   :   [ ]

10. Loss of balance   :   [ ]

11. Giddiness (vertigo):   [ ]

12. Difficulty chewing   :   [ ]

13. Difficulty swallowing :   [ ]

14. Bladder/waterworks problems   [ ]

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15. Bowel problems   :   [   ]

16. Problems with sexual function   [   ]

Description of above symptoms :_____

_____

_____

_____

_____

_____

_____

_____

_____

B. Previous Neurological investigations

----

                          date: findings:

    1. C. T. scan   :

    2. Angiograms   :

    3. Neurosurgery   :

    4. Neurovascular   :

       surgery

C. Pre-operative Neurological examination

----

    1. Speech   normal : 1   [   ]

              dysarthria : 2

           dysphasia (minor motor) : 3

         dysphasia (> minor motor) : 4

    2. Gait   normal : 1   [   ]

             abnormal : 2

       specify...

    3. Upper limb dyspraxia   [   ]

             present : 1

             absent : 2

    4. Dyscalculia   [   ]

             present : 1

             absent : 2

    5. Finger agnosia   [   ]

                p : 1

                a : 2

    6. R / L disorientation   [   ]

                p : 1

                a : 2

    7. Constructional apraxia   [   ]

                p : 1

                a : 2

8. Dressing apraxia   [   ]

        p : 1

        a : 2

9. Dysgraphia   [   ]

        p : 1

        a : 2

10. Dyslexia   [   ]

        p : 1

        a : 2

11. Colour anomia   [   ]

        p : 1

        a : 2

12. Cranial nerves   normal : 1   [   ]

               abnormal : 2

present : 1

absent : 2

                         Rt.   Lt.

      a) anosmia   ....

      b) retinal art. occlusion ....

c) ptosis ....

d) nystagmus (gaze towards).................

e) nystagmus (gaze vertical)................

f) horners syndrome ....

g. optic disc appearance ....

h. visual acuity ....

i. visual fields ....

j. pupillary reflexes ....

k. extraocular movements ....

l. corneal reflex ....

m. facial sensation ....

n. facial power ....

o. hearing ....

p. palatal power ....

q. sternomastoid power ....

r. tongue power ....

Summary of cranial nerve abnormalities :..................

....

....

13. Limb Examination

        normal : 1   [   ]

      abnormal : 2

a) muscle tone   normal : 1   u.r. [   ]

                  increased : 2   u.l. [   ]

                  decreased : 3   l.r. [   ]

                                   l.l. [   ]

b) muscle power   normal : 1   u.r. [   ]

                  U.M.N. : 2   u.l. [   ]

                  L.M.N. : 3   l.r. [   ]

                                   l.l. [   ]

c) involuntary movements

                present : 1   u.r [   ]

                 absent : 2   u.l. [   ]

                                l.r. [   ]

                                  l.l. [   ]

d) cerebellar function

                normal : 1   u.r. [   ]

              abnormal : 2   u.l. [   ]

                                  l.r. [   ]

                                  l.l. [   ]

e) deep reflexes

                              normal : 1

                          hyperactive : 2

                             reduced : 3

                              absent : 4

                                   Rt.   Lt.

SUPINATOR

BICEPS

TRICEPS

FINGER JERK

KNEE

ANKLE

        normal : 1

      abnormal : 2

                                   Rt.   Lt.

f. plantar reflexes

present : 1

            absent : 2

    g. primitive reflexes

            grasp :

    palmomental :

            pout :

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h. sensory system

normal : 1

abnormal : 2

	u.r.	u.l.	l.r.	l.l.
pain and temperature	[ ]	[ ]	[ ]	[ ]
tactile	[ ]	[ ]	[ ]	[ ]
position	[ ]	[ ]	[ ]	[ ]
vibration	[ ]	[ ]	[ ]	[ ]
cortical	[ ]	[ ]	[ ]	[ ]

i. motricity index

arm score   [...]

leg score   [...]
------------   -----

TOTAL SCORE   [...]

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The post-operative examinations were performed at the times shown in Table 1. and the examinations took the form, once again of either a checklist or representational assessment. - Table 4.

This included the pre-operative neurological examination protocol, as stated above (Table 3. section C), but in addition, two extra sections were added. The first took the form of a modified Glasgow coma scale and was used as a means of assessing progress in the first 12 - 24 hours post-operatively. Secondly , a section was added to contain a written daily diary, containing the individual progress of each patient.

Major neurological abnormalities were reported to the consultant/senior registrar in the department of neurology who on then visited the patient in question within 4 hours, following which he made a written entry concerning the likely nature of the problem.

An arrangement was made for any patients showing signs of persistent severe neurological deficit to be transferred to the Regional Neurological unit where a C.T. scan was performed. In addition to the routine post-operative follow up in the cardiac surgical department, provision was made for any patients with major deficit to be also re-assessed by a senior neurologist when they returned to the hospital six weeks after their operation.

Table 4.

PROTOCOL OF NEUROLOGICAL EXAMINATION - POST-OPERATIVE :

Assessment of level of consciousness :

----

1. Coma / altered level of consciousness   [   ]

        present : 1 ,   absent : 2   if present ;

a) eye opening   [   ]

    spontaneous : 1,   response to verbal stimuli : 2

    response to noxious stimuli : 3,   none : 4

b) motor response   [   ]

    obeying commands : 1, localising : 2, withdrawl : 3

    abnormal flexion : 4, abnormal extension : 5

c) verbal response   [   ]

    orientated speech : 1, confused conversation : 2

    inappropriate speech : 3, incomprehensible : 4

    no speech : 5

d) corneal responses   [   ]

        present : 1, absent : 2

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e) pupils   [   ]

   reacting both equal : 1, reacting one only : 2

   non reacting equal,2mm : 3, non reacting equal,4mm : 4

   non recting unequal : 5

f) spontaneous eye movements   [   ]

   none : 1, roving dysconjugate : 2, roving conjugate : 3

   orienting : 4, lateral deviation -> rt. : 5

   lateral deviation -> lt. : 6, other : 7

g) oculcephalic   [   ]

   absent : 1, reduced : 2, normal : 3

h) oculovestibular   [   ]

   absent :1, dysconjugate : 2,

   tonic conjugate deviation : 3, normal : 4

i) grimace   [   ]

   present :1, absent :2

j) respiration   [   ]

   ventilated : 1, periodic : 2, ataxic : 3, regular : 4

_____

2. Delirium / psychosis   [   ]

   present : 1, absent : 2

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3. Confusional state   [   ]

    present : 1, absent : 2

4. Seizures   [   ]

    myoclonus : 1, asterixis : 2, focal : 3

    generalised : 4, focal and generalised : 5, none : 6

The pre-operative neurological examination was then repeated
at this stage, and the results collated as in Table 3, section C.

BRIEF SUMMARY OF NEUROLOGICAL ABNORMALITIES

Day 1:_____

_____

Day 2 :_____

_____

Day 3 :_____

_____

Day 4 :_____

_____

Day 5 :_____

_____

Day 6 :_____

_____

Day 7 :_____

_____

b) Psychometric assessment

Neuropsychological testing has been used on many occasions in the past, to assess changes in cognitive function following cardiac surgery. Available results would suggest that at the present time it is the best method for obtaining a quantitative assessment of cognitive function post-operatively; and this view is reinforced by the finding that score changes following surgery correlate well with biochemical markers of brain damage (90,91,92).

The tests that we have used for our assessment, together with short explanations concerning their application are shown in Table 5. and the timing of the tests in Table 6.

We have attempted to employ tests which have a high test-retest reliability coefficients and so we would normally expect the scores to remain unchanged or to improve due to practice when the tests are repeated after a short interval. It is vital to differentiate between the generalised malaise associated with surgery in general with the more specific cognitive losses that have been reported in the past associated with post-bypass patients. In an attempt to resolve this issue we have subjected all the Group C patients to the same battery of psychometric analysis.The majority of available evidence would suggest that general surgery and conventional anaesthesia produce very little drop in psychometric function (93-97).

There have been five major studies utilising psychometric analysis of patients undergoing coronary artery bypass surgery. Four of them implicate the perfusion period as the most likely source of post-operative deficit, (although the percentage of patients with deficit appears to be related to the number and sensitivity of the tests used), and also find no evidence of similar deficit in the control groups (21,97-100).

The fifth study, while showing a deficit in the cardiac group of very similar proportions to the others also , rather surprisingly also showed a substantial degree of deficit in the non-cardiac control group. The one year follow up of patients in this study added considerable weight to the argument that the deficit may, in a considerable percentage of patients, represent a permanent cognitive loss (25).

For all of the psychometric tests the instructions were carefully and slowly explained to the patients before each assessment. The patient was given an opportunity to ask for clarification on any points prior to the original testing, pre-operatively. Any point that was raised was noted, and clarification of that point was then repeated prior to any subsequent examinations.

All tests, (both pre- and post-operatively), on every patient were performed by the same trained assessor. This person was highly skilled in the administration of the range of psychometric analysis that we had constructed.

These assessments, as with all other assessments of outcome, were performed "blindly", in all cases; the assessor having access to neither study protocol, nor results.

The choice of the contents of the psychometric "battery" was decided upon both from the results of previous work and also following consultation with neuropsychologists in the Department of Neurological studies at Atkinson Morley's Hospital.

TABLE 5. - PSYCHOMETRIC ASSESSMENT

---------   -----------------------

a) Cognitive assessment

-- --------------------

TEST 1. : Trail making A.

TEST 2. : Trail making B.

TEST 3. : Visual reproduction.

TEST 4. : Mental test score.

TEST 5. : WMS (Wechler memory scale) - mental control.

TEST 6. : WMS - digits span.

TEST 7. : WMS - associate learning.

TEST 8. : Frenchay aphasia screening test A.

TEST 9. : Frenchay aphasia screening test B.

b) Psycho-social assessment

-- -----------------------

              Frenchay activities index
    TEST 10 : <

              Activities of daily living (Barthel)

Additional assessment : Hospital anxiety/depression score.

TESTS 1 and 2 :   Trail making A + B (Halstead-Reitan)
----------------   -------------------

(psychomotor speed, flexability and visuospatial organisation)
(101,102)

The Trail making test part A consists of a sheet of paper on
which are drawn 25 circles each numbered from 1 to 25.

The examinee is instructed to connect the circles in numerical
order as quickly as possible.

Part B, is again composed of 25 circles, containing the numbers 1
to 13, and the letters A to L.

Here the examinee is instructed to connect the circles in
ascending order, as quickly as possible while alternating between
numbers and letters.

     (i.e. 1 - A - 2 - B - 3 etc.)

Errors were brought to the attention of the examinee, who was instructed to correct them. We then scored the test as following;

score :

10	no mistakes + < 4 minutes
9	no mistakes > 4 mins or 1 mistake < 4 mins
8	1 mistake > 4 mins
7	2 or 3 mistakes < 7 mins
6	4 or 5 mistakes < 7 mins
5	complete 5+ mistakes
4	complete 10+ mistakes
3	incomplete > 5 mistakes, 7 minutes
2	incomplete > 10 mistakes, 7 minutes
1	unable to perform test

TEST 3. : Visual reproduction
-------   --------------------

(visual memory, visuospatial ability and visual neglect)

The examinee is asked to view three cards for a period of
approximately 10 seconds each, after which the card in question
is then withdrawn and an attempt made to reproduce the previous
drawing as originally constructed. The attempts are then scored
by refering to the appropriate section in the Wechler Memory
Scale (WMS) handbook (section 6.). Each subtest was scored
independently and a total score obtained for each examinee.

Assessment also utilised the present standard method of visual
neglect testing, the drawing of the Greek Cross. This further
subtest was performed on each psychometric examination.

In addition to testing for visual neglect these other subtests
examine both visual memory and visuo-spatial ability, and have
been subjected to previous, extensive analysis with reference to
an identical population group (58,103).

TEST 4 : Mental test score (Hodkinson 1972)

-------- ----------------------------------

This test concentrates almost exclusively upon memory, both recent and longterm. This form of assessment has been well validated with regard to the neuropathological findings characteristic of dementia (104,105) and has recently been applied to the assssment of the acute stroke (106). The simple advantage of this test is that extensive cognitive testing is often limited by the setting in which it is conducted, especially in the immediate post-operative period. The mental test score overcomes these problems and allows assessment even when circumstances are difficult. It has however one disadvantage, in that some of the questions relate to current affairs matters which may not be appropriate to the individual examinee. The questions asked are scored below - each correct answer obtaining one mark.

AGE

TIME NOW (to nearest hour)

ADDRESS GIVEN (for recall at the end of the test) 42 WEST ST

NAME OF HOSPITAL

YEAR

DATE OF BIRTH

MONTH

YEARS OF FIRST WORLD WAR

MONARCH

COUNT BACKWARDS   FROM 20 - 1

TEST 5 : WMS - Mental Control

--------- ---------------------

This test consisted of three subtests :

Counting down from 20 - 1 ,

Repeating the alphabet ,

Counting in 3's up to 40 (starting at 1) ,

Both the total time taken to complete the subtests and also the number of errors are used to calculate the eventual score. It has been shown to be a sensitive index of both attention and also the powers of concentration by other workers in this same field of investigation (93).

TEST 6 : WMS - Digits Span

------ --------------------

The patient is required to repeat a digit series forwards and then a different series backwards. The score is the longest series remembered correctly.The test examines both attention span and also audioverbal immediate memory and is regarded as a general indicator of cerebral dysfunction without any special localising value (103).

DIGITS FORWARD	score	DIGITS BACKWARDS	score
2-8-6-1	4	7-5-1	3
7-4-2-9-6	5	3-5-8-	4
8-4-2-7-5-1	6	4-7-1-8-6	5

etc. - all 3,4,5,6,7and 8 number sequences are repeated twice although only one sequence for each is shown above.

TEST 7 : WMS - Associate Learning

------   -------------------------

Ten pairs of words are read to the patient who is required to
learn them in three trials. Each time the words are presented
however the order is slightly altered. Some of the pairs of words
are recognised as being "easy" while others are recognised as
being "hard". A system of scoring is again supplied with the
test.

It is recognised to be an assessment of both auditory memory and
also new learning ability (103).

FIRST PRESENTATION   SECOND PRESENTATION   THIRD PRESENTATION

metal - iron   rose - flower   baby - cries

baby - cries   obey - inch   obey - inch

crush - dark   north - south   north - south

school - grocery   up - down   school - grocery

rose - flower   fruit - apple   cabbage - pen

up - down   school - grocery   up - down

obey - inch   metal - iron   fruit - apple

fruit - apple   crush - dark   crush - dark

cabbage - pen   baby - cries   metal - iron

A total for both easy and hard recall is then calculated for each
of the 3 attempts. The final score = "easy"/2 + "hard".

TESTS 8 and 9 : Frenchay Aphasia Screening Test A and B
--------------   --

Aphasia is the commonest disorder of communication after stroke,
and therefore warrants careful examination with respect to post-
operative deficit (106).

It is possible that comprehension recovers before expression and
as a result it would seem important to examine separately these
two aspects of aphasia.

The major prognostic factor would seem to be the severity of the
initial loss. Age may have an indirect influence in that younger
patients appear to have predominately expressive aphasias which
tend to recover more fully.

The following test was devised at the Frenchay Stroke Unit,
Bristol.

The examinee is given the picture shown below and asked the following questions;

"show me the bridge."

"point to the man walking the dog"

"point to the tallest tree"

"point to the mans left leg and then the canoe"

"before pointing to the duck near the bridge, show me the middle hill"

"point to the square....the cone.....the oblong and the square...... the square,the cone and the semicircle...

the one that looks like a pyramid and the one that looks like a segment of orange."

EXPRESSION - TEST 9

---------- ------

Using the picture, the examinee is given the following
instructions;

"describe all that is happening in the picture"

SCORE: 5 - proper sentences naming 10 items - 4 phrases.

        4 - 4 phrases or 10 items but not normal performance

        3 - 3 phrases and > 5 items

        2 - 2 phrases

        1 - words only

"you have 1 minute to name all the animals you can think of"

SCORE: 5 - names 15

        4 - names 11 - 14

        3 - names 6 - 10

        2 - names 3 - 5

        1 - names 1 or 2

READING TEST	:	WRITING TEST

"point to the dog....point to
the man on the barge....to the
boys feeding the ducks...touch
the bottom of the card then the
top...touch the left hand corner."

score 5 - proper
sentences,
->
score 1 -
words only

An individual score was then calculated for both receptive
and expressive capabilities.

Figure 1 :   Frenchay Aphasia Screening Test - Pictorial
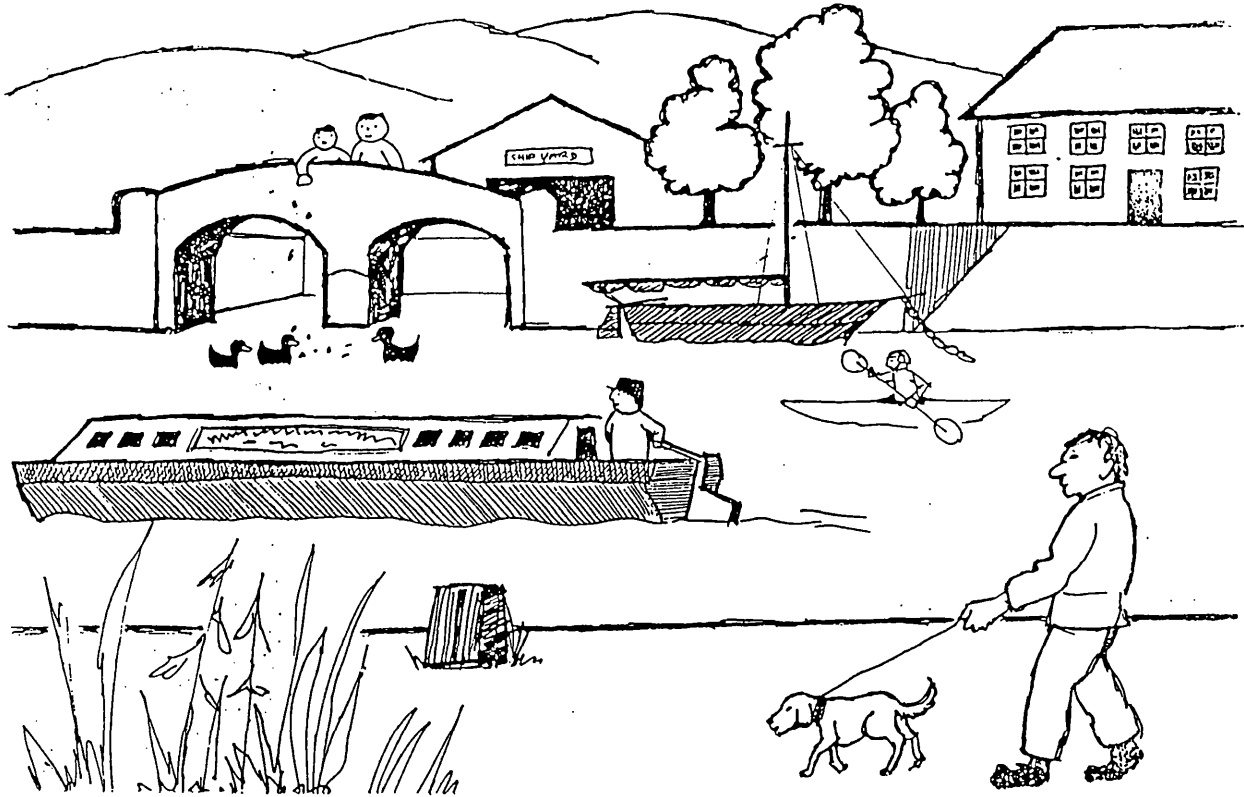
TEST 10 : Activities of Daily Living (Frenchay and Barthel)
-------   --

Tests examining activities of daily living have been used in many different contexes to assess post-event morbidity, whatever the cause. A large amount of nominitive data suggests that they offer an excellent insight into both the speed and extent of recovery; while having the inherent advantage that they examine factors, intrinsic to the psychological well-being of the patient.

The following two tests while overlapping to a small extent, do in fact complement each other well, and a combined score was obtained for all patients.

The advantages of the above assessments are that firstly, as they can be sent through the post, and therefore can be repeated as often as required in the post-operative period without the need for further hospital recall. Secondly, they result in a summary score, so allowing an interpretation of trends and also allowing appropriate statistical analysis (107,108)

The Hospital Anxiety and Depression scale is a self assessment scale which has been designed to detect states of anxiety and depression in the setting of either a hospital ward or in the hospital medical outpatient enviroment (109).

The Frenchay Activities Index

In the last 3 months;   code:

1) preparing meals

                                               1=never

2) washing up   2=under 1 /week

                                               3=1-2 / week

                                               4=most days

3) washing clothes   1=never

4) light housework   2= 1-2 in 3 months

5) heavy housework   3= 3-12 in 3 months

6) local shopping   4= at least weekly

7) social outings

8) walking outside > 15mins

9) actively pursuing hobby

10) driving car/bus travel

In last 6 months;   code:

11) outings/car rides   1= never

12) gardening   2= 1-2 / 6 months

13) household/car maintenance   3= 3-12 / 6 months

14) reading books   4= at least weekly

15) gainful work

                    TOTAL =

The Barthel Score

The stairs assessment was withdrawn from the list as this proved impossible in the immediate post-operative period.

1. feeding
2= independent, 1= needs some help
0=needs to be fed

2. bathing
1= able to wash all over,
0= needs help

3. grooming
1= totally independent
0=dependent in some way

4. dressing
2= independent, 1= needs some help
0= unable to do without help

5. bowels
2= no accidents, 1= occ. accidents
0= incontinent

6. bladder
2= continent, 1= occ.accidents
0= incontinent

7. toilet
2= independent, 1= minor
assistance
0= unable to use

8. transfer
3= totally independent, 2= minimal
help, 1= sit unaided,major help
0= unable to transfer

9. ambulation
3= independent for 50 metres
2= walk 50 metres with help
1= independent in wheelchair 50m.
0= immobile

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A score for the above two tests was calculated in each case and
the two scores added together to give a combined activities of
daily living assessment.

In addition the hospital anxiety depression scale shown below was
also tested on all willing participants.

Table 6. : Timing of psychometric assessments

-------- ----------------------------------

The complete battery of 10 psychometric tests plus the hospital anxiety depression scale were performed on all test occasions.

 Pre-operative : 1 - 2 days prior to surgery

 Post-operative : 2 - 3 days post surgery

 : 7 days post surgery

 : 6 weeks post surgery

Longterm follow-up will also be attempted

c) Ophthalmological assessment

All trial patients underwent detailed ophthalmological examination once, on the day prior to surgery and then again on three occasions in the first post-operative week.

Assessment consisted of testing ;

1. Visual acuity, with adequate correction

2. Visual fields using a goldman perimeter at one third of a metre using standard, and hence repeatable target size and intensity.

3. Extra-ocular movements

4. Fundoscopy, utilising a direct and indirect ophthalmoscope, following pupillary dilatation with 1% tropicamide.

All assessments were made by the same, senior member of the ophthalmological department. It is important to point out that the members of the ophthalmological department involved in the trial were completely "blind" to any changes in per-operative parameters. They were only informed at the end of the completed trial that the patients were from two cohorts.(i.e. controlled / uncontrolled PaCO2).

Although it was fully appreciated that additional information could possibly have been provided by retinal angiography (57), it proved impossible to obtain ethical clearance for the performance of such investigations; (the local ethical committee considered that the risk of anaphylactic reaction following intravenous injection of labelled red cells was of an unacceptably high order).

The timing of the various parts of the ophthalmological assessment are shown in Table 7. below.

Table 7. : Ophthalmological assessments
-------   ----------------------------

Time :	VIS.ACUITY :	VIS.FIELDS:	E.O.M:	RETINA
Pre-op	*	*	*	*
Post-op				
1 day	/	/	/	*
2/3 days	*	*	*	*
7 days	*	*	*	*
6 weeks	*	*	*	*

5.3 : Per-operative Anaesthetic and Surgical protocols.

65 patients undergoing isolated coronary artery bypass surgery and 15. patients undergoing peripheral vascular surgery,were admitted to the study, and a standardised anaesthetic and surgical protocol adopted.

a. Anaesthetic protocol

Pre-operative assessment was conducted as normal, with the anaesthetist unaware of the patients selected for entry into the trial until the morning of the operation.

A standard premedication - Papaveretum (0.3mg/kg) and Hyoscine(0.06mg/kg) was administered to all patients one hour prior to surgery.

On entry to the anaesthetic room all patients were given Diazepam (0.15mg/kg) to provide further sedation prior to the insertion of all monitoring lines under local anaesthesia (Lignocaine 1%). Careful monitoring of cardiovascular parameters was performed manually until the insertion of the direct monitoring lines.
An electrocardiograph was sited on admission to the anaesthetic room and was monitored throughout the peri-operative course.

The following monitoring was applied to all 65 patients, in the order shown, prior to the induction of anaesthesia.

1:   Peripheral intra-venous infusion - 14G cannula (Venflon).

2:   Radial arterial cannula - 20G (Wallace)

- connected to a 10cm length, of fine bore manometer tubing (priming volume 0.2ml) and a 3-way luer-lock tap (Discofix 3), all of which had been pre-flushed with an appropriate volume of heparinised normal saline (500 i.u. Heparin in 500ml 0.9% sodium chloride). The 3-way tap was inserted to allow easy aspiration of arterial samples for per-operative analysis:

- this was then connected to a pressurised fluid filled transducer/pressure system (Intra-flow) which was electrically transduced to the Hewlett-Packard monitoring system, so providing both continuous visual display and also a permanent record by means of a 4-channel chart recorder (Siemens). This system was calibrated both before and after the operations with standardised pressure loads.

