TOWARDS THE DEFINITION, MEASUREMENT AND ASSESSMENT OF THE ANAESTHETIC STATE.

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SUMMARY

The definition of the anaesthetic state is discussed. We see the anaesthetic state as a central nervous system state, which results from the interaction between the effects of anaesthetic dose and the effects of surgical stimulation on that system. However, the effects of surgical stimulation, although they may be described as an ordered sequence of events, cannot be quantified. And the wide variation in anaesthetic requirement means that anaesthetic dose can, at best be, defined with respect to a single point (or points) on a qualitative scale. It is therefore difficult to assess the various techniques proposed as monitors of the anaesthetic state.

These techniques are reviewed and it is apparent, that without a clear definition of the anaesthetic state, these techniques cannot be fully assessed. There is therefore a need for an individually valid anaesthetic state ("gold standard") to which other methods can be compared.

Clinical signs form the basis for the administration of thousands of successful anaesthetics each day and, despite some inadequacies, are currently the only practical, universally accepted indicators of anaesthetic adequacy. However, their interpretation is both subjective and variable. A reproducible, individualised description of the anaesthetic state, based on clinical signs would allow this and other techniques to be more fully assessed.

The objective of the work presented in this thesis was to investigate whether a clinically acceptable anaesthetic state could be produced by a control system

designed to maintain the patients systolic arterial pressure (SAP) at a predetermined level by altering the inspired concentration of enflurane or isoflurane. Such a control system, though limited in that it uses only one clinical sign, should help to standardise the management of the anaesthetic state.

A proportional - integral control system was set up with an RML 380Z-D computer interfaced to a Critikon Dinamap 1846 and a vaporizer controller. A program, written in BASIC, was designed to maintain the patients SAP at 90% of that predicted from age and sex standardised tables. The controller took data from the Dinamap, which was set to cycle at one minute intervals, and changed the inspired volatile concentration via the vaporizer controller.

In a preliminary study some patients were hypotensive, relative to the target SAP, following induction but prior to surgery. These patients therefore received minimal concentrations of volatile anaesthetic initially. Others received a relative overdose of anaesthetic during the procedure. Two additional rules were incorporated in the control algorithm to limit these effects. First, a minimum inspired concentration of 0.6% was delivered for the first 10 minutes and second, if the inspired dose of volatile anaesthetic exceeded a preset limit, the controller instructed the anaesthetist to give a bolus of morphine and reset the integral. This limit was defined as a total inspired concentration of more than 15% over 5 consecutive vaporizer settings with each individual setting exceeding 2.5%. This rule could only be activated

once in 15 minutes.

The study was carried out on 57 ASA I and II female patients admitted for routine gynaecological surgery. All patients were artificially ventilated and received a standard, nitrous oxide based anaesthetic supplemented with morphine at induction, and enflurane (22 patients) or isoflurane (35 patients). The dosage of volatile anaesthetic and the requirement of additional morphine were determined by the controller.

During surgery cardiovascular data and the inspired volatile requirement were recorded every minute and clinical signs "scored". Recovery times were measured and all patients interviewed post-operatively to discover whether they had been aware during anaesthesia.

An adequate anaesthetic state was defined by strict criteria based on cardiovascular variables, the goodness of control, recovery time and absence of awareness post-operatively. No patient recalled any intraoperative event. Overall, 53.8% of cases satisfied all criteria. A failure to achieve two or more of these criteria occurred in 7.5% of patients in the groups not requiring additional morphine compared to 83.3% of the patients who did require additional morphine.

The use of SAP as the sole variable to control the delivery of anaesthetic agents, can be criticised on several grounds. However, it is one of the few quantifiable indices available and increases in SAP are commonly treated with anaesthetic agents. Further, we carefully excluded those cases in whom SAP is likely to unreliable e.g. hypertensive patients.

Although our method of selecting the TSAP is crude, and those patients who required additional morphine may reflect those in whom the TSAP is low, the controller achieved the immediate aim of controlling SAP and also produced a pattern of clinical signs recognisable as general anaesthesia.

Pupil diameter was measured in 34 patients. A significant correlation was found between pupil diameter and SAP in 5 cases. There was no difference in the clinical anaesthetic state in those patients in whom a significant correlation was found and those in whom there was no significant correlation.

Spectral edge frequency (SEF) was measured in eight of the patients who received isoflurane using a Neurotrac monitor. Due to limitations in data recording we were not able to correlate SEF with SAP. However, SEF was plotted against SAP for seven patients during relatively stable periods of SAP control. A visual relationship was apparent between SAP and SEF in 4 cases. The significance of this finding is unknown. In a further case the EEG became isoelectric at the time a morphine bolus was requested by the computer. The processed EEG may be a better method of assessing a relative anaesthetic overdose than SAP alone during nitrous oxide-morphine-isoflurane anaesthesia.

In summary, a computer control system has been developed and tested. The controller achieved the immediate aim of controlling SAP and also produced a pattern of clinical signs recognisable as general anaesthesia.

INTRODUCTION

WHAT IS "GENERAL ANAESTHESIA" ?

The introduction of the word "anaesthesia" into the English language is generally attributed to Oliver Wendell Holmes. It is currently defined in the Oxford dictionary as "Absence of sensation, esp. artificially induced insensibility to pain". This definition of "Anaesthesia" refers only to sensory block, and as such does not clearly define the state induced by, or the objectives of, general anaesthesia. Although the introduction of new terminology has been suggested (1), the term is deeply entrenched and it is now more appropriate to redefine what the term "general anaesthesia" actually implies.

A HYPOTHETICAL DEFINITION OF THE STATE OF ANAESTHESIA.

The anaesthetic state is a functional state of the central nervous system which results from the interaction between anaesthetic drugs and surgical stimulation. As adequate general anaesthesia exists when the anaesthetic state is appropriate for surgery, the true definition of anaesthesia will be synonymous with the criteria which define this state. Therefore, anaesthesia should ideally be defined with reference to a specific level (or levels) of central nervous system activity.

However, although the intra-operative anaesthetic state, as we see it, results from the "balance" between the effects of surgical stimulation and the effects of anaesthetic dose on the central nervous system, it is not known if any of the methods proposed as as monitors of anaesthetic adequacy truly reflect this balance, if they monitor it completely or what level (or levels) of CNS

activity are most appropriate during general anaesthesia and surgery. Therefore, anaesthesia cannot currently be defined in these terms.

It should be noted that this hypothesis assumes that an "ideal" anaesthetic state can be described which is appropriate to all patients and all types of surgery, and that the determinants of the anaesthetic state are anaesthetic dose and surgical stimulation.

ALTERNATIVE DEFINITIONS OF ANAESTHESIA.

White recently described general anaesthesia as "... a reversible state of depression of the central nervous system of such a degree that consciousness is lost and that on recovery nothing is recalled relating to the period of anaesthesia " (2). This approach is fraught with difficulty as it involves circular arguments. Not only must each individual aspect of the definition be defined before the description can have any real meaning, but also these criteria may be fulfilled during surgery when the patients degree of responsiveness suggests that the anaesthetic state is inadequate i.e. when the clinical signs are untruthful.

Prys-Roberts (3) has argued that the only common effect of all general anaesthetic agents is "the suppression of perception" and, that anaesthesia should be considered as "that state which ensures the suppression of the somatic and visceral sensory components [to the noxious effects of surgical stimulation], and thus the perception of pain". And he suggests that analgesia, muscle relaxation and the suppression of autonomic activity should not be considered as components of

anaesthesia (4,5) but as desirable supplements to the anaesthetic state. As the perception of any sensation requires an awareness of that sensation (i.e. consciousness) this definition is, in essence, identical to that of White.

These definitions seem to imply that the only necessary "component" of anaesthesia is lack of awareness. It follows, that the anaesthetic state which achieves this objective, in conjunction with the suppression of peripheral responses to surgical stimulation by non-anaesthetic drugs (e.g. vasodilators and adrenergic blocking drugs), would be considered adequate. While this may be true, the author believes that the "ideal" anaesthetic state is likely to require the central suppression of more than memory function.

THE OBJECTIVES OF GENERAL ANAESTHESIA

The objective of general anaesthesia is to safely provide the best possible conditions for surgery. The anaesthetist therefore aims to produce a reversible state which includes:

1 Hypnosis, that is the patient should have no recall of intra-operative events.

2 Maintenance of physiological variables within boundaries, defined by himself for each case, and which depend on:

a) Patient factors ie disease status.

b) Surgical factors e.g. the provision of hypotension or muscle relaxation.

(continued)

3 The degree of reflex suppression to surgical stimulation necessary to attain the first and second goals.

4 A safe and comfortable post-operative recovery, which can be defined as the rapid recovery of protective reflexes, physiological stability and adequate analgesia.

DEFINING ADEQUATE GENERAL ANAESTHESIA.

Adequate, as opposed to inadequate, general anaesthesia may be defined as the intra-operative anaesthetic state which allows these goals to be fulfilled. Modification of these goals is necessary when specific types of surgery, drugs or pathological condition are considered e.g. a rapid recovery may not be a desirable objective following maxillofacial surgery. In general failure to achieve these objectives implies that the anaesthetic state induced was inadequate. As achievement of these goals cannot be confirmed until the post-operative period "anaesthesia" is a retrospective diagnosis.

The quality of anaesthesia may be considered relative to these goals and considered adequate or inadequate. And, if inadequate, as insufficient or excessive i.e. the difference between the anaesthetic state and these anaesthetic goals is the basis, of the concept, of anaesthetic depth.

THE CONCEPT OF ANAESTHETIC DEPTH.

Depth of anaesthesia is a concept used to describe a patients anaesthetic state relative to an assumed scale

which could range from full consciousness to death. Although this scale is related to anaesthetic dose, individual variations in drug response and the confounding effects of drug combinations and surgical stimulation mean that the relationship is not simple.

As the mechanism of action of anaesthetic drugs is unknown, no technique can be proven to assess anaesthetic depth. Further, if the depression of multiple nervous system sites is necessary or desirable for the achievement of adequate general anaesthesia then assessment of 'anaesthetic depth' may involve more than one technique and more than one scale.

With this in mind it is reasonable to describe any technique which improves the description of the anaesthetic state, and therefore allows the objectives of general anaesthesia to be more reliably attained, as a monitor of anaesthetic depth.

THE DEFINITION OF SOME POINTS ON THE ANAESTHETIC SCALE.

If a single scale can be used to describe the anaesthetic state then some points can be provisionally identified (Figure 1).

CONSCIOUSNESS.

At induction and during recovery a transition between the conscious and unconscious states occurs. Consciousness is however difficult to define. The definition most relevant to this aspect of anaesthesia depends on the ability of a patient to register, integrate and recall information from his memory. Aspects of consciousness assessed by other mental functions (e.g. arithmetic

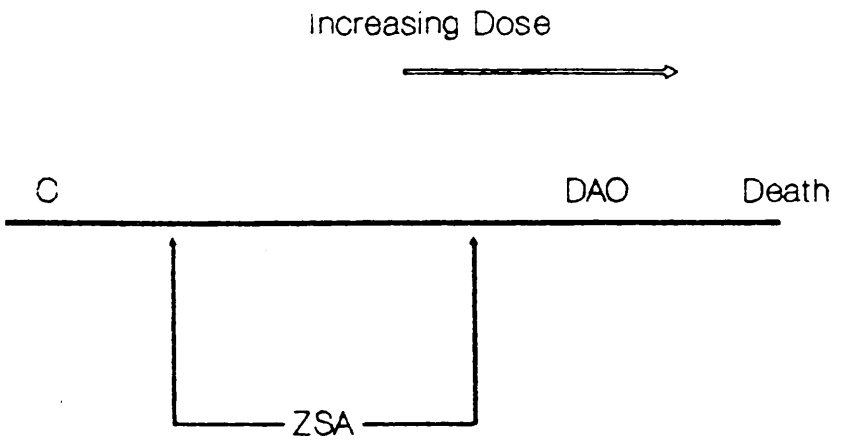


Figure 1.

Some points on the anaesthetic scale

C = Conscious

DAO = Dangerous anaesthetic overdose

ZSA = Zone of surgical anaesthesia

(see text for details)

performance) or by psychomotor reaction times are irrelevant during anaesthesia while definitions relating to enviromental inter-action (e.g. responses to pain) are only important if patient should move (disrupting surgery) or recall the precipitating event (e.g. skin incision). Unconsciousness will occur when one or more of the processes involved in memory function is disrupted to the necessary degree.

DANGEROUS ANAESTHETIC OVERDOSE.

Dangerous anaesthetic overdose is a more clinically relevant end-point than death and may be defined as the dose of anaesthetic at which physiological parameters (e.g. blood pressure) cannot be maintained within safe limits. These limits will depend on patient factors (e.g. hypertension or cerebro-vascular disease), drug factors (e.g. the concomitant use of vaso-dilators or beta-blockers) and anaesthetic technique (e.g. ventilated or non-ventilated patients).

A ZONE OF ANAESTHESIA.

Between these ill-defined extremes a zone of surgical anaesthesia (ZSA) can be described. This zone may be defined as the spread of drug dose over which all the anaesthetic goals defined above are achieved.

DEFINING THE OF THE ZONE OF ANAESTHESIA.

Individual anaesthetists achieve the goals of anaesthesia in most of their patients. Each anaesthetist does this by anaesthetising to his/her own personal "standard" and it follows that each anaesthetist can clinically identify a ZSA, for individual patients, with

the techniques he uses. The exact location and best definitions for the boundaries of this zone are unknown but, in the establishment of their personal standard, general 'thresholds' of response (the limits within which an anaesthetist allows a variable or group of variables to change before taking action) must be made. Defining these thresholds should allow the clinical boundaries of this zone to be described.

