THE REFINEMENT AND ASSESSMENT OF A TECHNIQUE FOR GENERAL ANAESTHESIA MAINTENANCE BY FEEDBACK CONTROL

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Summary

The objectives are to improve the quality of control obtained in a previous work which developed a system to maintain anaesthesia by feedback control of systolic arterial pressure (SAP). The study also aims to further validate the anaesthetic state produced by this system.

The relationship of arterial pressure (AP) on admission to hospital and in the anaesthetic room to resting values is examined in a preliminary study, bearing in mind the recognition of the phenomenon of "white coat hypertension".

Resting SAP, measured by an automatic monitor (Dinamap 1846), is then used to determine target SAP, which is the controlled variable in the feedback control system.

Also, fentanyl analgesia is substituted for morphine in 20 of the 64 patients undergoing anaesthesia in this way. This narcotic has a more rapid onset of action than morphine, and it was thought that this would smooth anaesthesia and improve the SAP control.

There has been no conscious awareness in patients undergoing anaesthesia by this method, and in this work we aim to further investigate the level of cognitive function during anaesthesia. We use a sensitive technique based on homophone priming in 24 patients.

The anaesthetic state is assessed by the quality of SAP control, the absence of conscious awareness, the safety of the recovery period, and by the value of physiological variables during anaesthesia.

INTRODUCTION

INTRODUCTION

This work develops the concept that a fully reproducible, clinically acceptable "state of anaesthesia" may eventually lead to a tighter definition of anaesthesia. Existing methods, purporting to measure anaesthesia, could be validated.

The Definition of Anaesthesia

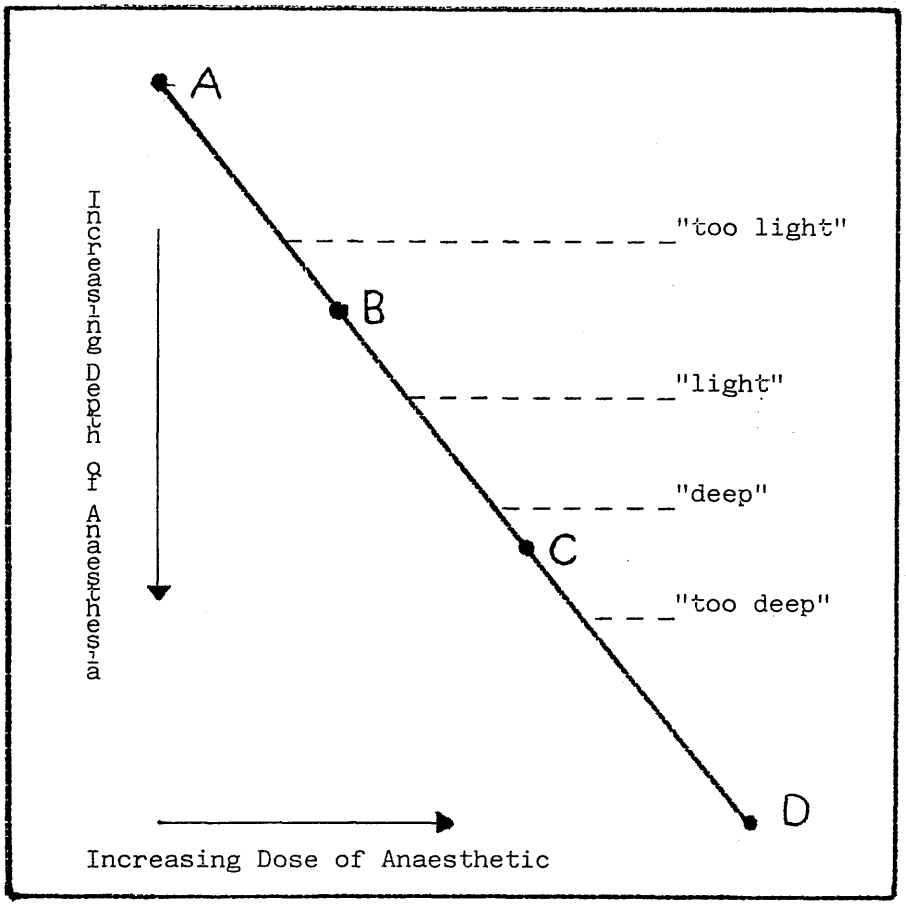
At present, a working definition of clinically acceptable anaesthesia is " the state which satisfies the following criteria;

1. A physiologically acceptable state
2. Facilitation of surgical procedure
3. Absence of awareness
4. A safe, short recovery period."

From this, it follows that clinically acceptable "anaesthesia" will only be an appropriate title after satisfactory recovery has been achieved consequently, and awareness proved absent. Furthermore, the moment of beginning and end of anaesthesia is unclear.

By imagining a line drawn from full consciousness to death by anaesthetic overdose we could represent anaesthesia as part of that line (figure 1). Representation by a line rather than a point means that our criteria are satisfied over a range of points. Also, the boundaries of the line are set by the "tightness" of the definition of anaesthesia; the tighter the definition, or the more strict the criteria, the shorter is the length of the anaesthesia part of the

Figure 1.



A = Fully conscious
B = The beginning of "adequate" anaesthesia
C = The end of "adequate" anaesthesia
D = Death by anaesthetic overdose

AB-Conscious awareness
Autonomic/somatic reflexes largely unattenuated

BC-Adequate anaesthesia
Autonomic/somatic reflexes attenuated
Satisfactory recovery

CD-Vital functions depressed
Prolongued recovery period

imaginary line.

It may be too simplistic to view anaesthesia as a length on one line; it may prove more apt to view anaesthesia as the intersection of several lines (figure 2), each of which represent the criteria to be satisfied and which have complex relationships to one another. For example, let two of these lines represent "physiological variables" and "awareness": a patient's state could lie within the anaesthesia part of "physiological variables" but just short of the anaesthesia part of "awareness" before the surgeons' incision. The response to stimulation (of incision), is enhanced due to the position occupied on the "awareness" line: this directly affects the position occupied on the "cardiovascular variable" line. Essentially, this analogy takes account not only of variability of response between individuals to anaesthetic drugs, but of variable systemic responses within each patient.

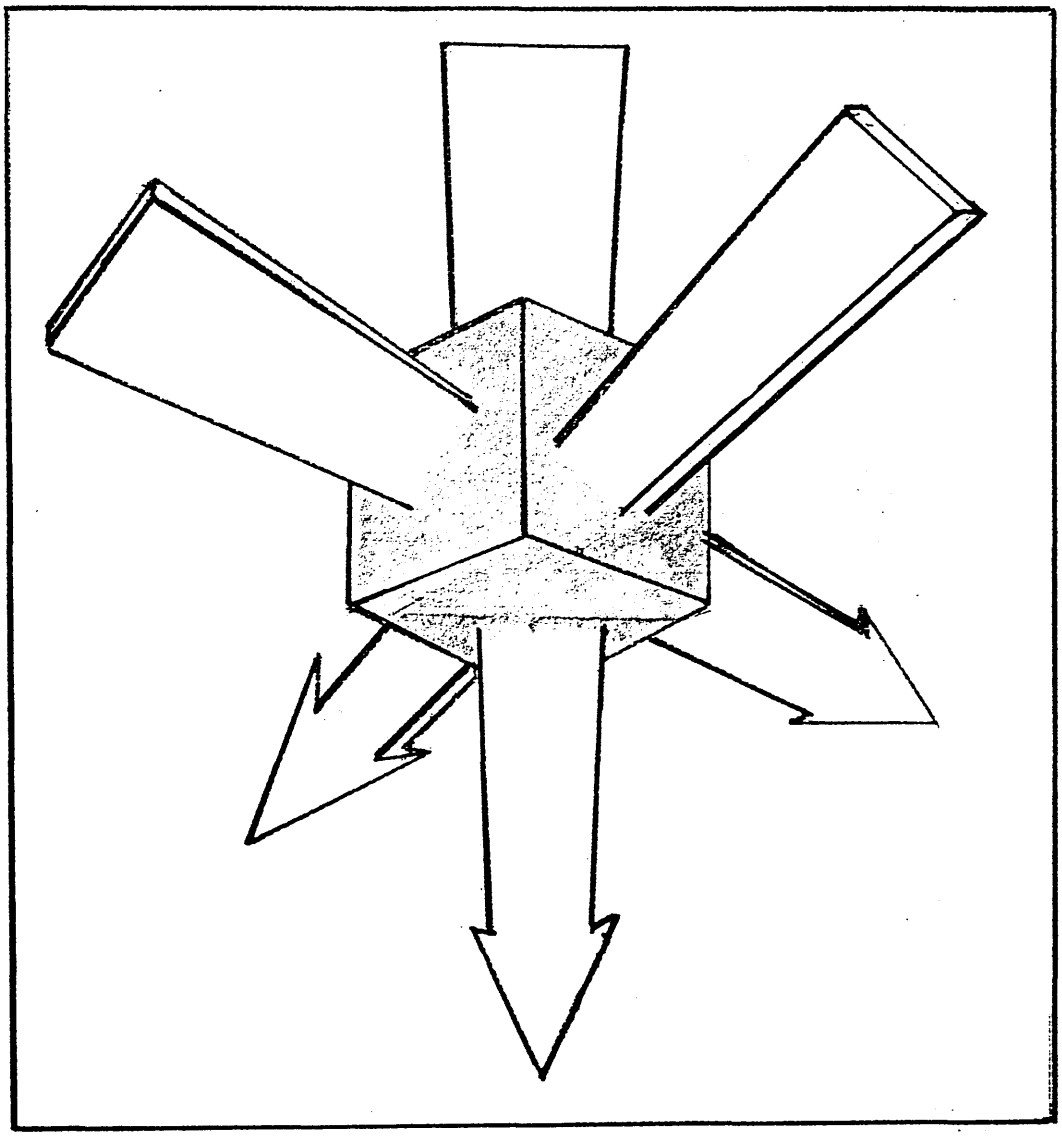
The Definition of Awareness

Awareness could most easily be seen as part of an imaginary line beginning in consciousness and ending somewhere before the portion representing "anaesthesia" (figure 2). Presently, awareness is defined as

> "the ability to recall, with or without prompting, any events which occurred during the period at which it was thought the patient was fully unconscious".

This definition re-iterates the initial difficulty that anaesthesia is a presumptive diagnosis, partially confirmed when awareness is excluded. Two forms of awareness are

Figure 2.



i) The arrows, (three are shown) can be seen to represent various components of anaesthesia, eg, conscious level or physiological variables, each of which has its own continuum.

ii) The shaded box represents the zone within which all the criteria for adequate anaesthesia are satisfied.

iii) The arrows start in the non-anaesthetised state, pass through the zone of adequate anaesthesia, and emerge to descend towards moribundity.

recognised;

1. Spontaneous recall.

In this case the patient remembers events which have taken place at surgery or during the time between administration of anaesthetic agents and commencement of surgery.

2. Sub-conscious or cued recall.

In this case, the patient is unable to volunteer information about perioperative events, but if given a "cue" demonstrates that there has been a degree of perception of the latter. And, the more sensitive the test for cued re-call, the higher is the incidence.

There is evidence, (see later), that awareness during operations can cause syndromes of psychosis, nightmares, panic attacks and insomnia if it is unrecognised. Informing the patient that awareness has occurred is generally effective treatment in these cases. It is also conceivable that patients may not remember being aware, but they have certainly stored, perhaps incompletely, information which could later affect behaviour. So, "sub-conscious awareness" may be clinically significant.

The study of the anaesthetic state

The analysis of anaesthesia may only begin when the state is supposed to exist as we cannot define the true moment of its beginning. To break into this chicken-egg cycle, in every-day practice, we use a set of guidelines for anaesthesia, and every anaesthetist has his own. The formula is the result of

personal experience and learning processes, and is not foolproof: a "good anaesthetic" remains a retrospective diagnosis.

Feedback control of Systolic Arterial Pressure

In this work, we use a "formula" for anaesthesia which was developed by Robb [1], in 1988. The technique involves a programme in BASIC which commands a proportional-integral feedback control system to maintain anaesthesia. The system comprises a Critikon Dinamap, an RML 380ZD computer and a vaporiser controller. Systolic arterial pressure (SAP), the controlled variable, is measured by the Dinamap each minute and the error between SAP and the pre-determined target SAP (TSAP), is calculated. The TSAP is 90% of the predicted SAP, based on an age-sex relationship. The magnitude of the error, the integral component and the proportional gain determine the dose of anaesthetic. The controller automatically adjusts the vaporiser to the correct setting each minute; thus anaesthesia is maintained. The programme also incorporates a rule governing administration of additional narcotic boluses: if the total of each % concentration of isoflurane delivered exceeds 15 over 5 minutes, and each % concentration exceeds 2.5%, the system instructs a narcotic bolus to be given. It is apparent that control is bad if this point is reached. This rule does not operate for ten minutes after a bolus is given.

SAP is routinely monitored during anaesthesia today and provides a cardiovascular window on events occurring in the central nervous system (CNS). However the window does not

show us the entire picture; i.e. the SAP represents the product of reflex reactions to surgical stimuli and effect of anaesthetic drugs on the CNS and cardiovascular system. Many other factors may cloud the picture, e.g. the presence or absence of normovolemia, administration of drugs affecting heart rate, the degree of abnormal "reactivity" seen in the arterial tree of hypertensive patients. For these reasons, SAP as the single controlled variable during anaesthesia can be critisized, but it remains an important guide to the adequacy of anaesthesia in practice: i.e. anaesthesia is inadequate if important physiological variables fall outside acceptable, safe limits.

Robb's technique is suitable for this work because:

1. Computer control provides a highly standardised method of administering anaesthesia and is thus an absolutely reproducible method.
2. Standardised technique speeds up the normally slow learning processes associated with heuristic methods of administering anaesthesia.
3. Until standardisation of anaesthesia is "tight", the validity of methods purporting to measure it cannot be assessed.

Using this system, Robb acheived the aim of controlling SAP in 55 out of 57 patients. However, the "goodness" of control (see below), varied considerably. Anaesthesia was adequate (in respect of all the foregoing criteria), in 53.8% of 52 remaining cases, (the protocol was breached in 3 cases). Adequacy was assessed from criteria based on

1. cardiovascular variables

2. "goodness" of SAP control
3. recovery time
4. absence of awareness

A striking difference in incidence of failure to acheive two or more of the above occurred between the patients who required extra narcotic boluses and those who did not: in the former group 83.3% failed to satisfy two or more of the criteria, compared to 7.5% in the latter. This merely reflects that overall poor SAP control prompts narcotic administration. Also, significantly more of the patients receiving enflurane required additional morphine than those who received isoflurane.

The Aims of The Study

The aims of the work in this study were:-

1. To improve the "goodness" (vide infra) of control of SAP, and
2. To demonstrate the absence of awareness ocurring during anaesthesia produced by the system.

1.Improving the control of SAP.

By improving the "goodness" of control, we may be able to better satisfy our criteria for adequate anaesthesia, and reduce variation in the state we mean to study. The "goodness" of SAP control is assessed by examining all the SAP values and calculating

i) The root mean square deviation (RMSD) of SAP.

This corresponds to the better known statistical standard

deviation, but here the "mean" is replaced by the TSAP.

ii) The points ratio (PR).

This is the ratio of % number of points above TSAP to that below TSAP.

iii) The mean deviation from TSAP.

This is the mean of the deviation of all SAP points during the control period from TSAP. The units are mmHg, and it may be positive or negative.

The best SAP control was acheived by Robb in patients who received isoflurane, rather than enflurane. Again, of that group, the control was better in those who did not require additional narcotic boluses. In this work, the 65 patients studied all received isoflurane. Also, two modifications to the original technique are explored with the aim of improving control;

1. The selection of the target SAP, or TSAP.
2. The use of fentanyl, a narcotic with a shorter latency of onset than morphine.

1. The selection of the TSAP.

Values for SAP based on age-sex relationships are based on population studies. There are two reasons for concern here;

1. Increasing evidence suggests that arterial pressure values obtained by random measurements may not represent true resting pressure.
2. Age and sex are the only considered factors, and individual variation is unaccounted for.

Therefore, we made a preliminary investigation of pre-operative arterial pressures with two aims in mind: first, to confirm that the presence of a doctor could transiently raise

arterial pressure, and second to estimate true resting AP. We could then not only examine the relationship between random and resting AP, but also obtain resting AP to use as TSAP.

In 40 of 64 patients studied, 90% of resting SAP provided the target for feedback control. The rationale that anaesthesia should physiologically resemble sleep, and that SAP asleep is even lower than resting SAP lies behind the use of 90% of resting SAP as a target. However, in the presence of surgical stimuli these stipulations need not necessarily hold true, and we chose to use resting SAP per se in 20 patients. Furthermore, TSAP based on 90% resting SAP tended to be lower than TSAP based on 90% SAP predicted from tables; by using resting SAP per se, the higher value of the two, we would hope to reduce any tendency to overdose by the system.

2. The use of fentanyl.

Analgesic drugs are used to reduce the pain of surgery, and during anaesthesia, also to reduce the requirement of anaesthetic agents. Indeed, some have used narcotic analgesic drugs in high doses with nitrous oxide alone to avoid using volatile agents. Clearly, these drugs contribute to the level of anaesthesia produced by a given brain concentration of volatile agent; the higher the dose of narcotic, the less volatile agent required to some extent. It would be desirable, therefore, to have a steady background level of narcotic when assessing the effects of a volatile agent on SAP in a feedback control system.

In Robb's work, 0.1mg/kg morphine at induction formed part of the anaesthetic technique. Although the system commenced immediately after entry into theatre, the results were

calculated using data obtained after the first ten minutes. This allowed the system to gain control and he presumed adequate anaesthesia only after this period. The use of morphine at induction, however, means that the CNS narcotic level both rises and falls after the initial 10 minute period. This reflects the relatively low lipid solubility of the drug causing slow penetration into the CNS. This is important because we have already said that the concentration of narcotic affects anaesthetic requirement. Therefore, by choosing a narcotic which penetrates the CNS more quickly we could eliminate the phase in our examination where narcotic CNS concentration is rising.

Fentanyl, a relatively highly fat soluble synthetic narcotic drug penetrates the CNS far more quickly than morphine and has maximal effect after 6 minutes.

The second reason for selecting fentanyl is that its effects on the cardiovascular system are less than those of morphine. This increases the confidence in SAP as a measure of anaesthesia when using fentanyl rather than morphine. A narcotic with no cardiovascular side-effects infused to effect a steady-state CNS concentration would be ideal. Twenty patients in the study received fentanyl, and in this group, TSAP was 90% of resting SAP.

The Investigation of Awareness

Our definition of anaesthesia, (see above), is a broad but practical one; it includes all aspects of the state which are necessary in practice. However, Prys-Roberts argues that the definition of anaesthesia applies only in terms of the

ability of the patient to consciously perceive or recall noxious surgical stimuli. The remaining requirements are met pharmacologically, either by the side effects of anaesthetic agents or by specific effects of other drugs. Thus anaesthetic agents should specifically prevent conscious awareness and recall only.

He goes on to say that "loss of consciousness is a threshold event" and "it follows that anaesthesia is an all or none phenomenon", there being no such thing as "depth of anaesthesia". There are several points here; firstly, loss of consciousness may not be a threshold event, but graded in terms of response. Consciousness itself cannot be defined objectively, except in terms of response i.e. conscious behaviour patterns. Secondly, conscious and unconscious awareness themselves represent a dose-related graded response to anaesthetic agents. Therefore, this definition of anaesthesia is another way of expressing anaesthesia beginning at a point on the imaginary line (see above) where awareness ends. Furthermore, this argument re-iterates the retrospective nature of the diagnosis "anaesthesia", and is of little help in understanding the spectrum of states for which anaesthesia may easily be mistaken.

Awareness of surgical stimuli is a terrifying and painful experience; the patient, unable to communicate, hears conversation and feels surgical manipulations. In less well understood forms of awareness, long-term psychiatric morbidity may result. On the imaginary line from fully conscious through anaesthesia, we do not know exactly where conscious awareness ends (and thus anaesthesia begins), nor

if unconscious awareness does end somewhere on the anaesthesia part of our line.

Presently, the ability to detect awareness depends on the sensitivity and specificity of the methods employed; simple tests of memory may be unable to retrieve information from events at anaesthesia. However, this information may be retrieved using more sensitive methods. Thus information is stored (completely or incompletely) but which may subsequently emerge to influence behaviour postoperatively, and this can be assessed objectively.

Understandably, the public at large as well as the medical, (and now legal), profession concern themselves with the problem of awareness under anaesthesia. This is supported by much media coverage in this area. In this study, we use a technique involving "homophone priming" to test for awareness in 24 patients receiving isoflurane in the feedback control of SAP.

Homophone priming is a sensitive technique because the task performed by the patient takes place at a sub-conscious level. It therefore is independant of performance per se. We looked for a difference in awareness levels at high and low end-tidal concentrations of isoflurane. We were also able to compare the control of SAP to the level of awareness.

Of the total of 64 patients anaesthetised by the system, only one reported recall spontaneously, although all were directly questioned. The patient reported a dream during which she had the impression that a cut was being made in her abdomen. She had no other sensation, e.g. hearing voices, anxiety, and could not be sure whether this dream had occurred under anaesthesia or not. It is likely that she had

indeed experienced this as a form of awareness, and she was advised so. However, clinical signs did not indicate retrospectivly, (or indeed at the time) that anaesthesia would turn out to be an inappropriate title.

CHAPTER 1

THE VARIABILITY OF ARTERIAL PRESSURE MEASUREMENTS

The Significance of Arterial Pressure Measurement

We have known for over a century that chronic elevation of arterial pressure or hypertension lead to target-organ damage and increased mortality and morbidity [2]. Arterial pressure, (AP), measurement aims to identify those at risk of developing established hypertension and related complications, such as left ventricular hypertrophy, cerebro-vascular accident (stroke), or renal damage. These patients then receive anti-hypertensive management and therapy.

Also, mortality and morbidity associated with surgery and anaesthesia in the face of uncontrolled hypertension are significantly increased [3,4,5,6,7,8,9]; it is important to distinguish such patients pre-operatively, as the risks may be less if AP is controlled.

Furthermore, during anaesthesia, AP provides a guide to the adequacy of the anaesthetic state. This follows because in the present definition of anaesthesia, physiological variables must remain at acceptable values. What is acceptable is obviously a function of pre-existing patient factors, e.g. hypertension, and also of the clinical opinion of each anaesthetist. Clinical opinions are subjective, and thus allow variation within the limits of the foregoing definition. The amount of variation of "acceptability", therefore, varies inversely with the "tightness" of the definition.

The misdiagnosis of Hypertension

Many different "cut-off" points in AP have been proposed [10], above which the patients were to be labelled hypertensive (table 1). At present, in the United States, hypertension is diagnosed if AP is >140/90mmHg on the initial clinic visit [11]. However, there is a widely recognised discrepancy between random pressure measurements, such as these, and true daily average values. This goes beyond both the natural daily variation within individuals [12], and the tendency of AP to fall on repeated measurements [13]. As long ago as 1940 [14], it was suspected that, for some patients, the doctor's office may be the only place where the pressure is high. The introduction of automatic AP measuring equipment [15] has confirmed that ambulatory 24-hour AP is often normal in some patients, who tend to be hypertensive at clinics. This group is thought to include from 20-43% of all those seen with raised pressure at clinics in the U.S.A. [16,17,18]. The phenomenon is known as "white-coat hypertension" (WCH). The subjects have little excess risk of target-organ damage, [19,20,21,22,23], reinforcing that the latter reflects long-term AP elevation. However, it is important to identify this group because anti-hypertensive therapy would be inappropriate and may be dangerous, particularly in the elderly [24]. There is growing concern that excessive lowering of diastolic AP may compromise ventricular function and result in myocardial ischaemia [25,26]: this seems to depend on the degree of concomitant coronary artery stenosis [27].

The importance of misdiagnosis of hypertension extends to surgery and anaesthesia; on the basis of random preoperative

Table 1: Arterial pressure limits for normotension.

Systolic/diastolic AP cut-off point.	Source
120/80	Robinson, Brucer 1939
130/70	Browne to 1947
140/80	Ayman 1934
140/90	Perera 1948
150/90	Thomas 1952
160/100	Bechgaard 1946
180/100	Burgess 1948
180/110	Evans 1956

Some of several different proposed "cut-off" points, above which hypertension may be diagnosed. (from Pickering, 1972, [10])

pressure measurements, a patient found hypertensive may be postponed from surgery because of the increased risk, (vide supra). If further investigation reveals no evidence of hypertension, the inconvenience and stress for patients, and the waste of valuable theatre and clinic time is unnecessary.

Factors resulting in variations in AP values

There is an ever-increasing number of manual and automatic devices for measuring AP. The automated devices are technically complex and costly and are often successfully marketed without independant validation. Thus, we rely on clinicians to validate the accuracy and reliability of the various pieces of equipment.

In general, we recognise that variability of AP measurement stems from three main areas:-

i) Method of measurement

ii) Observer error

iii) Patient related factors

i) The method of measurement

Direct intra-arterial monitoring

The gold standard of AP measurement is that measured by arterial cannulation. The intra-arterial cannula, the fluid-filled manometer tubing, a transducer and the recording apparatus comprise a simple second-order system [28]. This is known as the "direct" method of intra-arterial pressure monitoring, and it allows continuous monitoring, accurately following rapid and large swings, without being subject to observer error. The pressure varies depending on the artery

used; systolic AP is higher, mean AP is lower, and diastolic is lower as the distance from the aortic valve increases. Information is given as a waveform, and the instantaneously highest and lowest points are systolic and diastolic pressure, respectively.

Sources of error are inaccurate calibration, inappropriate damping or an unsuitable frequency response of the measuring system. Under-damping results in "overshoot", where systolic pressure is over-estimated and diastolic AP underestimated. Over-damping not only results in under-estimation of systolic AP, but also reduces the definition of the wave-form and the information which we derive from it. In general, the higher the frequency response of the system, the less the waveform is detrimentally affected by an inappropriate damping coefficient, (figure 3). The dynamic response of direct AP measuring systems may be optimised using various mechanical compensation methods, [29,30].

However, the process of cannulating an artery is itself an invasive procedure and carries the risk of complications not associated with non-invasive methods of AP measurement (table 2).

Indirect methods of AP measurement

Auscultatory and oscillometric methods measure blood pressure non-invasively. Both may be performed manually or automatically, but manual techniques give rise to more "observer errors", (see below). The cuffs referred to in the text are placed around part of a limb, usually the upper arm, but larger cuffs allow AP to be measured in the thigh.

Table 2: Complications of arterial cannulation.