3: Right atrial lines - Leadercath (2) - inserted to the right internal jugular vein - allowing the continuous monitoring, via the Hewlett Packard system / Siemens chart recorder, of right atrial pressure while allowing the separate central administration of drugs and fluids.

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4: Jugular bulb monitoring (pressure and venous sampling).

Insertion : Direct approach utilising low route: strict asepsis

With the patient placed in the head-down position and the head turned to the right, the triangular gap between the sternal and clavicular heads of the sternomastoid muscle were identified immediately above the clavicle on the left (the terminal part of the internal jugular vein lying behind the medial edge of the clavicular head of the muscle at this point).

Local anaesthetic was infiltrated at this point and the position of the vein confirmed with a 21G needle connected to a 5ml syringe. Having identified the exact position of the vein a 14g cannula (cordis) was inserted, pointing upwards, into the lumen of the vein, advanced a further 5cm, and correct positioning confirmed by the ease of aspiration of venous blood. A guide wire was then inserted some 2cm beyond the end of the cannula (i.e. 7cm into the vein) and the original cannula withdrawn.

The Cordis - 5FG sheath with integral dilator was then passed over the guide wire and into the vein. A marked "give" was routinely felt as the sheath entered the vein, again position being confirmed by the ease with which blood flowed retrogradely when the infusion bag, connected to the side arm of the sheath was lowered to the floor.

The guide wire was then withdrawn through the self-sealing port of the sheath. The distance was measured from the point of entry through the skin to the angle of the jaw, and the cordis sheath advanced retrogradely 1cm greater than the above measured distance (mean length of sheath advanced = 11.5cm).

A 100cm long section of manometer tubing (rigid), with a priming volume of 1.77ml, was then connected to the side arm of the sheath and after further checks on patency was flushed with an appropriate volume of heparinised saline. This line was then used for the sampling of jugular bulb venous blood throughout the per-operative period.

Under sterile conditions a catheter tip transducer
(Camino 110-4) was then advanced along the cordis sheath a distance of 1cm greater than the amount of sheath in the vein (mean = 12.5cm). The transducer was calibrated in air prior to insertion and again at the end of the procedure. (None of the patient measurements made in this study showed any significant calibration variations between the pre- and post-procedure values).The system was then connected via the Camino master control interface to the Hewlett Packard monitoring stack and thence to to the 4 channel chart recorder. This allowed continuous monitoring, together with a permanent record of jugular bulb pressure. None of the data relating to any jugular bulb samples or pressures were available to the anaesthetist / surgeon until after completion of the trial.

5. Cerebral function monitoring

All patients were connected to the Cerebral Function Analysing Monitor (CFAM) prior to the induction of anaesthesia. In all cases connection was made using scalp electrodes and collodion jelly which were pre-fixed to the appropriate points on the scalp prior to the patient leaving the ward. This allowed standardisation of both points and mode of fixation and avoided unnecessary delays on entry to the anaesthetic room.

The CFAM machine was standardised prior to use, and connected to the patient as early as possible in the anaesthetic procedure. Using an RS232 interface a digital recording of the CFAM output was made on digital tape and stored for future analysis (Cristie CS2).

The CFAM trace was continued throughout the per-operative course, only being discontinued immediately prior to the patient leaving the operating theatre.

The CFAM machine was positioned in the theatre so as to allow the anaesthetist to view the trace throughout the per-operative course (the normal situation in non-trial patients) and to act upon the information supplied by the trace as appropriate.

Induction of anaesthesia was with sodium thiopentone (5mg/kg).
administered into a peripheral vein.

Maintenance of anaesthesia was with an opiate / relaxant
technique (Papaveretum / Pancuronium - doses at discretion of the
appropriate anaesthetist) supplemented with nitrous oxide (66%)
and Halothane 0.5%.

Portex cuffed endotracheal tubes (9.0mm ID for men, 8.0mmID for
women) were used in all patients and connected to a Servovent
ventilator.

In the first 35 of the coronary artery surgery patients (Group A)
the anaesthetist referred to the results of his own blood gas
analysis, before, during, and after the period of perfusion, for
the adjustment of ventilatory parameters.

In the next 30 of the coronary artery patients (Group B) the
anaesthetist and perfusionist were asked to maintain normocapnia
($PaCO_2$ 35-45mmHg./ 4.7-6kPa.) throughout the operation with the
aid of an end-tidal CO_2 monitor (Engstrom) before bypass and an
"in-line" $PaCO_2$ analyser (Cardiomet 4000,Biomedics), situated in
the arterial output line from the bypass machine during
perfusion, in addition to the results of any blood gas analyses
that they performed. All equipment used was calibrated against
standard samples at the begining and end of measurements.

In the remaining 15 vascular cases (Group C) ventilatory parameters were again at the discretion of the anaesthetist who was free to act upon the results of his own blood gas analysis as appropriate. No additional montoring, by way of end-tidal CO_2 monitoring was utilised (i.e. as with Group A).

In all cases, requirements with regard to both transfusion of blood or other colloids or the need for the use of cardioselective drugs were again left to the discretion of the anaesthetist involved.

Following the operation all patients were transferred to the cardiac intensive care unit, where they remained intubated, and connected to a ventilator for elective post-operative ventilation (mean time to extubation = 11.7hrs post-operatively). In all cases rigorous control of ventilatory parameters maintained arterial $PaCO_2$ levels between 35 - 45mm.Hg. until extubation had been performed.

Standardised post-operative treatment protocols were applied to all patients in the trial, their presence in the trial not influencing any management decisions throughout their peri-operative course.

Following a period of approximately 24hrs in the intensive care unit the patients were transferred back to their appropriate pre-operative ward.

b. Surgical protocol

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Access to the heart was achieved in the coronary artery patients
by means of a mid-line sternotomy and the appropriate veins /
arteries were prepared and tested prior to the commencement of
the perfusion period.

Following the onset of the perfusion period surgical technique
consisted of;
- intermittent ischaemic arrest;

> - whole body cooling to 31deg C;
>
> - a Stockert/Cobe pump; utilising non-pulsatile
>   flow;
>
> - a bubble oxygenator (Dideco D700S);
>
> - priming with 2.0L. Ringers Lactate solution;
>
> - no arterial filters;
>
> - a long aortic cannula with side holes;
>
> - a right atrial cannula;
>
> - no left heart venting.

Anticoagulation to appropriate levels was achieved utilising
heparin (3mg/kg) and reversal of heparinisation achieved with
protamine sulphate as determined by Haemachron (modified Lee-
White clotting time).

5.4 : Additional per-operative monitoring.

Per-operatively the anaesthetist had access to both arterial and right atrial pressures, the per-operative CFAM trace and the results of his personal blood gas analysis. Neither the additional data obtained from the jugular bulb cannula (pressure recording or venous sampling measurements) nor any of the results from additional arterial or venous blood sampling, listed below, were available to the anaesthetists or surgeon until after the completion of the trial.

The following investigations, together with the jugular bulb measurements, represent the basis for our statistical analysis of per-operative patient parameters with post-operative outcome and as such warrant further discussion about their relevance to the issue of neurological deficit following cardiopulmonary bypass surgery.

a. Arterial Carbon Dioxide tensions (PaCO2)

- ---

i. Introduction:

Cerebral blood flow is extremely sensitive to changes in arterial carbon dioxide tension, showing marked increases during moderate hypercapnia and reductions during hypocapnia.(110-115)

The size of cerebral circulatory responses is approximately 5% for each 1 mmHg change in arterial carbon dioxide (110,116). In contrast neither metabolic acidosis nor metabolic alkalosis, where the arterial CO_2 tension remains constant, have any appreciable effect on actual cerebral blood flow.

The calibre of cerebral arteries and arterioles is extremely sensitive to alterations in perivascular pH; acidosis provoking vasodilatation and alkalosis vasoconstriction.

The hydrogen ion content of the extracellular fluid is determined by the equilibrium of bicarbonate/carbon dioxide and the available evidence suggests that effects of carbon dioxide upon cerebral vessels are a direct consequence of changes in perivascular pH.

Additional factors can modify the above mentioned cerebrovascular responses to alterations in arterial blood gas tensions and in the clinical context are of vital importance. The most important of these is the fact that the cerebrovascular dilatation induced by hypercapnia is significantly attenuated by moderate hypotension (117-120).

Hypotension is associated with the dilatation of cerebral arteries and arterioles(i.e. the autoregulatory mechanism through which a constant cerebral blood flow can be maintained), and it appears that this reduces the ability of vessels to further dilate in response to additional stimuli (such as hypercapnia).

This is clinically important in two situations:

Firstly, where patients are exposed to periods of sustained hypotension, manipulation of arterial carbon dioxide tensions (i.e. induced hypercapnia) are unlikely to restore normal cerebral blood flows (121-123).

Secondly, and perhaps most importantly, where patients are exposed to significant hypercapnia, the vascular response to a secondary hypotensive insult will be severely diminished (i.e they may lose their ability to autoregulate cerebral blood flow at perfusion pressures as high as 80mmHg (124).

It has been shown conclusively that cerebral CO_2 reactivity is maintained during hypothermic nonpulsatile cardiopulmonary bypass (125-131), and as such the above facts are highly relevant when discussing neurological deficit in our study population.

While the above data would suggest that the ideal would be to maintain a state of normocapnia throughout the per-operative course, this again raises another controversial issue: what is "normocapnia" in a hypothermic patient.

As the body is cooled the solubility of carbon dioxide increases, so reducing the $PaCO_2$ and increasing the pH of the blood. From a theoretical point of view it would seem sensible to maintain a $PaCO_2$ in blood, which when measured at 37deg. C gives a pH of 7.4, since this represents an optimal situation for the vast majority of enzymic systems in the body (132-136).

Recent studies however,would suggest that at least 50% of centres carrying out cardiac surgery in the USA and the UK, including this study group, make temperature corrected measurements of $PaCO_2$.(132,137) Arterial blood samples are taken, the temperature of the patient noted, and the sample then analysed at 37deg C with a blood autoanalyser. Having obtained the value $PaCO_2$ at 37deg C a correction factor is then invoked, normally automatically by dialling in the patients temperature to the autoanalyser, and an estimation of the $PaCO_2$ in the blood at the measured temperature calculated.

The aim of introducing the above correction factor being to maintain a pH of 7.4 at the hypothermic temperature. As a consequence this sequence of temperature correction of blood gas analyses is known as "pH stat".

Opponents of this approach argue that the proper reference value is electrochemical neutrality, where pH = pOH (138). It therefore follows that this differential between the neutral blood value (6.8 at 37deg.C.) and the actual blood pH (7.4 at 37deg.C.) should be maintained, whatever the temperature; so maintaining a constant buffering capacity of the alpha-imidazole group of the histidine moiety of various blood proteins. In turn resulting in optimal performance of cellular enzyme systems. Cooling is associated with a rise in the value of the electrochemical neutral point of blood. In order therefore to maintain this differential of 0.6 pH units it is necessary to maintain actual pH and actual $PaCO_2$ levels markedly higher and lower, respectively, from those seen at normothermia under normal physiological conditions. This deliberate production of what would be a marked respiratory alkalosis at normothermia is known as "alpha-stat". These same protagonists of the "alpha-stat" method argue that the maintenance of a "pH-stat" regime will produce a biochemical environment identical to marked hypercapnia at a temperature of 37deg.C.: the deleterious effects of which, with regard to the formation of a pressure-passive system secondary to the loss of cerebral autoregulation, have been detailed above (110,116,117,139).

While the actual interpretation of measured blood gas analysis remains a matter of debate what has not been discussed previously is the necessary frequency with which analysis should be performed. A personal informal survey of cardiac surgery units in the London area would suggest that on average (excluding paediatric units) the majority of anaesthetists perform one blood gas analysis prior to the onset of bypass (often shortly after commencing ventilation), perhaps two to three times during the period of perfusion, and again, once, post-perfusion.

In comparison to the response to carbon dioxide, the level of cerebral blood flow is relatively insensitive to changes in arterial oxygen tensions over the normal physiological range. If the arterial oxyygen tension falls below 50mmHg.(6.67kPa) however there is a dramatic increase in cerebral blood flow such that at a PaO2 of 30mmHg(4kPa) the flow is almost double that at 100mmHg(13.3kPa) (110).

As stated above this response is dramatically altered if other factors have already maximised the cerebral response to adversity (i.e. hypotension or hypercapnia) (140).

Ventilation with 100% oxygen on the other hand has only a minimal effect on reducing cerebral blood flow (less than 10% reduction even under prolonged hyperoxic conditions) (110).

ii. Study method:

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In all patients of the three groups studied (A,B and C), arterial and jugular bulb samples were taken every 10 minutes throughout the pre-perfusion phase, every minute for the first 10 minutes of the perfusion period and then again every 10 minutes until completion of the operation.

In all cases arterial samples were taken, either from the radial arterial line (pre-perfusion), or from the arterial output of the pump (per-perfusion).

At the pre-designated times a sample of blood (2.5-5.0ml.)was withdrawn along the sampling lines, (having previously removed a volume greater than the priming volume of the respective line), and into labelled pre-heparinised blood-gas syringes. These were placed immediately into ice-water and stored at 4degC until analysis was performed.

The samples were immediately sealed to prevent changes in content and were then placed first into a blood gas autoanalyser (ABL3-Radiometer) maintained at 37deg C for the measurement of blood gas analysis by electrode. The patients temperature at the time of sampling was dialled in for the calculation of the likely partial pressures at the time of sampling.

The member of the research team responsible for the sampling and interpretation of the per-operative results was completely separate from the personnel involved in either the neuropsychometric or the ophthalmological assessments so maintaining the "blind" nature of the investigations.

In every patient in the trial, analysis of blood samples taken per-operatively was always completed within 2 hours of sampling.

The results from each patient were then sealed away in separate envelopes, together with all other other per-operative information. At the completion of the trial the per-operative parameters were then examined and compared statistically with the results of the ophthalmological and neuropsychometric assessments.

b. Arterio-venous Oxygen content differences (a-v O2ct.dif.)

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i. Introduction

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In the "normal" conscious brain , the level of cerebral blood flow is adjusted to the level of cerebral oxygen and glucose consumption, the two substrates whose catabolism is responsible for almost all energy generation in cerebral tissue.

When cerebral function is depressed, and the total energy requirements are reduced, as in coma or under general anaesthetic conditions, total cerebral blood flow, oxygen consumption and glucose utilisation are all much lower than in the conscious state (141-145).

The coupling that exists between blood flow and energy generating metabolic processes has been demonstrated in all anatomical and functional sub-units of the CNS. Thus the level of blood flow is greatest in areas of greatest glucose utilisation (such as the primary auditory nuclei and the neocortex), intermediate in regions where glucose metabolism is intermediate (such as caudate nucleus and thalamus) and lowest in regions where glucose uptake rates are lowest (such as globus pallidus and white matter) (110,146,147).

The survival of the central nervous system is totally dependent upon the continuous maintenence of its blood supply to provide adequate amounts of essential substrates (oxygen and glucose). Brain stores of these substrates are minimal, such that if cerebral tissue blood supply is completely interrupted for only a few seconds then consciousness will be lost (148).

Under these circumstances a simple equation relates the cerebral oxygen flux, and this is shown below (149):

| Cerebral Metabolic Rate for Oxygen (CMRO2) | = | Cerebral Blood Flow (CBF) | x | Arterio-Venous Oxygen content difference |

It would seem possible therefore with knowledge of values of two of these variables to easily calculate a value for the third. In the awake, conscious patient this is certainly true.

The least accessable of these values is undoubtedly the cerebral metabolic rate for oxygen, (accurate direct estimation presenting many practical difficulties); and therefore the above equation has been used to calculate a value for CMRO2 in a variety of circumstances where estimations of both cerebral blood flow and a-v oxygen content differences have been made.

These include the calculation of normal values for the conscious

patient but in addition both patients undergoing general

anaesthesia alone and also general anaesthesia plus pulsatile or

non pulsatile cardiopulmonary bypass procedures.

(128,139,149,150)

It now seems probable that both in the conscious patient and also

in patients undergoing relatively normothermic general

anaesthesia the flow-metabolism couple shown above does in fact

remain intact; while in circumstances of hypothermic non-

pulsatile cardiopulmonary bypass, especially when associated with

hypercapnia (i.e. temperature corrected normocapnia), the flow-

metabolism couple no longer appears to apply (128,139,150).

Modification of the flow-metabolism couple by pharmacological,

physiological or pathological factors can be broadly separated

into three predominant categories.

In the first, agents which primarily act by directly depressing

cerebral function in general (e.g. thiopentone or other

associated barbiturates) are likely to bring about similar

reductions in both blood flow and substrate usage in any

particular region such that the normal relationship between flow

and metabolism is likely to be maintained (147).

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Secondly, following periods of longstanding metabolic acidosis or following inhibition of prostaglandin synthesis it appears that the normal relationship between blood flow and glucose usage is preserved but the ratio between the two is altered to a similar extent in all areas of the central nervous system. This, alteration in the flow-metabolism ratio is being extensively investigated at the present time; and it is from this research that a greater understanding of the mechanism of regulation of regional cerebral perfusion is being achieved (110).

The third type of alteration in coupling is one in which the relationship between blood flow and glucose usage has been selectively and focally altered. This is normally associated with pathological conditions such as; subarachnoid haemorrhage, the presence of cerebral tumours, during and after seizures and in spreading cortical depression (151). The common feature of all of the above pathologies is the inability of the damaged tissue to maintain the normal flow-metabolism ratios. Evidence is now available concerning the flow-metabolism couple during periods of hypothermic cardiopulmonary bypass (150,152). It appears that during the pre-bypass phase and also during periods of pulsatile hypothermic bypass the normal flow-metabolism coupling, both globally and regionally, is maintained. In contrast during periods of non-pulsatile hypothermic bypass, while blood flows remained within the normal range, the glucose consumption declined so bringing about significant increases in the flow-metabolism ratio.

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If the above evidence can be substantiated then it considerably reduces the value of studies which have looked in detail at cerebral blood flows during cardiopulmonary bypass; many of which have produced contradictory evidence with regard to the effect of hypothermic bypass on cerebral blood flow.

These discrepencies can now perhaps be explained by the lack of standardisation of per-operative normocapnic levels in the respective studies (126,130).

Cerebral blood flow measurements are therefore unlikely to provide us with information relative to the flow (i.e. oxygen and glucose) requirements when we examine the results under hypothermic non-pulsatile bypass conditions; and are much more likely to correlate directly with the cerebral perfusion pressure (mean arterial pressure - cerebral venous pressure).

While the exact cause of this pressure dependent system remains uncertain, variations from normocapnia and the direct effect of non-pulsatile bypass remain the most likely contributory aetiological factors.

This concept of a total disruption of the flow-metabolism couple also must make us reassess the value of aterio-venous oxygen content values as an index of cerebral well being during periods of hypothermic cardiopulmonary bypass.

The arterio-venous oxygen content difference is an indirect measure of cerebral oxygen extraction and represents the supply and demand of essential substrates to the brain. As the estimation of the oxygen content difference is made on arterial and mixed venous blood it can only reflect "global" changes in oxygen extraction.

In the conscious or normocapnic patient under general anaesthesia the relationship mentioned above allows relatively easy and reproducible interpretation of a-v O2ct. differences. In the anaesthetised patient the CMRO2 is likely to be considerably reduced (110,153). A measured rise in a-v O2ct. differences can only be brought about by an equivalent fall in cerebral blood flow.

This fall in cerebral flow is likely to reduce the total amount of oxygen supplied to the brain; which in turn automatically increases the extraction of oxygen from the blood that is being perfused. The end result of this is that the oxygen content in the venous blood falls, so increasing the measured oxygen content difference, which can therefore act as a sensitive index of cerebral well being.

In the case of hypothermic CPB the cerebral blood flow may be either greater or less than that required to supply the metabolic demand as it is purely dependent upon the perfusion pressure (150).

In circumstances where it is considerably greater than is required one would suspect that all would be well, but this may be far from the truth. Ischaemic areas of the brain may lose their ability to autoregulate, as may areas that have suffered old ischaemic damage (110).

As a result under conditions which would normally result in cerebral vasodilatation (especially hypercapnia) the normal tissue vasodilates while ischaemic tissue is unable to do so. It is possible under these circumstances that the high a-v O2ct. differences generated by the hypoperfused ischaemic areas may be lost to view, when they are combined with the low a-v O2ct. differences of the relatively hyperperfused areas.

A low a-v O2ct difference cannot by itself therefore be taken as an indication of cerebral well being.

The converse however is more easily interpreted. A sudden rise, or sustained high a-v O2ct differences can only be brought about by a situation where "global" oxygen demand exceeds supply.

A high a-v O2ct difference, under any circumstances, is a reflection that tissue viability is being compromised to the measured degree and that prompt intervention is necessary.

ii. Study method

In all study patients the same sample used to estimate blood gas analysis was also used to supply the volume necessary to measure the arterial oxygen content levels.

In order to obtain the jugular bulb venous blood aspiration of the side arm of the retrograde cordis sheath was performed; having first removed a volume greater than the priming volume of the line (1.77ml).

A lag-time for the transference of blood across the brain was calculated (6 seconds); using normal values for cerebral blood flow and for cerebral venous volume (3ml/100g brain tissue) and neglecting tissue O2 stores which are minimal.

The venous samples were therefore withdrawn 6 seconds after the arterial ones; all samples then being immediately sealed , placed into ice-water and stored at 4deg C until analysis.

At the time of analysis all samples were placed into an automated haemoximeter (OSM3 - Radiometer) for the estimation of arterial and jugular bulb oxygen contents and saturations. This haemoximeter was calibrated daily to ensure uniform performance throughout the study period.

The results were then sealed away and were not made available to
the anaesthetist or surgeon, or any other of the patient
assessment team (i.e. neuropsychometry or ophthalmology until
after the completion of the trial.)

c. Cerebral Perfusion Pressure

i. Introduction

The Cerebral Perfusion Pressure (CPP), (defined as mean arterial pressure minus the cerebral venous pressure), is a prime factor in the supply of blood, and hence oxygen and glucose, to the brain.(148)

The cerebral circulation has the intrinsic ability to maintain a constant blood flow over a wide range of mean arterial pressures. This capability, known as "autoregulation" can also be demonstrated when a reduction in perfusion pressure has been brought about by an increase in either cerebral venous or intracranial pressure (154,155,156).

It is thought that autoregulation is brought about by the systematic dilatation of the cerebral resistance vessels during periods of hypotension; and their constriction during periods of hypertension. Cerebrovascular resistance is therefore either increased or decreased to maintain constancy of flow.

There are however upper and lower pressure limits to this concept of autoregulation; and beyond these two extremes cerebral blood flow is perfusion pressure dependent (110).

Understanding this mechanism of action also allows an appreciation of circumstances in which the autoregulatory capabilities of the cerebral circulation may not be present.

The first situation has already been illustrated in the previous section (i.e. - the role of arterial carbon dioxide levels on cerebral flow). Increases in PaCO2 levels will be associated with an increase in cerebral blood flow, brought about by vasodilatation of the cerebral resistance vessels. As the PaCO2 levels rise further a maximum level of vasodilatation is reached and the flow is unable to be increased any further. If at this point the mean arterial pressure also falls, with an associated reduction in perfusion pressure then the brain will be unable to compensate as the resistance vessels are already maximally dilated.

Hypercapnia will therefore be one of the prime causes of failure of the autoregulatory response in the normal brain. At this point cerebral blood flow will become pressure dependent and reduction in flow will occur at perfusion pressures that would otherwise be acceptable. In these circumstances, severe hypotension carries the risk of cerebral ischaemia while hypertension will possibly be associated with cerebral oedema (157). Autoregulation will also be severely impaired following periods of hypoxia, after carotid artery occlusion, in sub-arachnoid haemorrhage, following periods of cerebral ischaemia (74,110), and in situations associated with severe haemodilution (152).

While the majority of opinion would now seem to suggest that cerebral autoregulation is lost during periods of cardiopulmonary bypass , neither the speed or timing of the onset of this pressure dependent system, nor the duration, or effect on other cerebral metabolic parameters (CMRO2), can be agreed upon. (130,152,158,159)

Indeed it is even suggested that the origin of the reduction in cerebral perfusion pressure (i.e. whether it be a reduction in mean arterial pressure, an increase in intracranial pressure or an increase in cerebral venous pressure) may have a marked effect on the incidence of post-operative deficit: with reductions in perfusion pressure brought about by abnormally high cerebral venous pressures having the worst outcome (160).

In the majority of studies attempting to correlate cerebral perfusion pressures with the incidence of neurological deficit, consideration has been given only to the mean arterial pressure, with a total disregard for the other elements of the perfusion equation (68).

Evidence has been available for many years that elevation of cerebral venous pressure is associated with a higher incidence of both EEG abnormalities and also significantly greater abnormalities in cerebral oxygen extraction, than in other patients with the same mean arterial pressure (70-72,161-164).

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Recent evidence also suggests that cerebral venous pressure may show considerable peri-operative variations and thereby exert a variable but often dramatic effect on cerebral perfusion pressure.

ii. Study method:

Mean arterial pressure was continuously measured by means of a
fluid filled system from an in-dwelling radial arterial cannula,
connected to an external transducer, and thence to the monitoring
stack, and the chart recorder.

The method of insertion of the retrograde jugular bulb cannula is
also described above. The particular cannula used (Cordis-5FG)
offered both the facility for continuous sampling of jugular
venous blood from the side-arm, together with a sealable access
port, along which a catheter tippped transducer could be passed.

The Camino catheter tip transducer pressure monitoring system was
chosen because it contains a miniture transducer at the distal
end, so eliminating the need for a fluid filled system to carry
pressure waves to an external transducer. This offers a
significant reduction in signal loss due to either damping, or
other extraneous influences. This is especially important in the
measurement of venous pressures as the measured pressures are of
a smaller magnitude than arterial signals. The other major
advantage of this system in the measurement of jugular bulb
pressures is with regard to patient safety. The Camino catheter
is a fibre-optic device and as such does not have a lumen. There
is therefore no risk of air-embolism (c.f. fluid filled system).