For each patient the zone of surgical anaesthesia will lie between two physiological boundaries which are defined by the anaesthetist for that individual. If the patient's clinical state should reach a boundary the anaesthetist will always act by either increasing or decreasing the dose of anaesthetic. Interventions may be made prior to a boundary crossing, the action itself dependent on the degree, rate of change and "truth" of the variables monitored e.g. heart rate changes will have less significance after the administration of atropine.

THE BOUNDARIES OF THE ZONE OF SURGICAL ANAESTHESIA.

The lower boundary of this zone will lie within clinically accepted 'safety' limits and may be defined as the maximum dose of anaesthetic at which the criteria describing it can be maintained. The upper boundary describes the situation where the degree of physiological disruption is either deemed dangerous, or "cortical awareness" is felt to be likely.

The variables used to assess the anaesthetic state clinically are affected by other events and the anaesthetist takes these into consideration. In some

extreme situations, for example cardio-pulmonary bypass surgery, clinical signs may give no or minimal information about the patients anaesthetic state; in others complicating factors e.g. concomitant drug therapy may detract from the usefulness of clinical signs and increase the risk of a relative under- or over-dose of anaesthetic.

Figure 2 shows a possible relationship between the ZSA and the true anaesthetic state.

DIFFICULTIES IN MEASURING THE ANAESTHETIC STATE.

Although it is reasonable to assume that the anaesthetic state results from the interaction between two CNS "inputs", assessment of the various methods proposed as monitors this state is difficult because:

1 Surgical stimulation, although it may be described as an ordered sequence of events (Figure 3), cannot be quantified.

2 The large inter-individual variation in anaesthetic requirement means that anaesthetic dose can at best be defined with respect to a single point (or points) on a qualitative scale. This imposes severe limitations on its use. The limitations of anaesthetic dose as a measurement of anaesthetic adequacy are discussed further in the following section.

When these problems are considered, the most appropriate method of assessment is to determine an individually valid functional anaesthetic state ("gold" standard), to which other methods can be compared. Although several workers have used, or suggested, that a

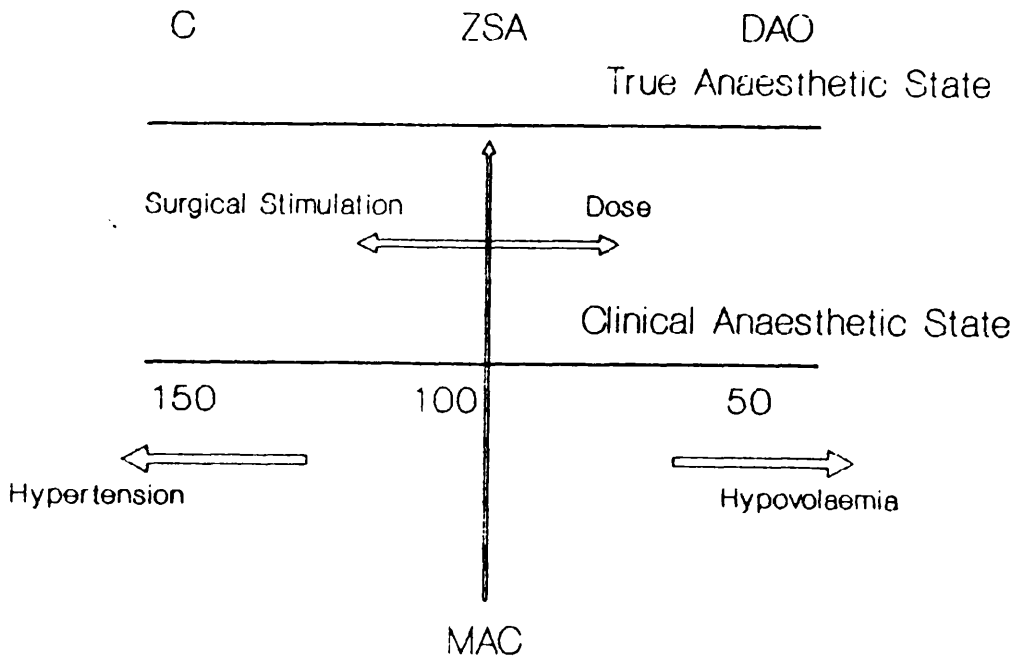


Figure 2.

A Possible Relationship between the ZSA and the True Anaesthetic State.

The upper line depicts the true anaesthetic state, ranging from consciousness (C) to dangerous anaesthetic overdose (DAO). The Zone of Surgical Anaesthesia (ZSA) lies between these points. The lower line depicts a representative clinical anaesthetic state defined, in this case, by Systolic Arterial Pressure (SAP). A relationship between these scales will exist, and may be measured at any fixed level of response (eg. MAC). However, the validity of the response is unknown and any change in the level of surgical stimulation or in drug dose may effect the true scale to a greater of lesser extent than the representative scale. Further, complicating factors eg. hypovolaemia or hypertension in the case of SAP may shift the representative scale relative to the true scale.

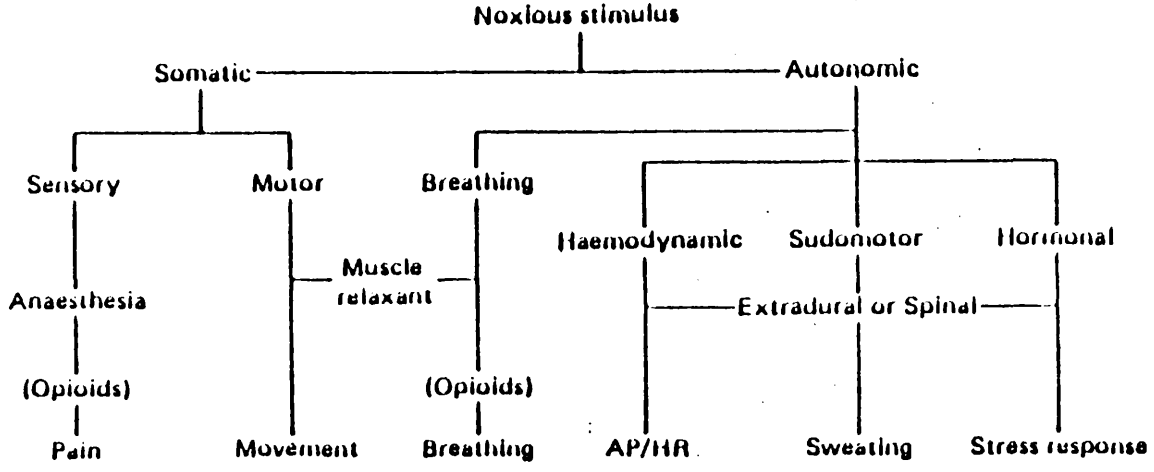


Figure 3 Surgical stimulation as an ordered sequence of events (from ref. 3)

Although surgical stimulation cannot be quantified it can be described qualitatively as a sequence of events, ordered by the dose required for their suppression (from left to right in the diagram).

specific mental state or level of autonomic activity (6,7,8,9,10) is the most appropriate method of assessing the various techniques proposed as monitors of anaesthetic adequacy, the use of this method has not become widespread. This may be because the definition and validation of such a state is difficult.

A CLINICAL STANDARD OF ANAESTHETIC ADEQUACY.

Clinical signs, despite some inadequacies (11,12), are currently the only practical, universally accepted, method of assessing the anaesthetic state. As such they are used successfully to guide the administration of thousands of anaesthetics each day. However, their interpretation is both subjective and variable. A reproducible, individualised description of the anaesthetic state, based on clinical signs and validated against the "goals" of anaesthesia, may allow the use of this technique as a gold standard. If another method (or combination of methods) should prove superior it should then be accepted as the new standard and the zone of surgical anaesthesia redefined with respect to this method.

Anaesthetic dose and surgical stimulation, the determinants of the anaesthetic state, are discussed in the following chapters and the validity of this approach in the final chapter.

CHAPTER 1

THE MINIMUM ALVEOLAR CONCENTRATION FOR ANAESTHESIA.

Many workers have concluded that the demonstration of a relationship between anaesthetic dose (usually expressed in terms of MAC) and a variable implies that a given technique measures anaesthetic depth; the effects of surgical stimulation being ignored. There are several limitations to the use of MAC in this context.

HISTORICAL ASPECTS AND THE DEFINITION OF THE MINIMUM ALVEOLAR CONCENTRATION FOR ANAESTHESIA.

Prior to 1946 agents were compared by the inspired concentration required in clinical practice. In 1946 Robbins introduced the AD50 as the anaesthetic vapour concentration at which 50% of mice failed to remain upright for 15 seconds, after 10 minutes exposure, in a jar rotating at 14 revolutions per minute (13). Using this value, and the FD50 (defined as the concentration causing respiratory arrest in 50% of mice after 10 minutes exposure); induction times, recovery times, safety margins etc. for volatile anaesthetic agents can be compared.

The term MAC was introduced by Merkel and Eger (14) in 1963 as an index of comparison between halothane and halopropane, being defined as the "minimal anaesthetic concentration required to keep a dog from responding by gross movement to a painful stimulus". This concept has been expanded and is now used as a major indicator of anaesthetic potency.

> MAC is defined in man as the alveolar concentration of anaesthetic vapour, expressed as a percentage of one atmosphere and held stable for 15 minutes, at which 50% of patients show no muscular response to an

applied noxious stimulus (e.g. skin incision or electric shock) (15). A positive response is taken as "gross purposeful muscular movement" (16); facial grimacing, coughing, swallowing etc. are considered negative (16,17).

FACTORS AFFECTING MAC

MAC may be effected by a number of factors and these are listed in Table 1. Although the effect of some variables (e.g. age) have a predictable effect on MAC which appears to be agent independent and corrections can be made, the effect of other variables differs between agents. For example, it has been shown in dogs that a decrease in temperature from 38 to 28 ^{o}C results in a 50% decrease in the MAC value for halothane but of only 25% in the case of cyclopropane (18).

In some studies (14,25) agents known to increase MAC e.g. cocaine (19) or decrease it e.g. thiopentone (16) were used. This may have effected the calculated values.

DIFFICULTIES IN TERMINOLOGY.

The term "Minimal Alveolar Concentration" has been described as "poor" (26), and may be misleading. MAC, as defined, describes a median effective value for the population with respect to one aspect of the overall response to a defined stimulus. MAC does not define a minimum alveolar concentration for anaesthesia in the individual.

De Jong and his co-workers (27) extrapolated 'MAC'_{95} values (the end-tidal concentration at which 95% of the population will shown no response to skin incision), for 9

Table 1. Some Factors That Affect MAC.

No or Minimal Effect	Decrease MAC	Increase MAC
Hypocarbia	Increased Age	Decreased Age
Hypercarbia	Hypothermia	Pyrexia
Hypoxia	Narcotics	CNS Stimulants
Metabolic Alkalosis	Sedatives	Alcohol Abuse
Stimulus Intensity	Muscle Relaxants	
Induced Hypertension	Nitrous Oxide	
	Acute Haemorrhagic Hypotension	
	Metabolic Acidosis	

References: 14,15,16,17,18,19,20,21,22,23,24

different volatile agents, using log dose-probit response lines, calculated from pooled data. In absolute terms these values are 5-40% greater than MAC*. These workers felt that a minimum, rather than a median, value would be more clinically useful. Knowledge of these values, or values described for other end-points is unlikely to alter the administration of drugs in clinical practice.

THE COMPONENTS OF MAC.

The determination of MAC requires the measurement of end-tidal anaesthetic concentration, the application of a noxious stimulus, and assessment of the subjects reaction.

END-TIDAL CONCENTRATION.

Waud and Waud (28) have suggested that the major contribution of MAC was the emphasis on end-tidal (alveolar) concentration rather than inspired concentration, a view reiterated by Quasha, Tinker and Eger in a recent review article (17). The alveolar concentration, after an equilibrium period, is used as an index of cerebral concentration, a useful trade-off between ease of sampling and indirectness of measurement, a vast improvement to the earlier emphasis on inspired concentrations.

* For clarity, "MAC" is used as an abbreviation for the classical minimum alveolar concentration, introduced by Merkel and Eger and defined on pages 27-28; " 'MAC' " is used as an abbreviation for "minimum alveolar concentrations" described by other workers for different end-points. These are differentiated in the text by the subscripts used by the authors who described them.

STIMULI AND END-POINTS OF RESPONSE.

Although the end-point and stimulus used in the calculation of MAC are well described, some workers have not adhered strictly to the criteria. Nicodemus et al (29) used "limb movements or facial grimacing" to indicate "lack of effective anaesthesia" which may explain the discrepancies between their results and previous work (30).

Some early work (16) suggests that some stimuli e.g. the tail clamp used in animal studies of MAC are maximal. That is, the application of two such stimuli do not increase MAC in that subject. Skin incision is not such a stimulus and it is debatable as to whether a 5 inch incision on the trunk is as "stimulating" as a 5 inch incision on the face where the pain receptors are more prolific. Further, this work suggests that, in the presence of a stimulus of varying intensity (e.g. during surgery) the anaesthetic dose required to prevent a motor response will itself vary. Work by Ausems (31,32) seems to confirm this, although autonomic variables were included in his definition of responders and non-responders (figure 4).

'MAC' AND OTHER END-POINTS.

'MAC' values have been described for a number of different stimuli and end-points.