1. Local haematoma formation, (with compression of surrounding tissues, and possible distal ischaemia)	due to failure to compress the artery after removal of puncturing cannula/needle.
2. Distal ischaemia,	if the cannulated vessel becomes occluded by the cannula, thrombosis, or if manipulation causes arterial spasm or physical trauma.
3. Infection i)	around the site of skin puncture.
ii)	ascending from flushing line to become systemic after colonisation of thrombus in the cannula itself.
4. Extravasation,	due to unnoticed disconnection of manometer tubing.

Table 2.

Figure 3.

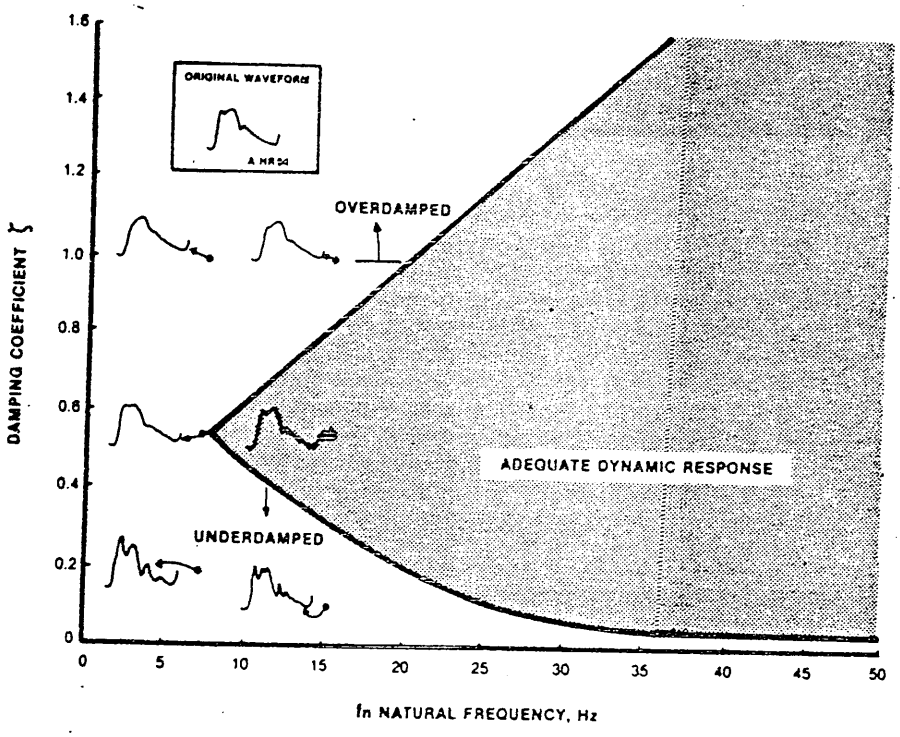


Figure 3

The plot shows the ranges of damping co-efficients and natural frequencies which do not distort the pressure wave-form (grey area).

The lower left area represents under-damping; over-shoot and "ringing" distort the wave-form.

The upper area represents overdamping; fine detail is lost, and systolic pressure is reduced.

1. Auscultation

The Korotkoff method [31] is widely used to measure AP by auscultation. This method makes use of a Riva-Rocci cuff, a column of mercury, (sphygmomanometer), and a device for detecting Korotkoff sounds (figure 4), over an artery distal to the cuff. These sounds are caused by turbulent, intermittent arterial blood flow as cuff pressure is allowed to fall from above to below arterial pressure. The sounds are classified into V phases; systolic AP corresponds well to phase I, and the diastolic pressure corresponds to phase IV. The average difference between phases IV and V values is 5mmHg, and for clinical purposes phase V may also be used to mark diastolic pressure.

The device used to detect the Korotkoff sounds may be a stethoscope or a doppler ultrasonic probe. Alternatively, pulsations may be palpated distal to the occluding cuff by an ultrasonic probe or photo-electric plethysmography.

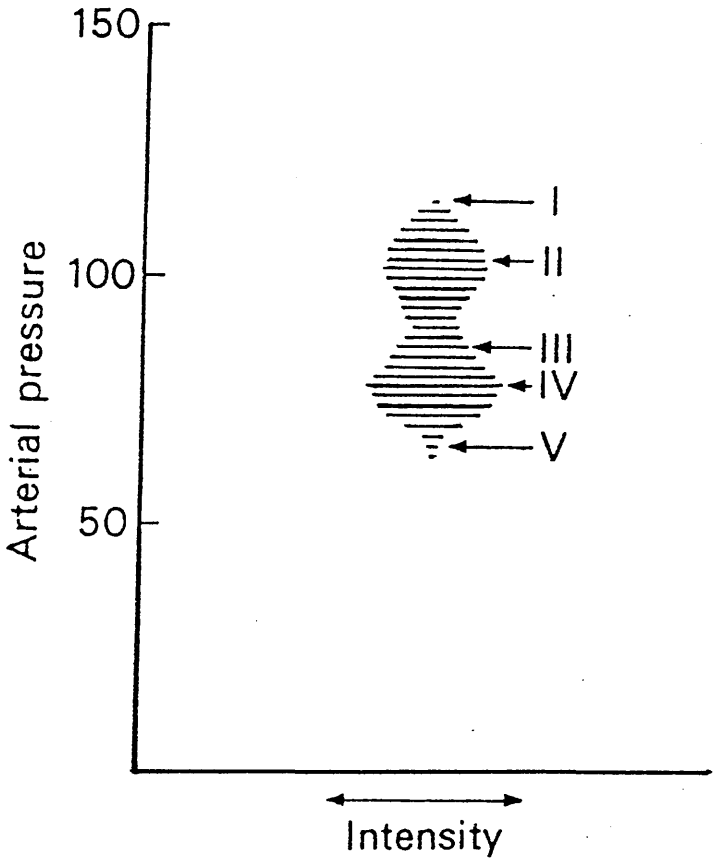
Van Bergen [32] compared auscultation with direct AP measurement; the errors for diastolic and systolic AP were as much as 20% and 30% respectively. These are extremes of inaccuracy: more commonly the error is of the order of 4 to 5 mmHg too low and 9 mm Hg too high for systolic and diastolic pressures, respectively.

Factors affecting the accuracy of auscultatory techniques include the following;-

1. The ratio of cuff width to arm circumference.

This should be from 0.4 to 0.6. Too low a ratio results in a falsely high pressure measurement, or the "fat-arm syndrome". Here, the cuff pressure is applied over a

Figure 4. The Korotkoff sounds.



I Clear tapping sounds, synchronous with heart beats.

II Quietening of these sounds.

III Again the sounds become louder, with a tapping quality.

IV Sudden muffling of these sounds.

V Sounds disappear altogether.

relatively smaller surface area and is dissipated by soft tissue in the arm before the artery is occluded. If the ratio is too high the reverse is true.

2. The ratio of the inflatable bladder to arm circumference.

The bladder inside the cuff should measure at least 80% of the arm circumference [33].

3. Gravitational effects.

Due to gravity, arterial pressure decreases by 2mmHg for every inch relative to the starting point. To avoid gravitational effects, the arm used for measurement, along with the base of the column of mercury, should be at the level of the heart, (aortic valve).

4. Speed of cuff deflation.

Using palpation of the distal arterial pulse alone, it is possible to under-estimate systolic pressure. This is because of the delay for the pulse to arrive as the cuff is still being let down and read simultaneously. The more quickly the cuff is let down, the greater is the problem. Petrie and O'Brien [33] recommend the speed of deflation should not exceed 2-3mmHg per second. The London School of Hygiene sphygmomanometer [34] automatically maintains speed of cuff deflation at 2mmHg per second.

5. Other

The hearing ability and sensitivity to pulse palpation of the operator, the sensitivity, design and positioning of the stethoscope and the calibration of the anaeroid manometer may contribute to inaccurate measurement.

2. Oscillometry

Originally described by Marey [35], this involves an air-filled cuff inflated to above systolic arterial pressure. With deflation of the cuff, blood begins to flow distally. This causes oscillations in the artery, which are transmitted, by the limb tissues, to the cuff. A pressure transducer senses the oscillations and takes the point at which they are maximal to be systolic AP. In the Von Recklinghausen oscillotonometer [36], the pressure oscillations are transmitted to the needle on a calibrated dial. Van Bergen's study [32] showed the accuracy of manual oscillometry to be slightly less than that of auscultation. Automatic devices based on oscillometry remove observer error but vary with design in their correlation to systolic, mean and diastolic pressures [37,38]. In general, they perform well enough to give reliable trend information , but may be inaccurate at very high or low AP, or when rapid changes are occuring.

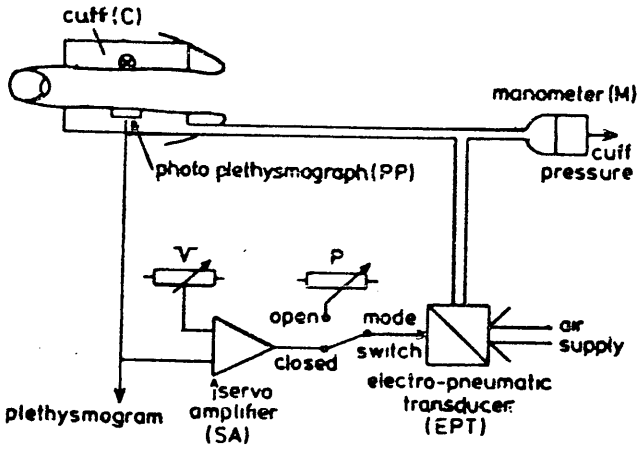
Plethysmography and oscillometry

A device recently introduced, and undergoing evaluation, combines oscillometry and photo-electric plethysmography (figure 5) to obtain blood pressure in a finger [39,40]. It is a non-invasive technique and is applicable only to extremities because of it's photo-electric component. In trials this device does reflect the changes in AP which pertain peripherally, i.e. finger systolic is greater than brachial artery systolic by 9mmHg or so.

ii) Observer Error

Using manual techniques, variations come from four sources;

Figure 5.



Block diagram of the Finapres. The manometer reads the pressure variations in the cuff, brought about by a source of pressed air. The air supply is regulated by an electropneumatic transducer and a fast-reacting servo-amplifier, guided by a plethysmogram taken from beneath the cuff. By the mode switch the instrument can be placed in the open mode for the calibration procedure. P = potentiometer to find the calibration pressure that has to be relayed to V as reference level for the servo-amplifier.

1. Observer-subject interaction,
2. Observer bias,
3. Digit preference,
4. Systematic observer error.

1. Observer-subject interaction.

Here, the procedure itself may actually alter blood pressure. Mancia and his colleagues saw this in 1983 [41]; they noted a transient pressor response (measured intra-arterially in the contra-lateral arm) when staff performed manual AP measurement. The effect was more marked when the observer was a doctor than when the former was a nurse. This evidence illustrates the phenomenon WCH, and suggests it is at least partly due to observer-subject interaction.

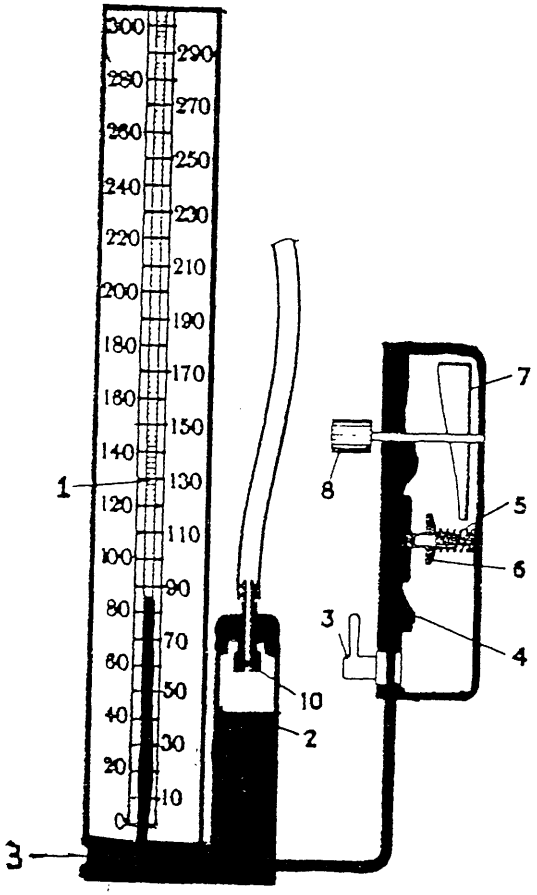
2. Observer Bias

This type of error results from the observer estimating AP closer to the value he expects than it actually is. This is obviously important in epidemiological studies, and experimental work, where a worker may anticipate a difference in means between two groups. One way to minimise this type of error would be to ensure that at least the experimenter is blind in the study. Also, observer bias can be reduced using a random-zero sphygmomanometer [42] (Figure 6): the zero is set at random before each measurement and is therefore unknown to the operator.

3. Digit Preference

(Terminal) digit preference refers to the increased likelihood that an observer may round up (or down) a value to

Figure 6. A random-zero sphygmomanometer.



1. A standard 0-300mmHg manometer.
2. Mercury reservoir.
3. Cock connecting the reservoir to a diaphragm chamber.
4. Diaphragm chamber.
5. Diaphragm spring acting to empty chamber.
6. Disc abutting onto spiral-faced cam.
7. Spiral-faced cam.
8. Knob to spin cam.

When the knob is spun, it comes to rest at random, thus setting the level of mercury in the reservoir at random. After cuff inflation, the cock (3) is closed, and arterial pressure is measured in the normal way. When the pressure in the cuff is released, the mercury comes to rest at the random zero. This value is subtracted from the arterial pressure readings to give the true pressure.

the nearest ten units subconsciously or otherwise [34]. The random-zero sphygmomanometer does not eliminate errors of this sort, which tend to be maximal at pressures furthest away from normal.

4. Systematic Observer Error

This really refers to faulty technique; for example, if the tendency of an individual is to overestimate AP, the mean AP of any group under study will be likewise affected. This is relatively easy to detect as a cause of distortion of results, and can be dealt with by various techniques to standardise observers, [34].

iii) Patient-related factors.

Age

In general, systolic and diastolic blood pressure increase with age (figure 7). Studies have shown that the rise in pressure is proportional to the starting level. At the age of two days, blood pressure rises until the age of six weeks. For the next four years it remains relatively stable. In the early years, systolic AP rises steadily until seventeen years of age, and at the end of adolescence the rate of rise slows. After about nineteen years, AP remains static until the late thirties. Similarly, diastolic pressure rises until adolescence, but then a rapid rise occurs before adulthood. The rise of blood pressure in adulthood is more gentle, diastolic pressure rising less per year than systolic: this results in a wider pulse pressure with increasing age. This is generally thought to be a result of decreased compliance of the resistance vessels which become affected by atherosclerosis.

Mancia and his workers [43] showed that AP variability increases with age, postulating that a given increase in stroke volume produces a higher pressure change in less compliant arteries.

Sex

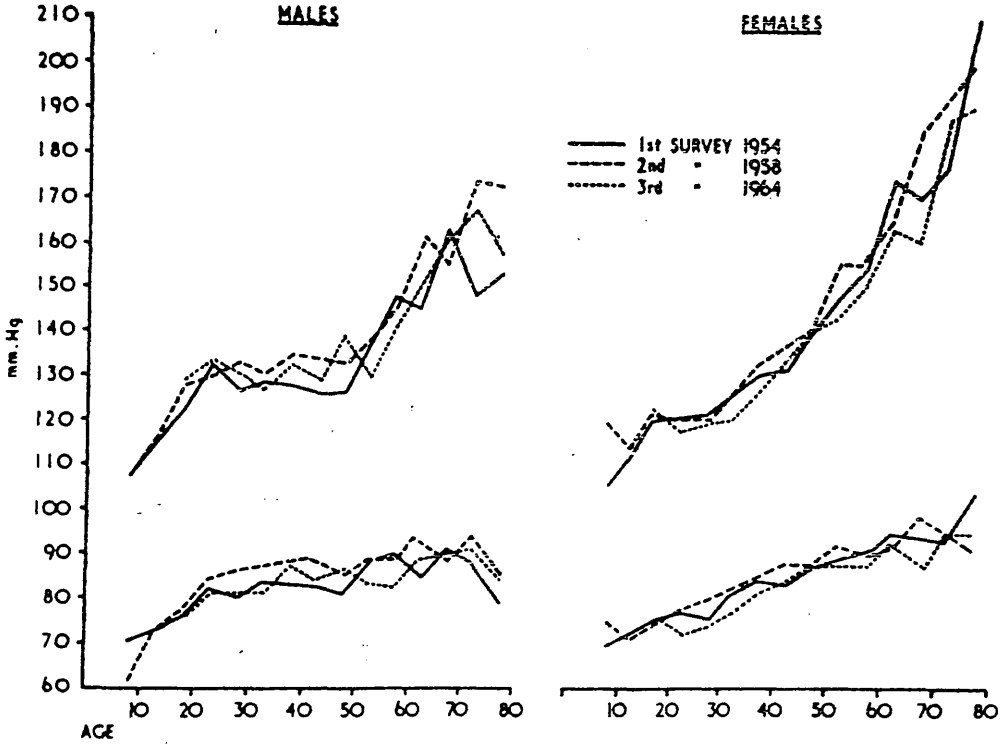
At all ages diastolic AP tends to be lower in men than women. Systolic AP, on the other hand, is higher in men until they reach the age of thirty, whereupon the converse is true.

Diurnal Variation

Blood pressure follows a pattern of circadian rhythm. This

Figure 7.

Relationship between age and blood pressure (in a Welsh population.)



(From Miall, W. E., and Lovell, H. G. 1967. Relation between change of blood pressure and age. *British Medical Journal*, 2, 660–664.)

The mean systolic and diastolic arterial pressure related to age in males and females from 3 surveys.

is illustrated by Drayer and his co-workers who studied normotensive individuals [12]. Blood pressures are significantly decreased at night, which means that average pressures over the whole day are less than than average taken during day-time hours. However, they suggest that in normotensive patients, the averages of a few or multiple readings taken between 8 and 10 am. in the morning are the best predictors of whole-day average.

Variability and Hypertension

"Variability" in this context is taken statistically from AP differences in the same individual. Standard deviation and variation co-efficient have been used to relate variability to blood pressure. Some authors conclude from very large studies that variability is proportional to the mean systolic pressure, but this is contested by others on statistical grounds. Furthermore, many studies have failed to demonstrate a positive relationship between variability and mean pressure. It is possible that the size of error inherent in non-invasive monitoring may itself correlate with mean pressure, thus distorting the results.

Mancia and his workers [43] studied hypertension, variability, age and baroreflex sensitivity. They showed, by direct arterial monitoring, that hypertensive patients demonstrate a higher degree of variability than normotensive patients. However, this only applied to absolute values and, when co-efficient of variation was used, the reverse became true. With his methods, baroreflex sensitivity could not be shown to have any relationship to absolute AP.

Environment

It is well documented by epidemiological studies that most blood pressures are higher when taken by a doctor in his office, clinic or in hospital. Mancia and his co-workers nicely demonstrated this significant, but transient, pressor response when a physician approaches the hospital bed to measure blood pressure. The response was less marked when measurements were performed by a nurse or technician.

Anxiety may account for high blood pressure in those who on subsequent readings have "regressed towards the norm"; they become more familiar with the environmemt. However, there is a group of patients in whom this phenomenon persists. In this situation, it has earned itself the name "white coat hypertension" (WCH). That is to say, patients are consistently hypertensive under the above circumstances, but have normal AP as measured throughout the day at home by ambulatory monitoring.

The relationship of this phenomenon to anxiety, the "orienting" reaction, or "regression towards the norm" remains unclear. Schneider [44] failed to show that there was a significant difference in the level of anxiety in patients who exibited WCH. However, the study showed a lower tendency to angry feelings, and less tendency to hold in these angry feelings in patients whose AP settled to normal at home.

It is possible that WCH patients have an increased level of sympathetic arousal when they first present for examination and AP measurement. This could lead to a conditioned response, (the "orienting" or "defence" response), of which they are unaware. Therefore, anxiety does not necessarily

contribute to white coat hypertension which persists after the first three or four visits.

It is not possible to accurately predict the patients in whom WCH occurs. However, Pickering and his co-workers [16] recently found WCH present in 21% of borderline hypertensive patients. These patients were more likely to be young and female, to weigh less, and to be recently diagnosed.

Conversely to the above situation, if a subject relaxes in a quiet environment, with closed eyes, has no distracting thoughts and is given repetitive mental action, the "relaxation response" is seen [45]. The EEG pattern differs distinctly from sleep or quiet sitting. There is a decreased level of autonomic activity so blood pressure is reduced significantly for the duration of the response.

Seasonal Variation

Large series of observations of blood pressure show significant changes with seasons of the year [46]. This related to temperature difference, blood pressures being significantly higher during the cold winter months.

Pain

Painful stimuli increase blood pressure.

Exercise

Immediately prior to exercise there is an anticipatory rise in AP. However, muscle metabolites and heat production cause peripheral dilatation and, despite increased blood flow, AP falls. It is thought that stimulation of skeletal muscle myelinated A(δ) and unmyelinated C afferent fibres cause reflex increased sympathetic activity. Tachycardia and raised

AP may also result during moderate exercise.

CONTROL OF ARTERIAL PRESSURE

1. Genesis of AP.

Arterial pressure is the product of blood flow, (cardiac output), and resistance presented to that flow by the arterial tree. The majority of the total resistance lies at the level of the arterioles. Since flow is laminar here, the relationship between flow and resistance obeys the Hagen-Posseuille equation for Newtonian fluids;

$$\text{Flow} = \frac{P \times 3.14 \times r4}{8 \times n \times l}$$

where P = driving pressure

r = radius of tube

n = viscosity

l = length

Note the influence of radius on resistance to flow; as the radius is halved, the resistance increases sixteen-fold. In other words, small changes in arteriolar calibre result in relatively larger changes in AP at constant flow rate.

The AP waveform is the sum of energy generated by left ventricular contractions and the resulting reflected energy from the elastic arterial walls. Myocardial work imparts kinetic energy to the flow of blood in systole and is also stored as potential energy. The potential energy overcomes and distends the elastic aortic wall during systole and is released in diastole so that flow continues throughout the cardiac cycle.

Circulatory Homeostasis

Circulatory homeostasis (figure 8) is effected by the autonomic nervous system (ANS). Integrated reflex responses (to intra-vascular distending pressure, PaCO2,) effect changes in arteriolar and venous calibre, and myocardial rate and contractility. Also, by controlling visceral activity, the ANS indirectly governs visceral blood flow (autoregulation). Autonomic reflexes also influence cardiac function. In addition, hormonally mediated control mechanisms assist in circulatory homeostasis. These regulate intra-vascular volume and operate over a longer time period than the autonomic reflexes.

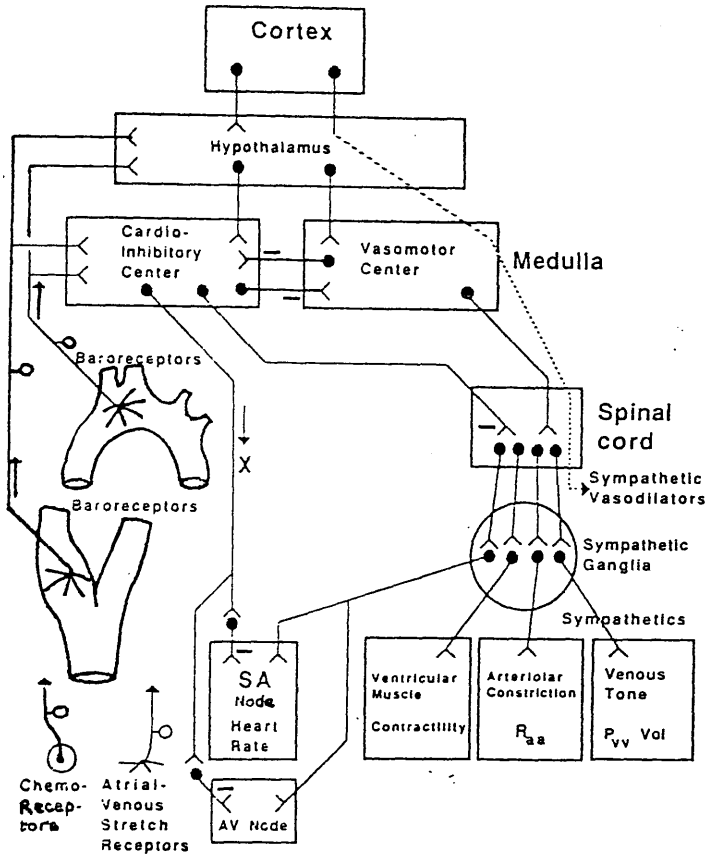
Autoregulation matches metabolic requirements to oxygen supply at the level of tissues. However, this fails if perfusion pressure falls below a critical level. Maintenance of AP is therefore vital.

Baroreflex Control of Arterial Pressure

The most rapid and first line of defence against increasing or decreasing AP is the baroreceptor reflex. Receptors lie in the walls of the internal carotid, brachiocephalic arteries, aortic arch, atria and lungs. The baroreceptors in the internal carotid arterial wall lie in a localised group of specialised cells; this is the carotid sinus, and their influence dominates integrated baroreceptor responses.

Baroreceptors are sensitive to stretch, so that a rise in AP causes an increased receptor firing rate. Furthermore the rate of AP change is important; the increase in firing is proportional to the rate of AP change at any given AP. The relationship between baroreceptor firing rate and AP is a

Figure 8.



A simplified diagram of the circuitry involved in the autonomic control of the circulation.

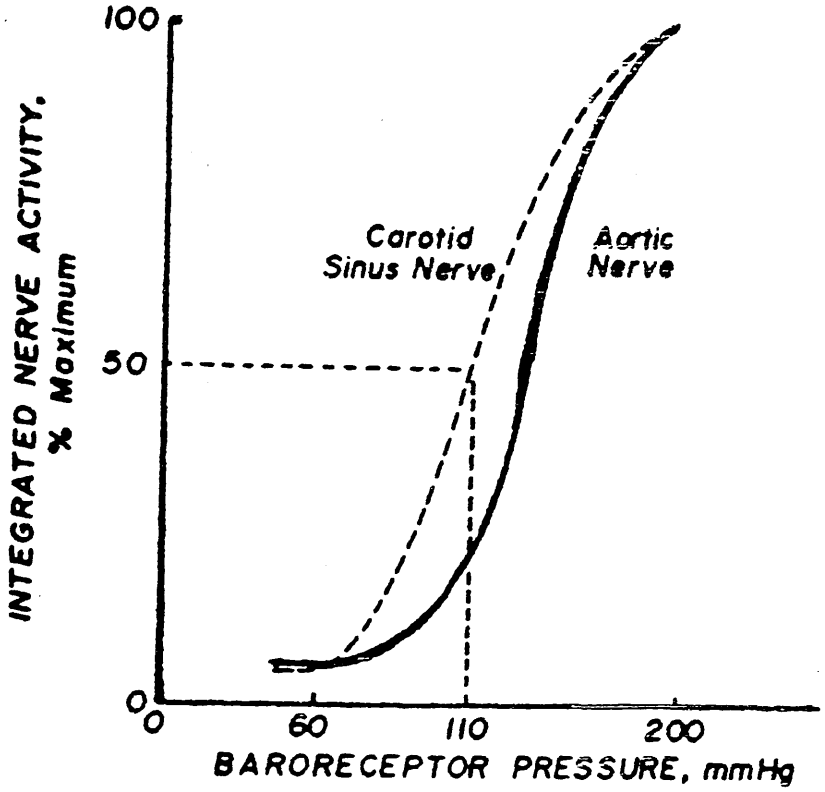
sigmoid curve, (figure 9); there is a firing threshold, a linear component and a saturation point [47]. Firing starts at about 65-70mmHg, but is maximal at 180mmHg. Baroreceptor sensitivity corresponds to the gradient of the slope of the relationship of heart rate (HR) and AP with "pressor/depressor" challenges or neck suction [48]. This relationship is only linear between AP of approximately 105-160mmHg. Furthermore, the reflex is asymmetrical; the response to increased AP is more rapid than to decrease in AP. Since vagal output corresponds to the early changes in SA node activity, and these are blocked by atropine, it is likely that early responses are mediated by cholinergic pathways.