The catheter tip transducer (model 110-4) was used in combination with the Camino 420 digital pressure monitor. Connection of this to the Hewlett-Packard monitoring stack and then to the chart recorder was then made.

Prior to insertion into the access port on the retrograde jugular bulb line the Camino catheter was checked and re-zeroed in air. The catheter was then advanced slowly along the cordis sheath for a distance 1cm greater than the length of the cannula. At this point the pressure wave was checked, and providing the trace showed an adequate frequency response, the transducer secured in place with both sutures and an occlusive dressing (Op-site).

On completion of pressure monitoring, and prior to the patient leaving the operating theatre, the transducer was removed from the retrograde cannula, and then rechecked in air to ensure that the per-operative drift was within acceptable limits. In all patients the measured per-operative error due to drift was less than 2mmHg.

The per-operative readings were then sealed away after each operation. As with the other parameters measured they were not made available to either the surgeon or anaesthetist until after completion of the study group,at which time analysis and comparison with the other measured parameters was made.

d. The Cerebral Function Analysing Monitor

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i. Introduction

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The introduction of the Cerebral Function Analysing Monitor
(CFAM) into clinical practice in 1979 (165-169) represented a
considerable technological advance over previously available
monitoring; especially with regard to the identification of
insults likely to result in post-operative neurological deficit
following cardiopulmonary bypass (170-173).

The predecessor of the CFAM was the Cerebral Function Monitor
(CFM), which, while providing a measure of amplitude variations
in the electroencephalogram (EEG), as recorded from biparietal
skin electrodes, gave no information regarding the frequency
distribution of the EEG signal.

Despite this limitation many authors at first claimed a very high
predictive capability for the apparatus, when used in the context
of identification of cerebral hypoperfusion during periods of
cardiopulmonary bypass (174-178).

It now seems most likely that some of the predictive ability of
this original apparatus was due to the fact that the neurological
deficit under examination was in fact major focal deficit which
as we have already stated occurs very infrequently (<4% cases).

When a major insult, of the size necessary to evoke focal post-operative symptoms, takes place, the amplitude changes will be both dramatic and also prolonged and the CFM is likely to show these changes.

Other methods of per-operative cerebral function monitoring, such as power spectrum analysis, linear display of the spectral analysis (CSA) and Grey-scale display of the spectral analysis (DSA), have all been successfully used in clinical practice in the identification of "focal" neurological deficit. They all however either require complicated analysis of results or suffer from problems of spectral "blind-spots". In addition they are all considerably more expensive, both to buy and to run, than the CFAM (179-188).

This study however, concerns itself with the more subtle changes seen in a much higher percentage of patients undergoing coronary artery bypass; and in these circumstances the lack of frequency information seen in the CFM record has been seen as a major drawback to its use (172).

In an attempt to greatly increase the amount of available information the Cerebral Function Analysing Monitor (CFAM) was developed (169). As with the CFM the signal is received from biparietal surface electrodes, secured with collodion to the scalp.

The CFAM however, gives a more detailed plot of the amplitude distribution and in addition gives an analysis of the frequencies of the EEG waveform. (The apparatus also has the capability to compute two channel evoked potentials and to write two channel EEG samples.)

The CFAM consists of a 6808 microprocessor system which controls both analog and digital circuitry, and a two-channel chart recorder. The EEG signal is detected by the surface electrodes and then passes to one or two isolation pre-amplifiers, A and B on extension cables.

Electrode impedance is also monitored, to ensure both integrity of the electrodes and also good skin contact at all times, by a low distortion sine wave applied across the elecrodes from a high impedance source. The 20kOhm impedance was used throughout our study, giving a 100 microvolt signal peak to peak.

The internal workings of the CFAM are complex and in the main beyond the scope of this text. It is however important to appreciate that the CFAM contains an asymmetric band-pass filter with a bandwidth from 1 - 27Hz and over the range 2 - 22Hz produces increased amplification of the signal with increasing frequency. This is essential if the underlying attenuation of EEG signals with increasing frequency is to be compensated for.

This would mean that without this asymmetric filter the CFAM trace would be completely dominated by the lower frequency waves of the EEG trace. As it is the frequency analysis is broken down evenly into the classical bands(beta : 13-27Hz; alpha : 7.5-13Hz; theta : 3.5-7.5Hz; delta : 1-3.5Hz), the record showing the percentage of total electrical activity occurring in each waveband.

In addition to the classical bands mentioned above, the CFAM also produces a record of the percentage of very low frequency activity (less than 1Hz) and also a suppression band which represents the percentage time that the weighted EEG is below a pre-set amplitude (adjustable from 1.0 - 10.5microvolts).

The amplitude trace also shows the mean, 10th and 90th percentiles of cerebral electrical activity, together with the minimum and maximum excursions in a 2-second epoch (see Fig.15).

The CFAM also has the facility of an RS232C data output terminal for the digital collection of data which can then be subjected to statistical analysis as appropriate.

ii.   Study Method:

All patients entered to the study were studied with the CFAM for the whole duration of their appropriate operation. The scalp electrodes were sited as soon as the patient entered the anaesthetic room and the recording started shortly afterwards. In all cases both a direct recording onto heat-sensitive paper, and also a permanent recording via the RS232C output to a digital cassette recorder (Cristie CS6) were obtained. This provided the capability for computerised assessment of the timing of amplitude and frequency changes with regard to other intraoperative events.

All recordings were obtained with silver-silver chloride dome electrodes,attached to the scalp with collodion, and electroconductive jelly inserted under the dome after first abrading the scalp. Three electrodes were used with the CFAM; two as active electrodes and the third as a guard electrode. All were terminated in sockets for attachment to the plugs on the header amplifier box. This was then positioned near the patients head and was connected to a socket on the rear of the CFAM. The guard electrode is isolated from the common zero voltage line, the mains earth and the metal of the instrument. This prevents artefacts caused by static charges on an un-earthed patient. The positioning of the electrodes is critical if reproduceable results are to be obtained and if inter-patient analysis is to be attempted.

In all of the study patients the vertex of the scalp was determined by the intersection of lines over the head joining the external auditory meati and joining the iion and the nasion. The recording electrodes were applied to the scalp transversely 3in (7.6cm.) apart and 2in.(5cm.) posterior to the vertex. The guard electrode was then placed anteriorly 1in.(2.5cm.) in front of the vertex in the mid-line.

The aims of this section of the study were to assess the sensitivity of the CFAM in identifying insults likely to be associated with the more diffuse cerebral deficit as previously described.

In order to document the incidence of significant CFAM changes it is essential to firstly define clearly what constitutes a "significant" CFAM change. At the present time there is no universally accepted definition of what changes in amplitude and frequency constitute a significant change.

For the purpose of this study an attempt has been made to amalgamate the classifications of earlier workers, who were performing a similar assessment of the CFM (148,174,189-195), together with some additional criteria more relevant to the increased information available on the CFAM.

A "significant CFAM change" is therefore defined as;

> " an acute change in both amplitude and frequency
> distribution which is maintained for a period of longer
> than three minutes and which cannot be accounted for in
> terms of alteration in either physiological or
> pharmacological environment".

6. RESULTS

In the following results the nomenclature given to each of the three sub-groups of patients is as follows:

Group A :   35 members: isolated coronary artery surgery. The per-operative ventilatory parameters were at the discretion of the anaesthetist who referred to and acted upon, the results of his own blood gas analysis as he felt appropriate.

Group B :   30 members: isolated coronary artery surgery The ventilatory parameters were adjusted as necessary in order to rigorously maintain a state of peri-operative normocapnia (temperature corrected $PaCO_2$ between 35 - 45mmHg. (4.7-6kPa.)). This was achieved by utilising an end-tidal CO_2 monitor in the pre-perfusion period, and a continuous in-line CO_2 sensor on the arterial side of the oxygenator during the perfusion period.

Group C :   15 members: peripheral vascular surgery. This group represented a control population. The ventilatory parameters were again at the discretion of the anaesthetist who performed blood gas analysis as he felt appropriate.

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All patients underwent identical pre- and post-operative assessments and were subjected to identical per-operative monitoring. The only variations in management related to the control expressed over ventilatory parameters as stated above.

In the following sections the results of each of the patient assessments (Neurological,Psychometric and Ophthalmological) were considered separately. In each case the results for the three respective groups (A,B and C) were identified and analysed.

The per-operative parameters measured (PaCO2, arterio-venous oxygen content differences, jugular bulb pressure, and cerebral perfusion pressure) together with the results from the peri-operative cerebral function analysing monitor tracings were also recorded separately. Again, in each case the results for all three groups were considered collectively. Further analyses relating to the incidence of post-operative neuropsychometric deficit in the respective groups was then made. Non-parametric statistical analysis was performed for all inter or intra-group calculations (Mann-Whitney U test); and 95% confidence limits calculated where appropriate.

The statistical correlation between per-operative parameters for the respective groups (together with the standard errors for those correlation coefficients) were also calculated.

6.1 Cohort characteristics:

The population statistics for the three groups, together with details of relevant pre-operative history and examination are shown in Fig. 1 and Fig. 2

Although no attempts were made at matching the patients with regard to any of the parameters monitored there were no significant differences between any of the measured parameters for Group A and Group B.

The members of Group C while being of statistically greater age on entering the trial ($P<0.05$), were not statistically different, with regard to the other measured parameters, from the other two groups.

Table 8 :   Mean cohort statistics for Group A, Group B and

---------   --

Group C

	Group A :	Group B :	GroupC
	(n=35)	(n=30)	(n=18)
1. Age (years)	58.75 (48-69)*	62.35 (52-68)*	71.2 (58-79)*
2. Sex	80% male	75% male	67%male
3. Previous focal neurology	11%	10%	0%
4. Number of Grafts	3.52	3.37	N/A
5. Duration perfusion (min)	83.6 (55-195)*	87.3 (60-145)*	N/A
6. Aortic Cross-clamp (min)	29.2 (14-39)*	28.4 (16-38)*	N/A

* ranges

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6.2 Incidence of post-operative deficit in Groups A, B and C

a) Neurological

- ------------

46% of Group A members, but only 27% of Group B and 20% of Group C showed evidence of new post-operative neurological signs.
Fig. 3. classifies the breakdown of neurological deficit in the respective groups.

b) Psychometric

- ------------

71% of Group A, 40% of Group B and 27% of Group C had evidence of significant post-operative neuro-psychometric deficit when examined on the third post-operative day.

The incidence had fallen to 26% of Group A, 13% of Group B and 13% of Group C by the time of discharge from hospital (7 days post-operatively in all cases).

Figure 2 shows the incidence of post-operative psychometric deficit in the respective groups together with an integral breakdown of the severity of deficit (moderate or severe) in each case.

Statistical analysis :

Neurological deficit

Although Group A had a greater incidence of post-operative neurological deficit than Group B as measured on two occasions in the first post-operative week, this failed to reach a level of statistical significance.

(Chi-squared = 2.38 ; Degrees of freedom = 1; 0.5 < P > 0.1)

There was no significant difference between the incidence of post-operative neurological deficit in Group B and Group C.

Psychometric deficit

Group A had a significantly higher incidence of post-operative neuropsychometric deficit than Group B.

(Chi-squared = 6.51; Degrees of Freedom = 1; 0.01 < P > 0.001)

There was no significant difference between the incidence of psychometric deficit in Group B and Group C.

Table 9 : Incidence of neurological deficit.

	Group A (n=35) %	Group B (n=30) %	Group C (n=15) %
1. Prolonged reduction conscious level	6	3	0
2. Stroke - definite	3	0	0
- possible	6	3	0
3. Eye Signs	20	0	0
4. Primitive reflexes	25	13	7
5. Psychosis	11	3	7
6. Peripheral neurological	14	7	7
7. Significant reduction Motricity Index abnormality	25	13	13
% WITH +VE NEUROLOGY	46	27	20

Fig.2 : Incidence of Psychometric deficit.

----- -----------------------------------

This figure shows the distribution of neuropsychometric deficit
in the three groups on days 3 and 7 post-operatively.

THE INCIDENCE OF NEUROPSYCHOMETRIC DEFICIT
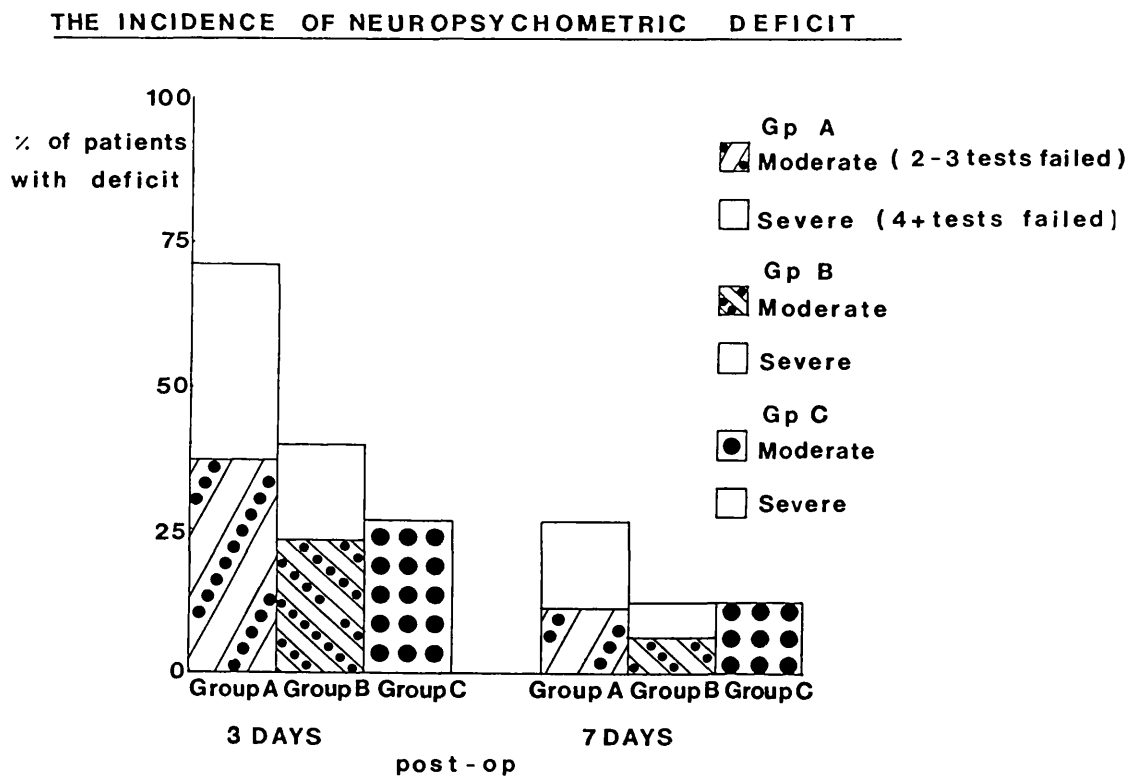
Table 10   Neuropsychometric deficit in the sample population

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Test :	% impaired by > 1 SD	% impaired by > 2 SD	% improved by > 1 SD
1.	26.2	9.2	3.1
2.	30.8	12.3	1.5
3.	32.3	6.2	0
4.	20.0	6.2	1.5
5.	12.3	7.7	6.2
6.	23.1	12.3	3.1
7.	36.9	9.2	1.5
8.	33.8	10.7	1.5
9.	10.8	1.5	3.1
10.	15.4	7.7	6.2

Table 11   Neuropsychometric scores pre- and post-operatively

Test	mean pre-op.score	mean change	range	Wilcoxon signed rank test
1.	55	+ 12.2	-7-+25	p< 0.01
2.	125	+ 37.5	-12-+68	p< 0.01
3.	8.25	- 1.2	-6-0	p< 0.05
4.	13.3	- 0.9	-8-+2	p< 0.05
5.	10.6	- 0.4	-9-+8	p< 0.01
6.	14.6	- 1.9	-11-+8	p< 0.01
7.	12.4	- 4.7	-8-+1	p< 0.001
8.	13.3	- 4.3	-9-+2	p< 0.005
9.	8.9	- 2.4	-9-+3	p< 0.05
10.	64.7	-7.2	-25-+12	p< 0.05

c) Incidence of post-operative Ophthalmological deficit

- --

Table 12 shows the incidence of ophthalmological deficit in the three respective groups at both 3 and 7 days post-operatively.

Following the incidence figures there is a description of the observed deficits in the appropriate subjects. Table 13

None of the patients examined (i.e. Group A, Group B or Group C) had any evidence of intraluminal emboli and no branch vessel embolisation was noted.

Statistical analysis :

_____

Group A had a significantly higher incidence of new post-operative ophthalmological signs.

(Fishers exact probability test - 2 tailed - $0.01 < P < 0.05$)

There was no statistical difference in the incidence of new ophthalmological signs between Group B and Group C.

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Table 12 : Incidence of ophthalmological signs in the 3 Groups.

Deficit :	Group A : (n = 35)	Group B : (n = 30)	Group C (n = 15)
Visual Field	0 (0%)	0 (0%)	0 (0%)
Visual Acuity	2 (6%)	0 (0%)	0 (0%)
Retinal changes	5 (14%)	0 (0%)	0 (0%)
% with ANY change	20%	0%	0%

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Table 13 : Classification of new ophthalmological deficit in

affected members of Group A.

Patient No.	Ophthalmological sign
1.	Cotton Wool spots / Disc haemorrhage
2.	Cotton Wool spots
3.	Cotton Wool spots
4.	Cotton Wool spots
5.	Cotton Wool spots
6.	Reduction in Visual Acuity ($\sim$ 20%)
7.	Reduction in Visual Acuity ($\sim$ 15%)

6.3   Per-operative arterial Carbon Dioxide tension measurements

The following diagrams show the per-operative measurements of arterial $PaCO_2$ for each of the three respective groups.

Each point on the diagrams represents a timed sample for an individual in that group.

Because of individual variation in timing with regard to many per-operative variables such as ;   the period of anaesthesia prior to perfusion, the length of perfusion itself and the period of post-perfusion anaesthesia, the only common point of reference is the onset of the perfusion period.

In all of the following diagrams looking at per-operative variables this common reference is shown as a vertical line and marked "onset". All timing are made around this point (i.e. + or - with regard to time).

Figure 3a shows the mean per-operative arterial $PaCO_2$ tensions for Group A; while Figure 3b shows diagramatically the range of individual values obtained (each point represents a timed sample from an individual member of Group A).

Figure 4 identifies the members of Group A who demonstrated severe neuropsychometric deficit post-operatively.

Figures 5a and 5b show the per-operative arterial $PaCO_2$ tensions

for Group B (5a = mean values; 5b = timed individual values).

Figure 6 shows the timed individual samples for members of

Group C.

Figure 3 : Per-operative arterial PaCO2 tensions for Group A.

ARTERIAL CO$_2$ TENSION Vs. TIME

a

ARTERIAL CO$_2$ TENSION vs TIME
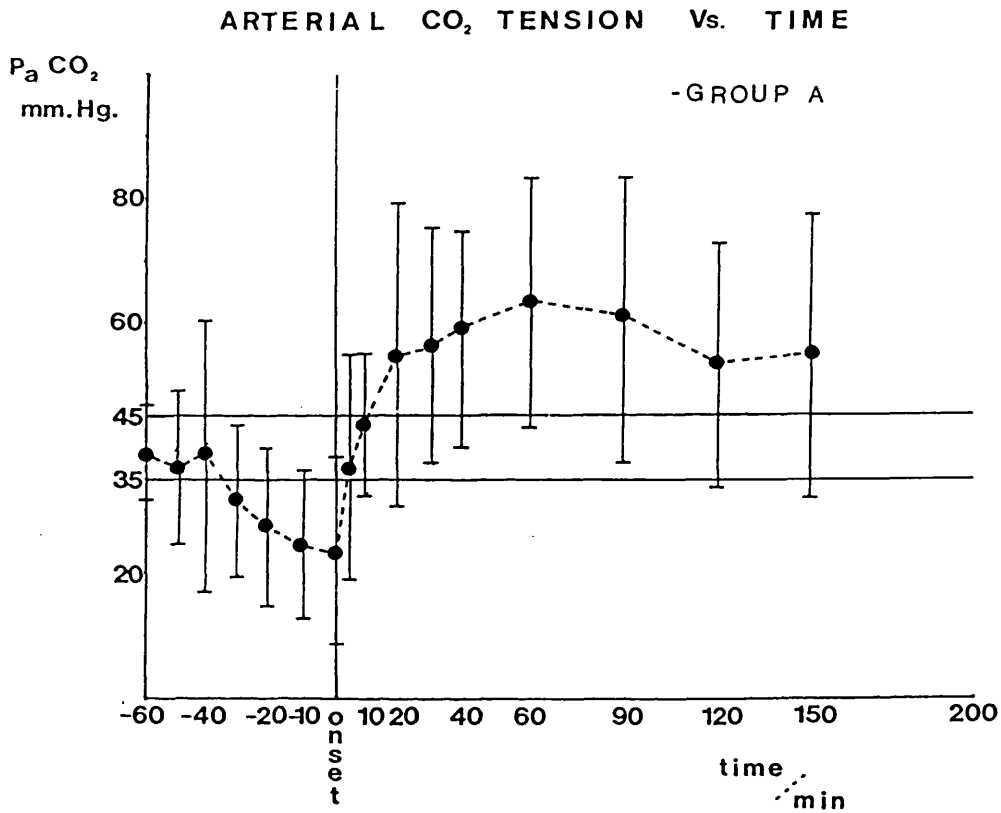
b
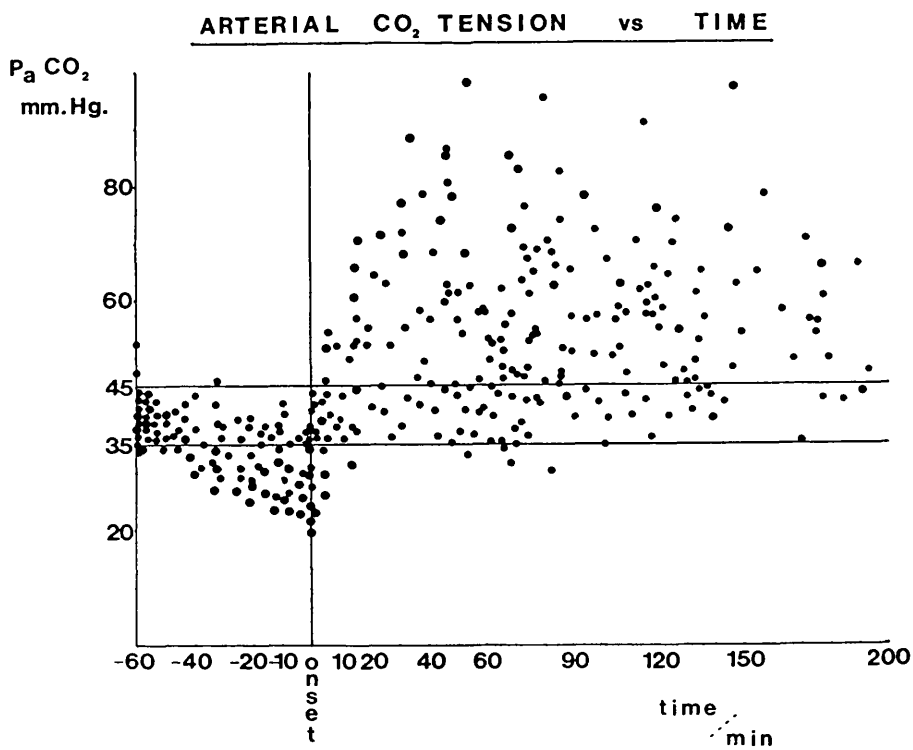
Figure 4 : Per-operative arterial PaCO2 tensions for Group A

with identification of patients demonstrating post-

operative deficit

The onset of the perfusion period is represented by the vertical

line marked "onset".

ARTERIAL CO$_2$ TENSION vs TIME
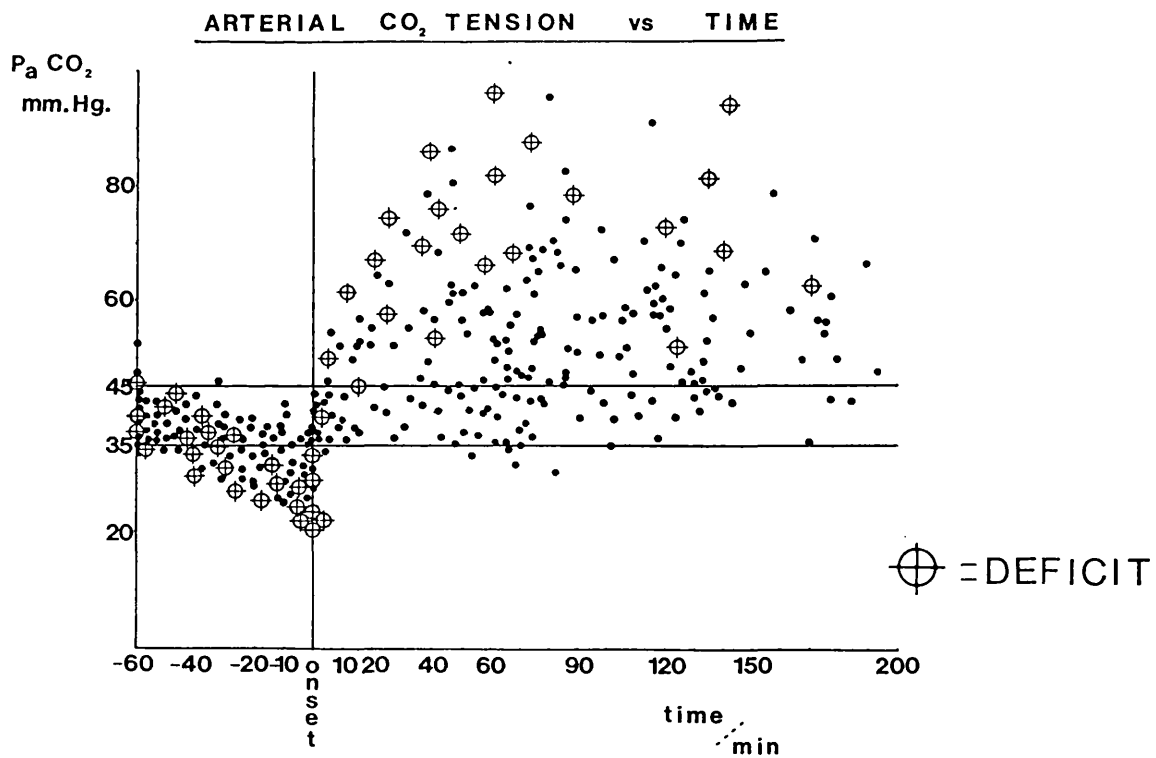
P_a CO$_2$
mm.Hg.