1 'MAC'_{BAR}, the age-adjusted anaesthetic dose required to block the adrenergic response to skin incision (defined as a 10% or greater increase in heart rate, blood pressure, pupil diameter or noradrenaline levels) in 50% of subjects. A value has been

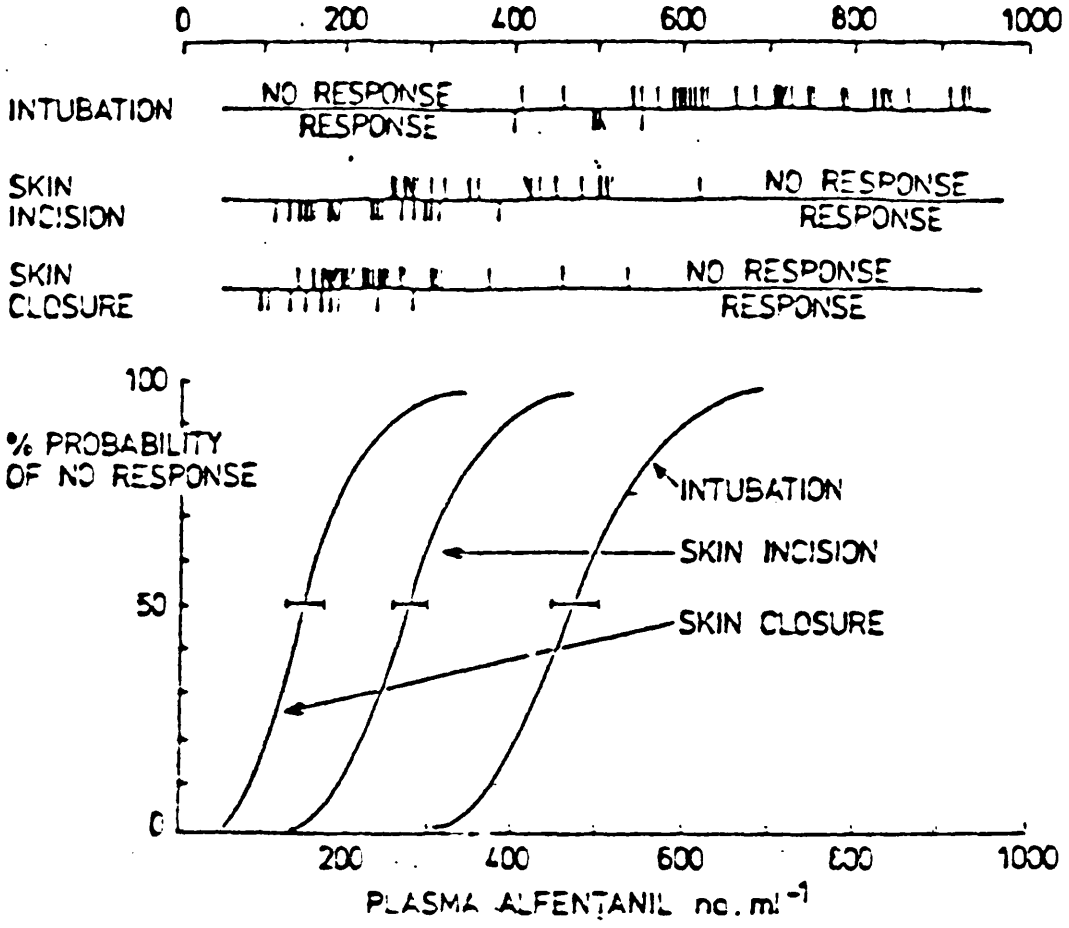


Figure 4 The dependency of dose-response curves on the type of stimulus.

Plasma alfentanil concentration-effect curves were determined for three stimuli (intubation, skin incision and skin closure) from the quantal date in the upper diagram by logistic regression. The bars indicate the standard error of the dose required to prevent a response in 50% of subjects (from ref. 32).

determined for halothane, enflurane and morphine (25). In each instance 60% nitrous oxide was given, all patients had their tracheas' sprayed with lignocaine (2mg/kg) and some received thiopentone at induction. With enflurane, the cardiovascular response to skin incision (as determined by changes in rate pressure product) was shown not to decrease with increasing doses of the drug, unlike those patients in the halothane and morphine groups. As pupillary changes were "estimated by approximation with a ruler", significant (10%) changes may have been missed.

2 'MAC'_{SI}, the alveolar concentration required to prevent a heart rate response to surgical stimulation in 50% of subjects. The value derived in this study was probably affected by the use of atropine as a premedicant (33).

3 'MAC'_{EI}, the minimal alveolar concentration required to prevent a motor response to intubation in 50% of cases and MAC_{ei}, that required to prevent a motor response to laryngoscopy in 50% of patients (34,35).

4 'MAC'_{awake}, the alveolar concentration at which 50% of people can be expected to respond to command (36). This study is complicated in that those patients anaesthetised with ether and fluroxene were volunteers and not exposed to surgery, while those anaesthetised with halothane and methoxyflurane were. The values determined in these studies are listed in table 2.

Although the number of stimuli and end-points

Table 2. 'MAC' Values determined for different Stimuli and End-Points.

AGENT	Mac Awake	Mac	Mac95	MacSI	MacEI	MacBAR*
Halothane	0.41	0.75	0.90		1.46	1.52
	0.57	1.00	1.20		1.95	2.02
Enflurane		1.68	1.88	1.97	2.93	3.66
		1.00	1.02	1.17	1.74	2.12
Isoflurane		1.2	1.63			
		1.0	1.36			
Methoxy-	0.08	0.17	0.22			
flurane	0.48	1.00	1.29			
Diethyl-	1.41	1.9	2.22			
ether	0.74	1.0	1.17			

The upper figures are the end-tidal concentrations (in %) required to fulfil the criteria of any given response and the lower figures represent the ratio of that dose to MAC. The responses are defined in the text.

* these values were determined in the presence of 60% nitrous oxide, 0.57 MAC has been allowed for the nitrous oxide.

See Text for References

available for study is almost inexhaustible, knowledge of the 'MAC' values which relate to them is unlikely to alter clinical practice (vide infra). The importance of using one group of subjects, to minimise experimental error, in the calculation of 'MAC' ratios has been stressed (28).

MAC AND COMBINATIONS OF ANAESTHETIC AGENTS

MAC values have also been calculated for combinations of anaesthetic agents (37,38,39,40,41,42). Although it is generally accepted (17) that combinations of anaesthetic agents are additive (figure 5), the number of combinations studied is small and both synergism and antagonism have both been demonstrated (43,44).

Little work has been done to determine whether anaesthetic agents are additive when different end-points of response are considered, however Stella and his co-workers (33) found that the end-tidal concentration of enflurane required to ablate the heart rate response to skin incision in 50% of subjects was only decreased by 53% when 70% nitrous oxide was added, less than would be anticipated from the additive effect of the nitrous oxide previously described (15,37,38,39,45).

MAC AND DOSE-RESPONSE CURVES.

MAC values are frequently used to derive dose-response curves. Waud and Waud have classified these (dose-response curves) as graded, quantal or ordered (28). Graded responses are those which can be measured on a continuous scale (e.g. blood pressure); quantal responses represent all or none responses in which the number of subjects reaching a defined end-point are plotted against

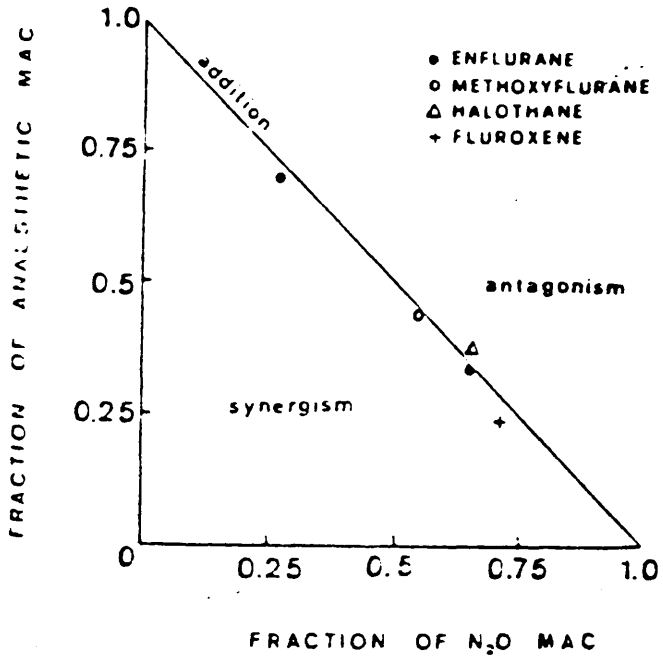


Figure 5. Combinations of nitrous oxide and volatile anaesthetic appear to be additive.

The vertical axis represents the fraction of MAC of four anaesthetic agents.. The value 1.0 represents 1 MAC of each agent. The horizontal axis represents the MAC fraction of nitrous oxide. The values obtained for the four anaesthetics fall near the line of simple addition. (from ref. 38).

concentration (eg MAC); and graded responses, empirical scales in which a number of end-points can be placed in order but in which the "distance between end-points" can have no meaning (e.g. Guedel's (46) classification of ether anaesthesia or Prys-Roberts (3) ranked suppression of noxious stimuli).

MAC refers to one point on a dose response curve. Comparison of anaesthetic agents using MAC is only valid at that point. Comparison using multiples or fractions of MAC can only be valid if the dose-response curves of the two agents are parallel (figure 6).

Although the ratios of anaesthetic requirement to MAC for a number of different end-points have been shown to be relatively constant for some agents (33,34,35) this is not always true

Kissin (47) derived 'MAC' values for three anaesthetic end-points (righting reflex, abolition of purposeful movement and heart rate response) for a variety of agents and concluded that the heart rate response to noxious stimulation, in contrast to the loss of righting reflex, has a constant ratio to MAC. Shim and his co-workers (48) found no common dose-ratio relationship for 4 different end-points (righting reflex, abolition of purposeful movement, respiratory and cardiac arrest) with 8 different agents.

Shim (48) has suggested that MAC results from the summation of different effects (eg. reflex suppression and analgesia) and therefore represents the sum of points on two or more dose response curves (figure 7). If this is true, MAC cannot be used to compare anaesthetic agents

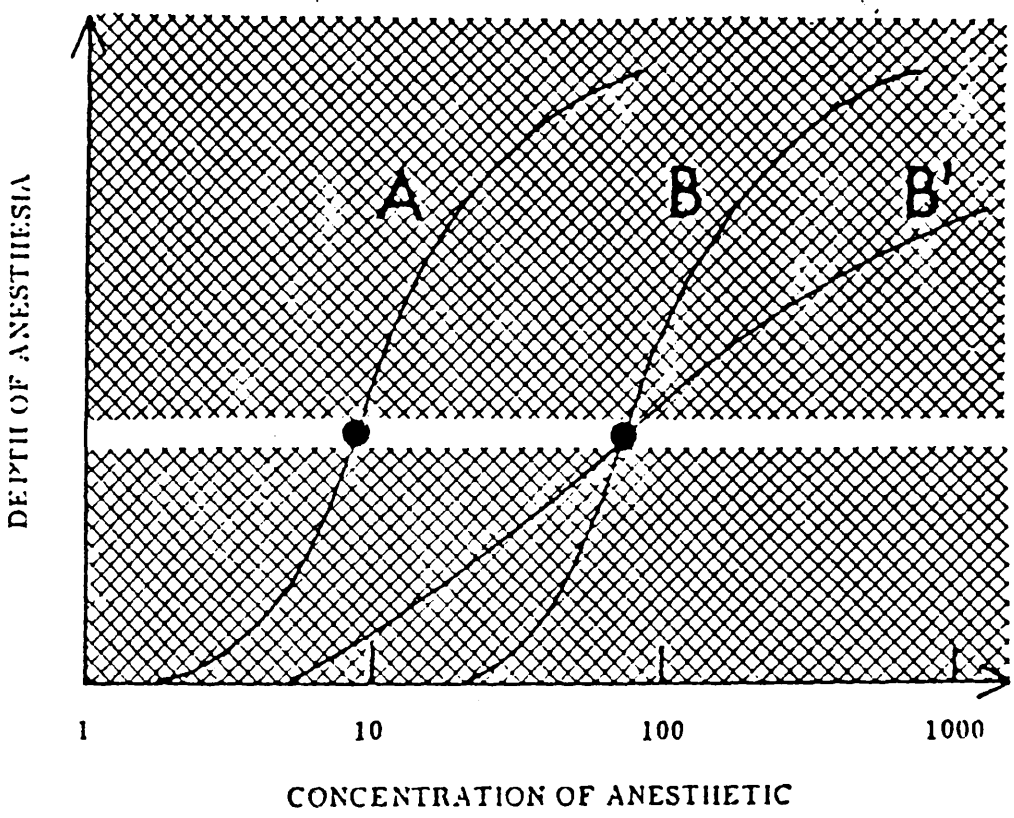


Figure 6. A limitation of MAC.

Anaesthetic depth is plotted against anaesthetic concentration and the dose response curves for three imaginary agents drawn. If the drugs are compared at one level of response (the window in the diagram), it is impossible to detemine if the dose response curves are parallel (from ref. 28).

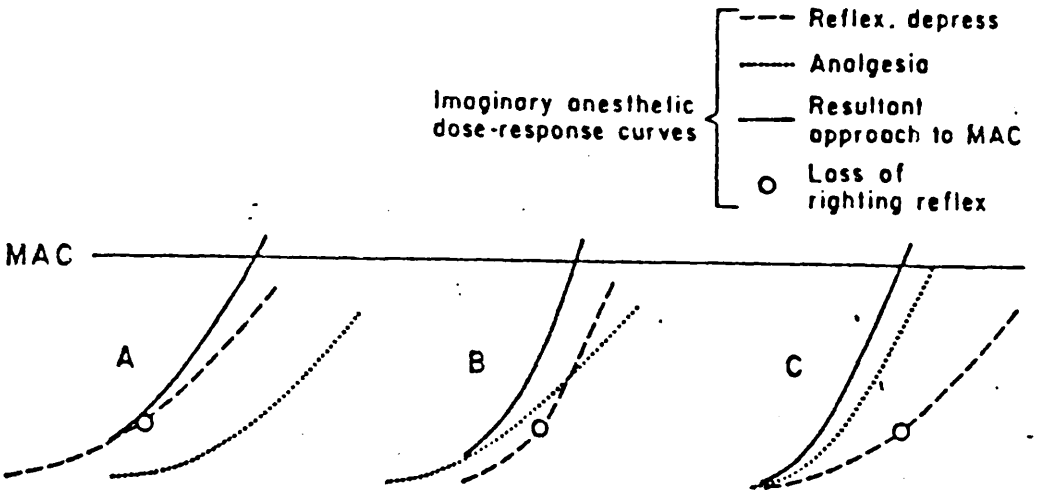


Figure 7. MAC as a combination of effects.