Baroreceptors may be reset; i.e. the position of the line representing the HR-AP relationship may be shifted to the right when a new AP level is "defended". This occurs when changes in AP persist. Resetting may account for the decreased baroreceptor sensitivity seen in the aged or in hypertensive patients.

Afferent information leaves the baroreceptors in the IX and X cranial nerves before synapsing on nuclei of the tractus solitarius. Projection onwards from this area is to three main groups of nuclei; paramedian reticular nuclei, dorsal vagal nucleus and ambiguous nucleus. These nuclei lie in the ill-defined region known as the vasomotor centre. The result of increased baroreceptor input on the vasomotor centre is-

1. Increased parasympathetic efferent activity
2. Decreased sympathetic efferent activity
3. Activation of parallel inhibitory sympathetic

Figure 9.



The relationship between carotid sinus and aortic arch pressure and activity in the afferent nerves from mechanoreceptors in their walls.

In the study from which the diagram was taken, significant changes in nerve traffic occur at an arterial pressure of 100mmHg for the aortic nerve compared with 70mmHg for the carotid nerve.

pathway within the spinal cord.

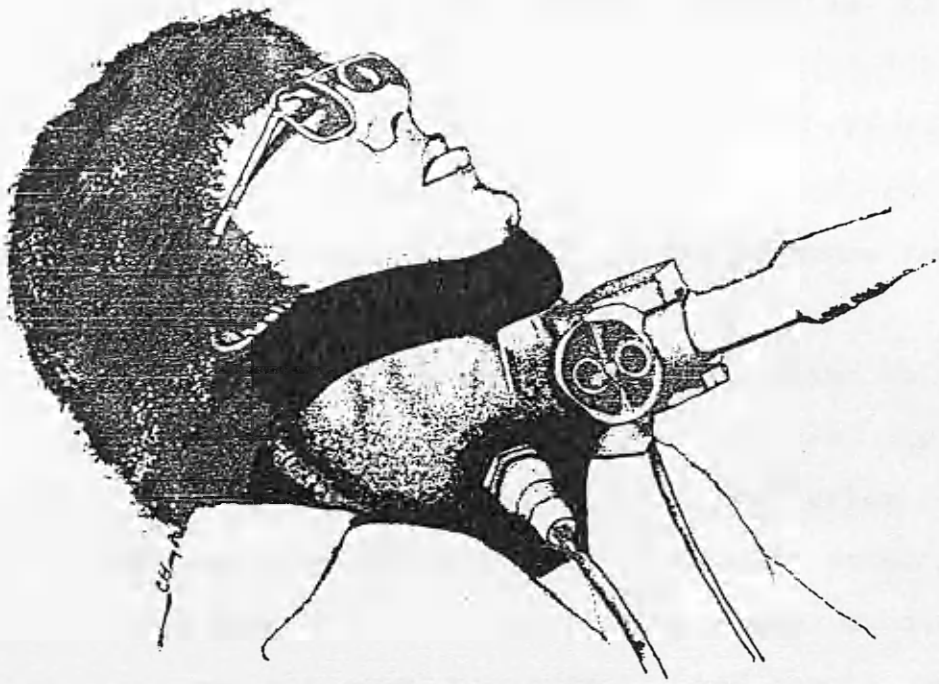
Understanding of the manner in which baroreceptor input modifies autonomic efferent activity is confounded by the old idea of a medullary vasomotor centre. The simplistic idea that baroreceptor input directly stimulates the "depressor" area of the vasomotor centre has not actually been shown. Furthermore, the hitherto assumed efferent pathways descending from the hypothalamus (anterior dorsal nucleus) to the vasomotor centre are unfounded in mediating baroreflexes. It is more likely that bulbo-spinal sympatho-inhibitory pathways are more important in mediating baroreceptor reflexes.

The efferent pathways for the autonomic reflexes are the parasympathetic and sympathetic nerves which synapse onto receptors within the effector organs: the blood vessels and muscle, conducting tissues and sino-atrial node of the heart.

The Baroreceptor Reflex and Anaesthesia

General anaesthetic agents affect baroreflex sensitivity, i.e. the R-R/AP relationship as tested by pressor/depressor challenges or neck suction (figure 10). This could be due to interference at any level of the reflex; eg., agents may act directly on receptors, on CNS pathways, or target organ receptors etc. Workers have attempted to show effects of anaesthetic agents on each stage of the reflex, but since detailed CNS mapping of pathways involved is unavailable, concrete evidence is generally confined to the peripheral elements. Indeed, authors disagree over the main site of inhibition of barorefex induced changes in peripheral resistance.

Figure 10. A neck suction device.



The chamber is used to alter carotid distending pressure experimentally. A strain gauge pressure transducer is mounted on the chamber. The hose (R) is connected to a continuous vacuum source. Pressure changes within the chamber are initiated by rotation of a solenoid-actuated valve.

Isoflurane, the volatile anaesthetic agent used in this study, depresses baroreflexes to increasing and decreasing arterial pressure at 1 MAC [49]. Although there is little further depression of the reflex to decreasing AP at 1.5 MAC, the response to increasing AP is progressively depressed. Isoflurane causes smooth muscle relaxation directly, but even if AP is maintained the depression of reflex response remains blunted at 1 MAC.

Thiopentone, the intravenous anaesthetic agent used in this study, also affects the baroreflex arc. Workers reported equal depression of pressor and depressor baroreflex limbs [50]. Thiopentone, also influences AP by direct effects on the cardiovascular system; these effects include myocardial depression, a possible vagolytic effect, and smooth muscle dilatation, and are independant of the baroreflex arc.

The net result of anaesthetic agents on baroreflex activity depends on the specificity of the agents for sites of action, the sensitivity to the agents of these sites, together with the prevailing dominance of each part of the reflex affected. Furthermore, it is feasible that the background CNS activity, on which the reflex is set, may be altered by the balance between surgical stimulation and CNS concentrations of anaesthetic agent.

CHAPTER 2

THE PRELIMINARY STUDY

Pre-operative Arterial Pressure Measurements: Their Relationship to Resting Values.

Introduction

We have seen that the phenomenon WCH may cause transient pressor responses in borderline hypertensive patients [16,18]. The evidence implies that random AP measurements may not represent true resting AP in that population.

We also know that AP may be unusually high prior to induction of anaesthesia [51]. Therefore, anaesthetists usually look to measurements made on the ward for baseline values. This is important in that, on the basis of these AP measurements, patients found hypertensive may have surgery and anaesthesia postponed. This is because of the well known increased morbidity and mortality associated with surgery and anaesthesia in the face of uncontrolled hypertension [3,4,5,6,7,8,9].

Admission to hospital for surgery and anaesthesia is a stressful time: with high anxiety levels and the hospital environment, it is possible that pre-operative AP could be affected in a similar manner to that seen in the WCH population.

Apart from causing unnecessary postponement, the implications of all this are of interest in two other respects: first, during anaesthesia, SAP provides a marker for the adequacy of the anaesthetic state, and in interpreting the values obtained, we depend on a baseline, representative of normal SAP in each patient. From the above, we have reason to believe that values based on manually

obtained measurements of SAP may not be truly representative. Second, for a target SAP during feedback control, a value based on true resting SAP may facilitate control obtained by the system, improving the quality as judged by our pre-defined variables.

This study compares random AP measurements, in the presence of the anaesthetist, with AP at rest in the absence of medical staff. The patients were not known to be hypertensive.

Patients and methods

Informed consent was obtained from 30 ASA 1 or 2 patients due for elective surgery. There were 21 females and 9 males, aged from 28 to 79 years. Those excluded were

i) known hypertensives
ii) patients with endocrine disease
iii) patients without a good understanding of English.

One patient admitted a history of antihypertensive therapy, but this had been discontinued for three years during which time she had remained normotensive.

Patients were studied in the late morning, one to two hours after admission to hospital. AP taken by nurses on admission was noted. After a routine preoperative visit, a Dinamap 1846P [38] measured AP at minute intervals for 15 minutes. After the initial reading, the patients were left undisturbed, supine and behind screens. They could not see the Dinamap display.

Premedication was 20mg temazepam orally two hours before induction of anaesthesia. In the anaesthetic room, the

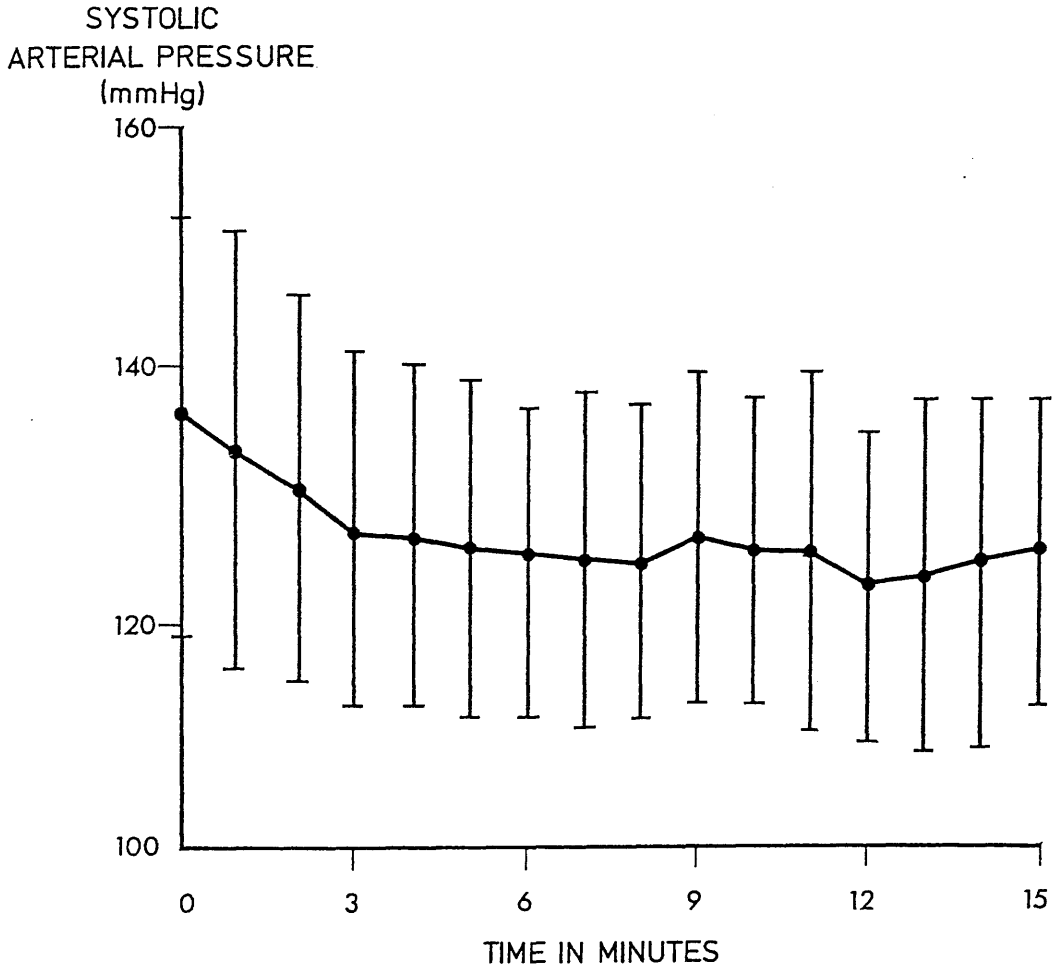
Dinamap took 10 consequetive readings ("stat-mode") in the presence of the anaesthetist. Unfortunately, to keep the operating lists on time, it was not possible to repeat the series of 15 AP measurements at minute intervals.

Results.

On the ward, in 29 out of 30 patients, AP was high initially (mean=136/78, SD17/12mmHg) then fell to a plateau, (mean =124/70, SD13/10mmHg). Figure 11 illustrates AP of all patients over 15 minutes. We defined plateau AP for each patient as the mean of the last five readings, and took the value to represent resting AP. The difference between initial and plateau pressure (paired t-test), was highly significant ($p < 0.001$), for systolic, mean and diastolic AP (table 3). In 18 patients, the initial systolic AP lay more than two SD above the plateau systolic AP. The mean time taken for systolic AP to fall to within 2SD of the mean plateau systolic AP was 92 seconds, (SD 154secs). Five patients were "hypertensive" initially (AP > 140/90mmHg), but their plateau pressures were normal.

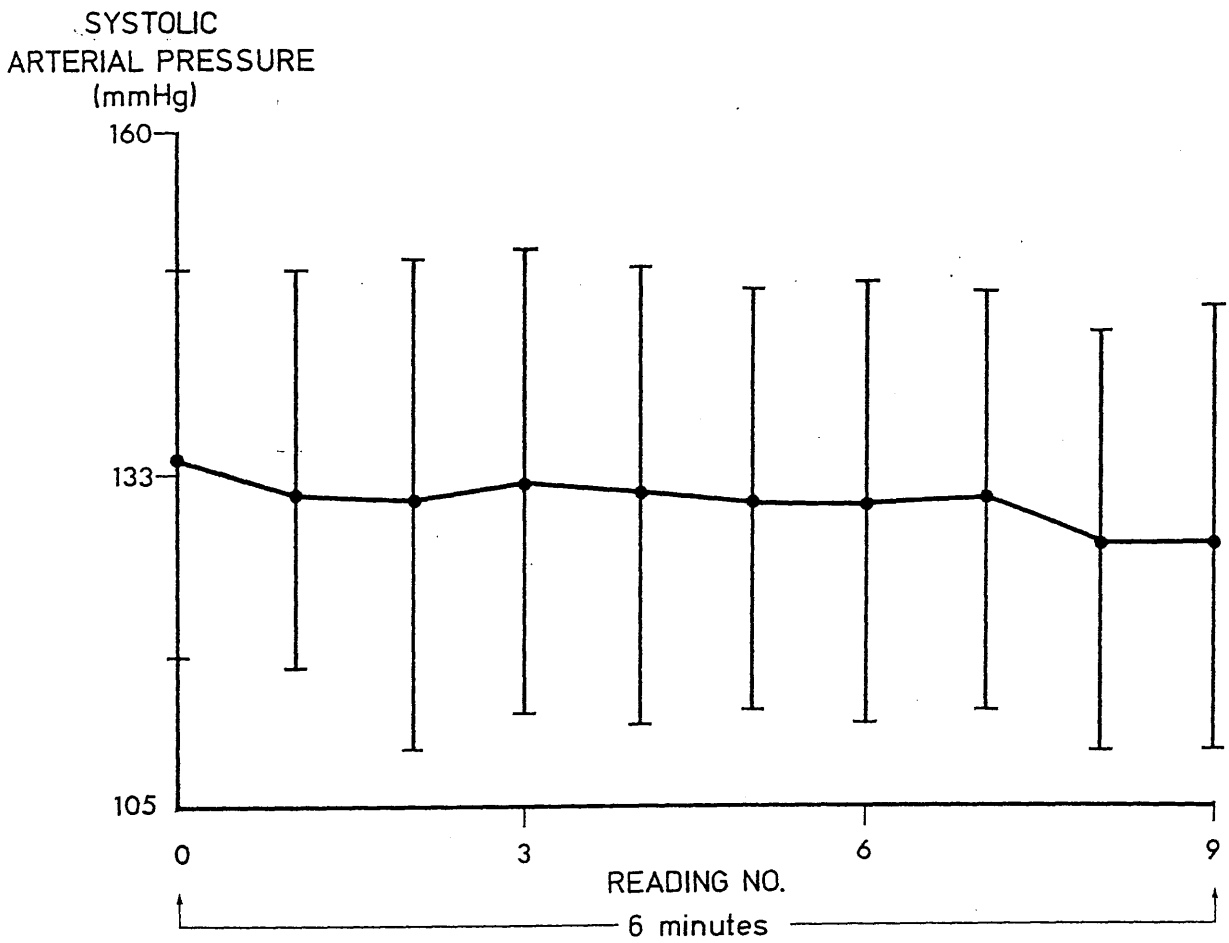
In the anaesthetic room (table 4) the initial AP mean was 134/80 mmHg, (SD16/16), whereas mean AP over 6 consequetive readings was 129/76 mmHg, (SD17/12). This difference was significant, although the magnitude of the fall less marked than that seen on the ward. Figure 12 shows mean SAP in the anaesthetic room. The lesser difference (in the anaesthetic room than the ward) between initial SAP and mean SAP may have been due to shorter recording time in the anaesthetic room, i.e. AP may have dropped further if we had measured over 15 minutes again. Or, it may have been due to the continuing

Figure 11.



Mean SAP at rest, recorded by a Dinamap 1846, over a 15 minute period, in 30 preoperative patients.

Figure 12.



Mean SAP, recorded by a Dinamap 1846, over 6 minutes in the anaesthetic room.

Table 3: Indirect arterial pressure measurements initially and after 15 minutes.

	systolic	mean	diastolic
Initial	** 136	** 102	** 78
	17	13	12
Plateau	124	91	70
	13	11	10

** $p < 0.001$ (paired t-test)

Mean values for systolic, mean and diastolic AP (mmHg + SD) on the ward initially and after 15 minutes (plateau), in 30 patients in the preliminary study.

Table 3

Table 4: Indirect arterial pressure in the anaesthetic room; initial and mean values.

	systolic	mean	diastolic
Initial	** 134	99	* 80
	16	16	16
Mean	129	96	76
	17	14	12

** $p < 0.001$
* $p < 0.05$

Mean values for systolic, mean and diastolic AP (mmHg + SD) in the anaesthetic room in 30 patients in the preliminary experiment. "Mean" refers to the average of 6 consecutive readings taken by the Dinamap 1846 on "stat-mode".

Table 4

presence of anaesthetic room personnel; the patients were not undisturbed during AP measurement in the anaesthetic room, as had been the case on the ward.

There were 8 patients who were "hypertensive" just prior to induction. One of these was the patient who had admitted a history of hypertension. She was never hypertensive on the ward during the study.

AP in the anaesthetic room differed significantly (paired t-test) from plateau values, ($P<0.001$ for systolic, mean and diastolic). Overall, anaesthetic room AP was closer to initial AP on the ward than to plateau AP (table 5).

AP recorded by the nursing staff (table 6) on admission (mean=130/81mmHg, SD13/7) also differed significantly from resting AP, ($p < 0.05$ for systolic, mean and diastolic). Furthermore, the correlation between the nurses SAP and resting SAP (table 7) was relatively poor, (0.475).

Inspection of values recorded by the nurses revealed evidence of digit preference [34].

The correlation (table 7) between systolic AP (SAP) in the anaesthetic room and plateau SAP, (0.695, Spearman), was less than the correlation between anaesthetic room and initial SAP (0.763).

Discussion

The results show AP in the ward and anaesthetic room to be significantly higher than at rest. The transient pressor response on the ward settled within 4 minutes in 28 out of 30 patients. Some evidence of a similar response was seen in the anaesthetic room, but AP was recorded over a shorter time.

Table 5: Indirect arterial pressure in the anaesthetic room and in the ward preoperatively.

	systolic	mean	diastolic
Anaesthetic room (initial reading)	134 16	99 16	80 16
Plateau/ Resting	** 124 13	** 91 11	** 70 1
Initial (ward)	136 17	102 13	78 12

** $p < 0.005$ compared with AP in the anaesthetic room.

Mean values for systolic, mean and diastolic AP (mmHG + SD) to show the differences between the pressures obtained in the anaesthetic room and both pressures obtained on the ward.

Table 5

Table 6

Automatic indirect arterial pressures measured preoperatively and in the anaesthetic room, and manual measurements made by ward nursing staff.

	systolic	mean	diastolic
Anaesthetic room	** 134 16	* 99 16	* 80 16
Plateau/ Resting	124 13	91 11	70 10
Initial	** 136 17	** 102 13	** 78 12
Nurses	* 130 13	* 97 8	** 81 10

** $p < 0.001$
* $p < 0.05$

compared to Resting/Plateau AP

Mean values of systolic, mean and diastolic AP (mmHg +SD) to show how other pressures obtained in the study compared with resting/plateau AP.

Table 6

Table 7: The correlation of resting systolic arterial pressure to that measured on admission to the ward both automatically and manually by nurses, and to that measured automatically in the anaesthetic room.

Initial SAP	0.87
Anaesthetic Room SAP	0.70
Nurses SAP	0.48

The correlations between the above listed mean SAP values and resting/plateau SAP.

Table 7

The premedicated patients were not left unattended, therefore, conditions under which AP measurements were made were dissimilar in the ward and in the anaesthetic room. AP measurements made on admission by nursing staff were poor predictors of resting AP, as measured by the Dinamap, and showed digit preference.

The difference between admission and "resting" AP is borne out in a large study of preoperative patients by Green [51]. However, in his study, admission measurements were made manually by nurses, and "resting" measurements by technicians. The magnitude of the difference in our study was greater, and this could be explained by the lesser effect of WCH when elicited by a technician, or nurse.

In our study, the Dinamap obtained readings in a standardised manner, eliminating observer bias and, more importantly, observer-subject interaction. In this way, values for "resting" AP (the plateau values) are validated. A routine preoperative visit from the anaesthetist provided a "standardised" stressful stimulus.

So what of the routine of AP recording on admission to hospital? These and other pre-operative measurements may not be representative of resting AP. Non-invasive, automated devices for AP recording provide more repeatable, reliable values. By distinguishing WCH from persistent hypertension, unnecessary postponement of surgery (with the stress, inconvenience and wastage of theatre time) need not occur. Although WCH patients do not have the same incidence of target-organ damage [21,22,23], there is still a cause for concern; workers have identified a positive correlation between the pressor responses to admission to hospital and to

intubation after induction to anaesthesia [8].

In addition to validating our concern over pre-operative AP, we have also validated our concern over the selection of target SAP (see introduction) for use in a feedback control system; errors of the nature seen in this preliminary study, may be inherent in the construction of population tables of AP. As SAP is a guide to adequacy of anaesthesia, the reference point, or baseline normal, must be genuine. Therefore, a more reliable method of selecting TSAP is necessary. We propose to use resting values determined by the automated non-invasive monitoring technique as the basis of TSAP selection in future.

CHAPTER 3

PROPORTIONAL-INTEGRAL FEEDBACK CONTROL OF SYSTOLIC ARTERIAL PRESSURE I:

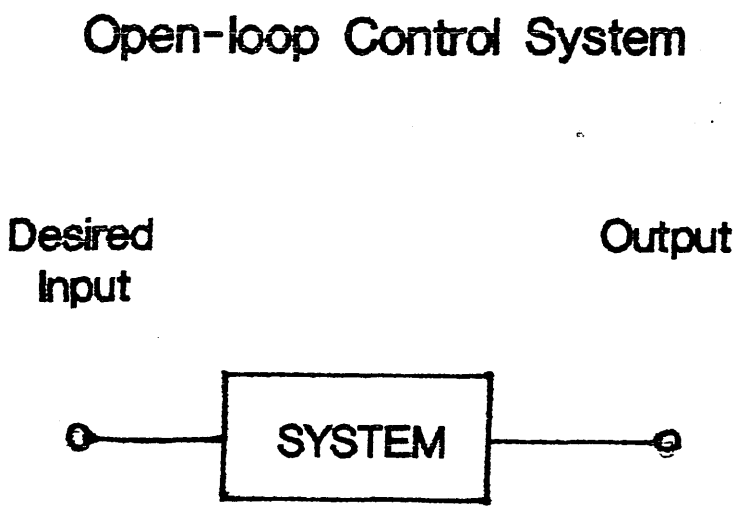
An outline of Control Systems

A control system is defined as "an arrangement of physical components connected or related in such a manner as to command, direct, or regulate itself or another system". Thus, our world contains innumerable control systems, ranging from relatively simple examples; refrigerators and electric ovens, to the most complex:- the human being.

Control systems are either open- or closed-loop, (OLCS or CLCS). A CLCS, also known as a feedback system, is defined as where "the control action is dependant upon the output of the system". In an OLCS the control action is unaffected by the ouput of the system, (figure 13). The difference between an OLCS and a CLCS is illustrated by comparing a micro-wave oven, (an OLCS), and a refrigerator, (a CLCS): in a microwave oven, once the timer is set, the microwaves (or ouptut), cook the food until the time elapses. The control action of this system is the degree of cooking food, and this depends on the setting of the timer, the power of the microwaves, and the size and original temperature of the food. These constitute the input to the system. Thus, the control action depends not on the output, but on the pre-set configuration of the system.

On the other hand, in the refrigerator system, the motor driving the cooler is controlled by a thermostat: thus the control action, (cooling), depends on the fridge temperature,

Figure 13.



The control action (of the system) is unaffected by the output.

(output). Figure 14 shows the arrangement of a CLCS. Note the relationship between the output, the reference (or target), and the error: the comparator calculates the error signal from the output, (hence "feedback control"), and reference values. Such a system is relatively complex in comparison to an OLCS, which has no target, or reference value. The CLCS, by constantly adjusting the control action, (depending on the output and reference value), is able to follow a target output with varying degrees of accuracy; there is potential for instability and oscillation about the target in the CLCS, (relatively more complex than an OLCS,) which result in deviations of the output from target value.