$\oplus$ =DEFICIT

Figure 5 : Per-operative arterial PaCO2 tensions for Group B
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(a = mean values; b = timed individual values)

ARTERIAL CO₂ TENSION Vs. TIME

a

b

139
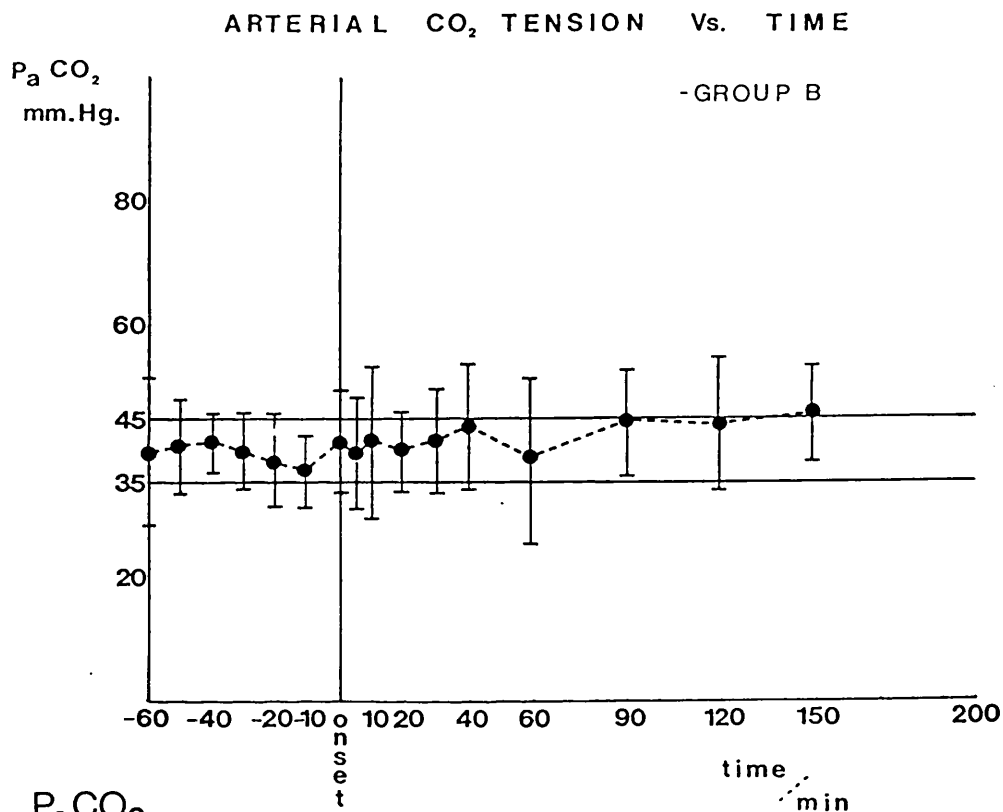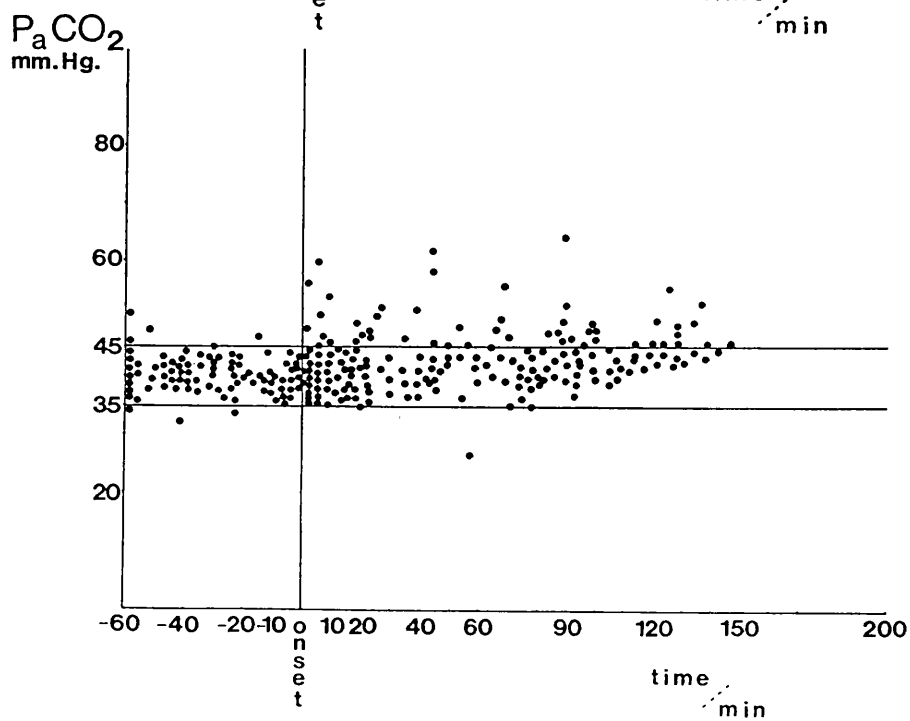
Figure 6(a) : Per-operative PaCO2 values for Group C

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Arterial CO_2 tension v time - Group C

$P_a CO_2$
mm.Hg.

time
min
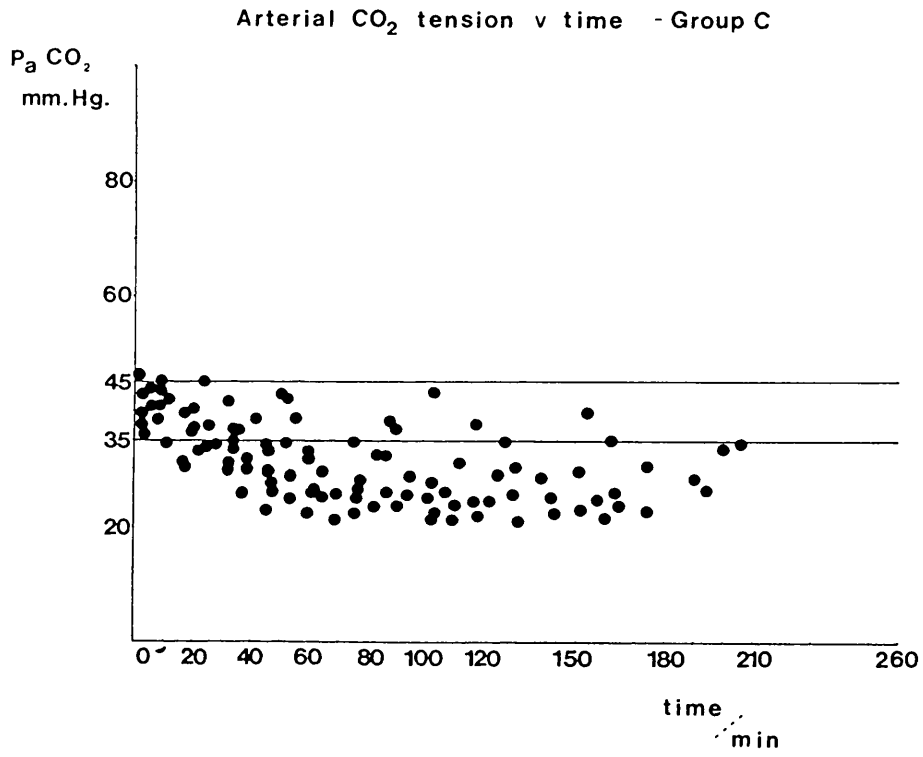
Figure 6(b)   : PaCO2, Blood Loss and Post-Operative Deficit for

Group C

MEAN PER-OPERATIVE P_aCO_2 v   BLOOD LOSS   -GROUP C
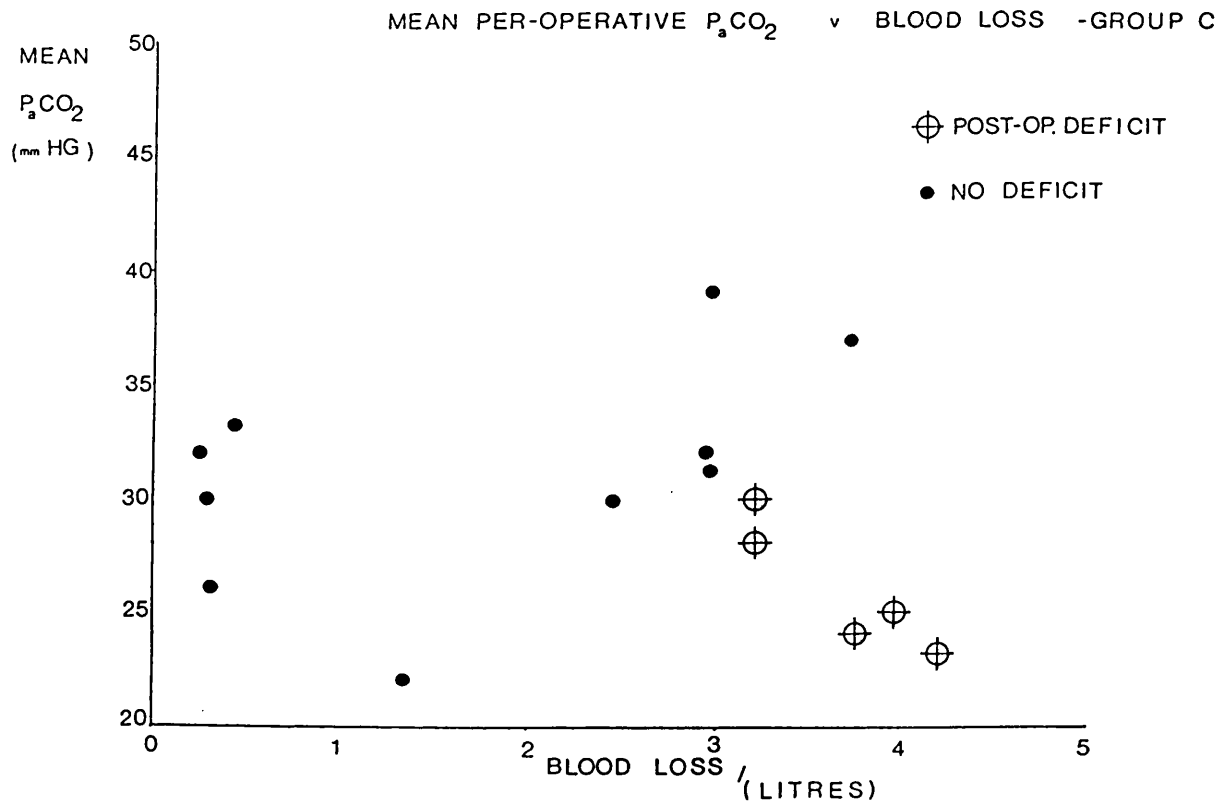
All members of the trial (Groups A,B and C) had measured carbon dioxide tensions within the normal range (35 -45 mmHg. (4.7-6kPa)) at the begining of any period of ventilation.

At the commencement of the perfusion period;
(mean time following commencement of ventilation; Group A = 56min, and Group B = 52min)

74% of members of Group A had a measured $PaCO_2$ less than 35mmHg. with 46% having a $PaCO_2$ value less than 30mmHg.

93% of members of Group B had $PaCO_2$ values within the normal range.
None of the Group B members had a $PaCO_2$ of less than 30mmHg.

For the control group a corresponding point in time was taken as 54 minutes following the commencement of ventilation. At this point; 80% of Group C members had $PaCO_2$ values less than 35mmHg; with 47% having a $PaCO_2$ less than 30mmHg

Examination of the per-operative arterial $PaCO_2$ results revealed two points to be associated with maximum inter-group variations. These two points, (immediately prior to; and immediately following the onset of perfusion) together with the results from all three groups at the commencement of ventilation, were the subject of statistical analysis.

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To compare inter-group variations in per-operative carbon dioxide tensions both the Mann-Whitney U test for unpaired data (two sample test) and also a two sample "t-test" were performed.
Prior to performing the "t-test" an assessment of the normality of the data was made by constructing a "Normal probability plot".

Regression analysis was used to clarify the relationship between peri-operative $PaCO_2$ measurements and the incidence of post-operative neuropsychometric deficit.

The results of the analyses are shown below and adjacent to each result is the appropriate reference (A1 -1 etc.), relevant to the statistics appendix. (A1)

Statistical Analysis : PaCO2

Appendix

Ref.

.

       a). Commencement of ventilation:

--   ----------------------------

       There were no statistical differences between the
       PaCO2 values for the three groups at this point. .

       b). Immediately prior to the onset of perfusion:

--   ---
       Group A had a significantly lower

(A1 -1)   mean PaCO2 value than Group B.   P < 0.001

       Group C had a significantly lower

(A1 -2)   PaCO2 values than Group B.   P < 0.001

       There were no significant differences
       between the PaCO2 values for Group A   P > 0.05

(A1 -3)   and Group C.

c). Immediately following the onset of perfusion

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The change in $PaCO_2$ values secondary

to the onset of perfusion was

significantly greater for Group A

(A1 -4)   than for Group B. $P < 0.001$

d). Regression Analysis

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The incidence of post-operative deficit correlated

well with both the pre-perfusion $PaCO_2$ value

(R-squared = 0.56) and also with the change in

$PaCO_2$ secondary to the onset of perfusion

(R-squared = 0.77)

(A1 -5,6)

6.4 Per-operative arterio - venous(jugular bulb) Oxygen content

differences. (a-v O2ct.differences)

The per-operative mean a-v O2ct.differences for Groups A,B and C are shown in Figures 7, 8 and 9 respectively.

The diagrams show the mean values, at timed peri-operative points, for each of the three groups; together with an estimation of the 95% confidence limits for those respective mean values.

Once again the onset of the perfusion is used as the common reference point for the comparison of timed individual samples.

(The units used for the measurement of a-v O2ct.difference is ml.oxygen per 100ml blood).

Figure 7 : Per-operative arterio-venous Oxygen content

differences for Group A.

ARTERIO-VENOUS O_2ct. DIFFERENCES v. TIME

147
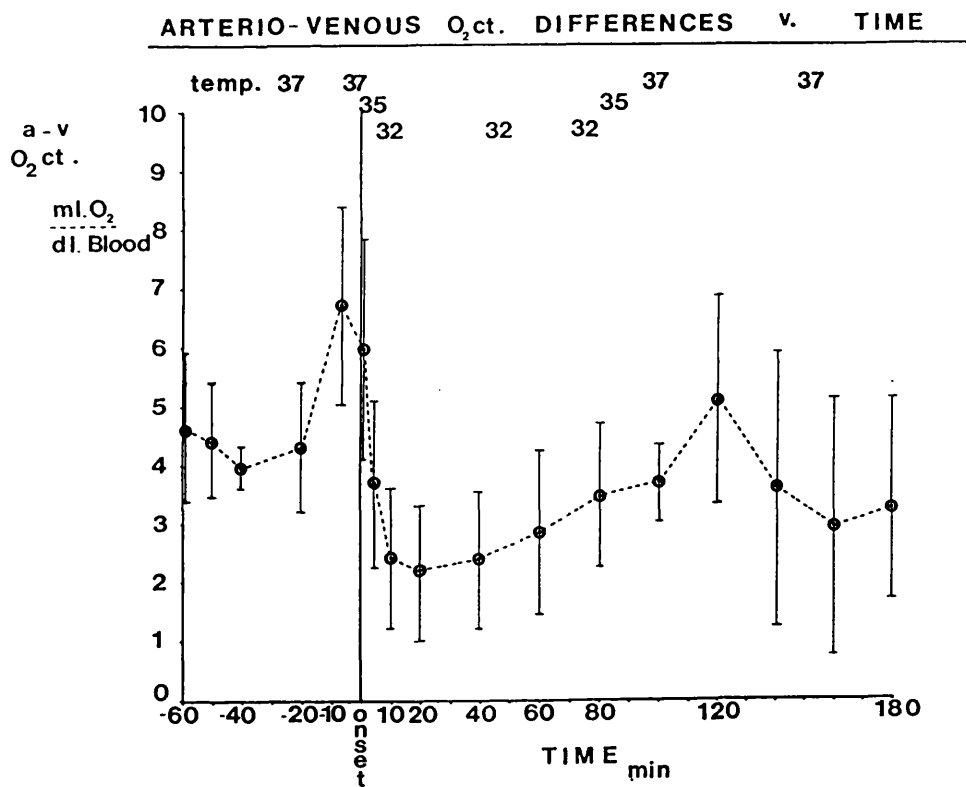
Figure 8 : Per-operative arterio-venous Oxygen content

differences for Group B.

ARTERIO-VENOUS O_2ct. DIFFERENCES v. TIME

148
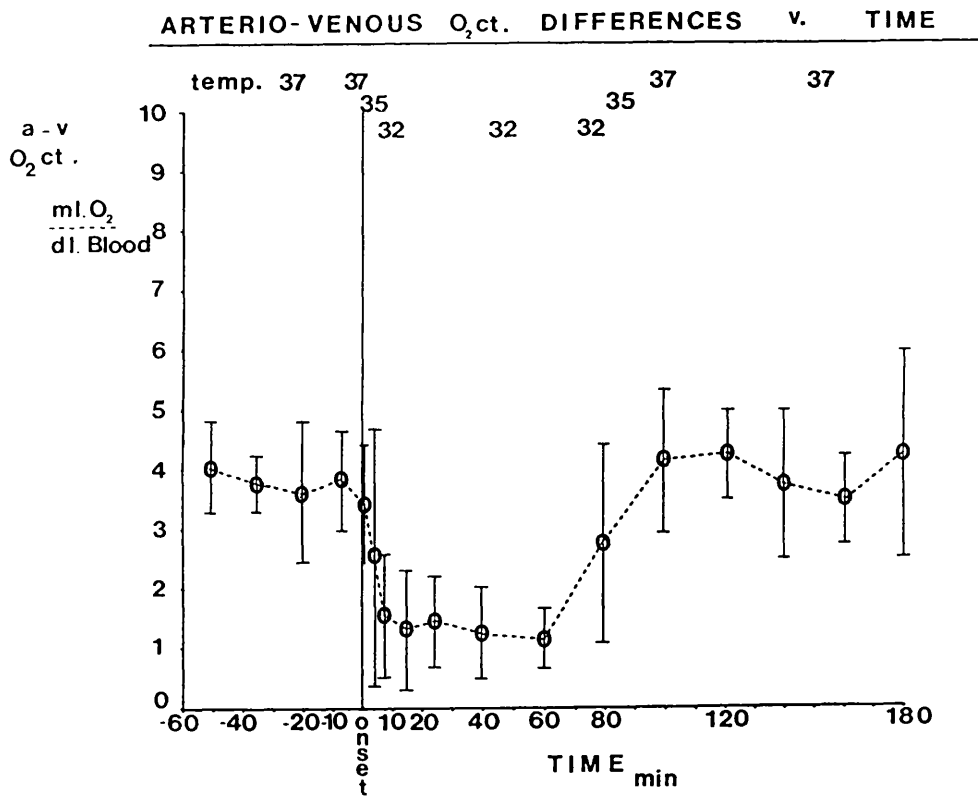
Figure 9 : Per-operative arterio-venous Oxygen content

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differences for Group C.

GROUP C
ARTERIO-VENOUS O_2ct. DIFFERENCES v. TIME

149
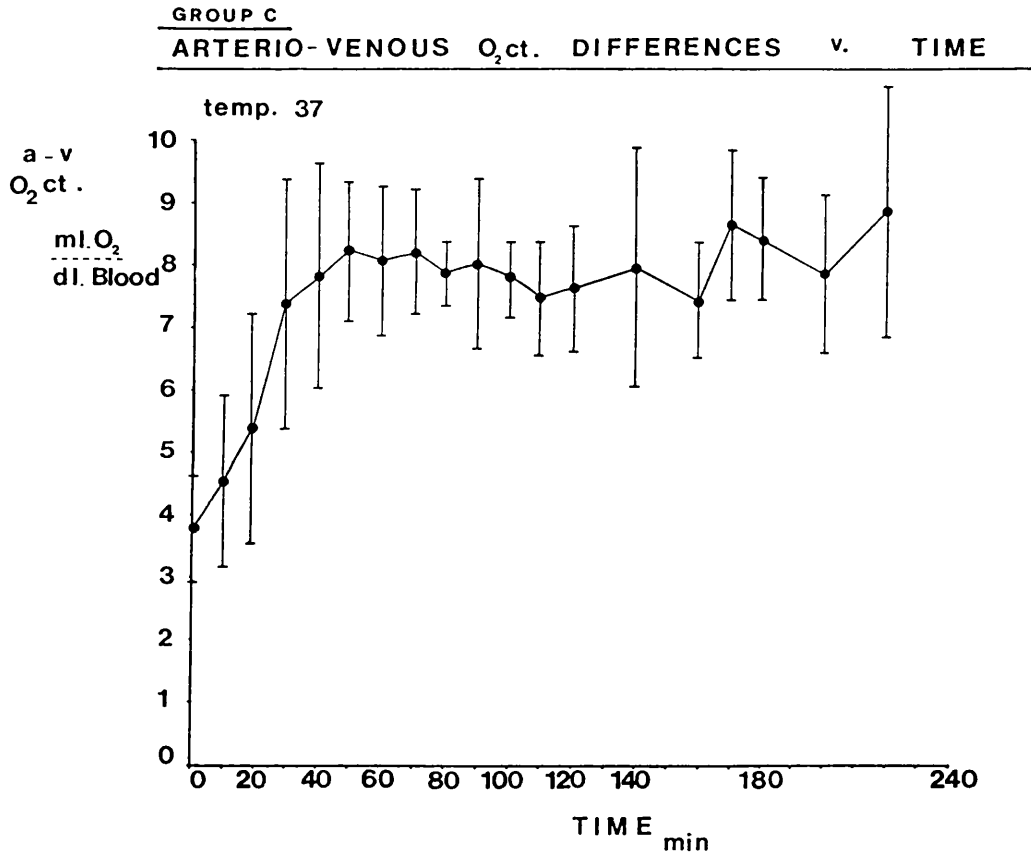
Maximum inter-group variations again occurred immediately prior to the onset of the perfusion period. This point, together with results obtained following the onset of perfusion were used in the statistical analysis.

Although there is no universally accepted "normal" range for a-vO2ct differences in patients undergoing general anaesthesia, it seems reasonable to assume that as there was no statistical difference between the three groups at the commencement of ventilation, that these values are within the normal range for the general population.

Figure 10 shows the intra-group a-vO2ct.differences for Group A members both with and without evidence of post-operative neuropsychometric deficit (mean values plus 95% confidence limits).

Statistical analysis is also provided relevant to this intra-group variation.

Mann-Whitney U-tests are also included to cover the observed data.

Figure 10 :   Intra-Group A variations in a-vO2ct.differences

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for patients both with and without evidence

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of post-operative deficit.

●———● :   Group A members with deficit.

●- - -● :   Group A members without deficit.

ARTERIO-VENOUS O_2ct. DIFFERENCES   v.   TIME
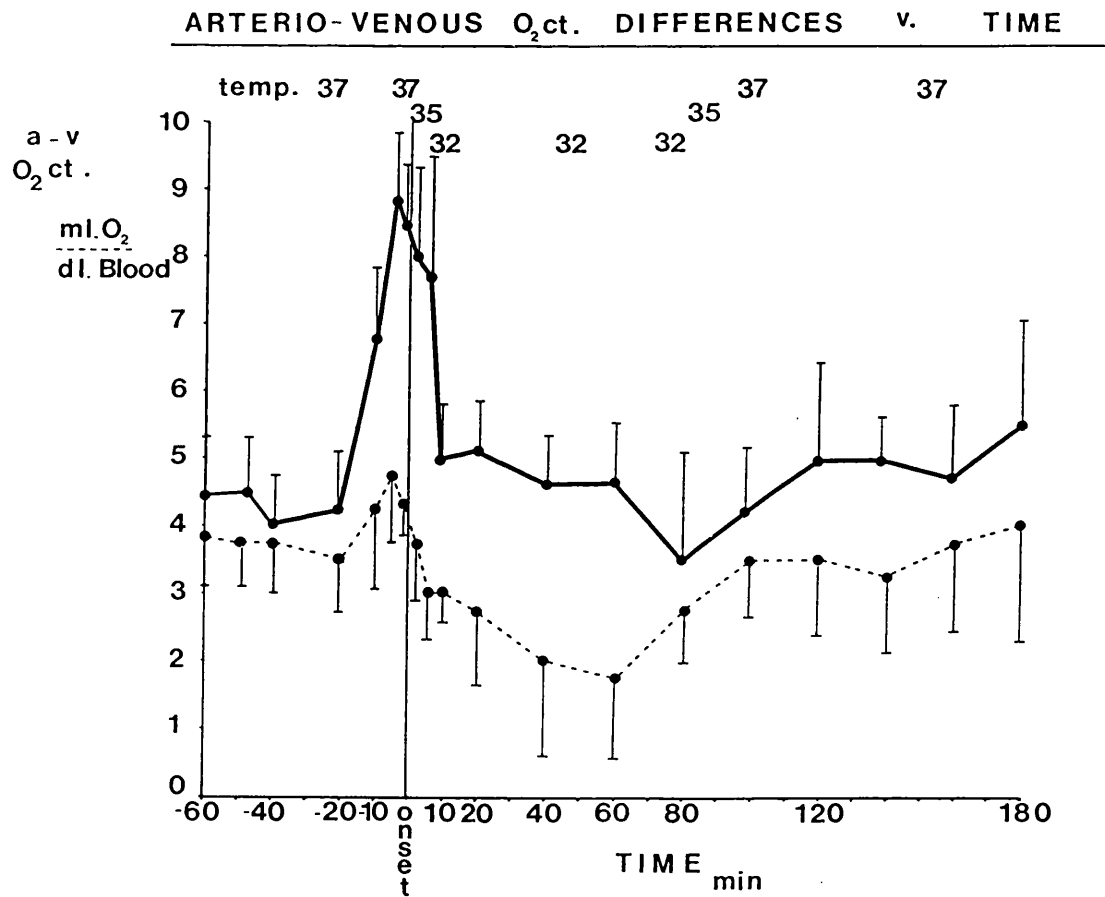
Statistical Analysis : a-vO2ct.differences

Appendix

Ref.