Hypothetical curves for three agents showing that unresponsiveness to skin incision at MAC may result from a combination of analgesia and reflex depression. The effect at MAC of agent A consists of 25% analgesia and 75% reflex depression; with agent B, 50% of each component; with agent C 25% reflex depression and 75% analgesia. As the righting reflex disappears at a certain level of reflex depression it would disappear well below MAC with agent A but at MAC with agent C (from ref. 48).

above or below the point of measurement i.e. the use of MAC multiples (or fractions) is meaningless.

Parallelism of dose-response curves, calculated for the volatile agents from pooled data, is the exception rather than the rule (27,49). This supports the view that the use of MAC multiples is scientifically not justifiable (28).

Further, the MAC value calculated for any given agent is very dependent on technique (50) and differences of over 10% are present in some studies done by the same group (16,51). Any error in the calculation of MAC would increase with multiplication and detract from any comparison made using MAC multiples.

USES AND ABUSES OF MAC.

MAC is a useful concept but the limitations inherent to its definition must be remembered. As the MAC value for an anaesthetic agent roughly corresponds with the concentrations which will be required in clinical practice it is a useful yardstick for the comparison of anaesthetic drugs with regard to physiological effects, side-effects etc.

However, MAC refers to the population and not the individual and although it (MAC) has been described as a point of "prime practical and theoretical significance" on the continuum from "analgesia to death" (52), MAC describes only one point on a specific dose-response curve, relates to only one aspect of the overall response to a set stimulus, is not directly applicable to the individual and cannot be applied to the multiple agent

techniques used in routine anaesthetic practice. Further, the presence or absence of a specific response (e.g. movement) is dependent on the balance between drug dose, stimulus type and stimulus intensity and cannot be defined with respect to one dose related parameter.

The usefulness of MAC in the assessment of techniques proposed as monitors of anaesthetic adequacy is limited.

CHAPTER 2

THE EFFECTS OF SURGICAL STIMULATION.

The anaesthetic state is clinically assessed by the patients residual responses to surgical stimulation. Some of the reflex responses evoked by surgical stimulation are discussed in this chapter.

REFLEX ACTIVITY AND SURGICAL STIMULATION.

A large number of somatic and autonomic reflexes can be initiated by surgical and other manipulations (eg laryngoscopy and intubation). Although these reflexes are suppressed in an ordered sequence by general anaesthetic agents (3) and a graded scale can be created (figure 1), it is not known if these reflexes are representative of the anaesthetic state.

AUTONOMIC NERVOUS SYSTEM.

The autonomic nervous system must be regarded as completely integrated, not as two mutually opposing parts:- the sympathetic and parasympathetic. The system consists of sensory organs, afferent and efferent pathways and numerous central connections. Although the limbic region may be regarded as the "visceral brain", both higher inputs and reflex activity (at various levels) determine the overall activity.

The most relevant reflexes are those in which the "end-organ" is the cardio-vascular system. Some of these reflexes will now be described in more detail:

1. Viscero-vascular reflexes.
2. Somatosympathetic reflexes.
3. Defence Reactions.

VISCERO-VASCULAR REFLEXES.

Experimentally, stimulation of abdominal and pelvic organs is associated with a variety of effects. For example, gallbladder distension in anaesthetised or spinal cat preparations initiate a hypertensive reflex, secondary to reflex vasoconstriction of the splanchnic vascular bed reinforced by catecholamine release from the adrenals. In the pelvis, stimulation of the rectum initiates a fall in blood pressure; with stimulation of the bladder having the opposite effect (53).

In patients with low spinal injuries (L2), bladder distension leads to reflex vasoconstriction of the lower limbs and an associated hypertension. Those with T5 lesions, suffer vasoconstriction of the upper limbs as well. In cats it has been demonstrated not only that both the renal and splanchnic vascular beds are involved but also that the rise in blood pressure is limited by the baroreceptors (53).

The haemodynamic responses of brain dead organ donor patients to surgical stimulation have been investigated (54). In the patient studied, and nine cases reviewed retrospectively, a pressor response to surgical stimulation occurred. The occurrence of a "mass reflex" was felt to be unlikely, and the authors concluded that residual lower medullary function (although compatible with the clinical diagnosis of brain death) may have been an aetiological factor.

Generally visceral reflex activity is increased in spinal preparations, whilst somatic reflexes are reduced. In decerebrate specimens the opposite tends to hold true:

somatic reflexes are increased, visceral reflexes being reduced (53). Wang (55) has shown that removal of the entire brain stem is necessary to abolish stimulus induced responses, except in chronic spinal preparations.

VISCERO-VASCULAR REFLEXES INITIATED BY ABDOMINAL SURGERY.

Manipulation of the upper abdominal viscera may lead to profound hypotension, with minimal change in the heart rate. Burstein (56) called this the coeliac plexus reflex and believed it was due to a sympatheticotonic state produced by the combination of atropine (as a premedicant) and ether, often in association with "light" anaesthesia. Smith (57) reported on 10 cases in 1953 and concluded that the fall in blood pressure was secondary to vagal cardiac inhibition.

In 1957 Roco and his co-workers (58) studied 68 patients undergoing laparotomy in an attempt to clarify the effect of manipulation on abdominal viscera. A variety of anaesthetic techniques were used. They found some areas (the upper anterior parietal peritoneum and the region of the common bile duct) to be particularly sensitive to stimulation. Hypotension, which the authors felt vagal in origin, occurred in 55 patients.

Folkow (59) studied 14 patients in 1961 and found hypotension and bradycardia to occur on mesenteric traction and hollow organ distension, a response which could be elicited by direct stimulation of the nerve fibers running to these organs. Vagal stimulation did not elicit this response and atropine, although reversing the bradycardia did not fully restore the blood pressure. As limb plethysmography suggested relaxation of capacitance

vessels as an aetiological factor the authors concluded that the reflex constituted a vagal bradycardia associated with a generalised decrease in sympathetic tone.

Seltzer (60) investigated this phenomenon in patients undergoing aortic aneurysm surgery. In these patients, suffering from a variety of pathological states, hypotension occurred in 19 out of 20 cases during controlled mesenteric traction. This was due to fall in systemic vascular resistance only partially compensated for by an increase in cardiac output. The maximal response occurred after 5-10 minutes, and was associated with flushing in some cases. These findings led the group to investigate a further 8 patients. They demonstrated that the fall in SVR was directly related to a rise in prostaglandin levels, confirming their suspicion that the primary effect was hormonal (61).

That Stoetling (62) was unable to show any effect after 30 seconds traction on the gallbladder was probably due to the short stimulation period and the short time for which the patients were monitored.

SOMATO-SYMPATHETIC REFLEXES.

Sato and his co-workers (63) studied the cardiovascular effects of cutaneous and muscle nerve stimulation in cats anaesthetised with chloralose and urethane. Their results are summarised in table 3. In those animals demonstrating a tachycardia, continued stimulation led to a fall in heart rate, which reached a plateau at around 50% of the peak value. No direct correlation between heart rate and blood pressure occurred

Table 3. The Effects of Stimulating Cutaneous and Muscle Afferents (after Sato et al, ref. 63).

Stimulated Nerve	Effect
Cut. Group II	No Effect
Cut. Group III	Bradycardia or tachycardia, direction of response unpredictable
Cut. Group IV	Tachycardia
Muscle Group I	No Effect
Muscle Group II	No Effect
Muscle Group III	Tachycardia or bradycardia(40%)
Muscle Group IV	Tachycardia, increase proportional to stimulus strength.

(Cut = Cutaneous)

Latency

Cutaneous 3secs(2.5-7.5secs), Peak change at 20-30secs

Muscle 10secs(8-16 secs), Peak change at 20-30secs

in this study. In some cases heart rate changes occurred in isolation and in others tachycardic responses occurred in association with hypotensive or mixed blood pressure changes. Sato concluded that the relationship between the somatic afferent system and the autonomic efferent system is much more complex than the concept of "pressor and depressor" afferents would suggest. And he proposed that the nature of the autonomic output would depend on the type, site and duration of stimulus as well as the general experimental conditions.

Kissin and his co-workers (64) demonstrated that the cardiac acceleratory response to stimulation of the superficial peroneal nerve in dogs is proportionally depressed by increasing end-tidal concentrations of halothane. They suggest that the autonomic response to stimulation, as measured by the cardiac acceleratory response to stimulation, might be used as a graded index of anaesthetic depth. These workers felt that their work confirmed the everyday practice of the anaesthetist who uses the cardiovascular response to surgical stimulation as a guide to anaesthetic adequacy. No information is given of blood pressure changes in this study.

Savege (65) investigated the cardiovascular response to tibial pressure in patients anaesthetised with althesin. Changes in cerebral activity, as measured by the CFM, did not correlate with the cardiovascular response to stimulation. Fentanyl obtunded the autonomic response to the stimulus, and did so during increasing CFM activity. The authors suggested that Althesin and similar agents should only be given in doses large enough to suppress

consciousness, as larger doses would not appear to effect the quality of anaesthesia.

DEFENCE REACTIONS.

Specific autonomic responses can be elicited by stimulating different hypothalamic regions. These reactions are complex and probably continually modulated by inputs from other centres. One of these reactions, the defence reaction, is a behavioural reaction which prepares the body for "fight or flight" (66). The response is present in all animals, and it would appear that although humans can override the initial emotional reaction, the individual organ responses persist. After decortication the response may be initiated by trifling stimuli, suggesting that cortical input is usually inhibitory. The cardiovascular response consists of:-

Sympathetic vasoconstriction in most vascular beds (including the renal and splanchnic circulations), an exception being skeletal muscle. The result is a tachycardia and increase in arterial pressure. This neurogenic response is reinforced by adrenal catecholamine release. The reflex is associated with strong inhibition of the baroreceptor reflex (66,67).

Although the full response is unlikely to occur in clinical practice, a modified response may be common intraoperativly. Workers in Sweden have investigated the comparative effects of a variety of anaesthetic techniques on the cardiovascular consequences of defence area stimulation in cats (68,69). Under both chloralose and fentanyl-diazepam-nitrous oxide anaesthesia somatic

afferent and defence area stimulation led to the sequence mentioned above, the degree of response being similar. Droperidol, despite minimal effects on resting arterial pressure, was found to greatly attenuate the vasoconstrictor response in both the renal and intestinal systems. The overall hypertensive response was also attenuated. Whether the effect was peripherally or centrally mediated is unknown. Isoflurane has also been shown to attenuate the response to both stimuli, in a dose related manner, when compared to the basic anaesthetic mentioned above (69).

CONCLUSIONS.

Surgical stimulation initiates a large number of somatic and autonomic reflexes. In clinical practice it is these reflex responses which are used to determine a patients anaesthetic requirement. However, some of the reflex responses used by the anaesthetist to determine the patients anaesthetic state may be poor indicators of the true anaesthetic state. The major difficulty of this approach is therefore to determine which reflex responses (autonomic, somatic, EEG etc.) are representative of the true anaesthetic state. These problems will be discussed later.

CHAPTER 3

METHODS OF ASSESSING THE ANAESTHETIC STATE

I) CLINICAL METHODS.

A. HISTORICAL ASPECTS.

From the time of Snow until the early part of this century anaesthesia was customarily divided into four stages (70):

Stage I (Stage of Induction): from the beginning of administration to the loss of consciousness.

Stage II (Stage of Struggling, or Breatholding, or Delirium, or Dreams): from loss of consciousness to the onset of surgical anaesthesia.

Stage III (Surgical Stage): characterised by deep, regular automatic breathing.

Stage IV (Overdose, or Stage of Bulbar Paralysis): not well described, but associated with shallow irregular respiration and fixed dilated pupils.

GUEDEL'S DESCRIPTION.

Guedel accurately described the clinical signs associated with di-ethyl ether (46). This allowed the clinical recognition of four stages and the subdivision of the third stage into four planes:

Stage I (Analgesia), from induction to loss of consciousness.

Stage II (Delirium). from loss of consciousness to the onset of automatic breathing.

Stage III (Surgical), from onset of automatic breathing to respiratory paralysis.

Plane (i) Indicated by regular respiration

Plane (ii) Indicated by cessation of eyeball activity. No change in respiration. (continued)

Plane (iii) Indicated by the start of intercostal paralysis

Plane (iv) Indicated by complete intercostal paralysis

Stage IV (Respiratory Paralysis), from respiratory paralysis to death.

The clinical signs used to indicate these relate to respiration, eyeball movement, pupil size, and the eyelid, swallowing and vomiting reflexes (figure 8).

Guedel recognised that different "levels" of anaesthesia are required to control the reflexes initiated by different types of surgery, and more specifically that operations not requiring muscle relaxation could be carried out in the lighter planes of Stage III. Use of his chart, in conjunction with the relevant section of his monograph, enabled the anaesthetist to attain the required "depth" for a wide variety of procedures (71). For example superficial operations might be carried out under Stage III(i) whilst the relaxation necessary for abdominal work would require Stage III (ii-iii).

SOME LIMITATIONS OF GUEDEL'S SIGNS.

Guedel recognised his chart to be accurate in only 90% of cases, accepting that "No set of signs can be constant.". He also appreciated that other factors (eg. premedication) might effect these signs and made allowances for some of these (71). Figure 8 demonstrates the effects of premedication on the pupillary signs.