Proportional-Integral Control

In a proportional feedback system, the output, (or control action), can be written as

$$[K_p \times e\ ],$$

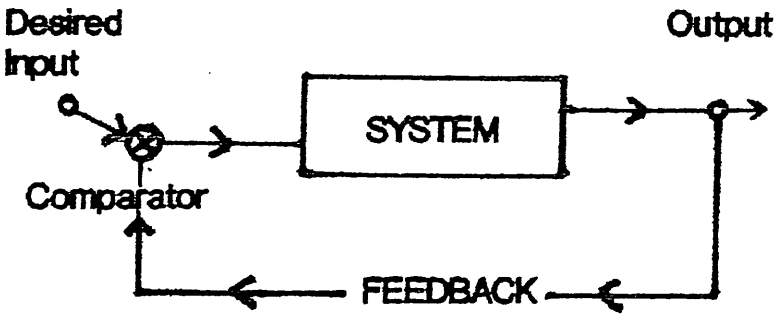
where K_p = proportional gain,

and e = error, or difference between any one output value and the target.

The output is therefore proportional to the gain. However, if the gain is high there is a tendency to overshoot and oscillation; if the gain is low, the corrective action may be inadequate. This system has a relatively crude control ability, and it fails to hit the target exactly, (for mathematical reasons). An integral component, which is the sum of all the errors, $[\Sigma e]$, may also be introduced and also requires a gain. The advantage of this is that it

Figure 14.

A Closed-loop Control System



The feedback carries information about the output back to the comparator. The comparator finds the error signal (the difference between the reference and the output), which then contributes (affects) the control action of the system.

reduces the offset, (the difference between the target and output at steady state), but at the risk of instability. Furthermore the integral may carry spurious information from previous error signals. The nature of a proportional-integral control system is that there will always be an offset. Mathematical analysis of such a system predicts the behaviour of the system with respect to oscillation and offset. The output of a proportional-integral control system is

$$[\ K_p \ x \ e\ ] \ + \ [\ K_I \ x \ \lessapprox e\ ],$$

where K_I is the gain of the integral component, and $\lessapprox e$ is the sum of all the errors, or the running integral.

The Feedback Control of SAP

In our control system, the output is an action which varies SAP, measured at minute intervals by a Critikon Dinamap, [38]. Our reference input is the target value, to which the output is compared; the difference is the "error" signal. The control director processes this signal, then directs the control effector (vaporiser) to adjust the dose of anaesthetic agent. Our control director is a BASIC programme, executed by a RML computer. The controlled variable is SAP, which we use as an index of the adequacy of anaesthesia. The vaporiser setting, (S_{vap}), is thus calculated;-

$$S_{vap} = [\ K_p \ x \ SAP_{error}\ ] \ + \ [\ K_I \ x \ \lessapprox (SAP_{error})\ ].$$

As before, K_p = the proportional gain

K_I = the gain of the integral,

and SAP_{error} = the difference between SAP measured by the

Dinamap and the target SAP, (TSAP).

$\sum(SAP_{error})$ = the sum of consecutive differences between SAP and TSAP; this is the running integral.

Note that if SAP is less than TSAP, the integral decreases and may eventually become zero. Also, it is written into the programme that if $S_{vap} < 0$, the vaporiser is set to deliver zero percent, (isoflurane).

After preliminary experiments, Robb set the values of K_p and K_I at 0.1 and 0.01 respectively. Furthermore, he set the value of the integral at the start to be 20 + [100 - age]. This is known as "preloading" the integral: the integral component must normally learn to deal with the offset, but pre-loading to a suitable value hastens this process. It also helps to ensure that anaesthetic dosage at the time of surgical incision, (early in the control period), is adequate and so the risk of awareness is lessened.

In addition to preloading the integral, (with adjustment for age), he also incorporated a rule in the BASIC programme that minimum isoflurane dosage would be 0.6% during the first 10 minutes of the control period: during the post-induction period but before surgical incision, low SAP (with respect to target SAP) could otherwise result in no anaesthetic being delivered. In the absence of integral preloading, this would have ensued immediately had the first SAP measurement been < TSAP. With the preloaded integral, this could still occur, after a few consequetive SAP measurements which fall significantly below TSAP. Thus, at incision, the otherwise exaggerated increase in SAP and risk of awareness are reduced

due to the incorporation of the "0.6% minimum for the first ten minutes" rule.

Another rule governed the administration of morphine boluses: if, over 5 consecutive minutes, the vaporiser output exceeded 2.5% isoflurane and the numerical total of those doses exceeded 15, the system instructed the anaesthetist to give a bolus of morphine. This rule could only operate once in every ten minutes, to prevent narcotic overdose, and the integral was reset to its initial pre-loaded value after each bolus.

The Use of Plateau Systolic Arterial Pressure as The Target for Feedback Control A Study of 20 Patients

Introduction

In this study of feedback control of SAP, we will use as the target SAP, (TSAP), individually obtained resting SAP; in Robb's work, TSAP was calculated using an age-sex rule, but we now have the means by which to obtain more reliable and accurate values for individuals, (chapter 2). We will compare the closeness and distribution of SAP points to and around the TSAP, (the ability of the system to hit the target, or quality of control), in our patients to the same variables in Robb's patients.

Patients and Methods

Written consent was obtained from 20 patients due to undergo elective, major surgery (table 8). The criteria for admission to the study included:-

i) ASA group I or II

ii) No uncontrolled hypertension. (A history of hypertension, or hypertension controlled by drug therapy did not exclude patients.)

iii) No previous reaction to anaesthetic agents, or history of asthma.

iv) Age between 18 and 75 years.

v) No CNS disease, treated or untreated.

After the pre-operative interview, a pre-calibrated Dinamap 1846P measured arterial pressure, (AP), at minute intervals

Table 8: Operations carried out on the 20 patients in the first study.

OPERATION	NO OF PATIENTS
Laparotomy	5
Hysterectomy	6
Pelvic Floor Repair	3
Mastectomy	3
Ovarian Cystectomy	1
Varicose Veins	2

Operations carried out on 20 patients in the first study undergoing anaesthesia by feedback control of SAP, supplemented by morphine analgesia.

Table 8

for 15 minutes. As in the preliminary study, (chapter 2), during this time the patients relaxed, supine, undisturbed with the screens pulled. The plateau SAP (PSAP) was the mean of the final 5 readings, (table 9).

Anaesthesia

Premedication was 20mg temazepam. In the anaesthetic room, before induction, a 16 French gauge intravenous cannula was sited in the wrist or fore-arm under local anaesthesia with 1% plain lignocaine. An infusion of Ringer's lactate solution commenced, and intravenous induction of anaesthesia began with 0.1mg/kg morphine sulphate, followed by sodium thiopentone (STP), in a dose sufficient to attenuate the eye-lid reflex; the dose was not pre-set. After vecuronium 0.1 mg/kg, ventilation was assisted, via mask, with 66% N_2O in O_2, and 0.5% isoflurane for two minutes before intubation. After tracheal intubation, transfer to theatre took place.

In theatre, artificial ventilation maintained end-tidal (ET) CO_2 between 28 and 35mmHg. The following monitors were connected;

i) ECG

ii) Dinamap for non-invasive AP measurement

iii) ET CO_2 and isoflurane monitors

iv) Digital pulse monitor

v) Nerve stimulator electrodes, (ulnar nerve).

After the first Dinamap AP reading, the control system was commenced. (Before induction, the PSAP had been set as target SAP.) For ten minutes, the minimum isoflurane concentration, ([isofurane]), was 0.6%. In most cases incision took place during this time. During the control period, additional

Table 9: Preoperative and target systolic arterial pressure in 20 patients in the first study.

Patient No.	INITIAL SAP (mmHg)	PSAP (mmHg)	PREDICTED TSAP (mmHg)
1.	128	124	135
2.	142	126	117
3.	141	127	104
4.	158	147	127
5.	213	184	137
6.	109	106	120
7.	136	119	122
8.	150	116	127
9.	130	119	124
10.	152	119	117
11.	119	116	110
12.	138	123	109
13.	113	106	117
14.	136	126	128
15.	142	146	134
16.	157	141	127
17.	126	109	106
18.	110	107	109
19.	148	128	114
20.	160	131	130
MEAN (SD)	140.4 (23)	126 (18)	120.7 (10)

SAP in 20 patients in the first study, on the ward (INITIAL and PSAP) and the values for TSAP calculated from the age-sex rule (PREDICTED TSAP).

N.B. Patient No. 5 had a plateau (resting) systolic arterial pressure of 184mmHg. TSAP was set at 150mmHg in this case, as the system demands that TSAP lies between 90 and 150mmHg.

The difference between initial and resting SAP was significant, ($p=0.002$) in a paired t-test.

The difference between PSAP and predicted target SAP was not significant.

boluses of morphine, (0.03-0.05mg/kg), were administered only if the system demanded, and vecuronium boluses were given if more than two twitches of the train of four were present. Also, if heart rate (HR) fell below 50, glycopyrolate 0.2mg was given; this was repeated after two minutes until HR rose above 50 bpm. The control system ran until 5 minutes before the end of surgery, (as anticipated by the anaesthetist), but if the operation time had exceeded 60 minutes, this time increased to a maximum of 10 minutes. Immediately after the last skin suture, the N_2O was discontinued, marking the end of anaesthesia.

The intravenous fluid regime included Ringer's lactate i) 5.4ml/kg ($\pm$1.8) before the control period began. This replaced the deficit from overnight fasting.

ii) 5-10mls/kg/hr as maintenance of basal requirement.

Blood loss was replaced with crystalloid or blood, at the anaesthetists' discretion.

Post-operative Recovery

Once spontaneous respiration was re-established, (in the presence of four twiches in the train of four with no visible fade), patients were extubated. They remained in theatre with the anaesthetist until simple commands were obeyed: this point was recorded as first response (FR) time. Eye-opening or protruding the tongue on command were both acceptable as first responses. After this, they remained in the recovery ward for 4-5 hours receiving routine post-operative care. Analgesia was provided with IM morphine.

Post-operative Interview

The interview took place 24 hours after surgery and the

following questions were put to the patient:

1. What is the last thing you remember before going to sleep?
2. Do you remember any dreams or hearing any voices that you think may have been during your operation?
3. What is the first thing you remember after your anaesthetic?
4. When you woke up, did you have pain?
5. Describe your pain; None - slight - moderate - severe.
6. Did you have nausea or vomiting?
7. How severe was this? None - slight - moderate - severe
8. How do think your anaesthetic suited you?
9. Would you have the same anaesthetic again?

The replies to questions 2, 4, 5, 6, 7, and 9 were noted; the other questions were intended to make the patient concentrate on thinking back to the time of the event.

Assessment of Control

The quality of control was assessed on all SAP points as follows;

1. The RMSD. This is the standard deviation of SAP points about the TSAP not the mean SAP.
2. The mean deviation of SAP from TSAP.
3. The points' ratio, (PR). This is the ratio of the percentage of SAP points above the target to that below.

This is the same way in which Robb assessed the quality of control. The criteria for good control were

1. RMSD < 10,
2. Mean SAP deviation between 5 and -5,
3. PR between 0.4 and 2.3

Adequacy of Anaesthesia

The criteria for overall adequacy of anaesthesia were

1. Physiological variables

   i) Mean heart rate (HR) between 50 and 100 beats per minute (b.p.m.)

   ii) Mean rate pressure product (RPP) < 12 000.

2. FR time from end of anaesthesia ⩽ 15 minutes was considered a satisfactory time for recovery. FR time >15 minutes indicated an inappropriately long time to the regaining of protective reflexes, as a direct result of anaesthetic overdose. However, to allow for variation in the time period from system discontinuation to end of anaesthesia, the corrected FR (cFR) was calculated as follows:-

   i) For surgery lasting < 60 minutes,

      cFR = STFR - 5 minutes.

      (STFR = Time from system termination to first response.

   ii) For surgery lasting ⩾ 60 minutes,

      cFR = STFR - 8 minutes.

   iii) In cases where cFR was calculated to be < 0, a value of 0 was applied.

3. No retrospective evidence of awareness.

Results

The mean "anaesthesia" time was 67.55 minutes, (SD 20), and mean age was 46 yrs, (SD 15.6). There were 18 females and 2 males.

On the ward, mean initial SAP was 140mmHg (SD 23). Mean PSAP was significantly lower, as in the preliminary experiment, (paired t-test), at 126mmHg (SD 18). SAP calculated from the

age-sex rule was 120.7mmHg (SD 10), which did not differ significantly from PSAP. (Table 9 gives details of initial SAP, resting SAP and predicted TSAP.) One patient had an initial SAP of 213 mmHg which fell to a PSAP of 184 mmHg; her diastolic AP was normal and she was a 71 yr old diabetic, well controlled on oral medication. The target was set at 150 mmHg in this case, as this was the highest target SAP the system would allow.

The mean STP dose was 4·8mg/kg (SD 0.6). Six patients (30%) required additional morphine. Mean blood loss in ml/kg was 5.7, (SD 7.5). However, in one case, surgery to a malignant ovarian cyst proved difficult. Bleeding was uncontrolled for several minutes, and total blood loss was approximately two and a half litres overall. No patients in the study required glycopyrolate, (mean HR 76.3 b.p.m., SD 16).

Patients received a mean of 20.78 mls/kg over the operative period. This was Hartmanns' solution, except in the case of the patient with the 2.5 litre blood loss: she received Haemaccel and blood as well.

The Control

The analysis of the quality of control did not include the initial 10 minute "settling down" period after the system was commenced.

Mean RMSD; 10.34 (SD 4.1)

Mean deviation from TSAP; -1.99 (SD 6.2)

Mean PR; 2.03 (SD 4.8)

The criteria for "good "control were satisfied as follows;

i) 35% of patients satisfied all 3 conditions,

ii) 65% of patients satisfied two or more conditions

iii) 70% of patients satisfied one or more conditions

iv) 30% of patients failed to satisfy any conditions.

RMSD correlated best to age, (Spearmann correlation 0.7, probability < 0.01) and also seemed closely related to PSAP and predicted SAP, (correlations 0.63 and 0.68, probabilities 0.003 and 0.001, respectively). There was no significant correlation between RMSD and cFR.

The Adequacy of Anaesthesia

1. Physiological variables.

i) Mean HR was 76 b.p.m. (SD 16),

ii) Mean RPP was 9366 (SD 2193).

In only two patients, did HR and RPP fail to satisfy the criteria for adequate anaesthesia. One patient developed an unexplained tachycardia, affecting RPP also; all the "good control" criteria were satisfied in this patient who had otherwise uneventful anaesthesia. In the other patient SAP control was more difficult; mean RMSD was 12.3, PR 22 and mean SAP deviation +7.78. Thus, none of the criteria for "good control" were satisfied, and SAP was the more important factor in raising RPP although HR showed a tendency to be >100 b.p.m.

2. Time to first response

The mean time from the end of anaesthesia to first response was 11.2 minutes, (SD 7.7). The cFR correlated well with mean vaporiser output, ($p = 0.02$), but correlation with RMSD was insignificant. The correlation between RMSD and response time improved from -0.15 to 0.24 when FR was corrected. Neither correlation was significant, but the suggestion is that, in discontinuing the system at the end of surgery, the

investigator may have been influenced by her impression of the quality of control, (and thus the amount of anaesthetic agent the patient had already received). Also, correlation between RMSD and cFR was limited because the mean SAP deviation was negative; RMSD increases as SAP points fall further below target, and low concentrations of isoflurane are delivered as a result. Thus cFR can decrease as RMSD increases. The mean vaporiser concentration setting was better related to cFR, (Spearman Correlation 0.51, $p < 0.05$). Overall, the suggestion is that increasing RMSD was related to SAP falling below the target.

Three out of 20 patients took longer than 15 minutes to obey commands. The first of these was a 23 year old male whose laparotomy took 112 minutes. His SAP control was such that he received two bolus doses of morphine during this time. During the control period, the mean vaporiser output was 2.5%. The system was discontinued 7 minutes before the end of anaesthesia, 28 minutes after which he obeyed commands.

The second patient of the three, a 71 year old lady, seemed relatively sensitive to isoflurane; SAP control over 43 minutes was satisfactory overall, and no morphine was required. Mean vaporiser output was relatively low, at 0.45%. The system was discontinued 1 minute before the end of anaesthesia, and after a further 24 minutes she was obeying commands. This was the same patient who had had a high PSAP >150 mmHg.

The third patient had undergone abdomenal hysterectomy, lasting 77 minutes. During this time, the system had requested a morphine bolus, as SAP control proved

unsatisfactory. None of the good control criteria were satisfied in this case, (RMSD=13.2, PR=2.61 and mean SAP deviation= +6.06). The mean vaporiser output in this case was 2.1%.

Awareness

No patients reported awareness of surgical events, or of dream-like experiences which may have been related to surgical events.

Post-operative pain, nausea, and vomiting.

Ten out of twenty patients reported pain on awakening from anaesthesia. The pain was described as "severe" in one case, "moderate" in six cases, and "mild" in three cases. The patient who had experienced severe pain was a 23 year old male; he was given 5 mg of intravenous papaveretum immediately in the recovery room, whereupon he settled down and went to sleep. Howevever, if roused and asked about his pain, he insisted it was still severe. He had had two bolus doses of morphine during his eighty minute laparotomy, and no further narcotic was given at that point for fear of CNS depression.

Three patients reported nausea of moderate intensity, in the immediate recovery period (first five hours post-op), and in one of these vomiting occured and was troublesome. The vomiting settled after prochlorperazine 12.5mg IM had been administered in the ward, some 12 hours later. This patient had undergone a seventy minute hysterectomy, and conditions for good control and adequate anaesthesia had been fully satisfied.

When asked if they thought the anaesthesia had suited them and whether or not they would have the same again, all the

patients except the one reporting "severe" pain on awakening replied that they would.

The criteria for overall adequacy of anaesthesia were satisfied then as follows;

60% of patients satisfied all the criteria,

15% failed only to satisfy the control criteria,

15% failed to satisfy control and response time criteria,

5% failed to satisfy the physiological variable criteria,

5% failed to satisfy physiological variable and control criteria.

N.B. To satisfy two out of three control criteria is here considered adequate for anaesthesia.

Comparison with Robb'S results

To compare these results with those of Robb, it is necessary to split the patients into two groups according to whether they received isoflurane only (group I_1), or whether additional morphine boluses had to be given (group I_1M). Additional narcotic boluses were necessary in 24% of his cases; in our study 30% required additional morphine.

Table 10 shows the mean values of RMSD, mean SAP deviation, PR, HR, RPP and % patients with cFR $\geq$ 15, obtained in Robbs' groups and our groups. Comparisons between our groups I_1 and I_1M were made using the Mann-Whitney U test.

a) The Control

i) Mean RMSD was higher than that obtained by Robb in both groups. However, as with his results, there was no significant difference between the RMSDs of our two groups, (10.5 and 10.3 for I_1 and I_1M respectively).

Table 10: Control data and physiological variables data from the first study and from a previous work.

	Patient Groups			
	Robb's groups		Our groups	
	Isoflurane only	Isoflurane + morphine	Isoflurane only, (I_1)	Isoflurane + morphine (I_1M)
No. of Patients	16	5	14	6
RMSD (SD)	7.0 (2.17)	8.48 (2.49)	10.5 (4.69)	10.28 (3.07)
Mean SAP Deviation (SD)	* 0.38 (3.09)	4.65 (1.55)	* -3.9 (5.96)	2.54 (4.1)
PR (SD)	** 2.64 (5.98)	3.24 (1.14)	** 0.66 (0.6)	5.24 (8.29)
HR (SD)	** 73.6 (8.06)	89.4 (9.78)	72.6 (15.44)	85.0 (15.2)
RPP (SD)	** 8677.4 (1144.5)	10634.0 (1030.4)	8741.2 (1832.4)	10823.1 (2429.1)
cFR	6.3%	60%	7%	66%

* $p < 0.05$
** $p < 0.01$ Mann-Whitney U test;

Mean values for the control and physiological variables in isoflurane only, and isoflurane and morphine subgroups of both our present (first) study and that of Robb [1].

Comparisons made only between our groups, (I_1 and I_1M), or between Robbs groups.

The cFR refers to the percentage of patients in each sub-group whose corrected time to first response was less than 15 minutes.

Table 10

ii) Mean SAP deviation in group I_1 was negative; in group I_1M, mean SAP deviation was positive, and as in Robb's study, significantly higher than that of group I_1.

iii) The mean PR was also significantly higher in the I_1M group; this was also Robb's experience.

b) Physiological variables

The mean values for physiological variables were notably similar to those obtained by Robb in both the I_1 and I_1M groups.

c) Response Time

Judged by the percentage of patients in each group who had a cFR time exceeding 15 minutes, there was no difference between these results and Robb's.

The "tightness" of the SAP control, reflected largely by RMSD was thus less good than that acheived by Robb. Despite this, the number of patients whose control proved inadequate at some time throughout anaesthesia, (i.e. the I_1M group), was similar. The difference in RMSD was more marked between the "isoflurane only" groups. This is easily explained; the morphine requiring groups represent patients whose SAP deviated mainly in an upwards direction from the target, and the control data will be affected similarly in these groups. However, the isoflurane only groups contain both well-controlled patients and those whose SAP deviated in a negative direction to the point where it would be considered poor, and result in a large RMSD; Indeed, examination of mean SAP deviation and mean PR in group I_1 reveals the distribution of SAP points to be mainly below TSAP, (mean SAP

deviation -3.9). We also see that the control data are affected especially by two cases where mean SAP deviations were -16.7 and -13.9. The RMSDs were 20.4 and 14.5 respectively, and were included in group I_1. Robb experienced the opposite; the majority of points were above the target, and he did not have large RMSDs as a result of SAP falling below target. Thus, the mean RMSDs in his two groups differed more than ours.

Overall, the negative mean SAP deviation and the low mean PR suggests SAP tended to fall below TSAP. Perhaps, this would be partially resolved by deducting 10% from PSAP and using this value as TSAP. This would allow for the effects of muscle paralysis and STP and morphine analgesia.

There are several factors which may influence the quality of control and which are pertinent here;

i) Initial SAP and/or a tendency towards hypertension. RMSD correlated significantly to initial SAP and PSAP; resting AP increases with arteriosclerosis, which produces a tendency for exaggerated swings in AP during anaesthesia [3, 4, 5, 6, 7, 8]. (We did not exclude controlled hypertensives, or those with a history of hypertension.)

ii) AP increases with age. Before the arbitrarily defined "hypertensive" point, physiological fluctuations, or variability in AP increase in magitude as mean AP increases. If mean and standard deviation are used to express variability, (as they are in our RMSD), then the latter becomes proportional to AP. To support this RMSD was significantly correlated to age and resting AP, between which there was the expected significant correlation. It may be more physiological, therefore, to assess deviation from TSAP

when the magnitude of the TSAP itself is taken into account. iii) Not only may the vasculature become more sensitive to anaesthetic agents with advancing years, the MAC of these agents is decreased and morphine requirements tend to be less [52]. This is related to changes in cerebral blood flow and neuronal density [53]. Although age was accounted for in the pre-loading of the integral, the proportional gain does not account for age. Nor did the investigator allow for decreasing morphine requirements with age.

A significant negative correlation between resting SAP and mean SAP deviation suggests that overall, sensitivity to isoflurane outweighed sensitivity to surgical stimuli under the conditions of our experiment.

Conclusion

Our overall results were similar to those of Robb, in terms of adequacy of anaesthesia and control. There was a notable difference in the distribution of SAP points around the target; whereas Robb had the majority of points above the target, our points were mainly below. The TSAP obtained from resting SAP was higher than that which would have resulted from the age-sex rule, which Robb used. On balance, our target was relatively high, perhaps taking 90% of resting AP would be more appropriate during anaesthesia, and help to improve the control. The elimination of other factors contributing to hypotension may also be of help in this respect; the use of morphine bears cause for consideration, in the next chapter.

CHAPTER 4

PROPORTIONAL-INTEGRAL FEEDBACK CONTROL of SYSTOLIC ARTERIAL PRESSURE: II

In chapter 3, we presented the results of a study of where we used feedback control of SAP to provide anaesthesia in 20 patients; as part of the protocol, we used morphine analgesia as an adjunct to anaesthesia and to help the system to provide adequate control of SAP. A discussion now follows on the rationale behind use of such potent analgesic drugs in this way, on the suitability of morphine itself; we also introduce the opioid fentanyl and aim to justify the view that it may be a more appropriate drug in this situation.

Terminology applied to morphine and it's derivatives

This will be outlined briefly, since confusion arises frequently; morphine, whose early use is referred to in the Old Testament, takes it's name from Morpheus, the god of sleep. Isolated by Serturner in 1803 from the opium poppy, ***(papaver somniferum)*** morphine and the other sleep producing constituents became known as "opiates". Analgesic properties led also to description as a "narcotic", from the greek prefix "narco" meaning to deaden or benumb.

The chemical structure of the drug was determined in 1923, and synthesis achieved in 1952. Other agents with similar structures were also synthesised and noted to produce similar effects, sedation, analgesia, respiratory depression, emesis, constipation, miosis and physical dependance. That these drugs acted via the same receptors was an obvious hypothesis; Acheson coined the term "opioid" to apply to all drugs acting

via these receptors. In 1974, Goldstein [54] showed "opiate" receptors to be widespread in CNS and at other sites. In 1983, a subcommittee on nomenclature at the International Narcotic Research Conference designated these receptors as "opioid" receptors, and by virtue of this, drugs active at these sites are "opioids". Note that opioids may have no analgesic properties, e.g. naloxone.

Opioids are of three types;

i) naturally occuring

ii) semisynthetic

iii) synthetic

Development of further opioids aims to produce drugs with high specificity and intrinsic activity at the receptor sites which lead to analgesia; thus for the same analgesic effect, lower concentrations, at sites other than the "analgesic" receptors, result in minimising unwanted side effects, (respiratory depression, nausea, vomiting etc).

The use of opioid analgesics in anaesthesia

In 1910, George Washington Crile of Cleveland, Ohio, published his theory of anoci associations [55]: during surgery, adverse psychic stimuli could be blocked by light anaesthesia, while the painful stimuli should be blocked by local analgesia. Shortly afterwards, in 1926, Lundy [56] used a combination of premedication, local and general anaesthesia, (with various agents), balancing unconsciousness and pain relief. The concept of such "balanced" anaesthesia was then brought to the fore after Griffiths and Johnson introduced curare into anaesthetic practice [57]: Gray and

Rees [58] defined anaesthesia to include

i) muscle relaxation

ii) analgesia

iii) narcosis.

However, it soon became apparent that techniques using N_2O for analgesia, and thiopentone for narcosis were resulting in unwanted autonomic activity and Woodbridge [59] added a fourth criteria to the definition of anaesthesia;- "abolition of autonomic reflexes". In order to satisfy these conditions, anaesthetists began to report their techniques using additional analgesic drugs during anaesthesia. These included pethidine, levorphanol, morphine, fentanyl and phenoperidine and when used in combination with other agents, a double-blind study failed to distinguish between them.