The results for all three groups closely conformed to
the ideal normal probability plot. Analysis relevant to
Normally distributed data was therefore considered

(A1-7)   appropriate.

a). Immediately prior to the onset of perfusion

--   --

Group A had a significantly higher mean

(A1-8)   a-vO2ct. difference than Group B.   P < 0.001

Group C had a significantly higher mean

(A1-9)   a-vO2ct. difference than Group B.   P < 0.001

There were no significant differences
between the a-vO2ct differences for

(A1-10)   Group A and Group C.   P > 0.05

The members of Group A with post-operative
deficit had significantly higher a-vO2ct.

(A1-11)   differences than those without deficit.   P < 0.01

b). During the period of perfusion

-- -------------------------------

There were no significant differences

between the a-vO2ct. differences for the

(A1-12)   two(A,B)groups during the perfusion period.

c). Regression Analysis

-- -------------------

Mean a-vO2ct.differences immediately prior to

perfusion showed a strong correlation (R =+0.8)

with the incidence of post-operative deficit.

(A1-13)   (R-squared = 0.64)

Mean a-vO2ct. differences also correlated well with

mean $PaCO_2$ values for the respective groups at the same

point, immediately prior to the onset of perfusion.

(A1-14)   (R-squared = 0.80)

6.5 Per-operative Jugular Bulb pressure measurements and

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calculated Cerebral Perfusion Pressures (CPP)

The mean per-operative jugular bulb pressures for Group A and Group B are shown in Figure 11 (95% confidence limits are also shown).

Figure 12 shows the per-operative relationship between jugular bulb pressure and right atrial pressure for members of Group A.

For each individual member of the trial, per-operative values for CPP were calculated for each of the timed recordings of jugular bulb pressure (CPP = mean arterial pressure - jugular bulb pressure).

These calculated values for CPP were then amassed for Group A and Group B and plotted as CPP against time, as shown in Figure 13.

Figure 14 shows the relationship between changes in both $PaCO_2$ and cerebral venous pressure, secondary to the onset of perfusion, in members of Groups A and B who showed evidence of deficit. The patients who still had a demonstrable neuropsychometric deficit one week following the operation are highlighted.

Figure 11 :   Per-operative mean Jugular Bulb pressure

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                measurements for Group A and Group B.

                Group A : dashed line.

                Group B : solid line

                (95% confidence limits are also displayed)

CEREBRAL   VENOUS   PRESSURE   v. TIME

155
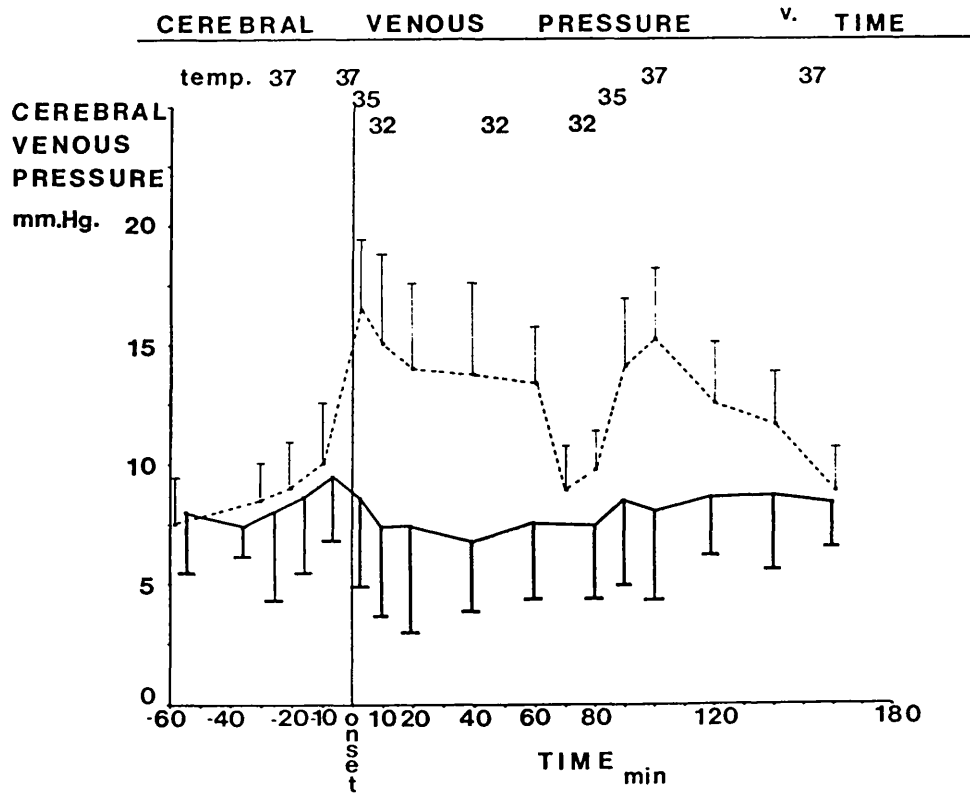
Figure 12 :   Per-operative relationship between Jugular Bulb
----------   ---

pressure and Right Atrial pressure - Group A.

CEREBRAL   VENOUS   PRESSURE   v. TIME

156
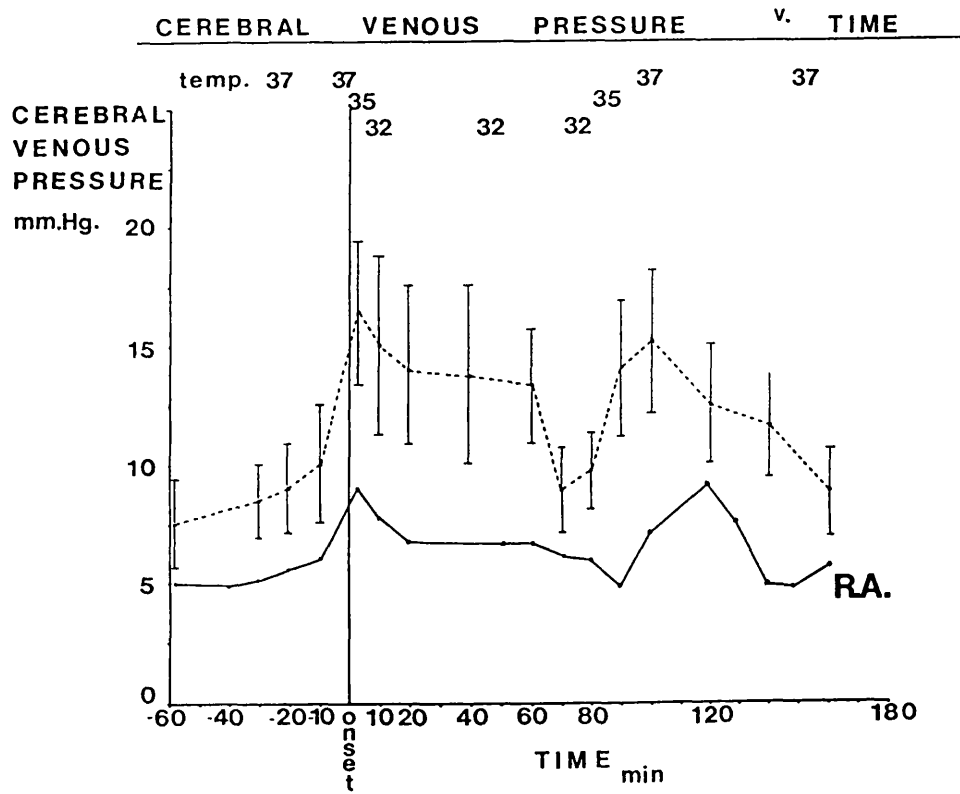
Figure 13 :   Per-operative values for individual measurements

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of Cerebral Perfusion Pressure (CPP) for members

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of Group A and Group B.

●   :   Group A members

·   :   Group B members

CEREBRAL   PERFUSION   PRESSURE
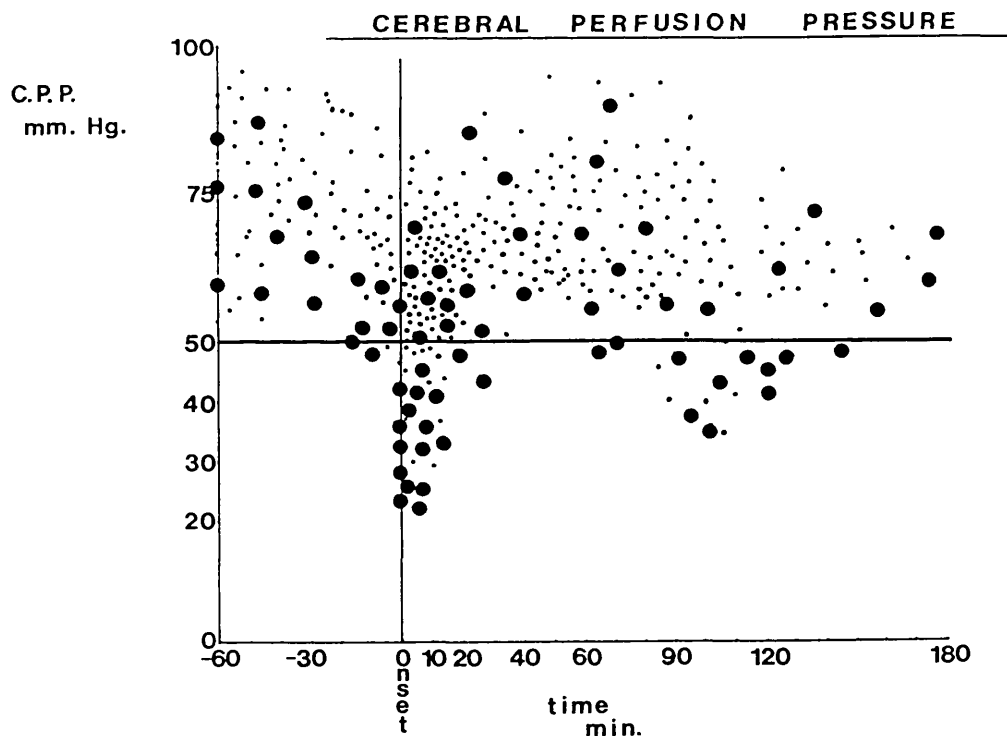
Figure 14 :   The relationship between the change in both PaCO2
----------   --

and Cerebral Venous Pressure secondary to the
----

onset of perfusion in members of Groups A and B
----

showing evidence of post-operative deficit

$\oplus$ = Residual deficit at seven days

●   = No demonstrable deficit at one week

158
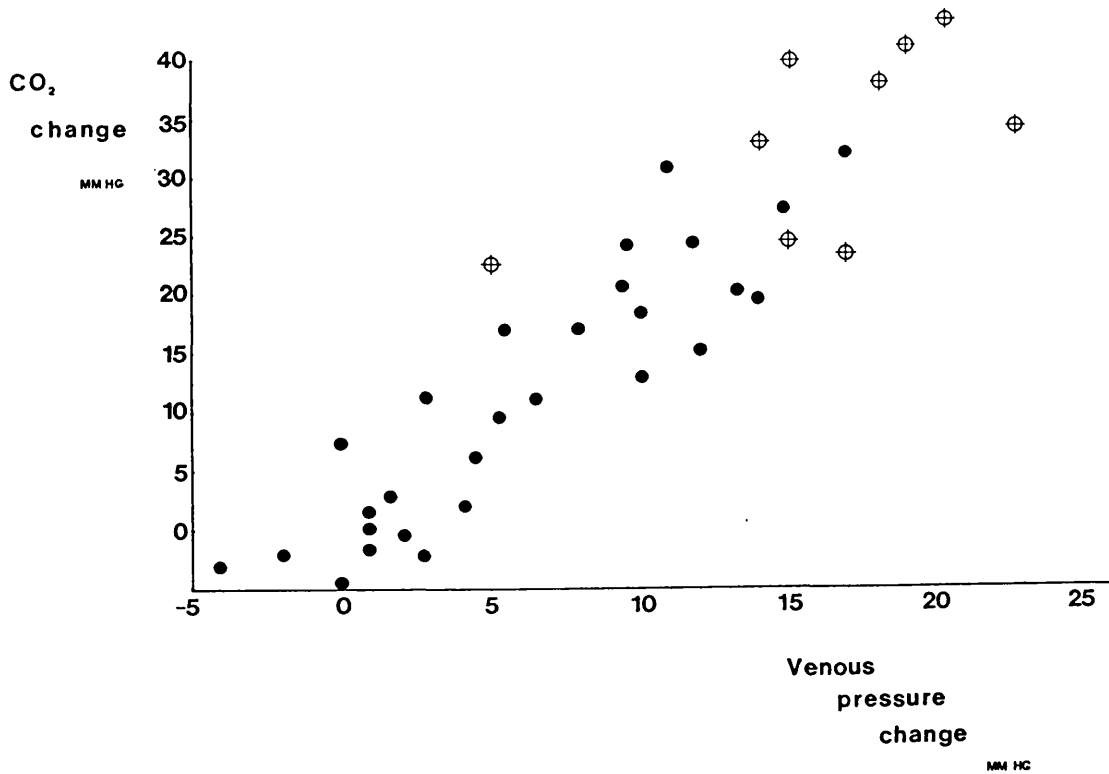
Appendix

Ref.

The per-operative results regarding both measured

jugular bulb pressure and calculated cerebral

perfusion pressure for Groups A and B closely

conformed to respective "normal" distributions and

were therefore subjected to appropriate methods of

(A1-15)   analysis.

a). Immediately following the onset of perfusion

--   --

Group A had significantly higher mean

(A1-16)   jugular bulb venous pressures;   P < 0.001

(mean Gp.A = 16.5; Gp.B = 8.3mmHg.)

and significantly lower Cerebral

(A1-17)   Perfusion Pressures than Group B.   P < 0.001

(mean Gp.A = 40.6; Gp.B = 51.7mmHg)

In addition the members of Group A

with evidence of post-operative

deficit had significantly higher

(A1-18)   jugular bulb pressures;   P < 0.01

(A1-19)   and significantly lower CPP's than

                 the Group A members without deficit.   P < 0.01

                 b).   Regression Analysis

                 ---   -------------------

                 Jugular bulb venous pressures

                 immediately following the

                 onset of the perfusion period

                 correlated well with;

(A1-20)   - the incidence of deficit   R-squared = 0.63

(A1-21)   - pre-perfusion PaCO2   R-squared = 0.70

(A1-22)   - change in PaCO2 @ perfusion   R-squared = 0.75

(A1-23)   - CPP immediately post-perfusion R-squared = 0.77

                 Cerebral Perfusion Pressures

                 immediately following the

                 onset of the perfusion period

                 also correlated with;

(A1-24)   - the incidence of deficit   R-squared = 0.63

changes in Group A and Group B

All patients were monitored with the CFAM throughout the peri-operative period, including the pre-induction period during which the patients were sedated but not unconscious.

Any significant change in both amplitude and frequency (as previously defined) of the CFAM signal was held to be a positive finding and recorded as such.

The characteristic changes that follow the administration of thiopentone and diazepam were discounted, as were the CFAM changes associated with hypothermia during the period of perfusion. (Figure 15)

Significant CFAM changes occurred throughout the peri-operative period; although examination of the timed incidence of all measured changes showed three points to be most regularly associated with abnormalities. (Figure 16)

Analysis of all traces revealed two particular CFAM trace abnormalities that, in a high percentage of participants, appeared to be closely linked with a significant post-operative deficit.

Figure 15 :   CFAM changes associated with Hypothermia and

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the intravenous injection of Thiopentone and

Diazepam.

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1 = i.v. Diazepam

2 = i.v. Thiopentone

3 = Hypothermic changes following onset of

    perfusion
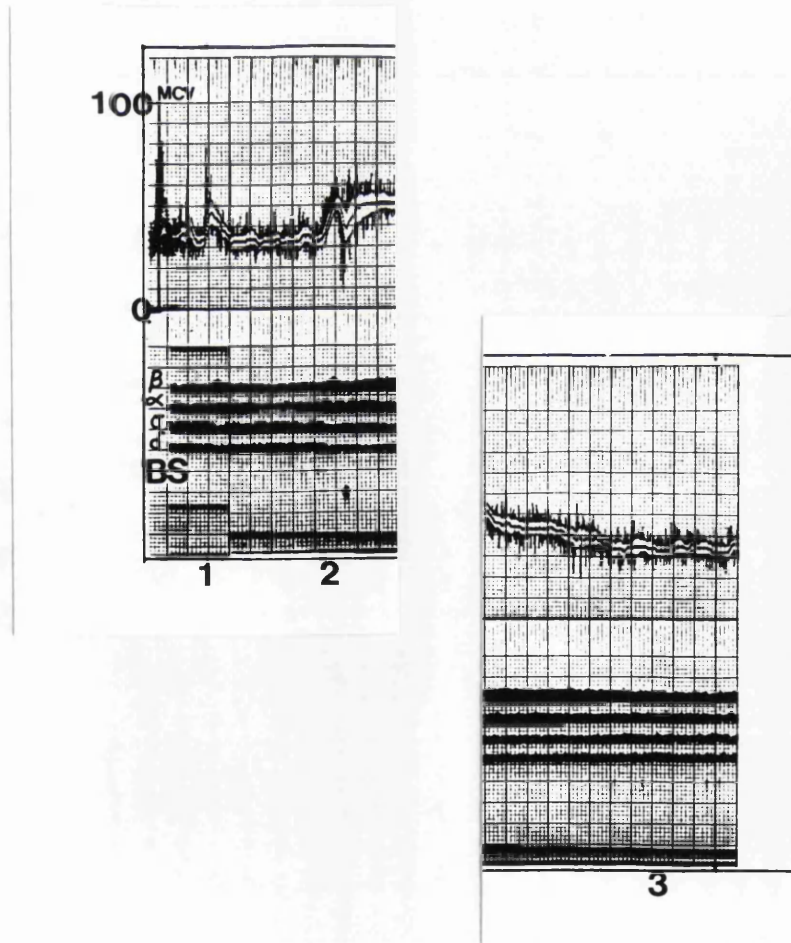
Figure 16 :   Timing of measured CFAM changes

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Total number of CFAM changes observed   = 61

Total number of patients showing changes = 38
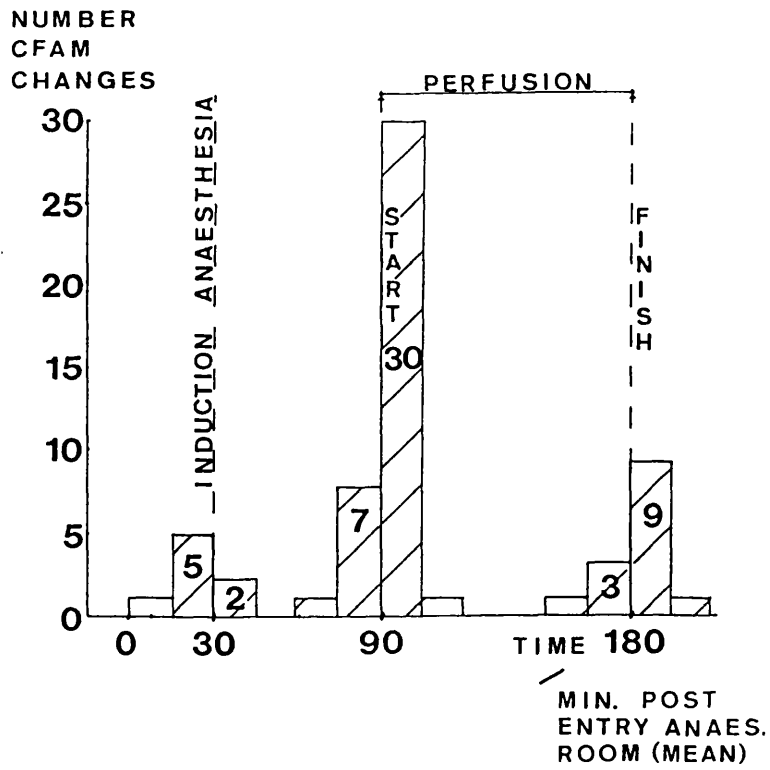
The first of these changes was a sudden reduction in amplitude of the trace associated with a reduction in fast wave activity (beta and alpha) and a simultaneous switch to a slow wave pattern (theta and delta). (Figure 17)

This was probably the most sinister CFAM change that was regularly found and in most cases its appearance was associated with dramatic alterations in cerebral perfusion pressure (mean arterial - cerebral venous pressure).

In cases where these changes persisted for longer than 5 minutes, or where return to pre-insult amplitude and frequencies was incomplete after 10 minutes then a significant post-operative neuropsychometric deficit was always found.

A second category of change was also identified, in which the patients CFAM trace showed no appreciable drop in mean amplitude voltage but instead demonstrated an opening up of the amplitude envelope (i.e. an increase in the 90th percentile voltage at the same time as a decrease in the 10th percentile voltage) together with a simultaneous increase in slow wave activity. (Figure 18) While this change was not always associated with post-operative neurology if occurring in isolation, the additional presence of one of the first type of changes, always resulted in the finding of a severe post-operative deficit. A significant proportion of patients (31%) showed more than one CFAM change during the peri-operative period.

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Figure 17 :   Significant CFAM changes: - (1)
----------   -------------------------------

               - Reduction in amplitude and associated change to
               ----
               slower frequencies.

C.F.A.M. trace
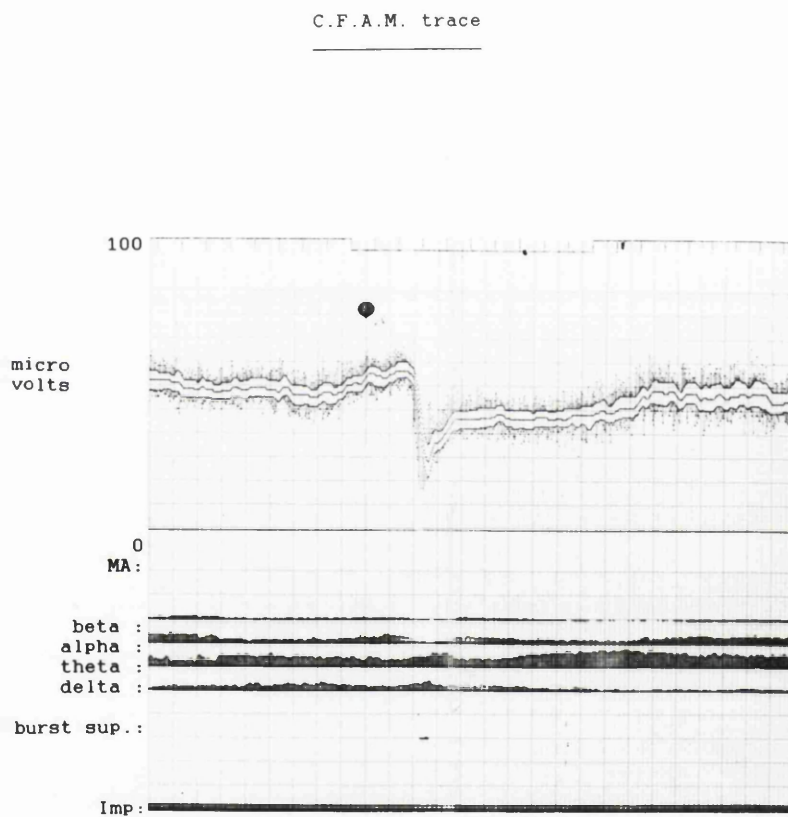
65 yrs: CABG: No evidence previous neurological disease.

1 = onset of perfusion ;   PaCO2 - 25mmHg (3.3kPa.)

Post-op.:   severe neuropsychometric deficit
            multiple retinal infarcts

165

Figure 18 :   Significant CFAM changes: - (2)
---------   -------------------------------

                - Opening of amplitude envelope without reduction

                ----

                in mean amplitude and associated switching to

                ----

                slower frequencies.

C.F.A.M. trace

Anaesthetic Room changes:

100

micro
volts

0
MA:

beta :
alpha :
theta :
delta :

burst sup.:

Imp:
1   **2 3 4**

59 yrs: CABG: No evidence previous neurological disease.

1 = Diazemuls ; 2 = head down for insertion of lines (shallow

respirations, difficult to rouse) ;   3 = jugular bulb pressure
                                                        (18mmHg)
4 = return to level position.