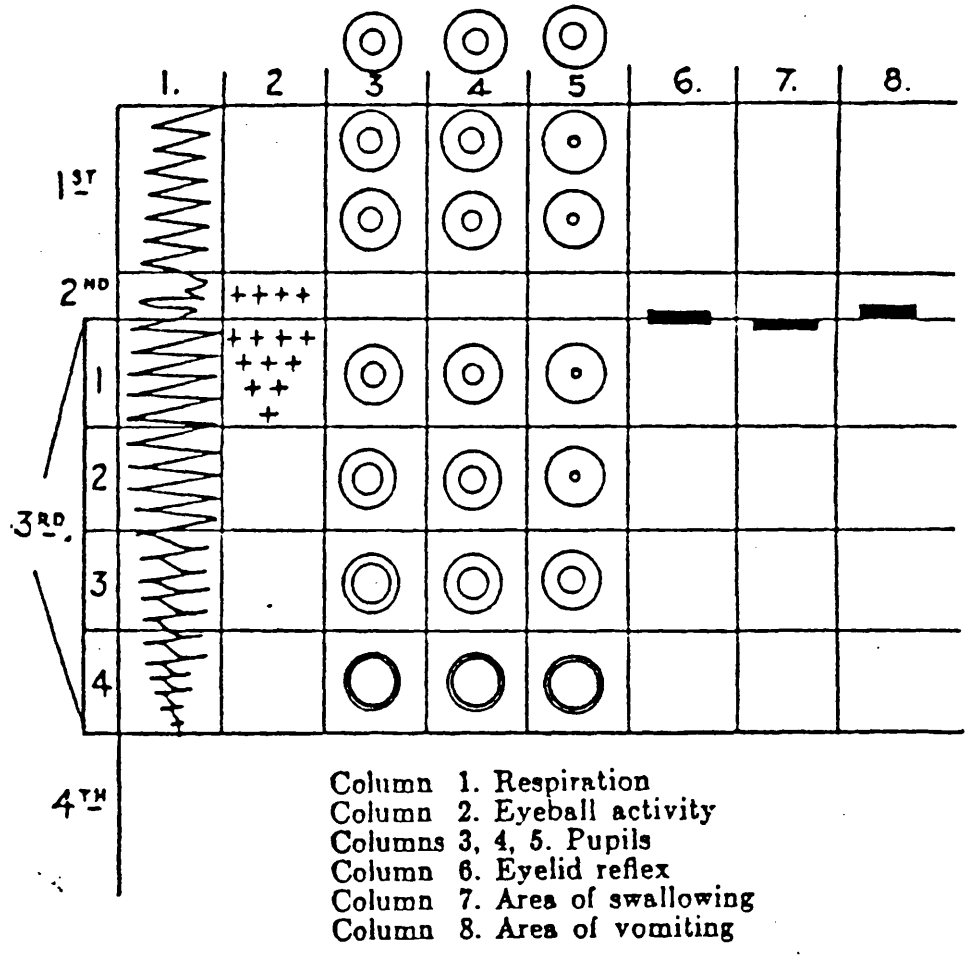


Figure 8. Guedel's signs and stages of anaesthesia.

The figure is explained in the text. Column 3 represents the eye signs in those patients not receiving premedication, Column 4 in those receiving atropine and Column 5 in those receiving morphine as premedication (from ref. 71).

FURTHER LIMITATIONS.

Clinical signs are dependent on a number of factors which relate to the patient, premedication, the anaesthetic agents used and the technique by which it is administered (46). Gillespie (70), citing cyclopropane as an example, emphasised that reliance on Guedel's respiratory signs, can be misleading:- especially if the airway is compromised. Having noted these inadequacies, and explained that the majority of difficulties which beset both the anaesthetist and the surgeon are caused by unwanted reflex activity, stressed the importance of reflex signs as guides to anaesthetic adequacy. Gillespie concluded that Guedel's classification of the stages and planes of anaesthesia should be retained, but equal importance given to signs of reflex activity (70). To this end he modified Guedel's chart, a version of which is still taught today (figure 9) (72).

CAN GUEDEL'S WORK BE MADE MORE RELEVANT ?

Mushin (73) stressed that the "signs" of anaesthesia are motor responses, elicited by an applied stimulus and, that in the absence of such a stimulus, it cannot be that implied a specific reflex is obtunded. This is especially relevant to ether, whose vapour represents such a stimulus. A patient breathing quietly on 10-15% ether will not react to skin incision, the same cannot be said for a patient breathing a less irritant vapour (eg. halothane or cyclopropane). Mushin felt that a better understanding of these signs, and the reasons for their demonstration with one agent (ether) would allow application of this knowledge to other agents.

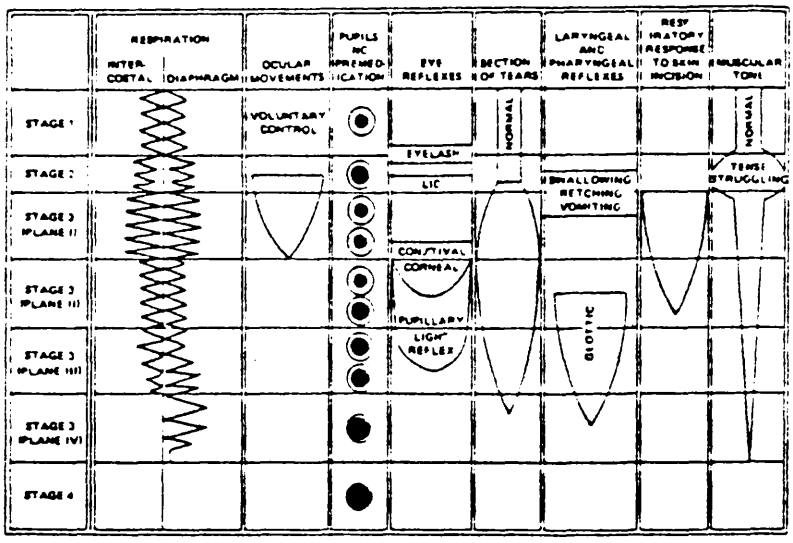


Figure 9. Guedel's chart "today".

A modification of Guedel's chart, based on work by Gillespie (70) and published in "A synopsis of anaesthesia" (from ref. 72).

Ellington has supported this view stating: "...the classification still gives considerable information that can, with exceptions, be used as a guide to "depth of anaesthesia" for various drugs " (74).

Although this approach is still taught today (75) its application would require learning complete sets of signs for each agent and combination of agents as well making allowances for the technique of administration and the quantity and timing of doses. A number of patient factors eg. concomitant drug therapy, the patient's disease status and the effects of surgical stimulation would also have to be allowed for.

OTHER APPROACHES.

Others have suggested that with redefinition and adaption, Guedel's observations may be applied to modern anaesthetic practice (76,77,78). Guedel's system is only applicable to ether. Stages and planes may be described for other agents but, for the reasons mentioned above, it is not practical. The limitations of Guedel's approach are not descriptive. They stem from its relevance to a single anaesthetic agent.

COMPONENTS OF ANAESTHESIA.

The introduction of specific pharmacological agents (and in particular muscle relaxants) highlighted the limitations of Guedel's approach. Patients apparently deeply anaesthetised with some agents (eg. thiopentone), as defined by Guedel, were found to respond to surgical stimulation. Gray suggested that a new approach to anaesthesia was necessary and introduced the "triad of

anaesthesia" (79) - narcosis, analgesia and relaxation. Later renamed narcosis, relaxation and reflex depression (which is more descriptively accurate) (4).

The reflexes he refers to are motor, visceral and endocrine. He summarises: "... these reflexes are open to modification by the anaesthetist and awareness of their presence and of the extent to which they can and should be depressed is of far more importance than any consideration of the "signs" of anaesthesia."

Woodbridge suggested a similar approach, although he described four components (1):

1. Sensory (afferent)
2. Motor(efferent)
3. Reflexes
4. Mental(sleep)

Woodbridge also suggested a scoring system for each of these components but the system is complex and not clinically applicable.

Although the approach these workers have taken is more relevant to today's practice they do not tell us how to measure anaesthetic depth but rather what is required from an anaesthetic.

More recently Pinsker (5) has suggested "..the concept that paralysis, unconsciousness, and attenuation of the stress response are the necessary and sufficient components of the anesthetized state." Defining paralysis as the absence of movement in the surgical field and emphasising that attenuation of the stress response only refers to those aspects of the whole which we can readily measure, and therefore control. The analgesic component

is not included as pain requires a conscious brain to "interpret the impulses from the periphery", a situation which does not occur if unconsciousness is achieved. This approach emphasises the importance of the patients response to surgery. It is this response by which a patients anaesthetic state is determined, not the patients response to anaesthetic agents.

DIFFICULTIES WITH TERMINOLOGY.

Prys-Roberts (3) in a recent editorial, suggested that difficulties in defining anaesthesia may be that "...successive generations of practitioners of the art have centred their concepts around the effects of the drugs available to them, rather than the responses of the patient to the trauma of surgery, and the suppression of those responses". A similar problem has arisen in the interpretation of clinical signs.

"Clinical signs" may reflect one of two effects (or a combination of the two):

1 Drug related effects.

2 The residual autonomic and somatic responses to surgical stimulation during anaesthesia.

In the fist case the signs are agent dependent e.g. the dose related fall in blood pressure associated with isoflurane or the tachypnoea associated with increasing halothane concentrations, are described as signs of "anaesthetic depth" in that they are dose related. These signs are agent dependent i.e. not all anaesthetic agents have these effects. Drug dependent effects are rarely used in the assessment of the anaesthetic state during surgery,

although they may complicate the interpretation of clinical signs (vide infra).

During surgery the anaesthetist assesses the clinical anaesthetic state from the residual autonomic and somatic responses to surgery. These responses reflect the balance between surgical stimulation and anaesthetic dose and are used by the anaesthetist to assess the patients drug requirement. Drug related effects (e.g. the cardiovascular stimulating effects associated with ketamine) complicate the interpretation of these reflex signs. A knowledge of the basic pharmacology of anaesthetic (and non-anaesthetic) agents is required to allow the anaesthetists to determine which signs reflect a patient's response to surgery; which signs reflect a patient's response to the drug; and which signs are invalidated (or have less meaning) due to concomitant drug therapy (e.g. heart rate changes in a patient being treated with B-blocking drugs).

That the anaesthetists is successful in achieving the ZSA in the vast majority of patients suggests that the autonomic and somatic responses are adequate predictors of the anaesthetic state in most patients.

METHODS OF ASSESSING THE ANAESTHETIC STATE

I) CLINICAL METHODS (continued).

B. THE CLINICAL ASSESSMENT OF THE ANAESTHETIC STATE.

After surgery has commenced the anaesthetist is guided by the patients residual autonomic and somatic responses to surgical stimulation. The range of autonomic response which can be measured is vast, however the constraints of surgery, ethics and the theatre environment limit the number which can be objectively monitored. The information presented to the anaesthetist may be qualitative or quantitative and results from the interaction between a large number of variables (figure 10). Each clinical index of anaesthetic adequacy will be considered separately.

INDICES USED IN THE ASSESSMENT OF ANAESTHETIC ADEQUACY DURING SURGERY.

A. CARDIOVASCULAR INDICES OF AUTONOMIC RESPONSE

1. Peripheral Circulation.

Digital plethysmography is now widely available and has been suggested as a monitor of anaesthetic adequacy (80). Johnstone suggests that the dose of halothane necessary for surgery in a paralysed patient may be defined as the minimal dose required to block the vasoconstrictor response to surgical stimulation. Difficulty in interpreting the trace might arise during hypocapnia, hypovolaemia or hypothermia and its use may not be applicable to other anaesthetic techniques.

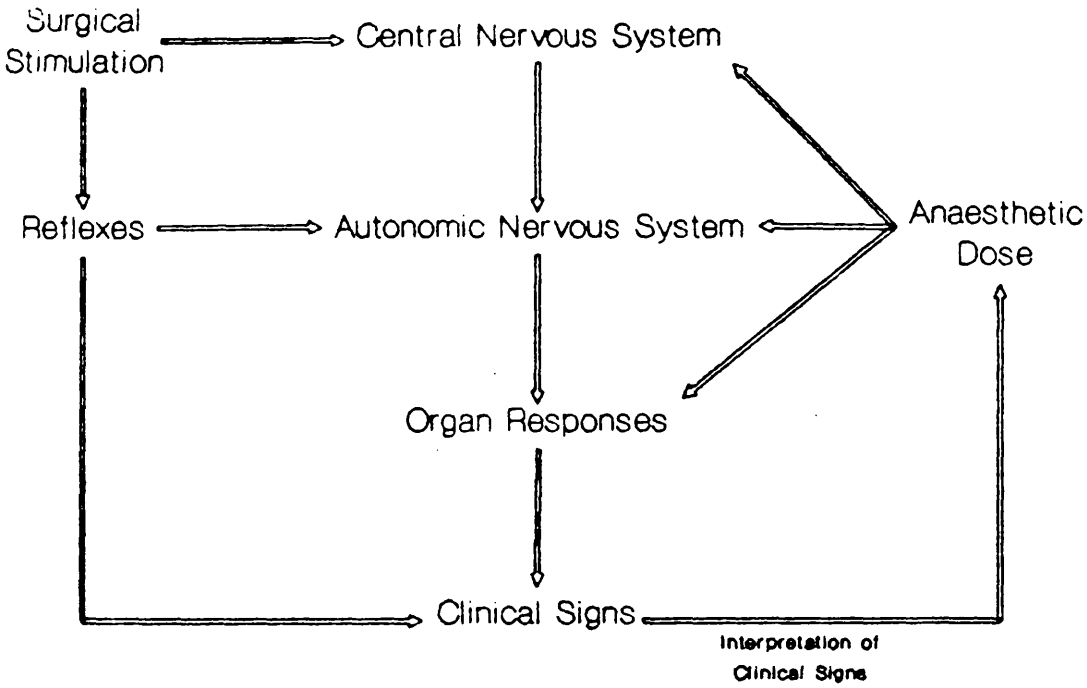


Figure 10. The determinants of the clinical anaesthetic state.