In current anaesthetic practice, the use of opioid drugs has survived as they confer the following advantages when used in combination with volatile agents;

i) Requirement of volatile agents are reduced

ii) Better analgesia is provided after surgery

iii) Autonomic reflexes are attenuated in a dose-related manner: large doses may abolish them completely.

iv) If awareness occurs, partial analgesia may lessen the atrocity for the patient. (Opioids must also decrease the incidence of awareness, provided that volatile agents are also used, since they decrease MAC.)

As well as providing analgesia in acute pain and as an adjunct to general anaesthesia, opioids have been used alone to provide anaesthesia: Lowenstein [60] successfully demonstrated that morphine 1 mg/kg could be used with 100% O_2 as a sole anaesthetic with minimal cardiovascular

haemodynamic effect. This became a popular technique in cardiac surgery, but it was soon apparent that significant disadvantages of morphine anaesthesia included incomplete amnesia, histamine-mediated reactions, markedly increased fluid and blood requirements and prolonged respiratory depression post-operatively. Furthermore, in contrast to Lowenstein's experience, cardiovascular stability was not always complete.

The opioid fentanyl

Fentanyl was introduced into clinical practice in the early 1960s, and is a synthetic opioid of the phenylpiperidine group. It is a pure u-agonist, introduced as an analgesic with a potency 50 to 100 times that of morphine and a shorter duration of action than morphine. At the time when morphine analgesia was popular, De Castro in Europe proposed that fentanyl also could, in high doses, be used as an anaesthetic. This was ignored at the time, but the problems associated with high dose morphine (see later) and other opioids prompted the search for "cleaner" opioids, with respect to the cardiovascular system.

Thus fentanyl became the subject of many pharmacodynamic and pharmacokinetic studies in animals and man. However, for various reasons, (eg. problems with assay techniques), the results are widely disparate. Fentanyl maintains a place in anaesthetic practice to-day, although its use may be superceded in the future by even more potent opioids whose clinical profiles are more precisely defined.

Clinically relevant pharmacology

Fentanyl is a tertiary amine with a pK_a of 8.43. It behaves as a weak base, and at body temperature and pH, it is 91% ionised and 80-85% protein bound [61]. Lipid solubility, as measured by the octanol-water distribution coefficient is greater than that of morphine; thus fentanyl crosses the blood-brain-barrier with greater rapidity than does morphine, and to a larger extent. This explains why fentanyl administered directly into brain is only twelve times as potent [62] as morphine, while 50 to 100 times as potent if given intravenously; higher lipid solubility of fentanyl means the drug has greater access to opioid receptors in brain.

Intra-venous fentanyl kinetics

After intravenous (IV) injection of fentanyl both 2 and 3-compartment models are described, in which the drug is introduced into the central compartment [63]. Plasma levels fall rapidly at first after IV injection due to redistribution into tissues. The volume of distribution varies between studies from 46 to 398 litres in humans [64]. Due to the high lipid solubility of fentanyl, the rate of uptake into tissues is limited only by blood-flow. Brain levels (cerebro-spinal fluid) of drug increase rapidly due to high blood flow to the brain, and onset of effect is rapid. The onset of effect begins 90 seconds after injection [64] and respiratory depression is maximal after 2 to 5 minutes, corresponding to increasing CSF drug concentration.

Concentration-time profiles of fentanyl suggest a central compartment which includes plasma, lung, spleen, kidney and

brain: CSF, muscle and intestine are seen as a compartment which equilibrates relatively quickly with the central one, and which is therefore filled relatively quickly: fat, on the other hand, is seen as a slowly equilibrating, large compartment. Maximal concentrations in fat, where perfusion is relatively poor, occur 30 minutes after IV injection. Thus, fentanyl fits the description of a drug whose duration of action is terminated by redistribution and single doses have a brief duration of action.

After equilibration with tissues (10-15 minutes), CSF and plasma fentanyl levels decrease in parallel. Fluctuations occurring during this phase, after 2 to 7 hours later [64]. Stoekel and his co-workers [65] suggested this was due to an ion-trapping effect of the acid gastric pH on the drug secreted in gastric juices. Mather argues in his review [62] that this sort of contribution to the secondary peaks would surely be negligible, bearing in mind the amount of opioid involved, first-pass effects (two thirds of the drug is removed in this case), volumes of distribution, and the effects of opiates on gastric emptying. It is interesting that in patients given cimetidine prior to surgery, the secondary peaks were absent. Mather suggests that it is more likely these peaks are due to fentanyl being squeezed out of muscle by the first movements after surgery.

Elimination of such a lipid soluble drug depends ultimately on biotransformation which enables renal excretion; 69% of the dose given is excreted in the urine as metabolites. Clearance of fentanyl has been estimated to be equal to hepatic blood flow and also to one third of the latter. There

is no evidence that clearance is related to initial dose, from studies using the same method for fentanyl assay and different doses. Elimination half-life, however is prolonged due to slow redistribution from poorly perfused tissues back into the central compartment from where it is eliminated. This means that

i) Repeated doses lead to accumulation.

ii) Large doses last longer because plasma drug levels do not fall below the threshold for central effects during redistribution phases.

iii) During the elimination phase, even a small increase in plasma fentanyl levels, (e.g. muscle movement), may cause an increase in the central effect.

Thus, while having a short duration of action in single small doses, repeated or large doses may produced prolonged respiratory depression.

Plasma fentanyl levels

In humans, the mean plasma analgesic concentration of fentanyl is between 1 and 3ng/ml. Respiratory depression is associated with this order of plasma level, but is not seen below 0.5ng/ml.

The effect of fentanyl on MAC

Animal experiments in dogs tested with tail-clamps have shown that fentanyl reduces the MAC of enflurane in a dose-related manner. However, there seems to be a ceiling effect; increasing the plasma level to 30ng/ml reduces MAC by 65%, but no further reduction can be achieved there after by further increasing plasma fentanyl levels [66]. The same

effect occurs with morphine.

The cardiovascular effects of fentanyl.

The cardiovascular effects of fentanyl are generally less than those seen with morphine. Fentanyl does not cause histamine release and hypotension is rare, with analgesic (2-10ug) and high doses [67]. Using (high dose) fentanyl to induce anaesthesia, heart rate, arterial pressure, pulmonary wedge pressure and pulmonary arterial pressure are largely unaffected. However, there is a reported incidence of a fentanyl-induced bradycardia at high doses; all opioids acting at u-receptors (except meperidine) stimulate the medullary vagal nuclei and this is thought largely to be the cause of the bradycardia. It may be minimised, but not prevented, by prior administration of anticholinergics and prevented by bilateral vagotomy. Myocardial performance is unaffected.

The Use of Fentanyl to Provide Analgesia, During Anaesthesia by Feedback Control of SAP: A Study of 20 Patients

Introduction

In the previous study of 20 patients, (chapter 3), the results overall showed mean SAP deviation falling below target SAP (TSAP). If this was a result of our technique, then the an undesirable consequence (apart from hypotension), could be awareness, because of persistently low inspired isoflurane concentrations. To offset this risk slightly, hypotension reduces MAC.

Our use of morphine analgesia may have contributed to this problem: cardiovascular side effects of this drug (in doses comparable to ours) include reduction in mean AP, consistent decrease in HR, and a transient decrease in systemic vascular resistance [68]. It is well known that histamine levels increase after IV morphine [69], and this is one mechanism by which AP may be reduced. Morphine decreases arteriolar and venous tone causing decreased venous return. The venodilatation is dose-related and may be the major contributor to the decreased venous return. The mechanism may be a central inhibition of sympathetic reflexes. Moreover, morphine may itself have a direct action on vascular smooth muscle.

In view of the above, we have chosen to use fentanyl analgesia in this study. Not only does fentanyl affect the CVS less than morphine (see above), but there may be other

advantages to using the drug; the high lipid solubility and more rapid onset of action of fentanyl, (2 to 5 minutes to peak effect v's morphine 30 (SD 15) minutes) means that analgesia levels should peak early in the control period, after IV fentanyl at induction. Thereafter, the levels will decline. This is in contrast to morphine; analgesic effect rises early in the control period, peaks, and then falls. Opioids affect MAC according to brain concentrations, so while a continuous infusion of narcotic at steady-state is the ultimate background against which to run our feedback control system, fentanyl would seem more suitable than morphine. Furthermore, after fentanyl boluses, brain concentration will increase relatively quickly and overall control should be improved.

One further adjustment to the protocol was to use 90% of resting/plateau SAP for the target SAP, or TSAP.

Patients and Methods

Inclusion criteria were identical to the previous study. Written consent was obtained from 20 patients due to undergo elective surgery, (table 11). After obtaining resting SAP on the ward as before, 90% of this value was used as TSAP.

Anaesthesia

Anaesthesia was identical to the previous study, except that at induction 2ug/kg IV fentanyl was given instead of morphine. In theatre, immediately before incision, a further 1ug/kg IV fentanyl was given. Further fentanyl boluses (1ug/kg) were ordered by the system according to the same rules as before, but the rule could be activated once in 10 minutes, (previously limited to 15 minutes).

Table 11

OPERATION	NO. OF PATIENTS
Hysterectomy	9
Pelvic floor repair	9
Oophorectomy	1
Ovarian cystectomy	1

Operations carried out on twenty patients undergoing anaesthesia by feedback control of SAP, supplemented by fentanyl analgesia, (the second study).

Table 11

Intravenous fluids were given in the same way as before, and recovery, post operative interview and analysis of results were also the same.

Results

On the ward (table 12), mean SAP was initially 138.8 (SD 20) mmHg, falling to a mean plateau value of 126 mmHg, (SD 15). The mean target SAP was 113.8 mmHg, (SD 13), and mean predicted target SAP was 121.6 mmHg, (SD 11). In this case, the difference between predicted target SAP and actual TSAP, (90% resting SAP), was highly significant ($p < 0.01$, paired t-test).

Mean anaesthesia time was 62.55 minutes, and mean age 48.8 years. All 20 patients were female, and the operations are listed in table 11. Five out of 20 patients (25%) required additional fentanyl boluses, and 7 out of 20 (35%) required glycopyrollate 0.2mg IV during anaesthesia.

The Control

Mean RMSD; 9.61 (SD 3.8)

Mean deviation from TSAP; 1.67 (SD 4.5)

Mean PR; 2.06 (SD 2.5)

The good control criteria (see chapter 3) were satisfied as follows;

i) 50% of patients satisfied all three criteria

ii) 65% of patients satisfied two or more criteria

iii) 90% of patients satisfied one or more criteria

iv) 10% of patients failed to satisfy any criteria.

There was a significant positive correlation between RMSD and target SAP obtained on the ward, ($p = 0.017$).

Table 12: Preoperative and target systolic arterial pressure in 20 patients in the second study.

PATIENT NO.	INITIAL SAP	PLATEAU / RESTING SAP	ACTUAL TSAP	PREDICTED TSAP
1.	149	123	112	131
2.	159	140	126	134
3.	151	126	113	134
4.	119	110	99	109
5.	140	131	118	117
6.	173	154	138	134
7.	120	116	129	113
8.	121	105	94	138
9.	119	118	106	120
10.	168	152	137	138
11.	159	143	129	114
12.	110	105	95	108
13.	145	119	107	128
14.	173	150	135	134
15.	120	123	112	123
16.	143	125	113	118
17.	121	121	109	106
18.	138	118	106	116
19.	128	126	113	122
20.	120	121	109	110
	---	---	---	---
MEAN	139	126	113	127
SD	20	15	13	11

Systolic Aterial Pressure, (SAP) in mmHg, in 20 patients (from the second study), from the ward (INITIAL and PLATEAU/RESTING SAP) and the derived value for target SAP, (ACTUAL TSAP) with TSAP calculated from the age-sex rule, (PREDICTED TSAP).

Table 12

The adequacy of Anaesthesia

a) Physiological variables.

Mean HR was 67.15 (SD 8) b.p.m. and mean RPP was 7968 (SD 1733). Two patients had a mean RPP > 1200, and both had a Mean HR < 100 b.p.m. SAP control was such that additional fentanyl boluses were required in both these patients.

b) Time to first response

The mean cFR time was 9.4 minutes (SD 6.3) minutes. Five patients took in excess of 15 minutes to obey commands. Only two of these had required additional fentanyl boluses.

c) Awareness

A 59 year old female patient reported a dream of "as if a cut was being made in the stomach". She remembered being put to sleep in the anaesthetic room, and waking up after she had reached the recovery room. She was unsure if this dream had occurred during her operation, and she had not been distressed fortunately, nor was the dream associated with hearing voices. She was told that this may well have been a direct result of a "light" level of anaesthesia, and was also questioned again after three days. She was unable to shed further light on the occurrence of her dream, nor had she remembered anything else about her operation. She said also that she would willingly undergo the same anaesthetic again. During her anaesthesia the control was not good; however, there was no indication from physiological variables, (or indeed other clinical signs), that she was consciously perceiving surgical events.

Post-operative pain, nausea, and vomiting

Two patients reported severe pain, 3 reported moderate pain, and 7 reported mild pain on awakening. Eight patients said they had no pain on awakening.

Only one patient reported nausea as a problem, and only this patient also reported vomiting.

All patients thought that their anaesthetics had suited them, and that they would agree to have the same anaesthetic again if necessary.

In this study, the criteria for overall adequacy of anaesthesia were satified as follows;

55% satisfied all the criteria,

5% failed only on the control criteria,

20% failed on control and response time,

5% failed only on physiological variables

5% failed on physiological variables and control criteria,

5% failed the corrected response time criteria only.

1 patient (5%), failed on control and was possibly aware.

Discussion

Although, the mean RMSD of this group, (9.61), differed little from mean RMSD in the previous study, (10.34), the difference between mean RMSDs in the isoflurane only group (I_2) and the isoflurane/fentanyl group, (I_2F), was greater than that between the two corresponding groups of the previous study. However, the difference did not reach statistical significance. Table 13 shows mean values for control data, physiological variables and response time in the two groups of patients, (separated according to whether or not they received additional fentanyl).

Table 13: control data and physiological variables data in the second study.

	PATIENT GROUPS		
	I_2		I_2F
NO. OF PATIENTS	15		5
RMSD	8.82 (3.4)		11.97 (4.6)
MEAN SAP DEVIATION	-5.3 (3.2)	**	6.84 (3.8)
PR	1.29 (1.8)	**	4.35 (3.1)
RPP	7405.0 (962.0)		9655.0 (2505.0)
HR	65 7.4		73 (b.p.m.) 7.9
cFR	8.2 5.5		13 (mins) 7.8

** $p < 0.01$, Mann-Whitney U test

Mean values (and SD) for control variables, physiological variables and response time in the groups I_2 and I_2F, (the second study).

Group I_2 required NO additional fentanyl boluses, and group I_2F were those who did.

Table 13

The distribution of SAP points around the target is clearly different from the first study; the PR in group I_2 reflects an even distribution, while in group I_2F, the points are mainly above TSAP. Mean SAP deviation in I_2 shows that the points in the group with better control were very close to the TSAP. This is in contrast to the corresponding group from the previous study; group I_1 contained patients whose control was poor because of points falling below TSAP. Clearly, the use of a lower TSAP and fentanyl analgesia in this study has minimised the appearance of such patients in the "good control" group, but has not significantly affected the number of patients whose SAP control has "escaped" in an upwards direction. All control criteria were satisfied by 50% of patients in this study compared with 30% in the previous study. By itself this does not tell us much; in as much as 25% patients in the previous study failed the "good control" criteria alone, (from our adequacy of anaesthesia criteria), the control becomes significant. In this study, only 5% failed on "control criteria" alone; this is obviously a less significant proportion.

Mean RPP values are again similar in both groups to the values obtained previously by us and by Robb. Mean HR, however, was significantly lower ($p = 0.03$, Mann-Whitney), in this study compared to the previous study with morphine, and 7 patients required glycopyrollate 0.2mg IV this time. It is well known that the combination of fentanyl and a muscle relaxant with no vagolytic action may result in bradycardia, especially in response to visceral stimuli. As a result of low HR and better overall control in this study, RPP was similarly significantly lower than in the previous study, (p

< 0.01).

In the I_2F group, the cFR time was longer than in group I_2, although this was not significant statistically. Forty per cent of group I_2F took in excess of 15 minutes to obey simple commands, compared to 20% in group I_2. Although there was no overall statistically significant difference in cFR between this and the previous study, there was a significantly increased cFR time in group I_1M compared to group I_2F: thus additional morphine boluses were associated with significantly more delay in recovery than additional fentanyl boluses. We predicted prolonged recovery times with repeated doses of fentanyl, but seem to have shown that repeated doses of morphine more markedly prolongs recovery; a possible explanation for this is that because morphine has a slow onset (low lipid solubility) of peak action in the CNS, (relative to fentanyl), the system regains control slowly after morphine boluses. During this time, high concentrations of isoflurane continue to be delivered, and overall, the patients tend to recieve more volatile anaesthetic with morphine than fentanyl, when control is poor and boluses are required.

Overall, the adequacy of anaesthesia was little changed with respect to the previous study, but significantly, we encountered a problem with one possible case of conscious perception. A post-hysterectomy patient needs only look at her abdomen to know that indeed a cut has been made; the report of a dream such as this is not necessarily evidence of conscious perception of surgical events. However, it is wiser to assume and deal with the problem as if it were evidence of

awareness, for fear of consequent harm to the patient.

The incidence and amount of pain on awakening from anaesthesia was strikingly increased in this study, reflecting the shorter duration of analgesic action of fentanyl compared to morphine. The cumulative CNS effect of repeated fentanyl boluses was not clinically significant in this study; cFR in group I_2F was 13 minutes, and 8.2minutes in group I_2, and the difference was insignificant.

Conclusion

Using fentanyl analgesia to supplement anaesthesia by feedback control of SAP, (90% of resting SAP), the "good" control criteria were better met than in a previous study using morphine, although the difference was of doubtful statistical significance. Overall adequacy of anaesthesia was little changed, except that in one case there was possibly awareness. Furthermore, the degree of discomfort in the immediate post-operative period, although not formally assessed, was increased compared with that reported by patients in the study where morphine was used. The subject of awareness is discussed and investigated next in this work.

CHAPTER 5

AWARENESS

Awareness is said to have occurred if a patient can remember specific events which occurred during anaesthesia, at a time when they were considered to be unconscious [70]. However, a patient may also give an investigator evidence that they have processed and retained, (perceived), information they received at such time. Since they cannot actively remember the information, but can often guess it (more than by chance alone), this phenomenon is called sub-conscious awareness. The patient is "unaware", therefore, of having perceived the information. To avoid confusion, we refer to conscious and unconscious perception to distinguish between the different categories of awareness.

It has been put forward by Professor J.G.Jones of Leeds that we may define 4 states which can exist (with respect to awareness during general anaesthesia)-;

1. The patient consciously perceives and remembers intra-operative events.
2. The patient consciously perceives but does not remember intra-operative events.
3. The patient unconsciously perceives: there can be no conscious (explicit) memory of an event which has never reached consciousness.
4. The patient perceives nothing at any level.

Going back to the idea that anaesthesia can be seen as a continuum, it is possible to visualise these stages ocurring on the "awareness" line as we go along from full consciousness to complete lack of perception. Progression from stage 1 to 3, (and indeed the existence of stage 2),

depends on the premise that general anaesthesia depresses memory before cognition is fully obtunded, and also that information is processed unconsciously initially. The latter is supported by psychological evidence [71], but the effects of general anaesthesia on memory are less well defined. Furthermore, while recognising the phenomenon where patients respond to verbal commands during anaesthesia and are later unable to remember so doing, we cannot know whether the actions were consciously initiated and forgotten, or unconsciously carried out.

While stage 1 is highly undesirable, and to be avoided at all costs, the possible long and short-term effects of perception during anaesthesia, (see later) make stages 2 and 3 certainly worthy of further investigation. Furthermore, these stages herald the onset of stage 1 on the continuum.

Consciousness

Consciousness itself remains a somewhat elusive entity; it is the means by which an individual experiences input stimuli, and thus shares his "knowledge" with himself. Therefore, it is an entirely subjective phenomenon, and as such, impossible to assess objectively. We can, however, make objective observations of conscious behaviour. Because a paralysed patient undergoing surgery cannot "do behaviour" or communicate with anyone but himself, we rely on his memory of, and his personal experience of events during surgery for evidence of conscious perception. Such memories vary from detailed accounts of surgical events and conversation, (especially personally directed derisory remarks), to vague dreams. Thus, it is sometimes difficult to assess whether the

dreams have taken place pre-operatively as a result of premedication, or post-operatively while an altered state of consciousness prevails.

Unconscious perception.

Information may undergo a complex degree of cognitive processing, prior to reaching consciousness, (pre-conscious processing). If the input stimulus is perceived unconsciously, it is referred to as "subliminal". Although subliminal information may affect behavioural responses, the individual cannot share this knowledge with himself. Another way to understand this is that the act of making this subconscious information conscious, (and thereby accessible to explicit memory), cannot be performed.

There is increasing evidence to support continuation of cognitive processing during anaesthesia (see later). However, in the absence of conscious perception, the stored information can only be retrieved by implicit memory tests (i.e. that the information/stimulus has been processed and stored is "implied" by a certain verbal/behavioural response to a subsequent test stimulus: conscious or intentional recollection is not possible). Explicit and implicit memory are independant; i.e. if information has never entered consciousness, then although stored, it may be accessible to implicit memory, but inaccessible to explicit memory.

We can see now that the retrieval of information perceived unconsciously is unlikely to yield much if testing involves a task of conscious recollection, or explicit memory. In other words, the sensitivity of tests for unconscious perception is least using explicit memory tests, and increases when

implicit tests are used.

The Significance of Unconscious Perception

We need to know to what extent unconsciously perceived information affects patients undergoing surgery and anaesthesia. We already know that disturbing psychiatric syndromes may result after conscious perception [73]. These syndromes resemble the "post-traumatic neuroses/psychoses" seen in survivors of combat after war, with vivid nightmares, pre-occupation with death, feelings of unreality, depression, anxiety, anger and frustration. The patients, unsure of the cause of their symptoms are afraid to complain in case they are thought insane. Although there is often no conscious perception, (or spontaneous recall), it may be that some information came very close to reaching consciousness; sleep, by depression of normal waking conscious mechanisms, allows the subconcious information to emerge vividly in terrifying dreams.

Evidence that unconscious perception may affect patient welfare post-operatively comes from two works presently; that of Evans and Richardson [74], and that of Bonke and co-workers [75].

Evans and Richardson played messages, pertaining to operation and post-operative recovery, through headphones to patients undergoing anaesthesia for hysterectomy. The messages included;

1. instructions on coping during the post-operative period, e.g. "How quickly you recover depends on you-the more you relax, the more comfortable you will be."
2. Positive suggestion type messages, e.g. "you will

not feel sick, you will not feel pain",

3. Third person suggestions, e.g. "the operation seems to be going very well and the patient is fine".

They showed a significantly reduced duration of and improved quality of post-operative recovery from abdominal hysterectomy. The incidence of post-operative pyrexia, bowel difficulties were significantly reduced, as was the post-operative stay.

Bonke and his co-workers performed a similar type of study in patients undergoing cholecystectomy. Their taped messages again pertained to the operation and post-operative recovery, and were mainly in the form of positive suggestions. They also added some third person messages, similar to those used by Evans and Richardson. They concluded that the post-operative stay, in the older age-groups only, was significantly reduced.

In this study, anaesthesia was standardised only by the use of the same drugs; we are not told the dosages for the majority of these, and the only other indication of adequacy of anaesthesia is the lack of conscious perception of the messages. Evans and Richardson give no information about the standardisation (or lack of it) of anaesthesia. This, unfortunately, makes it difficult to interpret the results.

Nevertheless, these findings may have considerable implications if validated in future; as Evans and Richardson point out, it may be that autonomic function is affected by unconsiously perceived information. The "stress response" to surgery and anaesthesia could be modified in this way, affecting post-operative recovery, e.g. resistance to infection, hormonal release etc.

In fact, one would expect this method of detection of unconscious perception to be most sensitive; autonomic function involves an absolute minimum of conscious processing (see above).

Similar studies, into the effects of suggestion on post-operative recovery, have been performed thirty or so years ago [76,77]. However, poor control and lack of information about the anaesthetic technique make these reports little more than anecdotal.

Testing for Unconscious Perception

Other types of psychological tests can be applied to the anaesthetic situation. The usual format is that of an auditory stimulus (given during surgery when unconsciousness is presumed), followed by a test which elicits a response, when consciousness has been resumed. The objective is to determine whether or not a particular response can be obtained significantly more often than would be expected by chance alone. If so, this influence on response is attributed to some degree of perception of the input stimulus.

The sensitivity of these studies may vary according to the design of both phases, and the anaesthesia involved:-

1. The stimulus

The input stimulus is more likely to produce an effect if pertinent to the patient. In a study by Levinson [78] in 1965 a crisis was simulated during the operation. Although no patient perceived this consciously, several patients were able to repeat the words used when hypnotised, one month post-operatively. Under hypnosis, some became so distressed

that the procedure was abandoned; the method is now, rightly, considered unethical.

Pertinent information may be brought to consciousness quickly, out of less important background noise. Thus, conscious mechanisms are "aroused" if the incoming stimulus is of importance to the "survival and needs" of the individual (the cocktail party phenomenon). Two things could be happening here;

1. The cognitive processes could arouse conscious mechanisms when vital information enters at a pre-conscious level, or
2. Vigilance mechanisms within consciousness may pull out from the pre-conscious pool information which it recognises as vital.

In either case, the result is that the input is more likely to be experienced consciously. This may explain anecdotal reports of patients complaining about personally directed derisory remarks during their operations [79]. (Note that in order to recognise information as vital, pre-conscious processing must occur.)

Bennett [80] puts forward a possible mechanism for this: the sensory input which is "last to go" in passing from conscious to unconscious is auditory input. However, the reticular activating system would re-inforce auditory information according to its importance. In turn, the importance of the information to the individual depends on the contents of his "knowledge-base" or long-term memory. Thus, "unimportant" signals do not cause activation, and the signal is less likely to be reflected into consciousness. Furthermore, at a level of anaesthesia where unimportant signals do not

activate consciousness, more important signals may well do so. The latter event would render anaesthesia inadequate.

Increasing the salience of input information can be achieved by preceeding the message by the patient's name or presenting information about the operation itself. We reasonably assume that such information pertains to the "needs" for survival, or well-being of the individual.

Workers have shown that salient auditory inputs produced significant galvanic skin responses, under nitrous oxide and halothane anaesthesia [81]. It is interesting that the investigators were unable to predict accurately what information would be most salient to any particular patient. Notably, the name of the miner's union leader (Mr. Arthur Scargill), at the time featuring in the national news, produced greater galvanic skin responses than the patient's own names. This supports the arguement that salience depends on individual differences in long-term memory, and varies subjectively with individual experiences.