166
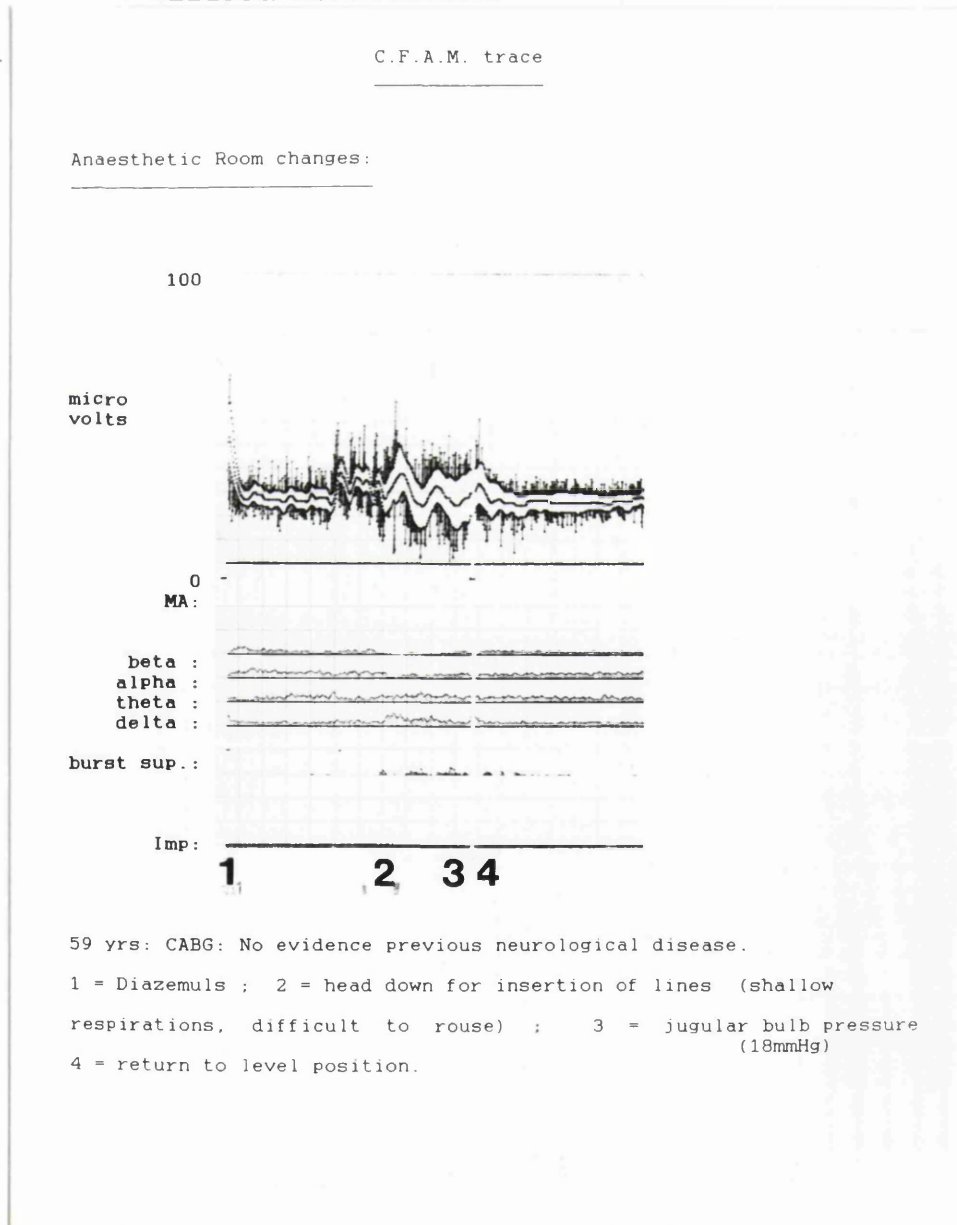
Table 14 looks at the relationship between the incidence of CFAM changes and the incidence of post-operative deficit for all 65 members of Groups A and B. Statistical analysis is with a Chi-squared test with Yates correction for small numbers.

Further statistical analysis looks at both the relative incidence of CFAM changes in Group A and Group B and also the relationship between the incidence of CFAM changes and other per-operative parameters abnormalities.

Table 15 examines both the incidence of both correct predictions of post-operative neuropsychometric outcome when using the CFAM trace alone; and also the incidence of false positive and false negative results. In addition calculation of both the sensitivity and specificity of the apparatus is made.

Table 14 :   Comparison of the incidence of neuropsychometric
--------   --

                  deficit with the frequency of individual CFAM
                  ----

                  changes

                  No. CFAM
                  changes   0   1   2   3

Neuropsych.

deficit

NONE (n= 28)   22   6   0   0

MODERATE (n=22)   3   9   10   0

SEVERE (n=15)   2   3   7   3

% with post-operative   18   67   100   100

deficit

Table 15 : The predictive capabilities of the CFAM :
-------- --

         as a sole estimation of post-operative outcome.

         Test   :   Deficit   :   Deficit
                          present   absent
         _____

CFAM +ve :   32   6

CFAM -ve :   5   22

The incidence of a positive CFAM in a patient with a post-
operative deficit   =   SENSITIVITY   =   32 / 37   =   86%

                        SPECIFICITY   =   22 / 28   =   79%

False positives (positive CFAM / no deficit)   = 6/28   =   21%

False negatives (negative CFAM / +ve deficit) = 5/37   =   13%

Statistical Analysis   :   Peri-operative CFAM changes.

Appendix

Ref.

The increasing number of significant

CFAM changes seen in association

with evidence of increasing neuro-

psychometric deficit is unlikely to

(A1-25)   be due to chance alone. $P < 0.001$

Group A patients had significantly

more peri-operative CFAM changes

(A1-26)   than Group B patients. $P < 0.001$

Group A patients had significantly

more peri-operative CFAM changes

(A1-27)   than Group C patients. $P < 0.05$

There was no demonstrable difference

between the number of peri-operative

(A1-28)   CFAM changes in Groups B and C. $P > 0.5$

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_____ _____

Arterio-venous oxygen content differences have been shown to correlate well with the incidence of post-operative neuropsychometric deficit (Al-21). This relationship is also represented diagramatically in Figure 19.

In routine clinical practice however this parameter is not always available; due both to the cost of the haemoximeter and also the need for jugular bulb access.

The marker of cerebral oxygenation and well-being that is most frequently used is the arterial Oxygen tension (PaO2); despite the fact that this is a measure of gas tension and by definition gives no direct information regarding oxygen requirements.

The clinical relevance of performing gas analysis on blood taken from a peripheral artery, with regard to the adequacy of cerebral oxygenation, has never been demonstrated. In an attempt to both clarify this matter, and also to identify the parameter most likely to give clinically relevant information regarding the state of cerebral well-being, further blood gas analysis was performed; and the results of these analyses (paired jugular venous and arterial samples), from patients demonstrating post-operative neuropsychometric deficit were compared with the results of simultaneous a-vO2.ct differences.

Figure 20 plots a-vO2.content differences against simultaneous jugular bulb and radial arterial paired PO2 tensions for all members of the trial showing deficit; samples being taken both immediately before and 10 minutes after the onset of the perfusion period (i.e. points in time where a-vO2.content differences are likely to be high and low respectively).

Jugular bulb PO2 tensions correlate very well with simultaneous a-vO2.ct differences. (R-squared = 0.79)

Radial artery PO2 tensions correlate badly with simultaneous a-vO2.ct differences. (R-squared = 0.04)

Figure 21 shows the poor correlation between the degree of neuropsychometric deficit and the absolute value for the minimum jugular bulb oxygen tension in all members of the trial.
(R-squared = 0.12)

Figure 19 :   Plot of a-vO2.ct differences(max.) against degree
----------   --
                of neuropsychometric deficit for all members of
                ----
                the trial.

Figure 19 :   Plot of a-vO2.ct differences(max.) against degree
----------   --

of neuropsychometric deficit for all members of

----

the trial.

----

a-vO₂ct max vs. NUMBER OF PSYCHOMETRIC
                      TESTS   FAILED

Figure 20 :   Plot of a-vO2.ct differences against paired,
---------   ---

               simultaneous, Jugular bulb and radial arterial PO2

               ----

               tensions in members of the trial showing post-

               ----

               operative deficit.

ARTERIO-VENOUS O₂ct. DIFFERENCES   v. P O₂

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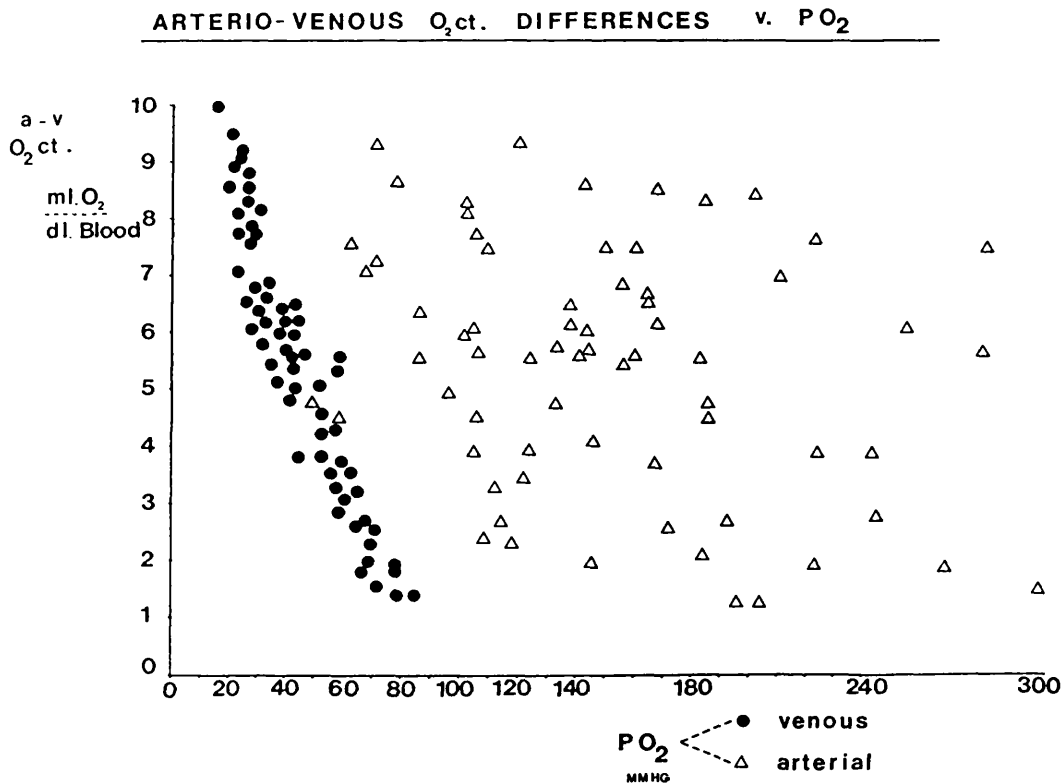
Figure 21 :   Plot of minimum Jugular bulb PO2 against the
---------   --

degree of neuropsychometric deficit for all
----

members of the trial.

P_vO_2 min vs. **NUMBER OF PSYCHOMETRIC**

TESTS   FAILED

175
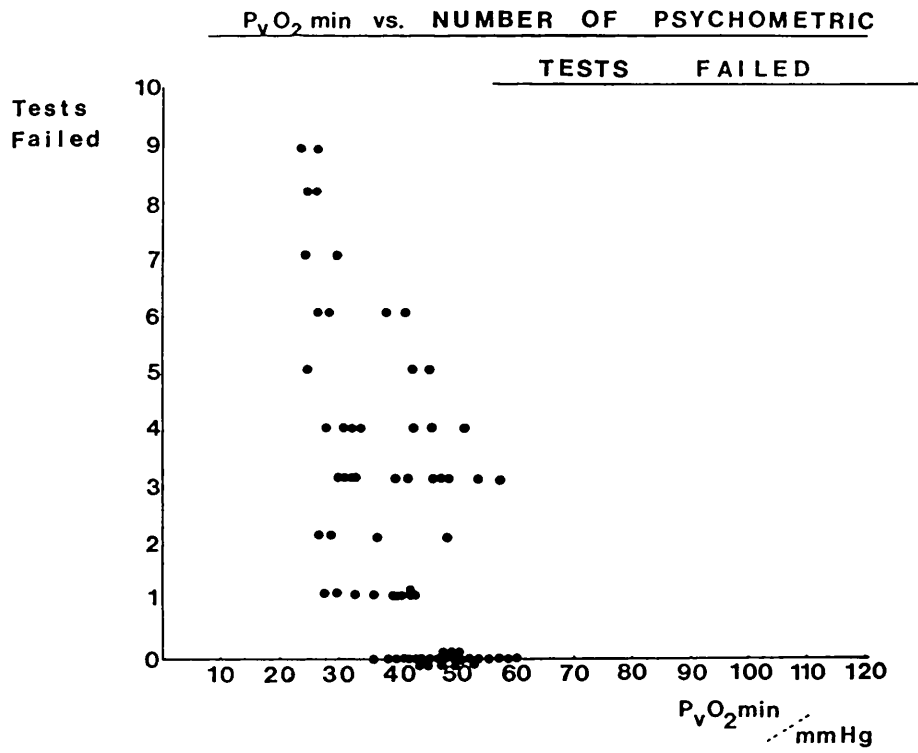
7. DISCUSSION

7.1 Sample population; Study method; Statistical analysis

___ _____

The random nature of patient selection, whether it be for the coronary artery surgery or peripheral vacular surgery patients, is likely to ensure that the patients slected are representative of the routine population undergoing their respective types of surgery at St.Georges Hospital.

It is also likely, because of the trial structure, that Group A patients conform as closely to "routine coronary artery surgery cases" as is feasibly possible in any experimental situation.

Group C also, have been selected randomly from a reasonably homogeneous population of patients awaiting peripheral vascular surgery, and as such are probably a good sample of patients undergoing non-cardiac surgery but in whom there is pre-existing arterial disease. The size of the groups was decided upon after careful discussion with the medical statisticians involved in the trial. It was felt that because of the structure of the trial that intra-group, as well as inter-group comparisons should be made with regard to both the per-operative monitoring and also patient outcome.

No exclusions were made from the trial on the basis of pre-existing disease.

The vast majority of patients undergoing isolated coronary artery grafting in the USA appear to have little symptomatology related to pre-existing neurological disease (19); an observation which also seems applicable to cardiac units in this country (25)

This may in part, however be due to the cursory neurological workup performed routinely in patients about to undergo cardiac surgery in this country. None of the patients involved in this trial, had undergone a full pre-operative neurological assessment,(i.e. involving examination of motor and cognitive capabilities, together with a basic assessment of cranial nerve function and retinal examination) prior to surgery.(Excluding Study Protocol)

While it may still be possible to recognize the post-operative appearance of discrete focal post-operative neurology under these circumstances it would be impossible to pick up the majority of the more subtle changes associated with the more diffuse type of neuropsychometric deficit that we have identified in this study.

The pre-operative neurological assessment must form the baseline for later changes that otherwise may well go unnoticed; and it is surely essential that this must be a prerequisite for entrance to a cardiac surgical programme.

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This problem of adequate peri-operative assessment is especially relevant in view of the recent confidential enquiry into peri-operative deaths (198),(as are the recommendations relating to basic monitoring requirements).

Without continuing patient assessment it is likely that the majority of patients with even severe psychometric deficits will be missed; and this may have major implications with regard to both the physical and psychological well-being of both the patient and also his immediate family.

It is only by careful pre- and post-operative documentation of neuropsychological parameters that any insight into the incidence of this deficit in the population as a whole can be made.

This of course will demand more resources to be applied, and this will meet with opposition, but it is vital to consider the longterm physical and psychological effects that such cognitive losses can have on patients, as well as the operation numbers, and survival rates.

It is important to note, however, that in those studies where detailed pre-operative assessment has revealed a significant degree of pre-operative neurological abnormality (25), then there was little correlation with post-operative outcome.

The structure of this study also warrants some further discussion. Before starting the study all participating parties were aware of the significance of undertaking sequential, rather than randomised allocation of patients into the two coronary artery groups.It was felt essential however, to allow the first group, Group A to approximate as closely as possible to normal clinical practice.

In order to do this it was essential that the anaesthetists involved had no idea that the results of the pilot study had suggested that pre-perfusion hypocapnia was possibly an important factor in the aetiology of post-operative deficit. This knowledge could perhaps, have unconsciously biased their management with regard to the frequency of blood gas estimation; thus jeopardising the whole point of the trial.

The advantages gained with regard to the "normality" of per-operative anaesthetic management for the patients in Group A, in our opinion, far outweighed any disadvantages with regard to the significance of statistical analysis. In an attempt to circumvent these statistical problems, a decision was made to carry out intra-group variation with regard to both per-operative monitoring, and also post-operative outcome.

Statistical analysis consisted of either Students "t" tests for parametric data; or the Mann-Whitney U test where data was either non-parametric or undefined.

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For statistical correlation between intellectual impairment and both the clinical signs of CNS dysfunction (neuropsychometric and ophthalmological) and also the incidence of other per-operative monitoring abnormalities,the Chi-squared test (with the Yates correction when necessary) and the Fisher's exact probability test, were used where appropriate.

Regression analysis using simple correlation parameters (Spearman's method) was performed to analyse the inter-dependance of peri-operative performance.

Although the percentage of patients with positive post-operative neurological signs was higher in Group A than Group B the difference between the two failed to reach a level of statistical significance.

This was in great contrast to the highly significant difference betwen the same two groups, in the incidence of post-operative psychometric deficit (A >> B).

The fact that the simple neurological examination failed to statistically demonstrate inter-group variation is perhaps of no great surprise. The tests are relatively simplistic and ,in the majority of cases, are screening tests looking for gross variations from normality. The interpretation of the findings then relies upon the experience of the person performing these simple tests in applying them to the clinical context. As has been stated from the outset, the post-operative deficit is likely, in the majority of cases to be subtle in nature, with little in the way of discrete localising signs. It is unlikely therefore, that an isolated neurological examination, even when performed by dedicated neurologists, will be able to clearly identify patients with moderate or even severe cognitive losses (as defined by the results of psychometric testing).

Further validity is added to this statement by the fact that when "hard" neurological signs were present, (i.e. the retinal changes identified by the ophthalmologists), they were in all cases immediately spotted during routine neurological examination. The level of competence of the neurologist involved is unlikely therefore to account significantly for the apparent failure of this line of investigation to demonstrate major inter-group differences.

It is perhaps realistic to suppose therefore that this insensitivity of neurological examination may also play some part in the fact that this whole syndrome of diffuse intellectual impairment following coronary artery surgery lay unrecognised for so long. It was only with the introduction of standardised psychometric testing that the true size of the problem could at last be fully appreciated.

The psychometric tests used in this trial have high test-retest reliability coefficients and the scores would normally be expected to remain unchanged when the same patient undergoes retesting after only a short period (93). The deficits that we have documented in the three groups are, by the very nature of the tests involved, highly unlikely to be the result of chance alone and are more likely to represent true inter-group variations secondary to per-operative factors.

71% of Group A had demonstrable psychometric deficit; and in 37% (13 patients), the psychometric deficit was said to be severe. Only one of these 13 patients was identified by the nursing and medical staff, responsible for their post-operative care, as having possible neurological sequelae. While this may lead sceptics of psychometric analysis to suggest that the tests are too sensitive; it is interesting to note that relatives of 6 of these 13 patients volunteered thoughts to our assessors that their relatives were "not quite the same", and three of the remaining 7 families offered similar comments when asked directly. The significance of these findings with regard to the presence of "true" abnormality cannot be overstated.

By the time of discharge the incidence of abnormality in Group A members had fallen to 26%; a figure below that recorded by other workers in this field at a similar post-operative point. This may represent that either the tests used here are if anything undersensitive to the presence of abnormality, or that the tests of others are oversensitive. This finding should not, perhaps, be totally unexpected. The tests are after all extremely sensitive both to the patients on whom the tests are performed, but also to the person who is performing the tests. It was for this reason that in this case it was deemed essential that all tests were performed by the same operator. This, unfortunately was not the case with all previous studies, and may have led to inter-operator error with regard to the identification of deficit.

The majority of Group A patients with deficit at 3 days post-operatively showed progressive improvement during the time prior to discharge; only 9 (26%) having demonstrable deficit at 7 days. All of these patients with residual deficit, had exhibited severe deficit when they were examined at 3 days post-operatively. Whether the natural progression of this recovery continues still remains to be documented, although evidence from other workers would suggest that even at one year post-operatively a significant proportion still have evidence of psychometric deficit (26).

What is certain is that Group B members suffered statistically less deficit when assessed at 3 days; and that this significant reduction in cognitive loss was maintained through to discharge.

Further questions however, must be raised by examination of the psychometric deficit in Group C, the control group of vascular cases. Statistical analysis of deficit revealed no significant difference between the deficits in Group B and Group C. This similarity once again was maintained through to discharge. In all of the affected Group C patients however the deficit was only moderate suggesting the possibility of varying aetiologies for the cardiac and non-cardiac groups. This finding, of a significant proportion of the "control" patients demonstrating neuropsychometric deficit is consistent with the findings of other workers in this field who have incorporated "control" groups of non-cardiac patients (25).

Of the seven, Group A patients, who demonstrated post-operative ophthalmological signs 5 showed retinal changes consistent with ocular hypoperfusion. All seven of the Group A patients with post-operative ophthalmological signs demonstrated in addition evidence of severe neuropsychometric deficit.

Retinal examination provides reliable information regarding the effect of external variables on the integrity of cerebral tissue, of which the retina is an outgrowth. As such it readily provides a unique insight into the post-perfusion brain (57).

Despite the ophthalmological signs noted on post-operative examination none of the 35 patients complained of visual symptoms.

Cotton wool spots represent focal retinal infarcts at the level of the nerve fibre layer, probably due to the occlusion of small pre-capillary arterioles. They may be a feature of blood dyscrasias or of ocular hypoperfusion as seen in carotid insufficiency (199-200).

Optic disc haemorrhage can be a feature of ischaemic optic neuropathy such as can occur in severe atheroscerosis or giant cell arteritis (201). However in these cases there is usually severe visual loss and an associated optic disc swelling, with a later secondary atrophy.

Optic disc haemorrhage is however, well recognised as a transient manifestation of raised intra-ocular pressure (I.O.P.) (202-205).

Per-operative I.O.P. recording during coronary artery surgery has demonstrated that at the time of change over to bypass, I.O.P. can often rise by up to 15mmHg (205). This correlates well with our own findings of a rise in cerebral venous pressure at the begining of perfusion, and may well represent a degree of venous stasis.

The above reported changes in intra-ocular pressure while within the normal range, may be of considerable significance when the ocular perfusion pressure is low. The results of this study would suggest that the start of the perfusion period is the point in time at which cerebral perfusion pressure (and hence ocular perfusion pressure) is most likely to be significantly reduced.

None of the patients showed any evidence of retinal microembolisation or branch vessel embolisation. Retinal angiography was not performed however due to ethical objections relating to the risks of anaphylaxis associated with the routine use of the appropriate isotope when injected intravenously.

Cerebral microemboli are thought to be an important factor in the production of neuropsychometric deficit following cardiopulmonary bypass surgery (45).

Despite the repeated documentation, by a variety of techniques, of the per-perfusion presence of both gaseous and particulate microemboli (206,207), quantitative estimates of the size and effect of these measured events have been lacking; and evidence for the hypothesis remains incomplete.

More recent evidence from centres concentrating on the role of microemboli in the aetiology of post-operative deficit would suggest that almost all patients undergoing cardiopulmonary bypass surgery can be shown to have retinal microemboli per-operatively (57). While the potential relevance of this data cannot be underestimated, the study in question failed to include any estimation of clinical outcome and as such leaves major doubts over the clinical relevance of the findings.

Although the exact size of the contribution of peri-operative microemboli to post-operative deficit remains unknown, a significant improvement in post-operative outcome has now been shown following both the introduction of 40 micron filters placed in the arterial limb of the bypass circuit (208-210), and also by a switch to the use of membrane rather than bubble oxygenators (61,62).

What is certain from this present study is that retinal microemboli, potentially difficult, if not impossible to manipulate per-operatively, were notable only by their absence.

This was also noted by other workers in similar prospective studies, involving neuropsychometric assessment (21), who found far greater ophthalmological evidence of ocular hypoperfusion than of retinal microembolisation.

Only 4 members of the study cohort were known to suffer from diabetes mellitus prior to surgery. One in Group A, one in Group B and the remaining two in Group C.

None of the diabetic patients showed any evidence of diabetic retinopathy pre-operatively: and none of the eye changes demonstrated were in any of the diabetic patients.

7.3 :   Per-operative arterial CO2 tensions.

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Methods of sampling, storage and analysis were standardised for all members of the trial. This, together with daily maintenance of all equipment ensured that both machine and operator error were likely to be minimal, but also uniform for all three groups.

As far as possible, the timing of per-operative sampling was standardised, using the onset of anaesthesia as the first reference point and the onset of the perfusion as the second.
All sampling was then performed at timed intervals around these two points (only onset of anaesthesia for Group C). On average five samples were taken from each patient for every hour that the operation continued. This frequency was increased in Groups A and B, immediately following the onset of the perfusion period, when dramatic changes in per-operative parameters warranted more detailed analysis.

All of the samples taken were measured using a CO_2 electrode at 37deg.C. and then corrected for the temperature of the patient at the time of the recording (pH stat) (the calculation being done electronically by the acid-base laboratory).While on theoretical grounds the basis for this "temperature correction" is highly debatable (132,133), recent polls of anaesthetists in the USA (133), would suggest that temperature correction remains the most popular method of assessing per-operative blood-gas analysis.