Although clinical signs, based on the patients' residual responses to surgical stimulation are used to assess a patients anaesthetic requirement, these clinical signs do not directly reflect the central nervous system balance which results from the interaction between the effects of anaesthetic dose and surgical stimulation.

2. Heart Rate & Blood Pressure.

Although heart rate and blood pressure are often used as part of the assessment of anaesthetic adequacy a number of complicating factors must be considered. Reflex changes during surgery may not always reflect changes in the anaesthetic state and use of these variables is complicated by changes in blood volume, carbon dioxide status, the anaesthetic technique used, a variety of disease states and the medications they entail.

3. Beat to beat heart rate variability (HRV)

Heart rate variability is a complex phenomenon which is incompletely understood. It is principally attributed to arterial pressure fluctuations, sinus arrythmia and variations in response to thermal regulation. Although HRV is associated with anxiety and pain (81) Carter and Asbury (82) found little correlation between periods of light anaesthesia and increased periods of variability.

B. EYE SIGNS.

1. Pupillary Diameter

The balance between sympathetic and parasympathetic tone is often said to determine pupil diameter, the situation is however extremely complex and involves both ascending and descending inputs (83). Although there is a close relationship between the spinal afferents associated with pupillary dilatation and the fibers carrying pain nerve impulses (53), the interpretation of pupillary signs during anaesthesia is difficult as a number of other variables are involved.

The volatile agents, intravenous induction agents,

opiates, and other drugs (eg atropine) all have different, and sometimes conflicting effects on the pupil. Mushin (76) has said that:

> "....importance should be attached to the size of the pupil only if it is other than the expected effect of the principle pre-anaesthetic drug which has been administered."

In anaesthetic practice today it may be difficult to determine which agent has the predominant effect and even when using "pure" volatile techniques determination of anaesthetic depth, on the basis of pupillary diameter, may be misleading. It is well known that large pupils may indicate both light and very deep levels of anaesthesia.

To measure pupillary diameter accurately requires specialised equipment, and although this has been developed (84) and used in clinical practice (85) the relevance of changes during anaesthesia are unknown. Evans felt that the variation in response to different agents was too great to warrant the inclusion of pupillary signs in a scoring system developed for assessing anaesthetic adequacy (86).

2. Pupillary Reflexes

The presence of the pupillary light reflex is generally taken as an indication of light anaesthesia, in the presence of miosis (eg. due to opiates) or mydriasis (eg. due to atropine) it may however be difficult to detect (86).

3. Oculo-micro tremor

Oculo-micro tremor is the smallest movement made by

the human eye. In 1976 Coakley demonstrated that the resting frequency decreased following induction with thiopentone (87). In one patient intra-operative recording was associated with a mean frequency some 40% below the control value. The sensitivity of the response to muscle relaxants would limit the use of oculo-microtremor as a monitor of anaesthetic adequacy should further evaluation demonstrate it to be of value.

C. LACRIMATION.

Increased lacrimation is often taken as a sign of inadequate anaesthesia. Although lacrimation can be assessed objectively, any interference with the eye (eg. wiping of tears) may be associated with increased lacrimation introducing artefacts. A further problem is establishing the relevance of tears in an eye in the horizontal position, and one that is not engaged in its normal function which directs tears into the nasolacrimal duct. Lacrimation may also be effected by anticholinergic agents.

D. SWEATING.

Sweating is another sign often taken to indicate light anaesthesia. Maryniak evaluated the production of palmar sweat and its correlation with heart rate in a group of patients undergoing cystoscopy (88). He demonstrated a close correlation between the two and concluded that palmar sweat production might be a useful indicator of the degree of sympathetic activity during anaesthesia and surgery. A previous study showed an increase in palmar sweat production following laryngoscopy

and intubation, despite abolition of the heart rate response, with a bolus of alfentanil (30ug/kg) (89).

Sweating is however dependent on a number of factors: humidity, body position (which effects collection), metabolic rate, inter-individual differences in rate, age (due to an intrinsic deterioration in function and an altered extrinsic factor which effects sensitivity to stimulation) as well as being site dependent (90). The use of anticholinergic agents detract from the usefulness of this sign.

Clinically three levels of sweating can be recognised; dry skin; feels moist; obvious beads of sweat (91). The complicating factors mentioned above, especially in relation to drugs and site of measurement, make assessment of this sign difficult.

E. RESPIRATORY SIGNS AND SKELETAL MUSCLE ACTIVITY.

Respiratory variables (tidal volume, respiratory rate etc.) are useful indicators of anaesthetic adequacy in the non-paralysed patient. While a skeletal muscle response to surgical stimulation, in the absence of neuromuscular blockade indicates (by definition) that anaesthesia is inadequate, both these signs are, at best, unreliable in the paralysed patient and will not be considered further.

The relationship between movement and consciousness in discussed later.

COMBINATIONS OF CLINICAL SIGNS.

From the above discussion it becomes apparent that no single clinical sign can be used as an indicator of anaesthetic depth in all cases. It also apparent that the

relevance of a particular sign may be decreased in specific instances. The most obvious example being somatic responses following the use of muscle relaxants.

In routine clinical practice anaesthetists use combinations of clinical signs to determine a patient's anaesthetic state. As discussed, the interpretation of clinical signs is not uniform. Evans and Davis have introduced a scoring system to "..collate these clinical signs and measurements into a single entity" (86). This system is based on four variables; blood pressure, heart rate, sweating and tear formation and is called the PRST system. A score value of 0 - 2 is assigned to each variable (table 4), and a global impression of the clinical anaesthetic state determined by summing the individual PRST variables (table 5). Drug effects may be allowed for (table 6). The PRST score has been used successfully to determine the anaesthetic requirement during surgery (91).

Other workers (9,10,31,32) have used combinations of anaesthetic signs to define the adequacy of anaesthesia. For example, Ausems and his co-workers (31,32) defined anaesthesia as inadequate if:

1. Systolic arterial pressure rose by more than 15mmHg above the patients normal (which was determined from preoperative and preinduction measurements).
2. The heart rate exceeded 90 beats per minute in the absence of hypovolaemia.
3. If any somatic response occurred.
4. Any other autonomic indicator of inadequate anaesthesia e.g. lacrimation or sweating occurred.

Table 4. The PRST scoring system.

Index	Conditions	Score
SAP (mmHg)	Less than Control + 15	0
	Less than Control + 30	1
	More than Control + 30	2
Heart Rate (bpm)	Less than Control + 15	0
	Less than Control + 30	1
	More then Control + 30	2
Sweat	None	0
	Skin moist	1
	Visible beads of sweat	2
Tears	No excess with eyes open	0
	Excess visible with eyes open	1
	Overflow with eyes closed	2

SAP = Systolic Arterial Pressure. Control values are taken prior to induction unless the patient is anxious when preoperative values are used.

(adapted from ref. 91).

Table 5. Assessing the adequacy of anaesthesia with the PRST score.

Total Score	Clinical Impression
5 - 8	Marked autonomic response - inadequate anaesthesia.
2 - 4	Acceptable level of response
0 - 2	Minimal response - evidence of adequate or excessive anaesthesia.

(adapted from ref. 91)

Table 6. The effect of some variables on the PRST score.

Variable	P	R	S	T
Atropine	+	+	-	-
Pancuronium	+	+	ns	ns
Curare	-	ns	ns	ns
Gallamine	+	+	ns	ns
Digoxin	ns	-	ns	ns
alpha-blocker	-	ns	ns	ns
beta-blocker	-	-	ns	ns
Hypovolaemia	-	+	ns	ns
Hypothermia	ns	-	-	ns

Several "non-anaesthetic" variables may effect the PRST score. They may either increase score ("+"), decrease score ("-") or have no effect ("ns"). These effects must be considered when the PRST score is used to evaluate the clinical anaesthetic state.

(adapted from ref. 91)

These criteria were used successfully to determine the alfentanil requirement in patients undergoing a variety of surgical procedures. The use of clinical signs as a "gold" standard is discussed later.

METHODS OF ASSESSING THE ANAESTHETIC STATE:
II) OESOPHAGEAL CONTRACTILITY.

ANATOMY AND PHYSIOLOGY.

The upper half of the human oesophagus is composed of striated muscle and the lower lower half of smooth muscle. Between these lies a transitional zone. The structure is innervated through the intra-mural and para-oesophageal plexuses which are supplied by the sympathetic and parasympathetic systems. The latter (via the vagus) is most important. Central neurological control of the oesophagus lies in the vagal motor nuclei and the adjacent reticular activating systems of the brain stem.

TYPES OF ACTIVITY.

Three types of activity may be recorded from the oesophagus:

1. Primary Peristalsis, activity initiated by swallowing and which conveys food down the oesophagus.
2. Secondary Peristalsis, activity arising in the main body of the oesophagus in response to a foreign body (e.g. food). This activity need not be preceded by swallowing and may be initiated by distending a balloon in the oesophagus (provoked lower oesophageal contraction - PLOC)
3. Tertiary Activity, non-propulsive activity which occurs spontaneously (spontaneous lower oesophageal contraction - SLOC). This activity appears to arise in the oesophageal motility centres of the brain stem.

MEASUREMENT OF OESOPHAGEAL ACTIVITY.

During anaesthesia and surgery oesophageal activity can be measured using a special probe e.g. Antec Lectron 301 (Antec Systems Ltd., Oxford). This system comprises a 35cm long oesophageal probe with a distal, liquid filled balloon connected to a pressure transducer; and a proximal, air filled balloon designed to provoke secondary activity. The technique can only be used in artificially ventilated patients, or variations due to oesophageal pressure change cannot be differentiated from changes due to ventilation.

THE RELEVANCE OF OESOPHAGEAL ACTIVITY.

Although oesophageal activity may occur as a local reflex there is evidence that secondary oesophageal activity is a reflex mediated at the brainstem. Changes in PLOC during anaesthesia may therefore reflect changes in brain-stem activity (92). As physiological stress and acoustic stimulation are associated with an increase in tertiary activity (93), increased SLOC activity might indicate inadequate ("stressful") anaesthesia.

THE EFFECT OF NON-ANAESTHETIC AGENTS ON OESOPHAGEAL ACTIVITY.

Smooth muscle relaxants such as glyceryl trinitrate and sodium nitroprusside decrease (and may ablate) lower oesophageal contractility (86). Skeletal muscle relaxants have no effect on LOC (94) but intravenous atropine and ganglion blocking agents produce substantial changes (86). Oesophageal disease can also be expected to affect activity.

CLINICAL EXPERIENCE.

An initial report (94) described an increase in the rate of SLOC, and increased amplitude of PLOC, when the dose of halothane and other anaesthetic agents was reduced. In a later study (95) the PRST score (vide supra) was used to determine the need for althesin increments, and LOC measured before and after each bolus. SLOC rate was shown to increase prior to each increment and decrease following it. No change in SLOC amplitude occurred.

However, SLOC amplitude has been used successfully to determine the requirement of fentanyl supplements in a small number (10) of patients (86).

A later study (92) investigated the relationships between LOC, MAC and clinical signs (assessed by the PRST score). This study confirmed that decreasing concentrations of halothane are associated with an increase in the rate of SLOC, an increased amplitude of PLOC and a rise in the PRST score. Further, increases in the PRST score, when the end-tidal halothane concentration remained stable, were paralleled by changes in LOC. This suggests that LOC is sensitive to surgical stimulation (assuming that the PRST score does reflect changes in the anaesthetic state).

Thomas and Aitkenhead (96) compared LOC activity in two groups of patients anaesthetised with 66% nitrous oxide in oxygen supplemented with 0.5% isoflurane. Paralysis was achieved with vecuronium. SLOC frequency and PLOC amplitude were significantly greater in the second group, who underwent abdominal hysterectomy, when compared to the first group, who underwent varicose vein surgery.

The groups were otherwise comparable. This suggests that LOC activity reflects the degree of surgical stimulation, which is presumed to be greater in the second group.

However, Cox and White (97) found LOC to be absent in 9 (out of 30) patients, despite clinical evidence of inadequate anaesthesia. And, in a study carried out pre-operatively (98), neither the rate and amplitude of SLOC; the amplitude of PLOC; or the oesophageal contractility index (which is derived from SLOC frequency and PLOC amplitude) could differentiate the conscious from the unconscious state in the individual. In this study diprivan was used as the sole anaesthetic agent and consciousness was defined as the ability to squeeze the investigators hand on command. Overall, statistically significant increases did occur during awakening and statistically significant decreases during induction in all the variables studied.

CONCLUSIONS.

Dose-dependent changes in LOC have been observed and these changes can be related to the clinical assessment of anaesthetic adequacy. Surgical stimulation appears to be associated with increased LOC activity. However, in individuals, lower oesophageal activity may be absent despite clinically inadequate anaesthesia. Further the susceptibility of this response to atropine and the large intra-individual variation which occurs on recovery from anaesthesia would appear to limit the usefulness of this technique. The possible relationship between "stress" and LOC deserves further investigation.

METHODS OF ASSESSING THE ANAESTHETIC STATE

III) ELECTROENCEPHALOGRAPHY AND RELATED METHODS.

INTRODUCTION.

The electro-encephalogram (EEG) monitors neuronal electrical activity. It has been suggested that this activity reflects the anaesthetic state. The purpose of this section is to clarify the use of the EEG and its derivatives in the study of anaesthetic depth.

A CLASSIFICATION OF THE EEG.

Monitors of cerebral electrical activity may be classified:

1 Raw EEG

2 Processed (non-evoked) EEG

   a) Time Domain Analysers e.g. the Cerebral Function Monitor (CFM) and the Anaesthetic Brain Monitor (ABM).

   b) Frequency Domain Analysers e.g. Compressed Spectral Array (CSA).

   c) Derived Univariant descriptors of EEG Activity e.g. Median Frequency (MF) and Spectral Edge Frequency (SEF).