2. Time interval between stimulus and response.

The time interval between anaesthesia and performing the retrieval task is also important. Adam [82] suggests that there is a dense amnesia immediately post-operatively, which recedes for up to two weeks. Since retrieval improves over this period, the post-operative deficit seems not to be in the incorporation of material in memory, but in the ability of conscious memory mechanisms to access the material. This may account for reports of post-operative difficulty with crossword puzzles; patients who previously had little trouble with crosswords found their skills diminished for several

days following cardiac surgery. (There may be other reasons why cognitive powers are reduced following cardiac surgery, of course).

Contrary to the above, in an unpublished study by Bonke, implicit memory for words decreased with time after anaesthesia; after a few hours, patients were less likely to respond with target words (as evidence of information perception). The author suggests that auditory stimuli under these conditions may only strengthen existing associations, (rather than be incorporated as "new" information); these effects may be short-lived, in contrast to the retention of actively learned material. There was no spontaneous recall in this study, but there was a significant effect on the generation of target words in implicit memory testing.

3. Method of retrieval

We have already stated that the method of information retrieval may greatly affect the sensitivity of the test; spontaneous recall is least sensitive, while autonomic responses could be considered the most sensitive, since they involve a minimum of conscious processing. In essence, a behavioural response is sought which occurs more often than it would by chance alone.

Verbal responses

Techniques which use verbal responses include free recall, recognition, free-association, spelling and the use of homophones.

In recognition tests, "cues" facilitate the tasks of recognising the input information. This would help the

patient to recall information which has been only weakly registered during a period of decreased consciousness. The patients are provided with lists of words, some heard during anaesthesia, and some not, and asked to guess which they have heard. The facilitation of memory tasks by "cues" is more sensitive than free recall, but free-association tasks are even less demanding of conscious, or explicit, memory.

Homophone priming [83] techniques take advantage of a natural feature of our language where a spoken sound has two (or more) meanings, eg. son/sun. A subject is "primed" with a phrase containing the less common element of a homophone pair, e.g. "a television SERIAL", and the homophone pair is cereal/SERIAL. This encourages the homophone to be encoded in memory in its less common form, perhaps strengthening existing associations. After priming, the subject is asked to spell, define or free-associate to the cue, when it is presented as an aural cue. Evidence of priming is when the less common meaning arises significantly more often than by chance alone.

Free-association ought to be the least demanding, and thus most sensitive retrieval method in homophone studies. In a study by Eiche and co-workers [79], there was no evidence that the elements of the homophone pairs had been encoded during anaesthesia. However, the study asked patients to recognise and spell the homophones, which may be more demanding memory tasks than free-association. Furthermore, the anaesthesia was not standardised, and the results' analysis has been critisised by Miller [84], on the grounds that performance parameters, appropriate in recognition testing, were omitted .

Priming with words from a semantic category may be used to influence the dynamics of verbal memory; within semantic categories, there is a hierarchical arrangement, whereby the more commonly used words in every day language are more likely to be generated by free-association. Exposure (priming) to less common words may raise their ranking within the semantic category, and increase the probability of their retrieval. Millar and Watkinson [85] demonstrated this effect in female general surgical and gynaecological patients.

Non-verbal responses

These tests involve the detection of behavioural responses in excess of normal. Studies of responses such as chin touching and ear pulling [86], after suggestion-type messages during anaesthesia, claim that behaviour is significantly altered post-operatively. However, in these studies there is no control of the pre-operative incidence of these behaviours, and the interpretation of actions such as these may be somewhat subjective.

Post-operative recovery patterns can be seen as behavioural responses, and some workers, (see above), have shown significantly improved recovery following suggestion-type messages. It is surprising that post-operative analgesic requirement was unaffected by the messages; however, there are many factors which uncouple amount of discomfort experienced and dose of analgesic received, e.g., the stoicism of the patient, the availability of nursing staff, etc. More interesting is the work of McLintock et al, assessing post-operative analgesic requirement objectively, (i.e. with patient-controlled analgesia), after soothing, re-assuring

taped messages played during anaesthesia. Although the results were not statistically significant, there was a decrease in the post-operative morphine requirements of the group who heard the messages compared to the control group (who heard white noise). The range of opiate requirements was also increased in the experimental group, and it is possible that this group included a sub-group whose requirements were significantly reduced. It has been suggested that pre-operative susceptibility to this sort of suggestion varies, (as it does to hypnotic suggestibility), and the sub-group may represent those whose susceptibility is high.

The implications that cognitive functioning continues under anaesthesia, from the above studies suggests that at the least during general anaesthesia, patient's ears should be covered, voices and extraneous noise should be kept to a minimum, and discretion observed when discussing the case in hand.

CHAPTER 6

PROPORTIONAL-INTEGRAL FEEDBACK CONTROL of SYSTOLIC ARTERIAL PRESSURE: III

Investigation of Conscious/unconscious Awareness

Introduction

In our previous group of 20 patients undergoing anaesthesia, by feedback control of SAP, using isoflurane and augmented by fentanyl analgesia, we reported one probable case of conscious perception. This was detected by spontaneous recall, and since this method is relatively insensitive, we appreciate that the incidence of perception (conscious or unconscious) may exceed this. It is surprising that this ocurred, in view of the fact that, with the system in its' present form, our patients have tended to have a relatively long first response time. This implies that their anaesthesia is relatively "deep" and in order to investigate cognitive function and perception, a sensitive method would be required.

For this reason a homophone priming technique was chosen (see chapter 5), and free-association was employed as the information retrieval method. In addition, the investigation was designed to examine the sensitivity to priming, at different end-tidal (ET) concentrations of isoflurane. Inherent in the sensitivity to priming during general anaesthesia are cognitive ability and level of consciousness at the time, so that a "depth" of anaesthesia continuum, could be validated for cognitive function.

Furthermore, we are in a position to standardise anaesthesia

in a reproducible manner with our system, where previous investigations into conscious and unconscious perception display a notable lack of standardisation. Those who conclude that there is an incidence of perception during general anaesthesia are unable to relate this to a particular state of anaesthesia.

In this series of 24 patients, the TSAP, or reference for the feedback control system was 90% of resting SAP, and supplementary analgesia was provided by morphine. Morphine analgesia was chosen rather than fentanyl because of the higher incidence of bradycardia, and the increased severity of post-operative pain seen when fentanyl analgesia supplemented anaesthesia in the previous series of 20 patients.

Patients and methods

Twenty-four patients, due to undergo elective surgery, (table 14) gave written consent to participate in the study. There were 4 males and 20 females, aged between 27 and 71 years, and the following led to exclusion;

i) uncontrolled hypertension
ii) a history of neurological damage
iii) psychiatric disease / medication
iv) neurological disease, including deafness

Preparation of audio-cassette tapes

Four audio-cassette tapes were recorded, in the voice of the investigator, in the recording room in the Glasgow University Audio-Visual department. Each tape began with the same message, instructing the patient to listen carefully, and that it was important to do so. Next came a list of ten

Table 14

OPERATIONS	NO. OF PATIENTS
Abdominal hysterectomy	11
Vaginal hysterectomy	4
Ovarian cystectomy	2
Pelvic floor repair	3
Inguinal herniorrhaphy	4

Operations carried out on 24 patients undergoing anaesthesia by feedback control, supplemented by morphine analgesia, (the third study).

Table 14

different phrases, a completely different list on each tape. The phrases each contained the less common element of a homophone pair in context, eg, ***a knight in shining armour***, where **night/*knight*** is the homophone pair, and ***knight*** is the less common element. The message and list sequence was repeated continuously, and the tapes were coded by the sound technician. The code was not broken until the conclusion of the study. Table 15 shows the homophone containing phrases used in the 4 lists, where each homophone is the less common element. The 40 homophones were chosen from normative data constructed by Galbraith & Taschman (2).

In a random double-blind manner, any two out of the four tapes were alloted to each patient as tapes A and B, to be played during anaesthesia according to the ET isoflurane concentration, (ET[isoflurane]); if ET[isoflurane] was $\leq$1.2% tape A would be played to the patient, and if ET[isoflurane] was > 1.2% tape B would be played. Thus, each patient would hear either one or two tapes out of the four, (according to ET[isoflurane], amounting to 10 or 20 homophone phrases out of 40.

Anaesthesia

The control system was programmed to set the TSAP at 90% of resting SAP, because, in our first series of 20 patients, (when we used morphine analgesia and TSAP was resting SAP per se), SAP had tended to fall below the target. Premedication and procedure in the anaesthetic room was identical to that in the first series.

After transfer to theatre, the control system was commenced immediately, and after a ten minute period, (for settling

Table 15

	List No. 1	
1.	bell / belle	the BELLE of the ball
2.	air / heir	the HEIR to the throne
3.	real / reel	an eightsome REEL
4.	pain / pane	a PANE of glass
5.	flea / flee	to FLEE from danger
6.	grown / groan	an agonising GROAN
7.	course / coarse	a COARSE material
8.	steal / steel	a rod of STEEL
9.	seen / scene	setting the SCENE
10.	weak / week	a seven day WEEK
	List No. 2	
1.	feet / feat	a FEAT of courage
2.	pale / pail	a PAIL of water
3.	fair / fare	to pay full FARE
4.	night / knight	a KNIGHT in shining armour
5.	hair / hare	as fast as a HARE
6.	steak / stake	a wooden STAKE
7.	sun / son	SON and daughter
8.	bore / boar	a wild BOAR
9.	seem / seam	the SEAM of a dress
10.	meat / meet	pleased to MEET you
	List No. 3	
1.	flower / flour	FLOUR and water
2.	hour / our	OURselves
3.	base / bass	a big BASS drum
4.	break / brake	apply the hand-BRAKE
5.	hear / here	HERE and there
6.	roll / role	an actor's ROLE
7.	sell / cell	a prison CELL
8.	colonel / kernel	a nut KERNEL
9.	him / hymn	a HYMN-book
10.	right / write	to WRITE a letter
	List No. 4	
1.	pray / prey	birds of PREY
2.	rain / reign	a REIGN of terror
3.	great / grate	a GRATE full of ashes
4.	one / won	we WON first prize
5.	cereal / serial	a television SERIAL
6.	plane / plain	PLAIN and simple
7.	toe / tow	a car on TOW
8.	tail / tale	to tell a TALE
9.	earn / urn	a grecian URN
10.	days / daze	going round in a DAZE

The forty homophone pairs and phrases into which the less common element was incorporated.

Table 15

down), either tape A or B was played into both ears of the patient through headphones. The volume was set at a comfortable listening level as judged by a theatre technician, so that the investigator remained blind to the list on that tape. End-tidal [isoflurane] was monitored using a Normac, and if the latter was $\leq$ 1.2% the patient heard tape A. If ET [isoflurane] was > 1.2% the patient heard tape B.

Post-operative interview

Twenty-four to thirty-six hours after surgery, the patients were interviewed; in addition to the same questions which were posed in the previous two series, the patients were asked to free-associate (respond promptly with their immediate thoughts) to all 40 homophones. The words were presented in a random fashion by the investigator, and other non-homophone words were inserted to try to prevent patients guessing the homophone nature of the test words. (It was envisaged that this knowledge may in some way have influenced their responses.)

If the patient free associated to the less common element which they had heard during anaesthesia, this counted as a HIT score. If the association was to the less common element which had not been heard during anaesthesia, this counted as a FALSE ALARM. Thus, the less common elements were the target responses, and were classified as HITS or FALSE ALARMS, depending on whether they had been heard during anaesthesia or not.

The interview was tape recorded in case responses were ambiguous, in which case there could be discussion with an independant interpreter; in fact no ambiguities arose and

Table 16: preoperative and target systolic arterial pressure in 24 patients in the third study.

Patient No.	Initial SAP	Resting SAP	Predicted TSAP	Actual TSAP
1.	127	125	117	113
2.	137	123	124	110
3.	125	120	107	108
4.	129	121	112	109
5.	150	136	127	122
6.	205	163	127	147
7.	135	120	134	108
8.	120	109	123	98
9.	136	126	114	113
10.	127	116	126	113
11.	129	124	120	108
12.	144	130	124	117
13.	136	128	137	115
14.	136	127	110	115
15.	144	133	129	121
16.	135	122	113	110
17.	136	129	112	116
18.	134	138	128	124
19.	121	123	113	111
20.	150	134	132	121
21.	160	129	117	116
22.	144	117	122	106
23.	145	123	120	111
24.	122	121	111	109
MEAN (SD)	138.6 (±17.3)	128.3 (±12.5)	120.8 (±8.2)	113.9 (±9.3)

SAP (mmHg) in 24 patients, in the third study, obtained on the ward (initial and resting SAP), TSAP predicted from the age-sex rule, and TSAP derived from resting SAP (actual TSAP).

Table 17: Control data from the third study.

Patient Group	RMSD	SAP Deviation (mmHg)	Points Ratio
Overall (n=24)	10.53 (4.8)	0.88 (6.8)	1.8 (1.6)
Group I_3 (n=9)	9.17 (4.3)	-2.76 (3.8)	0.92 (1.1)
Group I_3M (n=15)	12.82 (4.9)	6.94 (6.3)	3.24 (1.4)
	(p=0.04)	(p<0.001)	(p<0.001)

Mean values (and SD) for control data shown
i) overall for the third study group,
ii) for group I_3, and
iii) for group I_3M.

P values are from Mann-Whitney U-test, comparing groups I_3 and I_3M, for RMSD, SAP deviation and PR.

this was not necessary.

Results

Mean patient age was 48.6 years, (SD 14), and mean anaesthesia time was 60 minutes, (SD 22.4). There were 20 female and 4 male patients. Nine out of 24, (37.5%), required additional morphine during anaesthesia, but no patients required glycopyrrolate.

On the ward, mean SAP was initially 139mmHg (SD 17.3), falling to a mean plateau SAP of 128mmHg (SD 12.5): mean TSAP, at 90% of resting/plateau SAP was 114mmHg (SD 9.3), and significantly lower, ($p<0.01$ paired t-test), than predicted TSAP, (121mmHg, SD 8.2). Table 16 shows details of initial, plateau, target and predicted target SAP.

The Control Data

Mean RMSD = 10.53 ($\pm$4.8)

Mean SAP deviation = 0.88 ($\pm$6.8)

Mean PR = 1.8 ($\pm$1.6)

Table 17 shows the mean values for control data in the morphine-requiring and isoflurane only groups, (groups I_3M and I_3, respectively). The distribution of SAP points tended to be above TSAP in I_3M, but in I_3 the mean PR of 0.92 indicated a relatively even distribution (in contrast to our first study using morphine with a higher TSAP). Overall, the control criteria were satisfied as follows;-

i) 30% satisfied all 3 criteria,

ii) 66% satisfied 2 or more criteria,

iii) 88% satisfied 1 or more criteria,

iv) 12% failed to satisfy any criteria.

The 3 patients, (12%), who failed all the criteria, all had

a high RMSD due to persistence of SAP points well above TSAP, and therefore were in the I_3M group.

Physiological Variables

Mean HR (b.p.m.) = 74 (SD 12)

Mean RPP = 8620 (SD 1783)

One patient failed both the criteria (for adequacy of anaesthesia with regard to physiological variables). During her 44 minute abdominal hysterectomy, she developed a tachycardia and SAP was well above TSAP at the beginning of surgery. She received additional morphine, (ordered by the system), which eased control of her SAP, but the tachycardia persisted at > 100b.p.m. and RPP remained elevated, (mean 12894). Because SAP was controlled, mean RMSD was 9.0 and thus satisfied the criteria of RMSD < 10.

One other patient had a mean RPP of 12273. This patient was a 70 kg woman whose abdominal hysterectomy was less than easy, taking 106 minutes for the procedure. Three additional morphine boluses were required as SAP control was poor. In addition, HR tended to be between 90 and 100 b.p.m., (mean 97).

Table 18 shows mean RPP and HR for groups I_3 and I_3M, as well as overall. Note the significant difference between the mean values of the two groups, I_3 and I_3M.

Response time, pain on awakening, nausea and vomiting

Mean cFR was 8.2 minutes (SD 7.9). Four out of 24, (16%), had a cFR > 15 minutes, in all of whom control was such that additional morphine boluses had to be given. See table 18 for mean cFR in groups I_3 and I_3M.

Table 18: Physiological variables data and vaporiser output during the third study.

Patient Group	RPP	HR	cFR	Mean Vaporiser Output
Overall (n=24)	8620 (1783)	74 (13)	8.6 (7.9)	1.32 (0.86)
I_3 (n=9)	7195 (1342)	69 (8)	4.73 (4.6)	1.06 (0.51)
I_3M (n=15)	9793 (1872)	84 (12)	15.1 (8.2)	1.97 (1.03)
**p values	0.01	0.003	0.002	0.03

** Mann-Whitney U-test,
between groups I_3, and I_3M .

Mean values of physiological variables and vaporiser output during anaesthesia for 24 patients in the third study shown

i) overall,
ii) for group I_3, and
iii) for group I_3M.

Mean vaporiser output; figures refer to % isoflurane.

Table 18

Pain on awakening was decribed as severe by 6 patients, (32%), moderate by 7 patients, (29%), and mild by 10 patients, (41%). Only one patient claimed to have no pain on awakening.

Five patients complained of nausea post-operatively, in one of whom vomiting required administration of prochlorperazine 12.5mg IM.

Conscious and unconscious perception

There was no conscious recall of events during the time the patient was considered to be unconscious.

During surgery, the mean playing times (figure 15) of tapes A, (ET[isoflurane] $\leqslant$ 1.2%), and B, (ET[isoflurane] >1.2%), were 18.8 (SD 9.5) minutes, and 22.6 (SD 17.5) minutes. The difference was not statistically significant, (Wilcoxon signed ranks). Two patients did not hear tape A at any time, and two different patients did not hear tape B at any time. In these instances, the post-operative responses were included in the "unheard" category.

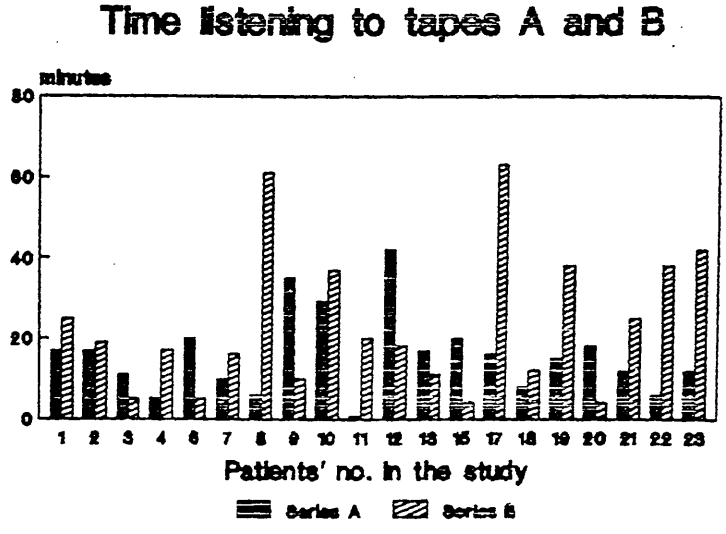
1. Responses to unheard homophones were analysed first; in 7 out of the forty homophones, the element thought to be LESS common was given spontaneously MORE frequently overall (table 19). Thus, the significance of this response after priming became doubtful, and the 7 words were excluded from the final analysis.
2. The FALSE ALARM scores were calculated for each individual patient from the lists which were unheard during anaesthesia. Mean FALSE ALARM score was 13.74% (SD 9.3).
3. For each patient, the incidence of HITS was calculated separately for tapes A and B, reflecting the effects of

Table 19: 7 homophones excluded from the final analysis.

	Homophone	Response Ratio
1.	EARN / urn	0.23
2.	GROWN / groan	0.31
3.	COURSE / coarse	0.23
4.	SEEM / seam	0.23
5.	HIM / hymn	0.46
6.	SEEN / scene	0.38
7.	REAL / reel	0.23

The response ratio is % frequency, (÷ 100), with which patients associated to the words in capital letters. These were considered to be the MORE common elements, and a response ratio of <0.5, in the absence of priming, indicates that the words were LESS common.

Figure 15.



Mean time on tape A = 16.8 mins (+/-9.5)
Mean time on tape B =22.6 mins (+/-18.6)

Twenty patients are represented here; the 4 patients who heard only one tape throughout anaesthesia are not represented.

priming at high, (>1.2%), and low, ($\leqslant$1.2%), ET-[isoflurane]. Mean HIT score on tape A was 15.53%, (SD 11.3), and on tape B was 8.6%, (SD 8.1).

In a Wilcoxon signed ranks test, the difference between tape A and B HIT scores was highly significant, (p=0.009). This reflected a greater number of primed responses at ET-[isoflurane]$\leqslant$ 1.2% compared to above that level.

However, the relationship between the FALSE ALARMS and the HIT scores overall, (tapes A + B; mean score 12.6%), was less clear; while there was no significant difference between these two, the incidence of HITS from tape B was significantly lower than the overall incidence of FALSE ALARMS. There was no difference between the mean HIT score on tape A and the FALSE ALARM score; thus the sum of the A and B HIT scores was less than the FALSE ALARM scores.

The correlations between time spent listening to either tape A or B and the HITS scored subsequently were not significant. The correlations which did exist suggested that as the listening time increased, the HIT score decreased. This effect seemed to be greater at the low ET [isoflurane], (Spearmann correlation co-efficients -0.4 and -0.2 for A and B, respectively).

Neither was there a significant correlation between the hit scores and the RMSD values, for either tape A or B.

To the investigator, there seemed to be circumstantial evidence that two responses were a direct result of priming; in two cases, the patient qualified their free association response by saying immediately "I've no idea what made me say that". They appeared surprised by their own replies, which

later turned out to be associations to the phrases they had heard during anaesthesia.

The adequacy of anaesthesia

In this study, the criteria for overall adequacy of anaesthesia were satisfied as follows;

63% satisfied all the criteria

17% failed only on the control criteria

8% failed on response time alone

4% failed on control criteria and physiological variables

4% failed on control criteria and response time

4% failed on all three counts.

Discussion

Since isoflurane depresses some cortical pathways in a dose-related manner, we expected that the pathways involved in processing and storage of auditory information might be similarly affected. In support of this, the results of this study showed a significantly increased incidence of primed responses at lower compared to higher ET[isoflurane]. However, we did not convincingly demonstrate a significant effect of priming overall. This could have been a chance statistical finding, due to small numbers, the lack of sensitivity of our protocol, or even an anti-priming effect of anaesthesia at higher ET concentrations. The incidence of spontaneous recall was zero.

Also, we were unable to demonstrate a relationship between the time spent listening to the tapes and the HIT scores; we had expected that at low ET concentrations of anaesthetic, (where presumably information storage and processing are not

totally disrupted), more exposure to priming would increase the HIT scores. It could be argued that 1.2% ET[isoflurane], in (66% N_2O and with morphine), is not a very low concentration, and even in the ET range of 0 - 1.2% we may have two opposing effects; increasing the priming time may well increase the HIT score below a certain "disruption threshold", while, on the other hand, the time of exposure to isoflurane anaesthesia may decrease the HIT scores after priming. Therefore, it is possible that the HIT scores consequent on tape A may have resulted from both effects, between which the study protocol was insufficiently sensitive to distinguish.

Another source of reduction in sensitivity was the loss of 7 out of 40 homophones in the final analysis. The normative data from which the homophones were chosen was collected from psychology students in the USA. Although care was taken to avoid pairs whose elements are pronounced differently in our local accent, words pertaining to current affairs, and even avoiding words thought salient in the life-style of our population, the use of the language clearly differred from that of our population. Normative data, from the population of patients under investigation, would enable this sort of study to be sensitive to the effects of anaesthesia per se on priming, and may validate any anti-priming effect suggested by the results of our HIT scores after tape B.

By preceeding the homophone phrases with a message instructing the patients to listen carefully, we sought to increase the level of attention; possibly a personal address would have been more likely to produce this effect. However, the content of the phrases themselves were not particularly

salient to the surgical patient. Since the CNS seems to respond preferentially to information pertaining to survival and well-being, salient information in this context would include subjects of post-operative well-being etc, as played to patients under anaesthesia by Evans and his co-workers [73]. There is evidence that retrieval ability improves for up to two weeks post-operatively, [81]; our post-operative interviews were performed after 24 hours. At first, it seems as though this was premature, but this evidence is based on tests of explicit memory whereas we were testing implicit memory here. Finally, RMSD did not correlate overall with HIT scores from either tape A or B. RMSD is a measure of the quality of SAP control, and is taken as one indication of the adequacy of the anaesthetic state in this work. However, we have already seen that a high RMSD may be a result of SAP falling too far below, as well as too far above TSAP. In the first instance, ET[isoflurane] would tend to be low, and in the second instance, ET[isoflurane] would tend to be high. This should be considered if we wish to relate the SAP control, (and adequacy of anaesthesia) to the "depth of anaesthesia" as judged by the effect of anaesthesia on priming.

In fact, in this study, using 90% resting SAP for TSAP, the RMSD values correlated well with mean vaporiser output. This, and the even distribution around SAP and small mean SAP deviation in group I_3, (those whose control was such that no additional morphine boluses were required), indicated that RMSD was not significantly affected by SAP points falling below TSAP. In group I_3M, mean vaporiser output (table 18)

and RMSD (table 17) were significantly higher than in group I_3, ($p=0.03$, and $p=0.006$, respectively; Mann-Whitney U-test).

It is of interest that the hit scores after tapes A and B were significantly different, (table 20), in group I_3M, ($p=0.017$, Mann-Whitney-U test), but not in group I_3. Thus, in the adequately controlled group, the ET[isoflurane] did not affect HIT scores, but where SAP escaped from the control, the ET[isoflurane] did seem to affect the HIT scores. Accepting SAP as a marker for the adequacy of anaesthesia, we could say that when SAP control is poor, surgical stimuli are over-balancing the effect of anaesthetic agents, resulting in excessive reflex autonomic activity. At this point, anaesthesia may also be such that cognitive processes are approaching the stage where they may be sensitive to priming; ascending stimuli have an arousing effect on cognitive processes, but these are more sensitive to increasing concentrations of anaesthetic agents, (than autonomic reflex activity). Thus, when SAP escaped far from TSAP, high [isoflurane], delivered consequently, precluded encoding of homophones to a greater degree than when SAP escaped TSAP by smaller amounts.

According to this argument, the degree of SAP control, (group I_3M represents those with poor control), has distinguished a group of patients in whom unconscious perception is related to ET[isoflurane]. Extending this argument, we could say that the degree of SAP control could be used to help recognise the point where anaesthesia may approach inadequate, (i.e. where conscious perception supervenes from unconscious perception on the continuum).