The author can add to this the results of an informal poll conducted at a recent meeting of perfusionists from the UK, held at the Brompton Hospital (unpublished data) in 1987. Of the thirteen centres represented at the meeting seven routinely used temperature corrected values (pH-stat) for per-operative $PaCO_2$ monitoring. Of the remaining centres, two more occasionally used temperature corrected values, depending upon the particular anaesthetist, while only four of the centres admitted to routinely using non-corrected $PaCO_2$ values (alpha-stat). Five of the seven centres utilising pH-stat admitted to routinely adding CO_2 to the bypass circuit at the start of the perfusion period.

Once again, for the purpose of this study the intention was to examine the normal practice of the cardiac institution in question, and this involved adopting the routine methods employed in that centre, at the time of the study. Temperature corrected $PaCO_2$ values were therefore used throughout.

Looking firstly at the per-operative $PaCO_2$ results for Group A (Figure 3) several points should be stressed :

Firstly, at the time of being placed onto mechanical ventilation, shortly after the commencement of anaesthesia, almost all of the group members had $PaCO_2$ values within the pre-defined "normal" range (35-45mmHg.).

There was therefore no evidence that these patients presented anything but a routine challenge, with regards to the accurate maintenance of per-operative PaCO2 normality.

By the time this group of patients entered the perfusion period however, all semblance of PaCO2 normality had disappeared.

In almost half of the patients PaCO2 values were less than 30mmHg.; a level that is likely to be associated with considerable increases in cerebrovascular resistance and in many cases with a concomitant reduction in cerebral blood flow(84). This reduction while often of considerable proportions, is unlikely to reduce cerebral blood flow below basal requirements, provided the cerebral circulation in question has adequate powers of "autoregulation". This of course cannot always be guaranteed, espacially in a population who by the very nature of their surgery have systemic arterial disease. While the actual direct harm done by this degree of pre-perfusion hypocapnia cannot be proven it surely cannot be in the interest of the patient to have its cerebral autoregulatory powers tested so vigorously.

Secondly, the onset of the perfusion period was associated with a dramatic change in PaCO2 values for the majority of patients in Group A. The greatest changes were seen in those patients whose pre-perfusion PaCO2 values showed the greatest degree of hypocapnia (Fig.8). In these patients the per-perfusion PaCO2 values were extremely high, and often fluctuated considerably during the course of the perfusion period.

Considering the fact that pH-stat management was being used, the degree of hypercapnia found in a high proportion of Group A patients following the onset of the perfusion period was likely to result in maximal vasodilatation of the cerebral circulation . The effect of this would be an obtunding of the autoregulatory response to any further reduction in cerebral perfusion pressure; and conversion of the cerebral circulation into a pressure passive system.

Group A, showed considerable variations from the normally acceptable range for per-operative normocapnia; despite the anaesthetists involved in the trial both wanting to, and also being under the impression that they were, maintaining a state of normocapnia.

Comparison with Group B (Figure 5) is startling. These patients despite being of similar age, sex and disease category presented no problems with regard to the maintenance of per-operative normocapnia. The answer must lie in the degree of monitoring. It would seem unreasonable, in an operation of this complexity involving fluctuations in electrolyte status, the instillation of an artificial, non-pulsatile perfusion circuit, considerable haemodilution and the addition to the circulating volume of large amounts of Ringers lactate solution, to expect any anaesthetist or perfusionist to maitain acid-base equilibrium on the basis of three or four blood gas analyses spread out over several hours. And yet this appears to be very often the case.

Further information obtained by the author at the above quoted meeting of UK perfusionists would suggest that on average only one blood gas sample is taken prior to the onset of the perfusion period; and this is often shortly after the patient is connected up to the ventilator.

The period of ventilation prior to perfusion normally ranges from 30 - 60 minutes, depending on whether internal mammary artery grafts are to be used. Any overestimation of ventilatory requirements by the anaesthetist at the outset (i.e tidal volume : frequency :minute volume), are likely to result in a considerable degree of hypocapnia one hour later if the original settings remain unchecked. Unfortunately this outcome would seem to be extremely likely in the context of present clinical practice, as documented in this study.

The period, following the start of artificial ventilation and up to the onset of perfusion is a busy time for the anaesthetist, involving the recording of baseline parameters, the infusion of any prescribed antibiotics, the drawing up of cardioreactive drugs for the peri-perfusion period, the heparinisation of the patient and in many centres with the preparation of the cardioplegia solution. There are many reasons therefore why the frequency of blood gas analysis may be limited during this period, and why often extreme degrees of hypocapnia and associated cerebral vasoconstriction may often go completely unnoticed.

In addition, the meeting of UK perfusionists suggested that during the perfusion period itself, only 2 or 3 blood gas analyses are performed on average, with a further sample at the end of the perfusion period and prior to extubation.

These findings suggest that a system of continuous,automated $PaCO_2$ estimation should be a mandatory part of pre-operative monitoring.

Pre-perfusion estimation can be provided by the routine use of the end-tidal CO_2 monitor while during the period of perfusion "in-line" CO_2 electrodes provide similar contiuous information. While the end-tidal CO_2 monitor presents some minor theoretical problems with regard to accurate moment to moment estimation of $PaCO_2$ levels, the results of the Group B patients shows that its use is consistent with the maintenance of per-operative normocapnia.

Calculation of an alveolar - arterial gradient at the commencement of ventilation, and the application of this calculation during the subsequent ventilatory period allows easy adjustment of ventilatory parameters so maintaining normocapnia without the need for further invasive monitoring. While it is true that there will be some variation in the alveolar-arterial gradient throughout the procedure it is likely to be small, and can be minimised further by additional calculations throughout the pre-perfusion phase.

The patients in Group C (Figure 6), the control group of patients undergoing peripheral vascular surgery, perhaps present the greatest questions with regard to the routine performance of general anaesthesia. Advancing age has been shown to be associated with both a reduction in cerebral blood flow to the cerebral grey matter, and also a slowing of cerebral autoregulation, secondary to decreased elasticity of the cerebral vasculature (172,173,174)

Patients in Group C showed degrees of hypocapnia that are of a similar degree as the patients in Group A.

Again the anaesthetist involved did not deliberately aim for a hypocapnic state, but merely assessed the patients, and instituted ventilatory parameters as he felt appropriate.

It was not routine practice, for the anaesthetist to use an end-tidal CO_2 monitor and any ventilatory adjustments were therefore based upon blood gas analysis as he felt appropriate. It is likely that the degree of hypocapnia seen in the majority of the patients in this group again reflects the paucity of arterial sampling. It should be of particular note, that, in both Groups A and C all anaesthetists were applying commonly quoted formulas for the calculation of ventilatory requirements: the use of a Manley ventilator, tidal volumes of 7.5-10ml/kg.body weight and fresh gas flows adjusted to give respiratory rates of 10-12 per minute.

While the hypocapnia immediately prior to the onset of perfusion in Group A, can be explained in terms of inadequate monitoring the possible explanation for the dramatic hypercapnia after the onset is slightly more complex.

For many years perfusionists in some cardiac centres have routinely added CO_2 (normally ~ 5%) to their gas mixtures for the perfusion circuit. The basis for this is almost certainly historical, dating back to the work of Severinghaus on children undergoing marked hypothermic cardiac surgery(159,160).

There is little evidence that patient outcome is improved, yet the practice persists.(99,101,102)

In addition to this historical basis the addition of CO_2 to the "pump", is looked upon by many perfusionists as a useful tool in rapidly correcting hypocapnia.

At St.Georges both of the above situations applied with the routine addition of 5% CO_2 to the pump at the commencement of bypass. This was then slowly reduced over a period of 10 to 15 minutes; a time interval which the perfusionist judged was long enough for the protective cerebral benefits of hypothermia to become fully established.

It is therefore evident that the perfusionist is consciously adding CO2, in the idea that this will either improve patient outcome or at the very least give the patient adequate cover against the harmful effects of hypocapnia.The method of adding the CO2 is however very inaccurate, (simply by turning on the CO2 rotameter) and once again the maintenance of PaCO2 control is based entirely upon intermittent blood gas analyses, performed by the perfusionist. Evidence at hand would suggest that the frequency of such analyses (paediatric surgery excluded) is grossly inadequate, and as a result per-perfusion control of PaCO2 leaves a great deal to be desired.

The fact that the patients who are most hypocapnic pre-perfusion are often those who become most hypercapnic secondary to the onset of perfusion would suggest that the crude manner of adding CO2 to the perfusion circuit, may in part, be responsible for the considerable rebound in CO2 levels.

The clinical implications of these findings are considerable; many of the Group A patients switching from a state of almost maximal cerebral vasoconstriction, (due to the measured hypocapnia), to a state of almost maximal cerebral vasodilatation, (secondary to the measured hypercapnia), almost instantaneously with the onset of the perfusion period. The effects of this dramatic change in cerebrovascular resistance on intracerebral blood volume have not been measured directly but the increase is likely to be significant.

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7.4 :   Arterio-venous oxygen content differences, Cerebral
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           venous and Cerebral Perfusion pressure measurements.

The per-operative diagram of mean a-vO2.ct differences for
members of Group A (Figure 7) shows several notable features.
Prior to the perfusion period the mean values are similar to
those documented by other workers looking at this parameter in
patients under general anaesthesia (i.e 4-5ml O2/100ml blood)
(114).

Within the 10 minutes prior to the onset of the perfusion a
dramatic rise in oxygen extraction occurs. This rise is
significantly greater in Group A than Group B. It is also true
that the rise in extraction in members of Group A who
demonstrated evidence of post-operative deficit, was
significantly greater than in those members of that same group
without deficit.

This peak in oxygen extraction corresponds both to the time of
maximal hypocapnia in Group A members and also to the point in
operative procedures where aortic and venous cardiac lines are
being inserted prior to connection to the bypass circuit. These
manoeuvres are often associated with considerable manipulation of
the heart and major vessels, often resulting in a reduction in
both venous return and cardiac output.

The onset of bypass is associated with a steep fall in oxygen extraction, coinciding with the onset of hypothermia, to a mean plateau level of around 2ml O2/100ml blood. This mean value was then continued through the period of perfusion, rising again with rewarming to similar levels to the pre-perfusion phase.

Group B, by contrast (Figure 8), show none of the sudden rise in the period immediately prior to perfusion. While the cardiac manipulation for the insertion of perfusion lines was just as likely to be troublesome in this group as in Group A, what differed was the degree of patient hypocapnia.

Group B again showed a fall to a plateau level of 1-2ml O2/100ml blood for the perfusion period rising again on rewarming. There was no significant difference between the O2 extraction levels of Groups A and B during either the perfusion or the post-perfusion periods.

There was however a highly significant difference between the oxygen extraction in Groups A and B prior to perfusion onset.

It has been suggested that the flow-metabolism link between cerebral oxygen requirements and supply may be broken down by the instillation of non-pulsatile cardiopulmonary bypass (128,150). In these circumstances the respective authors have suggested that the monitoring of a-vO2.ct differences may be misleading in that it will not correlate with cerebral metabolic rate for oxygen.

While the basis for this argument remains debatable, it is partially irrelevant to our findings as the major differences between the Groups A and B occurred prior to the onset of perfusion.

Group C (Figure 9) again show similar a-vO2.ct differences to the members of Group A. They differ however in that they are maintained at high levels throughout the period of the operation due to the lack of significant hypothermia. Again the oxygen extraction measurements show a highly significant correlation with both the degree of hypocapnia and also with the incidence of post-operative deficit.

The implications of these Group C findings have serious import on the conduct of anaesthesia for general surgery as well as cardiac surgery. The degree of neuropsychometric deficit, while not as high as in Group A patients is still significant; and appears to be related to the presence of unrecognised hypocapnia brought about by periods of prolonged hyperventilation. It may well be that in patients undergoing general surgery who are exposed to significant degrees of hypocapnia the associated reduction in cerebral blood flow never reaches ischaemic levels; unless a further cerebral insult intervenes. This may explain the improved correlation between PaCO2 and postoperative deficit in Group C members that can be achieved (R-squared improved from 0.56 to 0.72) by the stepwise addition of per-operative blood loss to mean per-operative PaCO2. (Figure 6b)

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Both cerebral venous, and cerebral perfusion pressures show significant variations between Groups A and B; with the maximum differences occurring immediately after the onset of the perfusion period.The rise in mean cerebral venous pressure secondary to the onset of perfusion is significantly greater in Group A than in Group B.(Figure 8). It is also significantly greater in those members of Group A demonstrating post-operative deficit, than in the group members without deficit.

There is also a significant correlation between this change in cerebral venous pressure and the change in arterial CO_2 tensions subsequent to the onset of bypass (Figure 14); with the patients with the most severe post-operative deficits having the greatest changes in both parameters.

The effect of these high cerebral venous pressures on cerebral perfusion pressures (CPP=MAP-CerVP) is considerable; possibly reducing many patients to sub-ischaemic levels, at a time when the protective effect of hypothermia is not maximal.

It is interesting to hypothesise that the measured increases in cerebral venous pressure secondary to the onset of perfusion are directly related to the opening up of the cerebral vascular bed, consequent upon dramatic fluctuations in PaCO2. The increase in intracerebral blood volume subsequent to this vasodilatation may indeed lead to considerable venous stasis, and susequent elevation of venous pressure.

This in turn may have a dramatic effect on cerebral perfusion pressure at a time when the system is pressure passive; with the potential for further reducing, the cerebral oxygen supply.

Our finding of a lack of significant a-vO2.ct differences between Groups A and B during the perfusion period perhaps adds weight to the idea of an absence of flow-metabolism coupling during non-pulsatile cardiopulmonary bypass.

As stated above, the first part of the perfusion period is associated with significant differences in both Cerebral perfusion pressure and also cerebral venous pressure between Groups A and B. It seems unlikely, that the a-vO2.ct differences, (possibly the most sensitive index of pre-perfusion cerebral insult), would not reflect these adverse conditions in Group A patients, if the parameter was a reliable index at that point in time; and perhaps we should therefore, question the value of this parameter during the perfusion period.

7.5 : The Cerebral Function Analysing Monitor and other additional montoring.

a). CFAM

The Cerebral Function Analysing Monitor (CFAM) produces a detailed analysis of the Electroencephalogram; utilising both the amplitude and frequency of cerebral electrical activity as recorded from biparietal electrodes applied to the scalp. The positioning of the electrodes is critical (168) and great efforts were made throughout this study to reproduce identical scalp placement.

Previous studies have identified characteristic CFAM changes associated with both the administration of drugs and also with variations in physiological variables such as temperature (169,194) and we have not included these in this study. We have been able to demonstrate two types of CFAM abnormalites that, in a high percentage of participants, appear to be closely linked with a demonstrable post-operative deficit.

The first of these changes is a sudden reduction in amplitude, associated with a reduction in fast wave activity (beta and alpha) and a simultaneous switch to a slow wave pattern (theta and delta) (Figure17).

This was probably the most sinister CFAM change that we regularly found and in most cases was associated with dramatic alterations in cerebral perfusion pressure (mean arterial - cerebral venous pressure).

In cases where these changes persisted for longer than 5 minutes, or where return to pre-insult amplitude and frequencies were incomplete after 10 minutes then a significant post-operative neuropsychometric deficit was always found.

Secondly, we identified a small group of patients in whom there was no appreciable drop in mean amplitude voltage but who instead showed an opening up of the amplitude envelope (i.e. an increase in 90th percentile voltage associated with a decrease in 10th percentile voltage), and a simultaneous increase in slow wave activity (Figure 18).

While this change was not always associated with post-operative neurology if occurring in isolation; the additional presence of one of the first type of changes, always resulted in the finding of a severe deficit. Prior to this study few authors had described CFAM changes occurring before the patient goes onto bypass. While it is true that the majority of our abnormalites occurred, as with other reports (170,175), at the start of the perfusion period, there were also a significant number at other times throughout the operation.

As the majority of patients undergoing coronary artery surgery have some limitation of cardiac performance it should not be surprising that any event likely to test cardiac reserve may well result in a degree of cerebral hypoperfusion and the associated CFAM abnormalities. This is even more likely to be significant if other physiological abnormalities associated with cerebral hypoperfusion are also present (e.g. arterial hypocapnia).

The results of this portion of the study serve to illustrate two important points:

Firstly, it is important to have the CFAM running throughout the operation, including the period in the anaesthetic room prior to the induction of anaesthesia which has previously been shown to be associated with arterial hypoxaemia in a group of cardiac surgical patients (214); and secondly, in agreement with other workers (16) that several sub- critical cerebral insults may be just as damaging as a single catastrophic event.

100% of patients with two or three peri-operative CFAM changes were found to have significant post-operative deficit.

21% of the members of Groups A and B, demonstrated false positive traces. That is to say, they showed positive traces without any evidence of post-operative deficit on psychometric assessment.

It is perhaps possible that this could suggest that the tests are simply too sensitive; but it is far more likely that it merely reflects present concepts regarding "ischaemic thresholds" (77). This theory states that as cerebral blood flow is progressively reduced a systematic series of physiological changes occurs. These changes are reflected in both general clinical and complex electrophysiological parameters (76), all of which are capable of providing information about the impending critical ischaemic level of cerebral blood flow. Only by being aware of these parameters suggesting sub-critical ischaemia is it possible to correct the reduced cerebral blood flow, thereby avoiding permanent damage.

Despite these findings of a reasonably high incidence of false positives, our research would suggest that at the present time the CFAM is likely to provide a practised observer with an excellent chance of identifying the occurrence of potential cerebral insults; and, in so doing, allow intervention to be taken before irreparable damage has been done. It is however not infallible, and as such may need to be combined with another index of cerebral well-being before we have enough strength of conviction to intervene at an early stage in every case demonstrating CFAM changes. If this improvement in specificity could be achieved then the regular use of the CFAM would surely be associated with a significant reduction in post-operative neuropsychometric deficit.

b).   Additional monitoring.

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Measurement of arterial oxygen tension (PaO2) is probably the most commonly applied parameter, in considering the adequacy of cerebral oxygenation, during cardiopulmonary bypass surgery.

While it is true that there is a well recognised relationship between the PaO2 and the percentage haemoglobin saturation (% Hb.O2) this involves the application of a complex mathematical equation in which there are many variables. The resulting sigmoid curve describing the relationship between PaO2 and % Hb.O2, is also affected by variables which can result in shifts of the curve either to the right or to the left. Temperature, PaCO2 and pH are three of the most important variables responsible for shifts in the oxygen dissociation curve; and as described in our study all three often vary dramatically during the course of cardiac surgery. It is essential therefore, to account for all of the above factors, before one can draw conclusions regarding the haemoglobin saturation from a simple measure of arterial oxygen tension. Even then, further regard must be paid both to the haemoglobin concentration and also the cardiac output before any accurate assessments of cerebral oxygen supply can be arrived at. Once again both of these parameters are likely to frequently alter during the course of both the pre- and per-perfusion periods; making rapid judgements on O2 supply exceedingly difficult.

It becomes increasingly obvious that the use of the PaO2 as a measure of the adequacy of cerebral oxygenation is, on theoretical grounds, open to major criticisms at every conceivable step. Despite this it remains the foundation of most per-operative assessments of the adequacy of cerebral oxygenation.

The pooled results of all patients in this study would suggest that one of the best per-operative indicators of post-operative outcome is the a-vO2.ct difference (max) of the individual concerned. While it would not be completely unreasonable to suggest that this parameter should be monitored routinely during the per-operative period, it is unlikely, partly due to the cost of the equipment involved that this suggestion is applicable to the clinical context. We therefore set out to compare the value of a-vO2.ct differences with the more readily available arterial (PaO2) and jugular venous(PvO2) oxygen tensions. The times chosen, immediately prior to and immediately following the onset of perfusion, represented a spread of a-vO2.ct differences as all members of the study were included.

The excellent correlation of a-vO2.ct differences with the PvO2 measurements , and the extremely poor correlation with arterial samples (Figure 20), serves to underline the theoretical objections to the routine use of PaO2 as the accepted standard assessment of tissue oxygenation.

PaO2 values can only really give us information about the efficiency of the oxygenator, through which the blood has circulated (lungs or oxygenator).

The evidence shown here would suggest that if we are to use an indirect assessment of cerebral oxygenation then the routine use of jugular venous oxygen tensions is likely to be most reflective of tissue demands.

Even this however is subject to certain limitations in that it will reflect only a global assessment, with areas of high PvO2, possibly cancelling out areas of the brain with low PvO2 values (secondary to reduced supply), when the venous drainage of all cerebral areas recombines in the cerbral venous sinuses.

It is, however, much more likely to reflect changes in cerebral oxygen flux, than the use of arterial sampling.

As with other parameters that have been examined in this study it is impossible to state minimum jugular venous oxygen tensions that are likely to be associated with a high degree of post-operative deficit. Figure 21 shows that the minimum PvO2 in patients with post-operative deficit is not significantly different from the minimum values shown for the patients demonstrating even severe deficit.

The message from this section of the study, as with the findings
of other groups (215), must surely be that a single measurement
of any parameter is unlikely to give enough information to make a
valid judgement regarding the presence or absence of a cerebral
insult; rather that the focus of attention should be on per-
operative parameter trends, in several interconnected variables.

Future research needs to be focused on the development of non-
invasive methods of cerebral oxygenation assessment. The need for
both high sensitivity and specificity, while minimising adverse
effects to the patient cannot be overstated. Despite some early
successes with infrared spectrophotometry in paediatric studies
(216,217) this ideal is still unattainable in adults.

It is likely that for the forseeable future, patient outcome will
be dependent upon the vigilance of both anaesthetists, surgeons
and perfusionists to continuously monitor presently available
parameters, both individually and in combination; so providing
the best overall assessment of cerebral well being.

CONCLUSION

This thesis documents the findings of a prospective investigation into both the size and severity of post-operative neuro-psychometric and ophthalmological deficit, in groups of patients undergoing coronary artery and peripheral vascular surgery. By means of intensive per-operative monitoring, an attempt has been made to draw conclusions regarding some of the factors which may be implicated in the aetiology of the measured deficit.

Pilot study results, revealed great individual discrepancies from expected arterial carbon dioxide tensions in a high percentage of patients. Because of the well recognised effect on cerebrovascular resistance of changes in $PaCO_2$, the coronary artery patients were separated into two groups. In the first group per-operative ventilatory parameters were at the discretion of the anaesthetist while in the second, additional monitoring was utilised so as to guarantee per-operative normocapnia. All other per-operative conditions were standardised for both groups.

Group A, in whom per-operative CO_2 values were not subjected to continuous monitoring suffered a higher incidence of both neurological, psychometric and ophthalmological deficit, than the controlled CO_2 group (Group B) when examined post-operatively.

Group A members demonstrated significantly lower PaCO2 values, immediately prior to the onset of the perfusion period, than Group B; a result presumably, of overenthusiastic ventilation.

The effects of this hypocapnia on post-operative deficit, cannot be accurately assessed in isolation, although results showed a significant correlation between the degree of hypocapnia and the incidence of post-operative deficit (R=0.75).It is almost certain that the degree of hypocapnia demonstrated in many of the Group A patients would be associated with a considerable degree of cerebral vasoconstriction; which while not certain to reduce cerebral blood flow below ischaemic thresholds in all cases, could considerably reduce their autoregulatory reserve. Measurements of cerebral oxygen extraction would reinforce the view, that this point immediately prior to the onset of perfusion, represents a considerable threat to the patient especially in the presence of severe hypocapnia.

The onset of the perfusion period, for Group A members at least, was associated with dramatic fluctuations in both PaCO2 values and also both cerebral venous and cerebral perfusion pressures. The cause for these significant changes can be explained, in part at least, by the attempts of the perfusionist to correct the previously unrecognised hypocapnia, secondary to the onset of perfusion.

In the majority of Group A patients, these crude attempts at re-attaining a state of normocapnia (by the addition of CO_2 to the perfusion circuit via a rotameter) resulted in a profound overshoot and the production of severe hypercapnia. The instantaneous opening up of the cerebrovascular bed, secondary to such excessive fluctuations in $PaCO_2$, will result in a significant degree of cerebral venous stasis; with a concomitant rise in cerebral venous pressure.

This considerable rise in cerebral venous pressure, as witnessed in many of the Group A patients, was by far the most important factor in the production of the significantly lower Cerebral Perfusion pressures seen in this group immediately following the onset of perfusion.

Hypercapnia, of the degree found in the greater proportion of Group A patients is associated with a loss of cerebral autoregulation and the production of a pressure passive system. Under these circumstances the measured reduction in cerebral perfusion pressure is likely to result in a significant fall in cerebral blood flow. Once again, while the significance of low cerebral perfusion pressures, cannot be judged in isolation the correlation between this parameter and the incidence of post-operative outcome was highly significant; as were the correlations with both the changes in $PaCO_2$ and also cerebral venous pressure, secondary to the onset of perfusion.

The significance of these documented changes should be judged in the context of their occurrence at the point in the perfusion period at which the cerebral protective effects of hypothermia are by no means maximal and at which mean arterial pressures can also fall to exceedingly low levels.

The remainder of the perfusion period was not associated with any further significant differences in the other measured parameters, despite considerable inter-group $PaCO_2$ differences.

This would suggest, that either the measured differences between the two groups were insignificant with regard to outcome; or perhaps more likely, that the parameters studied did not accurately reflect the state of cerebral well-being during periods of cardiopulmonary bypass.

The Cerebral Function Analysing Monitor, being used for the first time in conjunction with intensive per-operative monitoring and neuropsychometric assessments demonstrated a high incidence of abnormal traces (76%) in those patients who were later found to have a significant post-operative deficit. It also, however showed a reaonably high number of abnormal traces in patients who had no evidence of deficit (21%).