3 Evoked EEG (potentials)

   a) Auditory Evoked Potentials (AEP)

   b) Visually Evoked Potentials (VEP)

   c) Somatosensory Evoked Potentials (SSEP)

METHODS OF ASSESSING THE ANAESTHETIC STATE

III) ELECTROENCEPHALOGRAPHY AND RELATED METHODS.

1. THE RAW EEG.

The EEG is conventionally recorded from paired electrodes placed symmetrically, in standard positions on the scalp (99). Each record consists of signals containing different frequencies (0-50 Hz) and amplitudes (10-100 microvolts). These are nominally divided into five bands (100):

1 Delta waves (0.5-3Hz, 100uv): Asynchronous, symmetrical waves occurring in infants and sleeping adults, maximal in the frontal lobes.

2 Theta waves (4-7Hz, 10uv): Occur in the temporo-parietal region.

3 Alpha waves (8-13Hz, 50uV): Synchronous, symmetrical waves occurring in the parietal and occipital regions and augmented by closing the eyes and mental relaxation.

4 Beta waves (14-15Hz, 20uV): Asynchronous, symmetrical waves occurring in the fronto-central areas.

5 Gamma waves (26+ Hz, approx. 10uV): Rare in normal subjects.

The patterns, sites of maximal activity and amplitudes are different in children and infants. There is a large inter-individual variation. For example, in two thirds of the population the alpha rhythm disappears on eye opening, in one sixth it is present all the time and in the remainder tends to be absent when the eyes are closed (101).

USE OF THE RAW EEG IN THE ASSESSMENT OF ANAESTHETIC DEPTH.

Gibbs and his co-workers observed graded EEG changes in 3 volunteers under ether anaesthesia and suggested that the EEG might be used to assess anaesthetic depth (102). In 1950 Courtin and his associates further investigated the effects of ether on the EEG (103). They found consistent patterns and introduced a classification of anaesthetic depth based on these patterns (figure 11).

By the late 1950's the effects of several anaesthetic agents on the EEG had been documented. Martin (104) reviewed this work and concluded that anaesthesia tended to limit individual EEG variation, and constructed a general EEG classification associated with increasing anaesthetic dose. The 6 levels described were (figure 12):

1 At induction; an increase in frequency to 20 - 30Hz.

2 Associated with loss of Consciousness; large slow waves (1-5Hz, 50-300uV), that increase in amplitude as they slow.

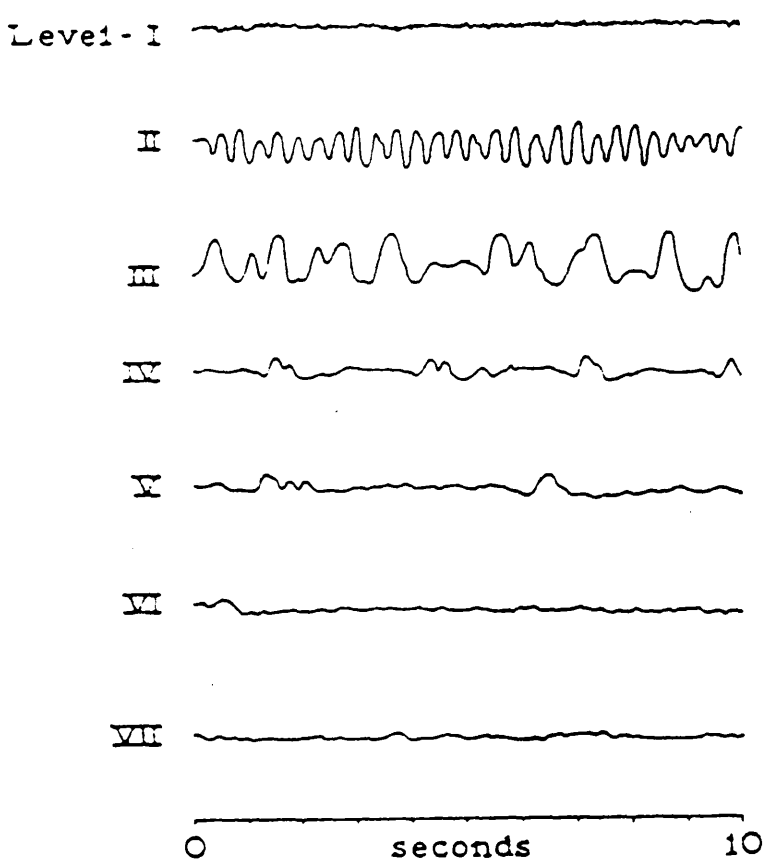
3 Increasing Depth; waves of irregular form and repetition time, which may have faster components superimposed as anaesthesia deepens.

4 & 5 Increasing Depth; falling amplitude with periods of inactivity (burst suppression). This period is divided into an early and a late phase.

6 Deep anaesthesia; isoelectric trace.

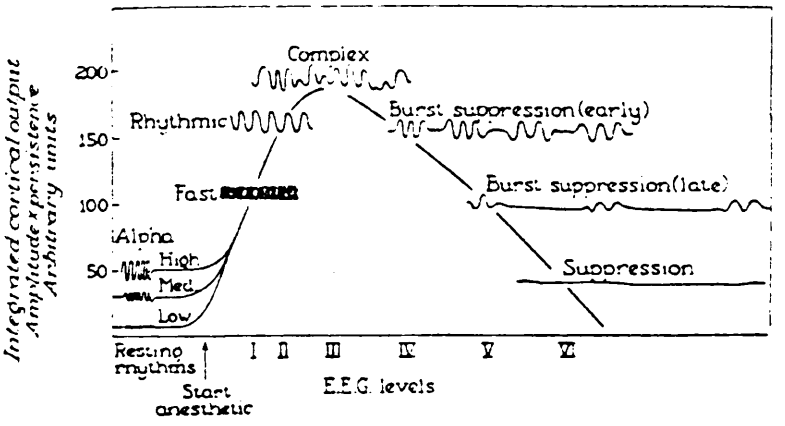
Faulconer and Bickford (105) cautioned that all 6 EEG levels did not occur with some agents and that a similar EEG level of anaesthesia does not necessarily indicate the same clinical state for different drugs. For example 7 EEG levels are described for ether anaesthesia (103); but only

Figure 11.



The seven electoencephalographic levels of ether anaesthesia described by Courtin and his associates (from ref. 103).

Figure 12.



A general classification of the EEG changes which occur during anaesthesia.

See text for details (from ref. 104).

6 for halothane (106,107) and cyclopropane (108); and 5 for thiopentone (109).

THE EXCITATORY AND DEPRESSANT NATURE OF EEG CHANGES DURING ANAESTHESIA.

Anaesthetic agents do not have a uniform effect on the EEG. For example, enflurane induces high voltage spike wave activity and burst suppression at high concentrations (110), not isoelectricity (as Martin's classification would require). Each agent, to a greater or lesser extent, does not fit Martin's general classification.

Clark and Rosner (111) suggest that drug structure systematically influences an anaesthetic agent's effect on neuroelectrical activity, with some agents causing central nervous system (CNS) excitation (figure 13). Winters (112) has proposed a multidirectional schema to link the clinical progression of the anaesthetic state to the excitatory and depressive effects different anaesthetic agents have on the EEG. This schema proposes that, after an initial excitatory phase, anaesthetic agents produce their clinical effect by drug induced CNS excitation or depression (figure 14). Both these classifications suggest that the EEG cannot be used as a simple, uniform measure of the anaesthetic state.

Further, the EEG trace from an anaesthetised patient may be indistinguishable from that recorded during normal wakefulness (113). And a normal alpha rhythm, in the immediate post-operative period, may be associated with a non-responsive patient (103). The EEG alone cannot differentiate the awake and anaesthetised states.

Chemical Group					Increasing CNS Irritability
Inorganic Agents	Hydrocarbons	Four-carbon Ethers	Three-carbon Ethers	Halogenated Hydrocarbons	
Xenon Xe Nitrous oxide N_2O	Cyclopropane $CH_2CH_2CH_2$	Diethyl ether $CH_3CH_2OCH_2CH_3$ Fluroxene $CF_3CH_2OCH:CH_2$	Methoxyflurane $CH_3OCF_2CHCl_2$ Forane $CHF_2OCHClCF_3$ Enflurane CHF_2OCF_2CHFCl	Trichloroethylene $CHCl:CCl_2$ Halothane, Chloroform $CHClBrCF_3$, $CHCl_3$	▼

Figure 13 Inhalational agents, arranged by structure and their neuro-electrical effects in man (from ref. 111).

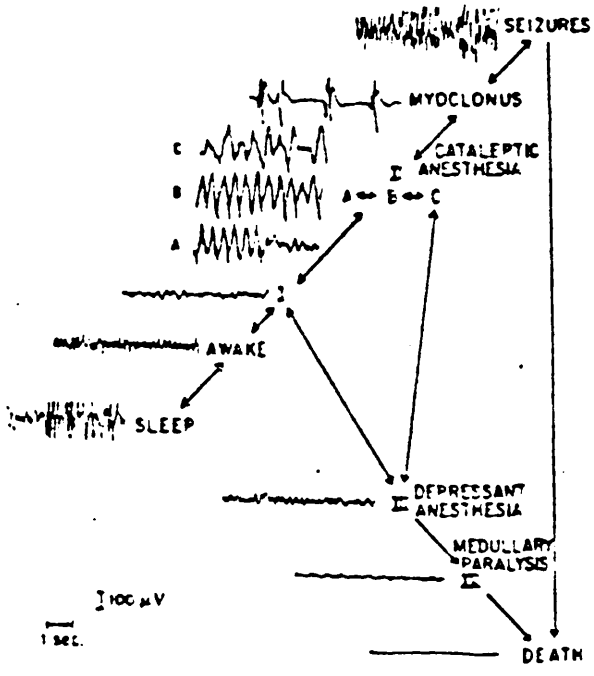


Figure 14 A multi-directional schema to relate EEG patterns to their clinical effects.

Anaesthetic agents may produce their effects by CNS depression or CNS activation. Winters constructed a multi-directional schema to relate EEG patterns to their clinical effects (from ref. 112).

THE RELATIONSHIP BETWEEN DRUG CONCENTRATION AND THE EEG.

Several studies have shown there is a good correlation between the EEG level of anaesthesia and drug concentration (108,114,115,116). The inter-individual variability between any single concentration measurement and EEG level was large. Both Faulconer and Possati (108,114) describe an "almost linear" relationship between drug concentration (of ether and cyclopropane) and EEG level. This relationship can only be fortuitous, as the units on the ordinate are empirical i.e. the EEG levels cannot be quantified but only placed in order of occurrence. Brand was unable to correlate EEG changes with plasma thiopentone concentration (117).

THE RELATIONSHIP OF CLINICAL SIGNS TO EEG.

Faulconer commented that correlation between EEG changes under ether anaesthesia and Guedel's signs was inconclusive (114). Galla (118), commenting that "..clinical signs and the electroencephalogram are variables related to the brain content of anesthetic" compared the traditional clinical signs of anaesthesia to visually recognised patterns of EEG activity; in an attempt to define the "clinical signs of anaesthesia most indicative of the anaesthetic state". He concluded that anaesthetic signs should be considered in terms of minimal necessary reflex depression and that a combination of these signs was a far more practical and sensitive indicator of anaesthetic adequacy than the EEG alone. Gain (106) failed to find any relationship between the EEG and clinical signs using halothane because "no reliable clinical signs" were present.

During their assessment of halothane as an anaesthetic agent, Robson and Sheridan (107) investigated the relationship between EEG changes and the clinical signs of anaesthesia described by Guedel. They found these signs of anaesthesia to be indistinct. The information given suggests that the same clinical level of anaesthesia may be associated with different EEG levels. Galla and his co-workers were only able to identify two EEG levels of anaesthesia with halothane and found clinical signs to be more reliable (115).

THE RELEVANCE OF RAW EEG CHANGES TO CLINICAL PRACTICE.

The dose of a drug required to produce all the EEG changes described for it are often far in excess of that required in clinical practice. Robson and Sheridan (107) noted "inadequate respiration" in one patient at EEG Level 3 under halothane anaesthesia and recorded systolic blood pressures of 60 mmHg or less at levels 4 to 6. Gain described profound hypotension at these levels (106). Galla (115) describes only two EEG levels under halothane anaesthesia and his conclusion, that clinical signs were more useful than the EEG in assessing anaesthetic adequacy, may be that the doses they used were in keeping with those required in clinical practice.

Similarly, it is unlikely (with the concomitant use of muscle relaxants) that an EEG level greater than 3 is necessary under di-ethyl ether anaesthesia or 2 of the 5 described (110) when enflurane is used. Similar comments may be made about most agents.

The corollary of this is, that a pattern of burst

suppression, which is generally assumed to indicate profound cerebral depression, may be associated with responsiveness to painful stimulation under hydroxydione anaesthesia (119), and retention of the eyelid reflex and "small jerky limb movements" following a bolus of althesin (120). In neither case can the patient be described as clinically anaesthetised. Brand (117) found that burst suppression during thiopentone anaesthesia, level 3 as described by Kiersey (109), can be associated with a response to minimal stimulation (venepuncture) in some cases, but be adequate for surgery in others.

PROBLEMS ASSOCIATED WITH THE USE OF THE RAW EEG.

Interpretation of the raw EEG requires specific training and is subject several problems (10):

1 Level definition: without a precise definition of anaesthesia the validity of the EEG as an indicator of anaesthetic adequacy is questionable.

2 Pattern definition: the subjective definition of what constitutes a pattern wave form is dependent on the observer.

3 Pattern variability: as different agents have differing effects on the EEG, pattern recognition is complex.

4 Inter-observer variability: experienced observers show a poor correlation with each other in the interpretation of individual EEGs (121).