Table 20

Patient group	HITS after Tape A	HITS after Tape B	FALSE ALARM Rate
** Overall (n=24)	15.5% (11.3)	8.6% (8.1)	13.7% (9.3)
I_3 (n=15)	12.8% (8.3)	9.0% (8.3)	13.2% (10.9)
** I_3M (n=9)	20.6% (14.9)	7.9% (8.4)	14.6% (5.9)

** indicates groups where A HITS are significantly greater that B HITS. ($p<0.01$ in both cases; Mann-Whitney U test.)

Mean HIT scores (and SD) and FALSE ALARM rates
i) overall in the third study,
ii) in group I_3, and
iii) in group I_3M.

Table 20

Equally important, in group I_3, there was no significant difference between HIT scores after tapes A or B. This suggests that patients with good SAP control are enjoying a relatively uniform anaesthesia, with respect to unconscious perception. Strictly, we cannot comment on conscious perception, since amnesia may preclude it's detection. However, since the majority of our patients tend to have a long recovery period, we believe anaesthesia to be relatively "deep", and conscious perception seems unlikely.

CHAPTER 7

PROPORTIONAL-INTEGRAL FEEDBACK CONTROL OF SYSTOLIC ARTERIAL PRESSURE:

A SUMMARY OF RESULTS OF 3 STUDIES.

We have now studied a total of 64 patients, undergoing elective surgery, and in whom anaesthesia was provided by feedback control of SAP. They are divided into 3 groups; 20 in groups I and II, and 24 in group III. In group I, TSAP was resting SAP per se, and intraoperative analgesia was provided using morphine. In group II, TSAP was 90% of resting SAP, and analgesia was provided by fentanyl. In group III, TSAP was also 90% of resting SAP, and analgesia was provided using morphine. There was no significant difference between groups with respect to age, sex, weight or resting SAP.

The 3 groups are themselves divided into two sub-groups, depending on whether or not the contol system demanded that additional boluses of narcotic be given during the control period;-

group I was divided into sub-groups I_1 and I_1M

group II was divided into sub-groups I_2 and I_2F

and group III was divided into sub-groups I_3 and I_3M.

Additional narcotic boluses were demanded by the system according to a rule, operating when high concentrations of isoflurane were delivered over 5 minutes, due to persistently high SAP with respect to TSAP; thus the control in this situation had become inadequate by definition. The percentage of patients in each group in whom this was the case (at any time), was as follows:-

group I :- 30%, (6 out of 20)

group II :- 25%, (5 out of 20)

group III :- 37.5%, (9 out of 24).

Control Data

The criteria for "good" control are outlined on page 8 of chapter 3, and the data were as follows in the 3 groups:-

	RMSD (SD)	SAP Deviation (SD)	PR (SD)
Group I	10.34 (4.2)	-1.99 (6.2)	2.38 (6.3)
Group II	9.61 (3.8)	+1.67 (4.5)	2.06 (2.5)
Group III	10.54 (4.8)	+0.88 (6.7)	1.8 (1.6)

For the purpose of inter-group comparisons, statistical significance indicated that $p < 0.025$, (Mann-Whitney U-test), since two comparisons were made in each case. There was no significant difference overall in RMSD or PR. However, SAP deviation was significantly lower in group I than in groups II and III, ($p = 0.002$ and 0.0014, respectively). This reflected the higher TSAP used in group I, (see above), and the resulting tendency for SAP to fall below target. This prompted selection of 90% of resting SAP to be used for TSAP in groups II and III.

RMSD and PSAP were significantly correlated, (positively), in all groups, ($p = 0.019$, $p = 0.006$, and $p = 0.022$ for groups I, II, and III, respectively); in other words, the higher the resting SAP, the less "good" was the control. We also know that increasing RMSD, in groups II and III, resulted from SAP lying too far above, rather than below,

TSAP.

Age also correlated significantly to RMSD in groups I and III, ($p = 0.002$ and $p = 0.03$, respectively). In view of the correlation between RMSD and PSAP, this was not surprising; resting SAP increases with age in the population. A significant correlation was not found in group II between age and RMSD, the reason for which is unclear.

Details and Control Data for Sub-groups

Bearing in mind the above, we would expect the control data to be more satisfactory, and mean age and PSAP to be lower in the isoflurane only, (IO), sub-groups than in the narcotic-requiring, (NR) sub-groups. The control data for the 6 sub-groups were as follows:-

Group	Mean RMSD (SD)	Mean PR (SD)	Mean SAP Deviation (SD)
I_1	10.53 (4.7)	0.66 (0.60)	-3.96 (5.9)
I_1M	10.28 (3.07)	5.24 (8.29)	+2.55 (4.15)
I_2	8.83 (3.4)	1.29 (1.81)	-0.05 (1.2)
I_2F	11.96 (4.59)	4.35 (3.08)	+6.84 (3.8)
I_3	9.17 (4.34)	0.92 (1.08)	-2.76 (3.84)
I_3M	12.82 (4.94)	3.25 (1.39)	+6.94 (6.33)

In the sub-groups pairs from groups II and III, RMSD is greater in the NR sub-group than the corresponding IO sub-group, but the difference is only significant, ($p < 0.05$), between I_3 and I_3M. We have already seen why this is not true

for group I: SAP fell far below TSAP to increase RMSD, rather than increasing RMSD being solely a result of SAP falling above TSAP. There were no significant differences in the mean RMSD values of the 3 IO sub-groups.

Similarly, mean deviation from TSAP is less in the NR sub-groups, significantly so for group I sub-groups, and highly significantly, ($p < 0.01$), so for the group II and III sub-groups. Note that the magnitude of the mean deviation in I_1 is actually greater than that in I_1M. Mean SAP deviation in I_2 was significantly higher, (less negative) than in I_1 and I_3.

The PR was highly significantly greater in each NR sub-group than in the corresponding IO sub-group; there was no difference at all between the mean PR values of all 3 IO sub-groups.

Thus, apart from the explainable discrepancies in group I control data results, our expectations are fulfilled in that there is significantly better control in our IO sub-groups.

It is interesting that our expectation that mean age and PSAP in the IO sub-groups would be lower, (than those in the NR sub-groups), was not confirmed. The mean age, weight and PSAP of each of the 6 sub-groups were as follows:-

Group	Mean Age in years. (SD)	Mean Weight in kg. (SD)	Mean PSAP/Resting SAP in mmHg. (SD)
I_1	50.4 (14.7)	62.3 (10.4)	127 (21.7)
I_1M	35.7 (13.3)	61.7 (9.3)	124 (4.9)
I_2	51.2 (16.4)	60.1 (6.8)	126 (13.8)
I_2F	42.2 (15.1)	62.3 (5.4)	129 (18.0)
I_3	52.7 (15.8)	68.6 (9.7)	130 (10.7)
I_3M	43.1 (8.8)	70.3 (9.4)	120 (5.7)

In each pair, mean age was less in the NR sub-group, although the differences were not significant. Average weight was similar throughout. Resting SAP, (PSAP), was also less in the NR sub-groups than in the corresponding IO sub-groups, but only significantly less in I_3M than in I_3. This is in contrast to expectations that age and PSAP would be greater in the NR sub-groups: these groups by definition had poorer control data, and this was borne out by our results shown above. RMSD, our main index of control adequacy, was seen to correlate significantly overall with age and PSAP, yet the results from the sub-group pairs confound this somewhat. This may be a chance statistical finding, due to smaller numbers arising when splitting groups into sub-groups. Two points merit consideration; first, patients with lower PSAP tend to be younger and fitter; MAC of volatile anaesthetic agents increases with age. Therefore, these younger patients may be less sensitive to anaesthetic agents, and require more isoflurane to stem autonomic reflexes. That is to say,

younger, fitter patients may be more difficult to control. Secondly, from this, as age and SAP increase and MAC decreases, it would seem that control should be easier. However, the increase in SAP seen with age may well be associated with pathological vessel changes, and a tendency to exaggerated swings in AP in response to the slightest stimuli. Although we excluded hypertensive patients from the study, the definition of hypertension, is arbitrary, (see chapter 1). In other words, our selected ASA I or II patients may include some "latent" hypertensive patients, i.e. those who may show exaggerated circulatory responses to surgical stimuli and anaesthesic drugs, but whose resting pressures are normal. In this way, age may sometimes be associated with increasing difficulties in control with our system.

In our 3 main groups, the "good" control criteria were satisfied as follows:-

	NUMBER OF CRITERIA SATISFIED			
	All 3	2 or more	1 or more	None
Group I	35%	65%	70%	30%
Group II	50%	65%	90%	10%
Group III	30%	66%	88%	12%

The results from group II appear marginally better at first glance, but we already know that there was little significant difference between groups overall.

The adequacy of Anaesthesia

In the introduction to this work, we defined the clinically acceptable anaesthetic state to include the following:-

i) normal physiological variables

ii) a safe, short recovery period

iii) absence of conscious awareness.

To assess the physiological state, we use heart rate, (HR), and "rate-pressure product", (RPP), since these variables are used most widely throughout current anaesthetic practice. Recovery is assessed by the (corrected) time to first response, (cFR), which is the time taken for the patient to respond to and obey simple commands after cessation of anaesthesia. In groups I and II, awareness was considered to have occurred if spontaneous recall occurred retrospectively. This is a relatively crude method of detecting awareness, and in group III, we used a sensitive method based on homophone priming for this purpose.

	PHYSIOLOGICAL VARIABLES (Mean & SD)		RESPONSE TIME (mins)	AWARENESS (no. of cases)
GROUP	HR	RPP	cFR	
I	76 (16)	9366 (2193)	11.2 (7.7)	0
II	67 (8)	7968 (1733)	9.4 (6.3)	1
III	74 (14)	8620 (1783)	8.6 (7.9)	0

Mean values for HR, RPP and cFR meet with our criteria for clinically acceptable anaesthesia. The single, (possible), case of conscious awareness, however, does not.

In group II, the fentanyl group, mean HR and RPP was less than in groups I and III. In this group, 7 patients had required IV glycopyrrolate during the control period, when HR fell below 50 b.p.m. In no patients of either group I or III had this been the case. The only significant difference, however, was that RPP in group I was greater than that in group II, ($p < 0.025$, Mann-Whitney U-test).

The differences in cFR were insignificant.

Just as we found significantly better control in the IO sub-groups compared to the NR sub-groups, the adequacy of anaesthesia was also significantly improved in the former:-

(Mean values & SD)

Group	HR (b.p.m.)	RPP	cFR (mins)	Aware (cases)
I_1	73 (15)	8741 (1832)	9.0 (6.3)	0
I_1M	85 (15)	10823 (2429)	16.0 (8.2)	0
I_2	65 (8)	7406 (962)	8.2 (5.5)	0
I_2F	73 (8)	9655 (2506)	13.0 (7.9)	1
I_3	69 (8)	7915 (1342)	4.7 (4.6)	0
I_3M	84 (13)	9793 (1872)	15.1 (8.2)	0

In each IO sub-group, the mean values for HR, RPP and cFR met the criteria for clinically acceptable anaesthesia. In contrast, in I_1M, mean RPP and cFR did not meet with these criteria. Similarly, in I_3M, mean cFR was above the pre-determined 15 minutes acceptable for this variable. Although mean values for all variables were more satisfactory in the IO sub-groups of each pair, the differences only reached statistical significance between I_3 and I_3M, (HR, RPP and cFR). No single IO sub-group met all our criteria significantl

better than both others, although mean cFR in I_3 was significantly better than that in I_1. Not unexpectedly, mean RPP in I_2 was significantly lower than that in I_1.

Our possible case of awareness occurred in I_2F, the NR sub-group of group II.

Thus, with better SAP control, we better satisfied our pre-determined criteria for clinically acceptable anaesthesia. It must be said, however, that overall, mean values met these criteria adequately, except for the one case of recall.

Awareness

In order to provide a more sensitive method of assessing the degree of awareness, we used a test of free association to homophones after priming during anaesthesia.

The 24 patients in group III underwent anaesthesia by feedback control of SAP, during which they heard tapes of homophone-containing phrases. The tape(s) which they heard depended on whether ET [isoflurane] was above, (tape A), or below, (tape B), 1.2% at any moment during anaesthesia. Priming during anaesthesia was assessed post-operatively using the number of HITS scored, on free association to the homophones. A HIT was scored if free association was to the less common homophone if it had been heard during anaesthesia on tape A or B.

Overall in the group, the HIT scores were significantly higher after tape A than after tape B. There was no significant correlation between HIT scores and RMSD, or time spent listening to either tape. There was also a confounding high incidence of FALSE ALARMS in the group, which resulted in the overall appearance of no statistical evidence of priming. However, the study design was not intended that the A and B HITS be grouped together in this way; we regarded the two groups as separate from the beginning.

The mean HIT scores after tapes A and B in groups I_3 and

I_3M, and the mean times spent listening to those tapes in each group are shown below:-

GROUP	A HITS (% & SD)	B HITS (% & SD)	TIME A (mins. & SD)	TIME B (mins. & SD)
I_3	12.8 (8.3)	9.0 (8.3)	17.8 (10.4)	13.1 (7.5)
I_3M	20.6 (15.0)	8.0 (3.2)	12.1 (9.2)	43.0 (15.0)

The higher incidence of HITS after tape A in I_3M than I_3 was insignificant, (Mann-Whitney U-test). Furthermore, the mean time spent listening to tape A was similar in both sub-groups. The incidence of HITS after tape B was also similar in both sub-groups. As we would expect, the time spent listening to tape B was significantly greater in I_3M; this group have a significantly higher RMSD, due to SAP falling above target. They therefore receive higher inspired [isoflurane], leading to higher ET [isoflurane].

In neither sub-group were there significant correlations between RMSD, HIT scores and time listening to either tape A or B.

However, in I_3M, the tape A hits were significantly greater, ($p = 0.017$, Wilcoxon signed ranks), than the tape B hits. This was not true for I_3.

Interpretation of these results was as follows; I_3 enjoyed a uniform depth of anaesthesia with regard to cognitive function, while in I_3M susceptibility to priming varied with ET [isoflurane]. Also, after tape A, in I_3M there was a higher incidence of primed responses, although not statistically significantly so, ($p = 0.27$).

We already know that the NR sub-groups, (of which I_3M is

one), had significantly less good SAP control and less adequate anaesthesia as judged by our criteria: it is possible that depth of anaesthesia in I_3M was similarly less adequate, and patients were more susceptible to priming. The high concentrations delivered when SAP deviated greatly from TSAP could have precluded priming, in the same way as, for example auditory evoked response pathways are depressed by increasing isoflurane concentrations. Thus, the quality of SAP control, (crudely defined by the IO and NR sub-groups), can not only distinguish more adequate anaesthesia, (physiological variables and recovery), but may also correspond with depth of anaesthesia with respect to cognitive function.

CHAPTER 8

MEASURING OF DEPTH OF ANAESTHESIA

Introduction

In 1920, Guedel [87] described the dose-related effects of ether on respiration, eyeball movements, pupil size and the swallowing, eyelid and vomiting reflexes: the plane of anaesthesia adequate for surgery could be accurately determined. Valid as the observations were for ether, they could not be applied when using other volatile agents, or the newly introduced intra-venous induction agents. Furthermore, the introduction of muscle relaxants [57] obscured many of the previously observed signs of ether anaesthesia, yet seemed to provide adequate operating conditions. Consequently there were several reports of awareness of events at surgery which prompted the search for some other reliable signal to measure the depth of anaesthesia.

To-day, most anaesthetists envisage the depth of anaesthesia as a continuum, often represented as a line drawn from full consciousness to unconcsiousness, which includes points at which various autonomic and somatic reflexes become depressed in response to increasing doses of anaesthetic drugs. We accept this, but add that with increasing anaesthetic doses, suppression of consciousness, somatic and various autonomic reflexes should be viewed on separate continuums; adequate anaesthesia exists when the "anaesthesia" points are occupied on each of these. We also suggest that in response to on-going surgical/noxious stimuli the point occupied at any one time on any one continuum may be displaced, and this may have a "knock-on" effect in displacing one or more points from their positions, (see Introduction).

Prys-Roberts [88] goes further, considering the supression of consciousness to be the only component of adequate anaesthesia. The effects on other variables, (such as arterial pressure, heart rate), are seen merely as "pharmacological attributes of the drugs" used in anaesthetic practice. This is reasonable; an important criterion for adequate (general) anaesthesia in the eyes of the profession and patients alike is the absence of conscious awareness of events. However, by regarding anaesthesia as an all-or-none phenomenon and denying anaesthetic "depth", he ignores that a consciousness continuum, or line, extends through areas which are often mistaken for "unconsciousness"; at these points cognitive functioning may still occur "subconsciously", and we do not know if a potential for harm exists in this area.

Our definition of clinically acceptable anaesthesia includes:-

i) absence of conscious awareness and recall for events during surgery.
ii) a short, safe recovery period.
iii) normal physiological variables.
iv) facilitation of surgical procedure.

While we concede that the absence of awareness is most important, if the patient suffers death by anaesthetic overdose, (and the "recovery period" is infinitely long), then the fact that the patient was not aware of events during surgery is irrelevant.

If we had a signal which reliably indicated whether consciousness was "on or off", we certainly could arrange the

pharmacological control of other reflexes to surgical or noxious stimuli, and achieve clinically adequate anaesthesia in this way. However, the signal would have to be independant of any of the reflex pathways we wished to suppress, or the information carried in the signal would become invalid. This is particularly difficult since many clinical signs purporting to represent anaesthetic depth involve autonomically mediated reflex pathways, eg. PRST scores, galvanometric skin reponses. Pharmacological interference with these parameters invalidates the signal, as the sole representation of the balance between anaesthesia and surgical stimulation.

Autonomic reflexes are primitive responses designed to promote survival of the organism. Conscious beings can override some of the motor responses, eg. withdrawal from pain. However, most of us could not control our tachycardia in response to pain. On the other hand, conscious mechanisms are highly developed and complex. Therefore, they may be more sensitive to disruptive influences; perhaps this explains why consciousness is suppressed first in response to increasing doses of most volatile anaesthetic agents, (except in the case of those with analgesic properties, like ether). Thus, at the point on the anaesthetic continuum where autonomic reflexes to surgical stimulation are moderately supressed, so too are conscious mechanisms.

A signal representing depth of anaesthesia ought to measure the balance, or imbalance, between surgery and anaesthesia. However, if we obtain a response to surgical stimulation which indicates inadequate suppression of consciousness it may already be too late. Also, while anaesthesia may be

adequate for a low level of surgical stimulus, it may not suffice if the surgical stimulus suddenly becomes intense; we are on a knife edge with regard to changing severity of surgical stimulation. Whereas the intensity of surgical stimuli may change rapidly, changes in brain concentrations of anaesthetic agents take longer.Thus, we require a signal which is sensitive to impending awareness, which has a fast enough response time to prevent development of the latter. Obviously, the crux of the matter lies in the quantification of surgical stimuli: if we could predict the change in our signal to an anticipated level of surgical stimulus we could ensure adequate depth throughout.

The ideal signal.

i) Sensitivity: the false negative rate should be of the order of 0.1%, for the incidence of awareness is already approximately 1% (Caesarean sections). Not only should the false positive rate be in the order of 5% [89], it is mandatory that the patient be protected from brain damage due to anaesthetic overdose.

ii) Specificity: the signal should correlate to the level of consciousness, and be unaffected by other factors, such as drugs used during anaesthesia, hypovolaemia, hypotension, or end-tidal CO_2.

iii) Uniformity: all anaesthetic agents should produce the

same dose-related signal changes. Surgical stimuli, and arousing influences, ought to reverse the signal changes seen with increasing dose of anaesthetic agents, since the anaesthetic depth is viewed as a balance between the two. Withdrawal of anaesthetics also should reverse the signal changes. Whether or not the signal should revert to baseline levels after surgery and anaesthesia cease is debatable; the stress response now becomes established, and pre-operative baseline measurements would seem an inappropriate target.

iv) Readability: signal changes should be clear and easily interpreted.

vii) Application: the means to obtain the signal routinely at operation should be practically unobtrusive.

Methods of measuring depth of anaesthesia.

Several methods of obtaining a signal to assess the depth of anaesthesia have been proposed. The signals are obtained from information based on

i) Traditional clinical signs

ii) Other autonomic activity

iii) The electro-encephalogram (EEG), or derived measurements.

The clinical signs which we routinely monitor are themselves mediated by reflex autonomic activity; however, we distinguish "traditional" clinical signs, which are routinely monitored, (eg. heart rate, pressor responses), from those which are not, (eg. lower oesophageal contractions, frontalis muscle elecromyographs), and which have not been adopted for routine monitoring by all.

Traditional Clinical Signs

The traditional clinical signs have stood the test of time and continue to provide anaesthetists with a guide to the "adequacy" of anaesthesia. This follows because we define adequate anaesthesia to include satisfactory physiological variables. In the anaesthetised patient, these signs include changes in arterial pressure, heart rate, sweating, tear secretion, pupil size, and peripheral perfusion in response to surgical stimulation.

Increasing concentrations of individual anaesthetic agents alone have different effects on each of these signs [90]; the changes are dose-related, show similar overall trends and are graded, for the most part. Cullen and his co-workers also showed that surgical stimulation does reverse some of the changes.

From the above, it would seem that clinical signs are well on the way to fulfilling the criteria for the ideal signal. However, as we know, clinical signs used by clinicians are not foolproof in preventing awareness, and there are a number of other problems with interpretation of clinical signs:-

i) Drugs acting on the autonomic system used during anaesthesia, (eg. atropine, B-blockers,) affect

clinical signs; thus the signal becomes non-specific.

ii) Discrepancies arise from the effects of surgical stimuli on heart rate in the anaesthetised patient: usually surgical stimulation will partially reverse the anaesthetic induced decrease in rate, but it may also result in profound bradycardia.

iii) Heart rate and arterial pressure are not independant of one another.

iv) Although changes in HR and AP can be easily and objectively measured, many of the clinical signs are assessed subjectively, eg. tear secretion, sweating. A more objective assessment of sweating may be obtained by measuring the galvanic skin response [91]; using this method, (which is related to sympathetic cholinergic activity), there is a profound reduction in sweating with induction of anaesthesia, and more graded reductions in reponse to "bursts" of halothane during surgery.

v) Cardiovascular and autonomic status affect interpretation of arterial pressure and heart rate responses.

vi) Most importantly, narcotic drugs may be given in doses which completely abolish the cardiovascular reflexes to surgery. Furthermore, these drugs do not all produce unconsciousness.

Because we are a generation of anaesthetists taught to routinely observe these various signs, we have, from experience, familiarised ourselves with these various interactions. We reject certain information from clinical signs and attach importance other data, depending on the

validity of each. This we assess using our experience of the drugs we use and how they influence the anaesthetically attenuated autonomic reflex responses to surgical stimuli.

Accepting these limitations, there is no doubt that signals obtained from a number of clinical signs can be used to "drive" satisfactory anaesthetics. The anaesthetic dosage can be calculated according to a pre-set formula, which takes into account the error in the signal, (see chapter 4). We have done this ourselves using arterial pressure, and Evans and his workers [92] used a combination of arterial pressure, heart rate, sweating and tear secretion, (PRST score).

In our study of 24 patients, we used arterial pressure as the signal to provide a reproducible state of anaesthesia. It has already been shown that volatile anaesthetics significantly depress cardiovascular responses to noxious stimuli at approximately twice the concentration required to depress somatic motor responses [93]. At this point, in unparalysed patients, the lack of movement in response to surgical incision almost certainly indicates unconsciousness. We validated our technique with respect to awareness using a sensitive test. The quality of control varied, but with our particular pre-set formula, we found ourselves far enough down the "physiological variables" continuum, (i.e. reflexes were suppressed to the extent), to also ensure unconsciousness, using our anaesthetic technique for various types of (major) surgery.

Other autonomic activity

i) Lower oesophageal contractility (LOC).

As is true for the American opossum, the human lower oesophagus is formed of smooth muscle; thus, the presence of skeletal neuro-muscular blockade does not affect its contractility. Secondary peristaltic, (or provoked), contractions and tertiary spontaneous contractions have been recently investigated by several workers.

In 1984 Evans and his colleagues made a preliminary communication proposing LOC as a new monitor of anaesthetic depth [94]. They described dose-related reduction in the amplitude of provoked contractions, and dose-related reduction of the frequency of spontaneous contractions. With increasing anaesthetic vapour concentrations, spontaneous LOC was completely suppressed. The amplitude of the spontaneous contractions, however, was unaffected over the clinical anaesthetic concentrations. After further confirmation [95], this led the authors to regard the spontaneous contractions as "on-off" or "all-or-none".

The effects of anaesthetics on LOC were investigated by several more workers; a Belfast group obtained a similar pattern of results, stating that the pattern of LOC related well to the clinical state, although we are not told how the clinical state was assessed [96]. These authors felt that the LOC pattern preceeded clinical signs in the indication of lightening anaesthesia. Thus, it would seem that LOC is more sensitive than clinical signs alone in assessing at least the adequacy of anaesthesia.

Results vary, however; Cox and White reported that 9 out of

30 patients showed clinical signs of inadequate anaesthesia when no provoked or spontaneous contractions were present [97]. Isaac and Rosen, while finding the same overall dose-related changes in LOC with increasing anaesthetic concentration, reported that such changes did not always occur [98].

It also appears that LOC is sensitive to the balance of effects of surgery and anaesthesia [99]; at steady state halothane concentrations, changes in LOC are paralleled by changes in clinical state, as judged by PRST score. Also, a study of varicose vein versus hysterectomy surgery [100], LOC was significantly increased in the hysterectomy group (at similar anaesthetic concentrations).

Whether or not LOC correlates with level of awareness has been crudely investigated; during induction and emergence from anaesthesia, responsiveness to hand squeeze commands was shown to correlate significantly with LOC changes [98].

LOC is also affected by drugs with cholinergic and anticholinergic activity, such as atropine. This is a limitation on its validity in anaesthetic clinical practice, as is the presence of achalasia or autonomic neuropathy. Also, drugs with a direct action on smooth muscle, such as sodium nitroprusside, greatly affect LOC. However, minor oesophageal disease, such as oesophagitis, does not affect LOC significantly.

In their preliminary report, Evans and co-workers reported that the suppression of LOC was not only related to increasing concentrations of volatile anaesthetic, but also to increments of fentanyl. (Fentanyl is an opioid and therefore not expected to prevent awareness [101]). This

action of fentanyl on LOC may at first seem to cast doubt on the validity of the signal, but considering that spontaneous LOC is stress-related, this is to be expected; the analgesic action of the drug blocks part of the ascending surgical stimulation and so reduces the opposition to the anaesthetic effect. Thus, stress is reduced and with it spontaneous LOC. Presumably by the same mechanism, fentanyl and other narcotics reduce MAC. In the absence of painful stimuli, fentanyl may not influence LOC; this remains to be borne out.

ii) The electromyograph (EMG)

Frontalis muscle activity is partially resistant to neuromuscular blockade, perhaps reflecting its partially autonomic innervation via the facial nerve. Frontalis muscle EMG activity varies with a) level of vigilance

b) cognitive function

c) auditory stimuli.