While this high incidence of false positives may limit the application of the CFAM as a sole predictor of neurological outcome , there was an excellent correlation between the number of CFAM abnormalities seen on any one trace and the degree of post-operative outcome; with all patients demonstrating 2 or more abnormalities ending up with severe post-operative deficits.

Great doubt has also been cast upon the wisdom of routinely using the arterial oxygen tension as a marker of cerebral oxygenation. While the arterio-venous oxygen content difference probably remains the most reliable guide to cerebral oxygen requirements the jugular venous oxygen tension also appears to give a reliable estimation of cerebral well-being; provided we concern ourselves with the monitoring of measurement trends rather than absolute values.

Taken together, this study would suggest that where methods of monitoring demand that intermittent blood sampling and analysis is performed, then it is likely (especially in the charged atmosphere of a cardiac theatre) that the sampling will occur infrequently. As a result, errors in the original estimation of ventilatory parameters may be amplified by this paucity of pre-perfusion sampling and by the duration of the pre-perfusion period.

This is likely to result in a high proportion of the patients entering the perfusion phase markedly hypocapnic; and the detrimental effect of this on cerebral blood flow is then likely to be compounded, if crude attempts at CO_2 correction are instituted following the onset of perfusion.

What is certain is that it is possible to maintain a state of per-operative normocapnia in the vast majority of patients undergoing coronary artery surgery if a system of continuous $PaCO_2$ monitoring is applied; and that this greater control of per-operative $PaCO_2$ values is associated with a significant reduction in post-operative morbidity.

It is highly unlikely, that such a system of intensive monitoring will completely eradicate the occurrence of post-operative neuropsychometric deficit; indeed this study has shown that it will not. What should be stressed however, is that all the variables measured were open to per-operative manipulation and that by careful attention to these measured parameters a significant reduction in morbidity was achieved.

This project, although now completed highlights wider issues, which have implications for anaesthesia in general and which deserve extensive exploration. It has been shown that a high percentage of our control group were subjected to severe cerebrovascular stresses by virtue of severe unrecognised hypocapnia (Figure 3).

A reasonably high percentage of these patients showed moderate psychometric deficit post-operatively, despite the maintenance of adequate cerebral perfusion pressures throughout.

How commonly is the degree of hypocapnia seen in Group C found in patients undergoing routine general surgery; and how does the aged, arteriosclerotic brain respond to these hypocapnic stresses, as witnessed in members of this study?

In addition it is also worth considering the effect on cerebral blood flow of a hypercapnic enviroment, (and the production of a pressure passive circulation); frequently encountered during anaesthesia involving spontaneous respiration.

Future investigations will need to be thorough and extensive, for the effect on both the routine performance of general anaesthesia and on the recognised statutory minimum monitoring requirements may be considerable.

It is possible however, to take encouragement from our completed study; for, as a result of meticulous attention to peri-operative detail, a previously unrecognised and potentially harmful sequence of events has been highlighted and a change in accepted clinical practice introduced. This, in turn, has resulted in a significant reduction in peri-operative neurological morbidity.

PaCO2 levels immediately prior to onset of perfusion

Patient	Gp.A	Gp.B	Gp.C
1	26	33	24
2	21	30	22
3	20	36	25
4	24	36	23
5	28	36	28
6	27	37	29
7	30	37	26
8	26	37	33
9	29	38	32
10	34	38	34
11	32	38	30
12	36	39	32
13	37	39	36
14	39	40	37
15	38	40	39
16	41	40	
17	37	41	
18	36	41	
19	37	38	
20	40	38	
21	32	39	
22	33	39	
23	34	45	
24	34	45	
25	30	44	
26	30	44	
27	29	37	
28	29	37	
29	28	37	
30	27	35	
31	27		
32	26		
33	26		
34	27		
35	30		

Variable:	Gp.A PaCO2	Gp.B PaCO2	Gp.C PaCO2
Sample size	35	30	15
Average	30.8571	38.4667	30
Median	30	38	30
Mode	26	37	32
Geometric mean	30.4088	38.3297	29.5566
Variance	28.0084	10.8092	28.1429
Standard deviation	5.2923	3.28773	5.30498
Standard error	0.894561	0.600255	1.36974
Minimum	20	30	22
Maximum	41	45	39
Range	21	15	17
Lower quartile	27	37	25
Upper quartile	36	40	34
Interquartile range	9	3	9
Skewness	0.0987469	0.0666374	0.0695566
Standardized skewness	0.238496	0.149006	0.109979
Kurtosis	-0.627324	0.995194	-1.08892
Standardized kurtosis	-0.757566	1.11266	-0.860871

Two-Sample Analysis Results   (A1 - 1)

		Gp.A PaCO2	Gp.B PaCO2	Pooled
Sample Statistics:	Number of Obs.	35	30	65
	Average	30.8571	38.4667	34.3692
	Variance	28.0084	10.8092	20.0913
	Std. Deviation	5.2923	3.28773	4.48233
	Median	30	38	36

Conf. Interval For Diff. in Means: 95   Percent
 (Equal Vars.)   Sample 1 - Sample 2   -9.83865 -5.3804   63 D.F.
 (Unequal Vars.) Sample 1 - Sample 2   -9.76661 -5.45243   57.8 D.F.

Hypothesis test for H0 : Diff = 0   Computed t statistic = -6.82325
                    vs Alt : NE   Sig. Level = 1.53775E -7   at
Alpha = 0.05   so reject H0

	Gp.B PaCO2	Gp.C PaCO2	Pooled
Sample Statistics: Number of Obs.	30	15	45
Average	38.4667	30	35.6444
Variance	10.8092	28.1429	16.4527
Std. Deviation	3.28773	5.30498	4.05619
Median	38	30	37

Conf. Interval For Diff. in Means: 95   Percent
 (Equal Vars.)   Sample 1 - Sample 2   5.8793 11.054   43 D.F.
 (Unequal Vars.) Sample 1 - Sample 2   5.34171 11.5916   19.5 D.F.

Conf. Interval for Ratio of Variances: 0   Percent
                 Sample 1 Sample 2

Hypothesis Test for HO: Diff = 0   Computed t statistic = -5.45589
                vs Alt: NE   Sig. Level = 9.20825E-7
                at Alpha = 0.05   so reject HO.

	Gp.A PaCO2	Gp.C PaCO2	Pooled
Sample Statistics: Number of Obs.	35	18	53
Average	30.8571	29.7222	30.4717
Variance	28.0084	21.0359	25.6843
Std. Deviation	5.2923	4.5865	5.06796
Median	30	30	30

Conf. Interval For Diff. in Means: 95   Percent
 (Equal Vars.)   Sample 1 - Sample 2   -1.81679 4.08663   51 D.F.
 (Unequal Vars.) Sample 1 - Sample 2   -1.70372 3.97356   39.1 D.F.

Conf. Interval for Ratio of Variances: 0   Percent
                 Sample 1

Hypothesis Test for HO: Diff = 0   Computed t statistic = 0.524445
                vs Alt: NE   Sig. Level = 0.602383
                at Alpha = 0.05   so do not reject HO.

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Post-onset perfusion PaCO2 change   Gp. A   Gp.B   Pooled

Sample Statistics:		Gp. A	Gp.B	Pooled
	Number of Obs.	35	30	65
	Average	18.9143	7.8	13.7846
	Variance	112.551	29.5448	74.342
	Std. Deviation	10.609	5.43552	8.62218
	Median	17	7	12

Conf. Interval For Diff. in Means: 95   Percent

 (Equal Vars.)   Sample 1 - Sample 2   6.82636 15.4022   63 D.F.

 (Unequal Vars.) Sample 1 - Sample 2   7.00116 15.2274   52.3 D.F.

Hypothesis test for H0:   Diff = 0   Computed t statistic = 5.18087

           vs Alt: NE   Sig. Level = 2.55909E -6

         at Alpha = 0.05   so reject H0

Regression Analysis – Linear model: Y = a+bX   (A1 – 5)

Dependent variable: Pre-perfusion PaCO2

Independent variable: Post-operative neuropsychometric deficit

Parameter	Estimate	Standard Error	T Value	Prob. Level
Intercept	39.9776	0.561177	71.2388	0
Slope	-2.43028	0.18141	-13.3966	0

Analysis of Variance

Source	Sum of Squares	Df	Mean Square	F-Ratio	Prob. Level
Model	1629.2253	1	1629.2253	179.4699	.00000
Error	571.91316	63	9.07799		
Total (Corr.)	2201.1385	64			

Correlation Coefficient = -0.860334   R-squared = 74.02 percent

Stnd. Error of Est. = 3.01297

Regression Analysis – Linear model: Y = a+bX   (A1 – 6)

Dependent variable: Post onset perfusion change in PaCO2

Independent variable: Post-operative neuropsychometric deficit

Parameter	Estimate	Standard Error	T Value	Prob. Level
Intercept	3.82666	0.921661	4.15191	1.00927E-4
Slope	4.31511	0.297943	14.483	0

Analysis of Variance

Source	Sum of Squares	Df	Mean Square	F-Ratio	Prob. Level
Model	5136.3138	1	5136.3138	209.7581	.00000
Error	1542.6708	63	24.4868		
Total (Corr.)	6678.9846	64			

Correlation Coefficient = 0.876941   R-squared = 76.90 percent

Stnd. Error of Est. = 4.94842

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Normal Probability Plot

B:GA.VAR2,B:GB.VAR2,B:GC.VAR2
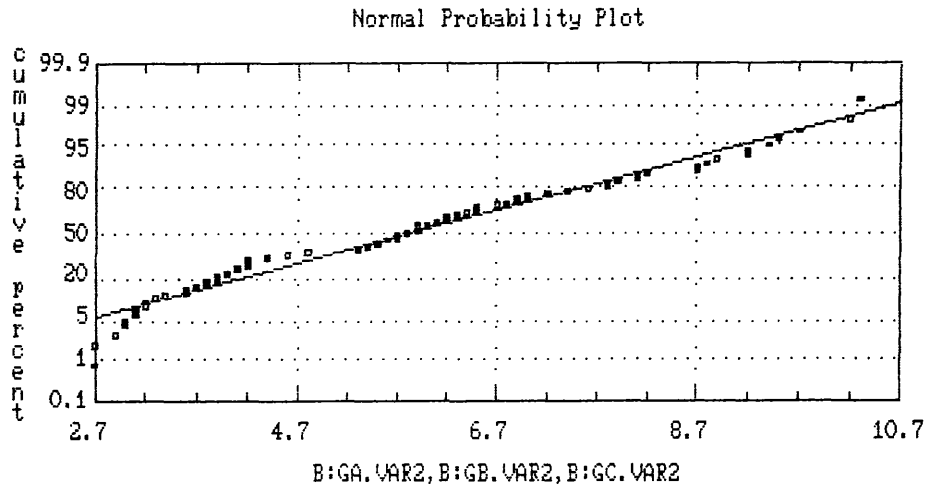
Estimated KOLMOGOROV statistic DPLUS = 0.109838
Estimated KOLMOGOROV statistic DMINUS = 0.105971
Estimated overall statistic DN = 0.109838
Approximate significance level = 0.999995

```
                  Gp.A(A-v02)  Gp.B(A-v02)  Pooled
Sample Statistics: Number of Obs.      35          30          65
                   Average         6.69714     3.94667     5.42769
                   Variance        1.78793     0.819816    1.34229
                   Std. Deviation  1.33714     0.905437    1.15857
                   Median          6.5         3.9         5.5
```

Conf. Interval For Diff. in Means: 95   Percent
  (Equal Vars.)   Sample 1 - Sample 2   2.1743 3.32665   63 D.F.
  (Unequal Vars.) Sample 1 - Sample 2   2.19022 3.31073   60.0 D.F.

Conf. Interval for Ratio of Variances: 0   Percent
                  Sample 1 Sample 2

Hypothesis Test for HO: Diff = 0   Computed t statistic = 9.56791
                 vs Alt: NE   Sig. Level = 6.81677E -14
              at Alpha = 0.05   so reject HO.

            Two-Sample Analysis Results   (A1 - 9)

                  Gp.B(A-v)   Gp.C(A-v)   Pooled
Sample Statistics: Number of Obs.   30   18   48
                   Average   3.94667   7.32222   5.2125
                   Variance   0.819816   4.22301   2.07752
                   Std. Deviation 0.905437   2.055   1.44136
                   Median   3.9   6.8   4.2
```

Conf. Interval For Diff. in Means:     95    Percent
  (Equal Vars.)    Sample 1 - Sample 2   -4.24076 -2.51035     46 D.F.
  (Unequal Vars.)  Sample 1 - Sample 2   -4.44008 -2.31103   21.0 D.F.

Conf. Interval for Ratio of Variances:  0     Percent
                  Sample 1  Sample 2


Hypothesis Test for HO: Diff = 0        Computed t statistic = 6.07061
                 vs Alt: NE             Sig. Level = 1.53182E-7
              at Alpha = 0.05           so reject HO.

|                              | Gp.A(A-v)O2ct. | Gp.C(A-v)O2ct. | Pooled  |
|------------------------------|----------------|----------------|---------|
| Sample Statistics: Number of Obs. | 35       | 15             | 50      |
| Average                      | 6.73143        | 6.82667        | 6.76    |
| Variance                     | 1.83634        | 3.53067        | 2.33052 |
| Std. Deviation               | 1.35511        | 1.87901        | 1.5266  |
| Median                       | 6.5            | 6.5            | 6.5     |

```
Conf. Interval For Diff. in Means:     95    Percent
 (Equal Vars.)     Sample 1 - Sample 2  -1.0427
 (Unequal Vars.)  Sample 1 - Sample 2   -1.21285

Conf. Interval for Ratio of Variances:  0    Percent
               Sample 1  Sample 2


Hypothesis Test for H0: Diff = 0       Computed t statistic = -0.202153
               vs Alt: NE              Sig. Level = 0.840652-7
           at Alpha  = 0.05    so do not reject H0.
```

	Gp.A deficit	Gp.A no deficit	pooled
Sample Statistics: Number of Obs.	25	10	35
Average	7.156	5.55	6.69714
Variance	1.3409	1.13167	1.28384
Std. Deviation	1.15797	1.0638	1.13307
Median	7	5.7	6.5

```
Conf. Interval For Diff. in Means:     95    Percent
 (Equal Vars.)     Sample 1 - Sample 2  0.743258 2.46874     33 D.F.
 (Unequal Vars.)  Sample 1 - Sample 2   0.747858 2.46414   18.0 D.F.
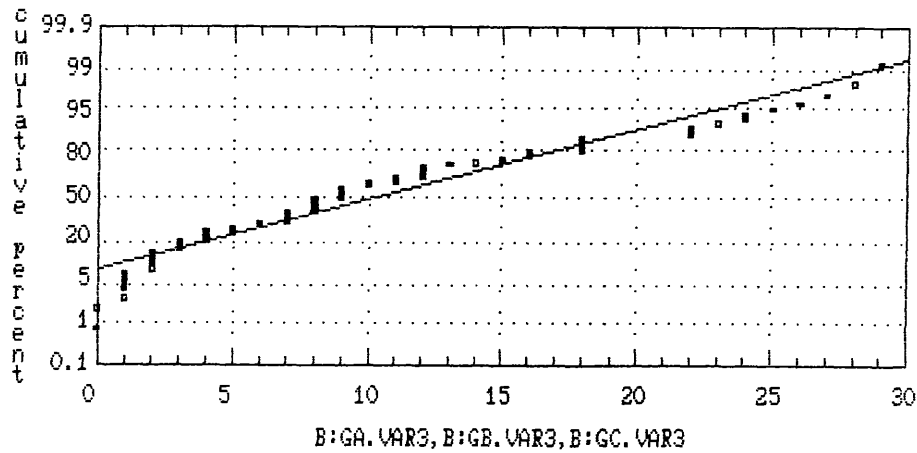
Conf. Interval for Ratio of Variances:  0    Percent
               Sample 1
```

		Gp.A mean A-vO2 ct.diff/perfusion	Gp.B A-vO2 ct./perfusion	Pooled
Sample Statistics:	Number of Obs.	35	30	65
	Average	3.10571	3.05333	3.08154
	Variance	0.167613	0.0722299	0.123707
	Std. Deviation	0.409406	0.268756	0.35172
	Median	3.1	3.05	3.1

Conf. Interval For Diff. in Means: 95   Percent
  (Equal Vars.)   Sample 1 - Sample 2   -0.122534 0.227296   63 D.F.
  (Unequal Vars.) Sample 1 - Sample 2   -0.117394 0.222156   59.2 D.F.

Conf. Interval for Ratio of Variances: 0   Percent
                  Sample 1

Regression Analysis - Linear model: Y = a+bX   (A1 - 13)

Dependent variable: Pre-perfusion (A-v)O2 ct.differences
Independent variable: Post-operative neuropsychometric deficit

Parameter	Estimate	Standard Error	T Value	Prob. Level
Intercept	3.83026	0.202668	18.8992	0
Slope	0.69222	0.0655159	10.5657	1.33227E-15

Analysis of Variance

Source	Sum of Squares	Df	Mean Square	F-Ratio	Prob. Level
Model	132.17670	1	132.17670	111.63354	.00000
Error	74.593456	63	1.184023		
Total (Corr.)	206.77015	64			

Correlation Coefficient = 0.799528   R-squared = 63.92 percent
Stnd. Error of Est. = 1.08813

Normal Probability Plot

B:GA.VAR3, B:GB.VAR3, B:GC.VAR3

Estimated KOLMOGOROV statistic DPLUS = 0.0741698
Estimated KOLMOGOROV statistic DMINUS = 0.0968143
Estimated overall statistic DN = 0.0968143
Approximate significance level = 0.999999

Normal Probability Plot

B:GA.VAR6, B:GB.VAR6, B:GC.VAR6

Estimated KOLMOGOROV statistic DPLUS = 0.121785
Estimated KOLMOGOROV statistic DMINUS = 0.0926123
Estimated overall statistic DN = 0.121785
Approximate significance level = 1

Dependent variable: Pre-perfusion PaCO2
Independent variable: A-v O2 ct.differences

Parameter	Estimate	Standard Error	T Value	Prob. Level
Intercept	50.2521	1.03868	48.3806	0
Slope	-2.92627	0.181803	-16.0958	0

Analysis of Variance

Source	Sum of Squares	Df	Mean Square	F-Ratio	Prob. Level
Model	1770.5804	1	1770.5804	259.0744	.00000
Error	430.55803	63	6.83425		
Total (Corr.)	2201.1385	64			

Correlation Coefficient = -0.89688   R-squared = 80.44 percent
Stnd. Error of Est. = 2.61424

Two-Sample Analysis Results   (A1 - 16)

	Gp.A CeVenPr	Gp.B CeVenPr	Pooled
Sample Statistics: Number of Obs.	35	30	65
Average	16.4571	8.26667	12.6769
Variance	46.7849	9.02989	29.4056
Std. Deviation	6.83995	3.00498	5.42269
Median	16	8	11

Conf. Interval For Diff. in Means: 95   Percent
 (Equal Vars.)   Sample 1 - Sample 2   5.4937 10.8873   63 D.F.
 (Unequal Vars.) Sample 1 - Sample 2   5.61706 10.7639   48.2 D.F.

Conf. Interval for Ratio of Variances: 0   Percent
                 Sample 1

Comparison of Two Samples   (A1 - 17)

Sample 1: Gp.A Cerebral Perfusion Pressures

Sample 2: GP.B Cerebral Perfusion Pressures

Test based on: Pairs

Average rank of first group = 18 based on 35 values.
Average rank of second group = 44.5 based on 18 values.
Large sample test statistic Z = 5.90848
Two-tailed probability of equaling or exceeding Z = 3.46447E-9

Comparison of Two Samples   (A1 -18)

Sample 1: Gp.A CerVenPressure / deficit

Sample 2: Gp.A CerVenPressure / no deficit

Test based on: Pairs

Average rank of first group = 22.12 based on 25 values.
Average rank of second group = 7.7 based on 10 values.
Large sample test statistic Z = -3.76072
Two-tailed probability of equaling or exceeding Z = 1.69477E-4

NOTE: 35 total observations.

Comparison of Two Samples   (A1 - 19)

Sample 1: Gp.A CPP / deficit

Sample 2: GP.A CPP / no deficit

Test based on: Pairs

Average rank of first group = 14.04 based on 25 values.
Average rank of second group = 27.9 based on 10 values.
Large sample test statistic Z = 3.59974
Two-tailed probability of equaling or exceeding Z = 3.18612E-4

NOTE: 35 total observations.

Regression Analysis – Linear model: Y = a+bX   (A1 – 20)

Dependent variable: Jugular bulb pressure

Independent variable: post-operative deficit

Parameter	Estimate	Standard Error	T Value	Prob. Level
Intercept	6.72493	0.778702	8.63608	2.77067E-12
Slope	2.5792	0.251729	10.2459	4.88498E-15

Analysis of Variance

Source	Sum of Squares	Df	Mean Square	F-Ratio	Prob. Level
Model	1834.9994	1	1834.9994	104.9794	.00000
Error	1101.2160	63	17.4796		
Total (Corr.)	2936.2154	64			

Correlation Coefficient = 0.79054   R-squared = 62.50 percent
Stnd. Error of Est. = 4.18086

Regression Analysis – Linear model: Y = a+bX   (A1 – 21)

Dependent variable: Jugular bulb pressure

Independent variable: Pre-perfusion PaCO2

Parameter	Estimate	Standard Error	T Value	Prob. Level
Intercept	46.0641	2.74363	16.7895	0
Slope	-0.971427	0.078708	-12.3422	0

Analysis of Variance

Source	Sum of Squares	Df	Mean Square	F-Ratio	Prob. Level
Model	2077.1508	1	2077.1508	152.3291	.00000
Error	859.06454	63	13.63595		
Total (Corr.)	2936.2154	64			

Correlation Coefficient = -0.841085   R-squared = 70.74 percent
Stnd. Error of Est. = 3.69269

Regression Analysis – Linear model: Y = a+bX   (A1 – 22)

Dependent variable: Jugular bulb pressure

Independent variable: Change PaCO2 with onset perfusion

Parameter	Estimate	Standard Error	T Value	Prob. Level
Intercept	4.75271	0.712226	6.67304	1.14102E-7
Slope	0.574859	0.0416251	13.8104	0

Analysis of Variance

Source	Sum of Squares	Df	Mean Square	F-Ratio	Prob. Level
Model	2207.1593	1	2207.1593	190.7275	.00000
Error	729.05608	63	11.57232		
Total (Corr.)	2936.2154	64			

Correlation Coefficient = 0.867008   R-squared = 75.17 percent
Stnd. Error of Est. = 3.40181

Regression Analysis – Linear model: Y = a+bX   (A1 – 23)

Dependent variable: Jugular bulb pressure

Independent variable: CPP immediately post perfusion

Parameter	Estimate	Standard Error	T Value	Prob. Level
Intercept	40.3086	1.93936	20.7845	0
Slope	-0.603919	0.0414517	-14.5692	0

Analysis of Variance

Source	Sum of Squares	Df	Mean Square	F-Ratio	Prob. Level
Model	2264.1963	1	2264.1963	212.2624	.00000
Error	672.01909	63	10.66697		
Total (Corr.)	2936.2154	64			

Correlation Coefficient = -0.878139   R-squared = 77.11 percent
Stnd. Error of Est. = 3.26603

Regression Analysis - Linear model: Y = a+bX   (A1 - 24)

Dependent variable: CPP immediately following onset perfusion

Independent variable: Incidence of post-operative deficit

Parameter	Estimate	Standard Error	T Value	Prob. Level
Intercept	54.455	1.12206	48.5313	0
Slope	-3.7705	0.362725	-10.3949	2.66454E-15

Analysis of Variance

Source	Sum of Squares	Df	Mean Square	F-Ratio	Prob. Level
Model	3921.6063	1	3921.6063	108.0542	.00000
Error	2286.4553	63	36.2929		
Total (Corr.)	6208.0615	64			

Correlation Coefficient = -0.794793   R-squared = 63.17 percent
Stnd. Error of Est. = 6.02436

Regression Analysis - Linear model: Y = a+bX   (A1 - 25)

Dependent variable: CFAM changes

Independent variable: Post-operative deficit

Parameter	Estimate	Standard Error	T Value	Prob. Level
Intercept	0.21952	0.121535	1.80623	0.0756596
Slope	0.324875	0.0392883	8.26898	1.20883E-11

Analysis of Variance

Source	Sum of Squares	Df	Mean Square	F-Ratio	Prob. Level
Model	29.113754	1	29.113754	68.376013	.00000
Error	26.824707	63	.425789		
Total (Corr.)	55.938462	64			

Correlation Coefficient = 0.721429   R-squared = 52.05 percent
Stnd. Error of Est. = 0.652525

Comparison of Two Samples   (A1 - 26)

Sample 1: CFAM changes GP.A

Sample 2: CFAM changes GP.B

Test based on: Pairs

Average rank of first group = 37.5286 based on 35 values.
Average rank of second group = 27.7167 based on 30 values.
Large sample test statistic Z = -2.19938
Two-tailed probability of equaling or exceeding Z = 0.027851

Comparison of Two Samples   (A1 - 27)

Sample 1: CFAM changes Gp.A

Sample 2: CFAM changes GP.C

Test based on: Pairs

Average rank of first group = 31.1 based on 35 values.
Average rank of second group = 19.0278 based on 18 values.
Large sample test statistic Z = -2.84347
Two-tailed probability of equaling or exceeding Z = 4.46258E-3

Comparison of Two Samples   (A1 - 28)

Sample 1: CFAM changes Gp.B

Sample 2: CFAM changes Gp.C

Test based on: Pairs

Average rank of first group = 25.6833 based on 30 values.
Average rank of second group = 22.5278 based on 18 values.
Large sample test statistic Z = -0.835638
Two-tailed probability of equaling or exceeding Z = 0.403356

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