The EMG recording itself is relatively easy to obtain; it involves skin surface electrodes, the placement of which does not present a problem during most anaesthetics.

At induction of anaesthesia, there is a profound fall in EMG activity, and gradation is not apparent [102]. Surgical stimuli may produce easily distinguished spikes of activity. This is said to indicate inadequate anaesthesia. During propofol anaesthesia narcotic boluses produced falls in EMG activity. Prior to the boluses the EMG seemed to be showing graded increases. Couture and his workers [103] showed that during clinically stable anaesthesia surgical stimuli did not affect EMG activity, which remained profoundly below awake levels. When consciousness is regained, EMG activity returns

to baseline values. Thus, some have attempted to assess depth of anaesthesia using EMG activity.

As we have said, EMG activity is not only affected by anaesthesia; acoustic stimuli may also increase EMG activity. This may result from either the acousticofacial reflex [104], or incomplete suppression of cognitive function during anaesthesia. It remains to be seen whether the pertinence of auditory stimuli affects EMG activity during anaesthesia.

Finally, EMG activity may be sensitive to cerebral ischaemia; the latter authors report increases in intra-cranial pressure corresponding with increases in EMG activity. However, this does not necessarily represent a reliable cause and effect relationship since the report comes from a comatose head-injured patient.

The EEG, and derived measurements.

The EEG is a recording of the electrical activity of the brain, which relates well to the level of cerebral blood flow and oxygen metabolism [105]. The potentials are in the order of 10-100uV, and of variable frequencies between 1 and 30Hz. The conventional EEG provides voluminous and complex displays, and changes occurring during anaesthesia are not easy to interpret visually. Volavka and his workers showed that even among expert encephalographers, the highest correlation was 56% with visual interpretation [106]. However, development of electronic techniques has assisted in this problem by reducing the data in various ways, (see below).

In 1952, Faulconer and his colleagues demonstrated several distiguishable EEG changes which correlated well with

increasing blood ether concentrations [107]. However, since the introduction of muscle relxant drugs, we now tend to carry out anaesthesia using a narrower range of volatile anaesthetic concentrations; the identification of EEG changes in response to small changes within this narrow concentration range is less easy and less accepted.

Despite some general similarities in EEG patterns as anaesthetic concentration increases, considerable variation in the detail of these changes exists with different anaesthetic agents [108]: the criteria of a "uniform signal" is therefore not satisfied. However, the changes seen with increasing doses of volatile anaesthetic agents, or some other drugs, (for example fentanyl), accurately reflect increasing brain concentrations. It is logical therefore that we have tried in various ways to extract information, and process the EEG to try to obtain a signal which may correlate to the depth of anaesthesia and awareness.

The EEG responses to superimposed surgical stimuli under halothane anaesthesia vary; high voltage slow frequency or low voltage high frequency patterns may be seen [109]. Thus, the EEG signal changes do not necessarily undergo graded reversal with surgical stimuli.

In its various processed forms, the EEG signal has been related to patient response to command, or to surgical stimulation, (see later). Not only does the EEG show changes in response to anaesthetic agents, there are specific changes with other drugs, such as fentanyl, and other physiological variables, eg. arterial PCO_2 and hypothermia. Unless we can be sure that these other factors do not change during EEG

measurement, any signal obtained will be less valid.

Clearly, although EEG recordings could not be said to satisfy several of our ideal signal criteria, (eg. ease of interpretation, uniformity, specificity), the signal changes in response to varying doses of different agents, arousal and surgical stimuli may prove useful in some way as a guide to anaesthetic depth.

The processed EEG

In an attempt to facilitate visual interpretation of EEG patterns during anaesthesia, and to simplify the information given by the EEG, various methods of processing the latter have been described.

i) The cerebral function monitor (CFM).

Developed by Maynard in 1979, the CFM produces an output voltage by the manipulation of a single channel of the EEG. The EEG signal firstly undergoes filtering to remove baseline drift and reduce emphasis on the lower frequencies (which are resistant to phamacological and hypoxic depression). Next, the average peak voltage is derived by rectification and averaging of the peak voltages. If very slow paper speed is used, (30 cm per hour), trends can be seen easily, but at the expense of small acute changes.

Because of the ability to show trend clearly, the CFM has been of use in the detection of cerebral ischaemia, where abrupt changes in the pre-existing trends are seen [110]. It is clear that the CFM signal is sensitive in warning of cerebral ischaemia; Branthwaite reported a 60% reduction of neurological sequelae following cardio-pulmonary by-pass by agressively treating CFM evidence of global ischaemia

[111]. The advantage over the raw EEG is that of ease of interpretation, but the disadvantage is that focal ischaemia is more difficult to detect, (single channel of the EEG is used). Two channel CFM monitors are more sensitive though. The other disadvantage of the processing involved is that, due to averaging, (see above), frequency bands are not considered independantly: thus changes in one part of the spectrum may cancel out changes in another. Information is "lost", and sensitivity to minor changes is decreased.

Attempts to relate CFM changes to depth of anaesthesia have met with varying success; biphasic changes were seen as anaesthesia was progressively "deepened", and the same authors found that CFM tracings at or near the pre-induction levels did not correlate to wakefulness, and awakening did not occur at the same pre-induction level [112].

Thus, the CFM signal is not very reliable, does not exhibit a graded response, and is not very sensitive to small changes.

ii) The Cerebral Function Analysing Monitor (CFAM).

The CFAM, was described by Sebel and his co-workers [113], and developed from the CFM; its advantages include a seperate display of frequency content of the EEG, as well as amplitude. Thus, less information is lost from the original signal. Also, an indication of electrode contact resistance is given, which allows the observer to judge the amount of artefact in the signal, eg. as a result of scalp muscle activity. This increases "confidence" in the signal. Furthermore, with the same apparatus, it is possible to

record and display the raw EEG, and evoked potentials (see later) from the EEG.

In an early study in primates, Prior and colleagues were able to characterise six different stages of anaesthesia using the CFAM, while althesin was given to maintain steady-state drug levels [114]. Other studies show clear and reproducible changes in the CFAM in response to halothane and nitrous oxide [115,116]. Also, some workers have demonstrated acute changes in the CFAM signal in response to surgical stimuli; these authors feel that these changes occurred in the presence of other signs (eg. cardiovascular) of "light" anaesthesia [117]. Proponents feel that the microprocessing of the CFAM signal may be ultimately of use in detecting "light" anaesthesia. However, no identical changes have been demonstrated for all anaesthetic agents, and such microprocessing techniques would depend on pre-programming of normative EEG data for each anaesthetic agent to be used. Validation of the technique would again depend on retrospective analysis of inadequate states of anaesthesia, with respect to awareness.

iii) Power Spectral Analysis.

By digitising the EEG signal and subjecting the waveform to Fourier analysis [118] at frequent time intervals, (epochs), all of the information in the original signal is retained. The power in each freqency band is calculated by squaring the amplitude of each. In this way, the complex EEG signal is transformed into a number of simpler sine waves, and ingenious methods of display facilitate interpretation of the otherwise massive amounts of data generated; the compressed

spectral array, (CSA), developed by Bickford [119] and density-modulated spectral array (DSA), by Fleming and Smith [120], are illustrated in figure 16.

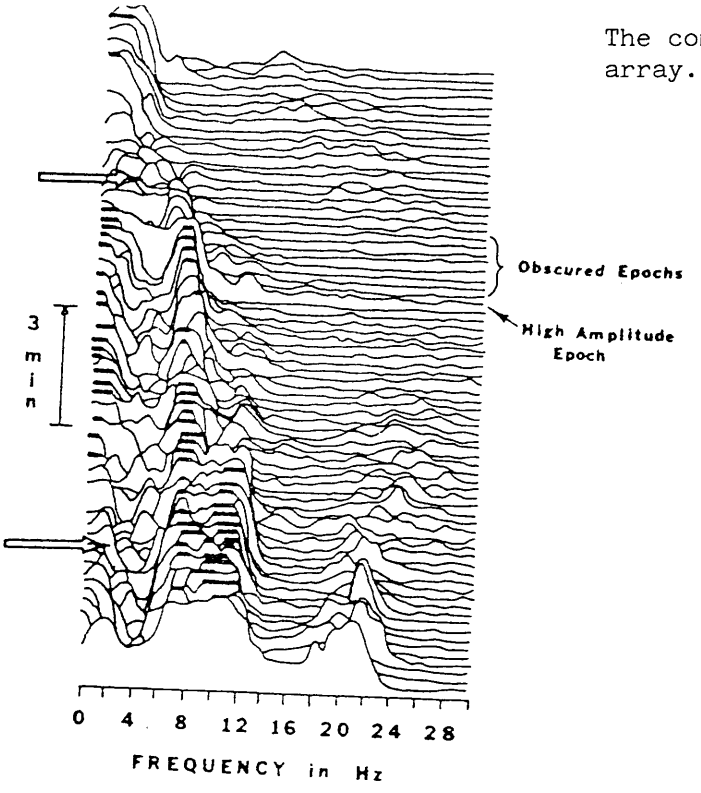
Although no information is lost in processing the EEG signal, it should be pointed out that, in the CSA display, information is obscured as a result of the "hills" casting a "shadow" on the changes occuring at similar frequencies in subsequent epochs. It may also be difficult to time the power changes, since power and time are represented on the same axis, (vertical). Offsetting the time axis, so that it lies at 45° to the power and frequency axes, (figure 17).

Again, this signal has been shown to correlate to the degree of hypotension during cardio-pulmonary by-pass and to cerebral circulatory changes at carotid endarterectomy [121,122]. Also, authors have demonstrated characteristic changes occurring with various anaesthetic agents. However, the changes are again not uniform, nor have they been shown to be reversed by surgical stimuli.

Berezowskyj and his colleagues [123] attempted to validate this signal as a measurement of the depth of anaesthesia in 1976; throughout surgery, a total of 341 EEG epochs were analysed by computer, using 13 frequency-domain variables. They simultaneously estimated anaesthetic depth, using the presence of movement, (unparalysed patients), heart rate and arterial pressure. Having this information as a data base, the ability of the computer to estimate the depth of anaesthesia from the EEG processing was 55-80%, depending on the method used to estimate performance. The authors point out that even 55% is comparable to the figure achieved by experienced electro-encephalographers, (see above) in visual

Figure 16.

i)



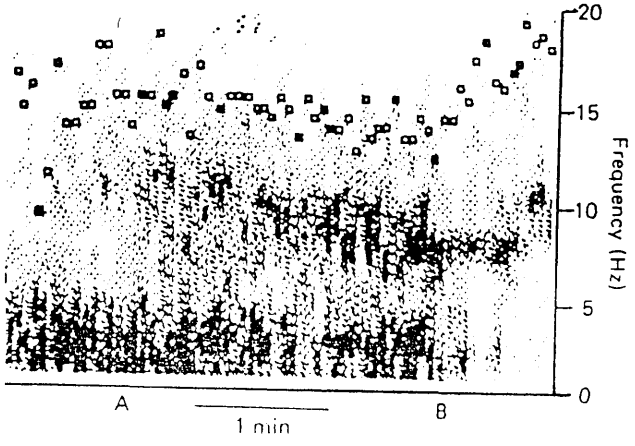
The compressed spectral array.

Problems with the linear display of the spectral analysis (CSA).

1) Loss of data. An epoch of high-amplitude activity is shown obscuring part of the data in subsequent epochs for almost 3 min. Any changes in the 0–7-Hz range of the EEG during this time would not be detectable. In an effort to prevent an even greater loss of data when very-high-amplitude activity occurs, "hills" may be truncated, as indicated by the heavy horizontal lines. Unfortunately, this only changes the nature of the data lost, it does not prevent the loss.

2) Confusion of time and amplitude. Because time and amplitude of the EEG spectrum are displayed on the same axis, an identifiable baseline is needed to estimate the amplitude. The low-amplitude, high-frequency segment of the epoch often serves as such a baseline; however, in areas such as those identified by the hollow arrows, it may be difficult or impossible to identify the baseline and estimate EEG activity.

ii)



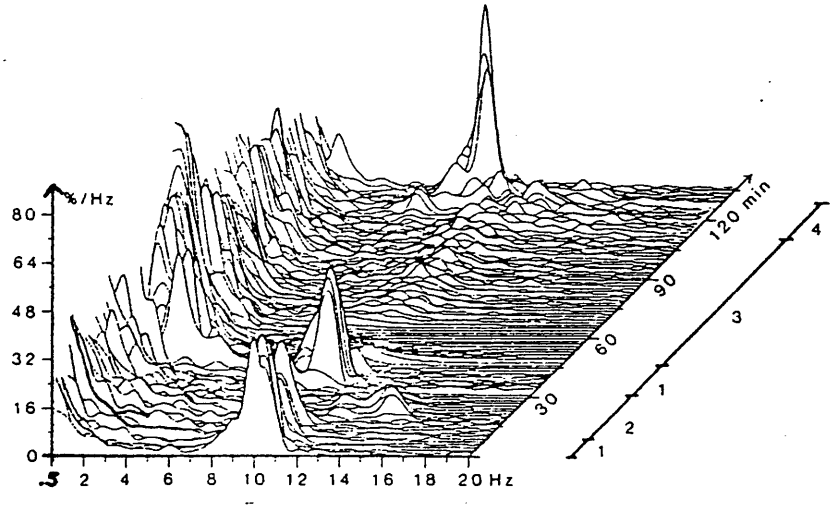
The density modulated spectral array.

(power spectrum v's spectral edge)

Spectral edge frequency is also shown (□).

In this recording
A=Anaesthesia
B=Intubation.

Figure 17.



The compressed spectral array; the time axis is offset at 45° to the other two axes, to minimise loss of data.

analysis of gross EEG activity.

Another group of workers, [124], also derived a scoring system based on power spectral analysis to predict the probability of patient movement in response to trocar insertion at laparoscopy; applying discriminant analysis to the scores from "move" and "no-move" patients, they were able to plot a "probability of move" curve for each of two anaesthetic techniques. Each curve illustrates the probability of movement against the EEG score.

The authors thus were able to correlate their signal to the MAC point on the anaesthetic continuum, where there is no movement in response to incision. However, they also addressed awareness in the study; patients were asked to squeeze the hand during the period immediately prior to insertion of the trocar, and whether or not they opened their eyes on hearing their names was noted. There was no significant difference in EEG scores between those who moved with trocar insertion and those who responded to their names.

The same authors, also reported interim findings of a subsequent study, using the same EEG scoring system with the same anaesthetic technique; awareness was assessed by means of a simple recognition test, where one of five sounds was played to the patient during anaesthesia. Although there was no conscious awareness, many patients had opened their eyes and squeezed their hands in response on command. Six patients said they clearly recognised one of the five sounds, which turned out to be the sound they had heard. Only two of these six were moving in response to surgery, but the EEG scores of all six were high relative to the rest of the study group. By

applying the "probability of move" curve, appropriate for each anaesthetic technique, the median probability was 90%. This indicates a light plane of anaesthesia, which was partly confirmed by clinical criteria, (MAC), but it also may be more sensitive; although patients did not move, they were probably nearer to the point of conscious awareness.

These studies illustrate that deriving signals by computer analysis may be clinically applicable in measuring depth of anaesthesia. This is despite the lack of uniformity of the signal changes for all anaesthetics. By facilitating the formation of large data bases, computerised systems may overcome this difficulty and provide reliable signals for at least a few basic techniques.

Thus, power spectral analysis provides a signal which is easily read and correlates clinically to depth of anaesthesia. Importantly, it is also sensitive to cerebral ischaemia, and perhaps to the level of awareness.

iv) Period analysis

One of simplest method of analysing an epoch of the EEG is to count the number of times the waveform crosses zero. Known as the zero crossing frequency, (ZXF), this measurement can be performed using relatively simple, inexpensive equipment and was one of the earliest EEG analysing methods used. Unfortunately, again much information carried by the original EEG is lost in such a reduction of data, and any one ZXF may represent a number of differing EEG patterns. Also, small amplitude changes in the low-frequency EEG component results in large increases in ZXF; thus the signal itself is over-sensitive at times.

Despite these theoretical objections, some have proposed that ZXF together with the mean rectified voltage, can be used to measure anaesthetic depth [125]. This is known as period-amplitude analysis. In a comparison of sensitivity of various methods of EEG analysis, ZXF with amplitude was one of the "safest" in the detection of cerebral ischaemia [126]. Others have examined ZXF, mean integrated voltage and the frontalis muscle EMG during anaesthesia [102]; despite good correlations between ZXF and with blood propofol levels, there was no relationship between the former and conscious level or awareness.

On the grounds that for multi-modal distributions, (such as the EEG frequency distribution), the median value represents the spread of data better than the mean, the median EEG frequency has received attention. The results are encouraging; not only are there dose-related changes with blood anaesthetic concentrations [127], (ketamine, methohexitone and etomidate), there is good correlation with the level of responsiveness, (loss of corneal reflex, orientation). Median EEG frequency and responsiveness also correlate well for isoflurane, halothane and enflurane. However, where the general EEG pattern does not slow with increasing blood anaesthetic concentrations, (propofol and thiopentone), the dose-related decrease in median EEG frequency is not seen. Thus, the criteria of uniformity is not completely fulfilled.

v) Evoked responses.

Computer averaging of EEG responses to sensory stimuli produces specific potentials, (figure 18), representing the

brain response evoked by a variety of stimuli. Time-locking the EEG and the stimulus removes the back-ground, non-specific part of the EEG. It is suggested that the effect of anaesthetics on such specific responses, and the pathways they represent, may be a better index of the anaesthetic depth than the EEG.

Three types of evoked response have received attention;

i) somato-sensory (SEP)

ii) visual (VEP)

iii) auditory (AEP).

The stimuli are thus tactile, visual, or auditory.

SEPs have been used extensively during neurosurgery, to monitor the integrity of ascending pathways during surgical manipulation [128]. The volatile agents halothane, enflurane and isoflurane have been shown to increase the latency of the cortical components of the SEP, and similarly to decrease wave amplitude [129]. In contrast, the sub-cortical components are largely unaffected.

The effect of anaesthesia on VEPs has been studied; while the potentials are qualitativly similar, during halothane anaesthesia, to those recorded in the awake condition, the latency of some of the component waves is increased by increasing alveolar anaesthetic concentration [130]. Latencies are measured to within 2 or 3 msec in clinical laboratories, so the maximum shift of 37 msec is easily detected.

Adam and Collins [131] also reported dose-related wave latency increases in some later VEP components in response to enflurane, (sub-anaesthetic doses). Isoflurane also has been

shown to increase the latency and decrease amplitude in the cortical part of the VEP [132]. Perhaps as a consequence of the shortness of the pathway itself, many of these "changes" were insignificant; this reduces the sensitivity of such a signal. However, Burchiel and his co-workers [133] examined the effects of enflurane on VEPs, (2.5-3.7%), and found large amplitude increases, but did not report any latency changes. Thus, the signal has not shown uniformity, but seems to be agent specific. These latter workers established that CO_2 levels may greatly alter the amplitude of VEP components; thus, variation in temperature and ventilation must be avoided for meaningful interpretation of this signal.

The study of VEPs during anaesthesia has by no means been exhausted, but incongruous results so far indicate that the signal is likely to be of limited use as a measure of anaesthetic depth.

On the other hand, AEPs have received much attention; Jones and his co-workers have investigated the effects of halothane, enflurane, and isoflurane and several intravenous induction agents on the AEP [134,135,136,137,]. They demonstrated common dose-related changes with increasing concentrations of these agents. However, the common amplitude changes, (reduced amplitude), were seen only in the early cortical components of the AEP, the brainstem potentials being relatively unaffected. The anaesthetics also produced dose-related graded increases in wave latency, in the early cortical part of the AEP.

The same authors have demonstrated reversal of the changes, (though incomplete), on withdrawl of the anaesthetic and, importantly, that the amplitude changes are reversed by

superimposed surgical stimuli [138]. The latency changes, however were not reversed by surgery and the authors felt that the progressive increases in latency throughout the period of anaesthesia were attributable to increasing brain anaesthetic concentrations.

They also attempted to validate the signal, using an isolated fore-arm technique to test awareness levels during anaesthesia [139]. An increased level of response was seen when wave Nb, (a component of the early cortical part of the AEP), latency was < 44.5msec. However, this particular component of the AEP signal, (early cortical latency), is not that which the authors demonstrated to be reversed by surgical stimuli, (amplitude of early cortical response). Therefore, it remains to be seen whether they can correlate a change in the level of responsiveness with amplitude changes in response to surgical stimuli.

This group of workers have methodically approached most of the criteria for a depth of anaesthesia signal. Their work is borne out by others [140], but the feasibility of adoption of routine neurophysiological monitoring is surely limited by the elaborate nature of measuring evoked potentials.

Thus, whereas the EEG and many of the other derivations are agent specific, evoked potentials seem to be affected in the same way by all anaesthetics. Several of the drugs used in conjunction with general anaesthesia, (e.g. benzodiazepines, opioids), have been shown not to affect the evoked potentials significantly. The evoked potentials are, like the EEG, sensitive to cerebral ischaemia, and are also affected by other variables, notably arterial CO_2 concentration, and

temperature.

Conclusion

No single method of monitoring fulfills all the criteria we previously set out as necessary for a signal representing depth of anaesthesia. The degree to which each signal correlates with conscious level is difficult to determine; many authors have related conscious level merely to whether clinical signs of light anaesthesia exist. Traditional clinical signs, as we have pointed out are not a "gold standard" by which new methods can be validated.

A simple scoring system was devised to assess the relative merit of each method in satisfying the proposed criteria for the signal, (table 21).

The method was based on the criteria was as follows:-

i) Sensitivity

For all the proposed signals, with the obvious exception of clinical signs, there are not enough cases to extract meaningful information about the incidence of awareness. Thus, the false negative rate remains undetermined in the majority of cases.

The same applies to the false positive rate. No score is therefore awarded to assess the latter two points.

A score of 0-2 was awarded for sensitivity to cerebral ischaemia as follows:-

0 - unreliable as an indicator of cerebral ischaemia.

1 - partially sensitive to cerebral ischaemia.

2 - of proven use as an indicator of cerebral ischaemia, the signal changes being a

Table 21

CRITERIA	CS	LOC	EMG	EEG	CFAM	CSA	AEP
Sensitivity	1	1	1	2	2	2	2
Specificity	0	0	0	0	0	0	1
Uniformity	1	1	1	0	0	0	1
Dose-related changes	1	1	1	1	1	1	1
Reversibility	2	1	0	0	0	0	2
Readability							
i)	0	1	1	1	1	1	1
ii)	0	1	1	0	1	1	1
iii)	1	1	1	0	0	0	0
TOTAL	6	7	6	4	5	5	9

Scores awarded to various proposed methods of monitoring depth of anaesthesia, according to satisfaction of the predetermined criteria. The higher the score (out of a possible =10), the better the criteria are satisfied.

CS : clinical signs
LOC : lower oesophageal contractility
EMG : electromyograph
EEG : the unprocessed electroencephalogram
CFAM: cerebral function analysing monitor
CSA : Compressed spectral array
AEP : auditory evoked potential (early cortical part).

Table 21

progression of the dose-related changes.

ii) Specificity

A score of 0 or 1 is awarded as follows:-

0 - the signal is affected by muscle relaxants and/or other drugs, and stimuli other than surgical produce changes in the signal.

1 - the signal is unaffected by drugs or other stimuli.

The level of vigilance and cerebral ischaemia do affect many of the signal changes, but since these are desirable qualities, these are not included in the first category. The level of vigilance, as already stated has not been fully investigated with regard to each signal.

iii) Uniformity

A score of 0 or 1 was awarded as follows:-

0 - different anaesthetic agents produce different characteristic changes.

1 - the changes in the signal are the same with all anaesthetics.

iv) Dose-related changes

A score of 0 or 1 was awarded as follows:-

0 - changes not shown to be dose-related.

1 - changes shown to be dose-related.

v) Reversibility

A score of 0-2 was determined as follows:-

0 - Surgical stimuli have no effect on the signal changes induced by increasing

anaesthetic dose.

1 - Surgical stimuli produce recogniseable changes in the signal, during anaesthesia.

2 - The signal changes produced by anaesthetics are reversed by surgical stimuli.

vi) Readability

The scores here were in three groups of either 0 or 1. Points were awarded for

i) objective measurement

ii) ease of interpretation

iii) signal clarity.

These scores were awarded as follows:-

0 - the signal is measured subjectively

1 - the signal is measured objectively

0 - the signal is interpreted subjectively

1 - the signal is interpreted objectively

0 - signal changes are small and difficult to distinguish in the range of clinical anaesthetic concentrations.

1 - signal changes are seen clearly.

Table 21 shows the AEP scores highest and the unprocessed EEG scores lowest. This system is not sensitive to several points however, notably that "clinical signs" differ individually with respect to each criteria. In this event, the lowest "reasonable" value applicable was given. This introduces a subjective element into the scoring system, which is compounded by subjectivity involved in deciding whether or not the signal changes are easily seen or not. This latter point was introduced to distinguish between the

signals which produce small changes and are of more use in indicating trend, eg CFAM. Also, to the naked eye, the changes in wave latencies of the AEP, measured in ms, are not immediately obvious.

The early part of the auditory evoked potential is itself a repsonse to a stimulus which is superimposed upon a prevailing background of surgery and anaesthesia. So too are provoked oesophageal contractions, and they also score highly with this system. It is not enough that a signal reflects brain anaesthetic concentration accurately, (this applies to EEG, CFAM, CSA etc.); in the face of changing levels of surgical stimulation, any particular brain anaesthetic concentration is unhelpful in calculating the balance, or imbalance, of surgery and anaesthesia. It seems likely that evoked signals could give a better indication of the latter, in patients with intact auditory pathways.

Although the AEP scores 90% towards criteria fulfillment, it remains to be seen whether the level of consciousness, or cognitive ability, correlates with the signal changes.

Conclusion

From our preliminary study, we concluded that AP measured on admission to hospital in the presence of a doctor, or manually by a nurse differs significantly from true resting pressure. Incorporating AP derived from true resting values into our feedback control system, we acheived SAP control in 100% of patients. In 33%, additional narcotic boluses were required, indicating that the control was less good in these patients. In the non-narcotic requiring groups, two or more criteria for clinically adequate anaesthesia were satisfied by 91% of patients, compared to 40% for those requiring additional narcotic boluses.

The use of fentanyl rather than morphine, did not affect the quality of control significantly, but did significantly alter values for physiological variables. In addition, it is possible that a patient in the fentanyl group may have experienced conscious awareness during anaesthesia, while there was no evidence of this in the other groups.

A sensitive test of cognitive function revealed no conscious awareness during anaesthesia, but there was evidence the cognition does continue to some degree under anaesthesia.

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