Excluding these difficulties (vide supra), there are problems with interference (e.g. diathermy) and interpretation in the presence of changes in blood

pressure, PaO2, PaCO2, surgical stimulation etc. The standard recording rate of over 10,000 cm/hour makes the following of trends impossible.

Combinations of anaesthetic agents makes interpretation of the EEG more difficult. Clark (111) has pointed out that the chaotic nature of the literature concerning the EEG effects of some drugs (halothane, ether and fluroxene) was due to the use of nitrous oxide by some workers. This "chaos" is likely to be greater in clinical practice where combinations of drugs are often used and other variables not controlled eg. blood pressure. Marshal (113) suggests that the effects of some factors may be additive e.g. moderate hyperventilation or a slight increase in inspired anaesthetic concentration may have minimal effects on the EEG alone but in combination produce marked changes.

SUMMARY.

The raw EEG will never be a practical tool in routine anaesthetic practice. Visual interpretation of the raw data requires expertise and is open to observer error. The EEG in isolation cannot differentiate the awake from the sleeping state and, although dose related changes do occur, the changes apparent within the clinical range are small and agent specific. The use of anaesthetic drugs in combination makes interpretation of these changes more difficult.

The literature on computer processed EEG techniques suggests that the EEG does contain sufficient information, inferring that automated analysis is required for its extraction. These techniques will be considered next.

METHODS OF ASSESSING THE ANAESTHETIC STATE

III) ELECTROENCEPHALOGRAPHY AND RELATED METHODS.

2. THE PROCESSED EEG.

INTRODUCTION.

Micro-processor based, on-line data acquisition techniques make it possible to transform, compress and display the raw EEG signal into more easily understood forms. These techniques derive frequency and amplitude data from the raw EEG signal but generally ignore aspects such as wave-form.

During signal quantification some of the information contained in the original EEG signal is lost while other aspects may be enhanced. As this is dependent on the processor used, it is important to appreciate how the characteristics of a given machine may effect the interpretation of a standard input signal.

THE FUNDAMENTALS AND LIMITATIONS OF SIGNAL PROCESSING.

Processing an EEG signal consists of 4 basic steps:- data acquisition, signal amplification, signal quantification and display of the processed signal. Each of these effects the way the information contained in the original signal is presented to the user.

1. Data Acquisition.

The electrodes are potentially the weakest link in any EEG system. The electrodes must be properly applied and impedance monitored to warn the operator of output changes due to electrode drift. As the optimal recording site for the various clinical applications of these

machines has not been determined some inconsistencies may be due to the use of different electrode positions.

Prior and Maynard (122) suggest the use of parietal electrodes as cerebral activity is maximal in this region during anaesthesia, it overlies the boundary zone between the three main cerebral arteries and minimises muscle artefact. The ABM (vide infra) uses a fronto-mastoid position to pick-up this "muscle artefact" which is then processed and displayed on a separate channel. Simple "stick-on" ECG electrodes can be used in the latter situation, which has an obvious practical advantage.

2. Amplification.

The ability of an EEG processor to accurately amplify the EEG signal depends on its sensitivity, linearity, frequency response, band-width, phase-shift distortion and noise rejection characteristics. As the amplifier characteristics of the various machines differ the output signal obtained from any given input signal varies between machines (figures 15 and 16).

3. Signal Quantification.

Although several automated analytical techniques have been used to quantify the EEG signal, few are available commercially (125). They may be divided into those analysing a period of time (time domain analysers) and those analysing a certain frequency range (frequency domain analyser). This distinction is historical and, to an extent, arbitrary but useful descriptively.

Time domain analysers determine the mean integrated voltage of successive EEG epochs to provide an overall

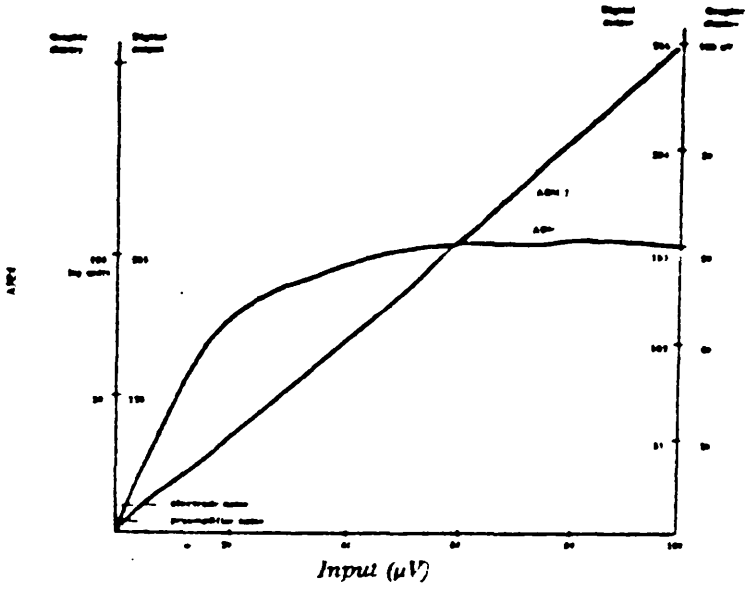


Figure 15. Processed EEG amplitude from the ABM and ABM2 Although the frequency response of the ABM and ABM2 are similiar; the output of the ABM2 is designed to be proportional to the input from 3-100 uv while the output of the ABM is proportional to the logarithm of the input from 3-60 uv (from ref. 123).

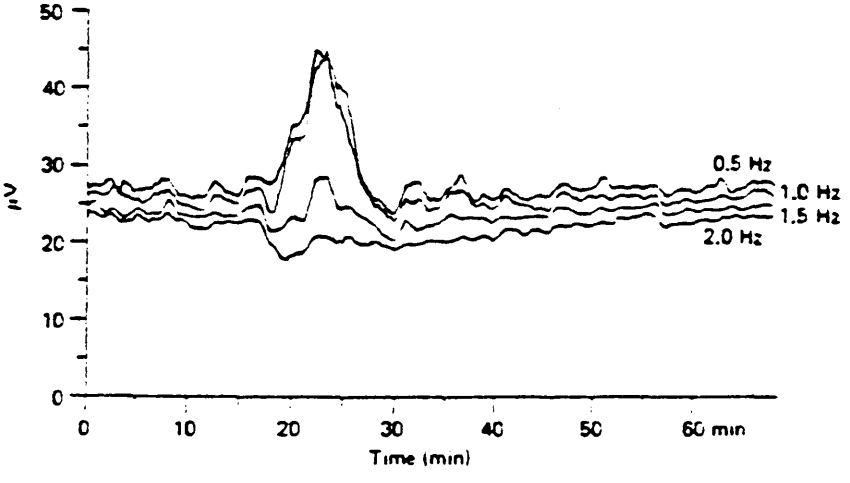


Figure 16. The effect of different low cut off filters. The time course of mean amplitude during carotid end-arterectomy. The four curves refer to four different low cut off frequencies. If a high cut off is selected a reverse in trend can be observed (from ref. 124).

indication of amplitude. Most processors of this type derive frequency information from the analysed epoch. The ABM and CFM are examples of this type of machine and are discussed in more detail below.

Frequency domain analysers, for example the Compressed Spectral Array (CSA), generate successive power spectra from short (2-30 second) epochs using fast fourier transformation. Each spectrum is represented as a smoothed histogram (figure 17).

4. Display.

The alternatives for display of processed EEG information determined in the time domain are, to an extent, limited. The frequency and amplitude characteristics being displayed separately against time. The type of display and scale used differ greatly from machine to machine.

Frequency domain analysers use pseudo-three dimensional plots of successive power spectra as a function of time. The method of display, duration and frequency of epoch analysis and amplitude scaling may effect the interpretation of data, obtained from the same amplifier.

ARTEFACT AND OTHER SOURCES OF ERROR.

Artefact may be intrinsic (ie. from unwanted biological sources eg. the heart, muscle and eye) or extrinsic (ie. from the environment eg. diathermy, faulty electrode contacts and the mains electricity supply). Artefact is detected in the raw EEG by visual examination, following processing this may be impossible. Automatic

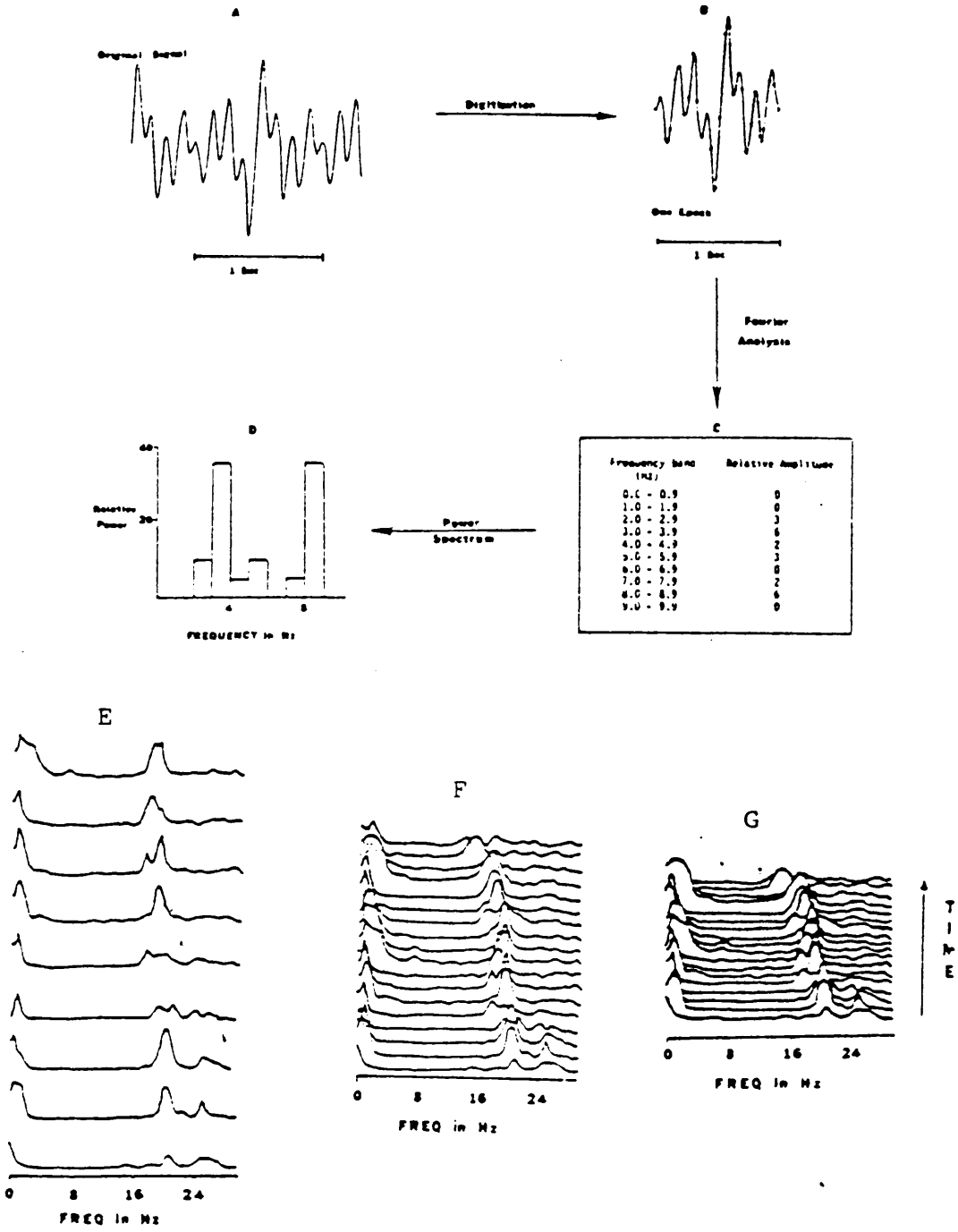


Figure 17. A schematic representation of the process of power spectrum analysis.

The original waveform (A) is digitised by repeated sampling at short intervals. Fourier analysis is carried out on each epoch of data (B). The results (C) give the amplitude of activity in each frequency band. These amplitudes are squared to produce power histograms (D) which are smoothed and plotted sequentially (E). Compressing (F) and suppressing lines that would lie behind a hill produces the final compressed spectral array (G) (from ref. 125).

artefact detection systems remain to be perfected, and this alone must limit the clinical usefulness of these systems (126).

NUMERIC EEG INTERPRETATION.

Further simplification is possible, with the original signal being represented by a single number (eg. spectral edge frequency, median frequency, median power frequency etc.). This type of approach may be used to generate enormous amounts of data. For example, a system has been reported which separates the EEG into 30 1-Hz bins (0.5 - 1.5, 1.5 - 2.5 Hz etc.) (126), and describes each bin numerically with regard to the number of waves and power present for any given epoch. This generates 153 numbers for each analysed epoch, which may itself be as short as 2 seconds. The validity of these numbers as a measure of the anaesthetic state is unknown.

OVERVIEW.

The presentation and content of the information derived from any given EEG signal is highly dependent on the EEG processor used, as different frequency and amplitude components contained in the original signal may be enhanced or suppressed during amplification, quantification or display. Some systems, such as the compressed spectral array, contain a lot of information but present it in a form which may itself require skilled interpretation. Others such, as the univariate descriptors of EEG activity may not adequately represent the multimodal power spectra often present during anaesthesia or fail to reveal some EEG patterns eg burst suppression

(127). Figure 18 shows how the spectral edge frequency may misrepresent overall EEG activity.

THE CFM, CFAM AND ABM.

The cerebral function monitor (CFM), cerebral function analysing monitor (CFAM) and the anaesthesia and brain monitor (ABM) have been most extensively studied in this field.

THE CEREBRAL FUNCTION MONITOR.

The CFM amplifies, filters, compresses and rectifies the original EEG signal to produce a trace on a slow speed semi-logarithmic chart (122). The trace is dependent on the frequency and amplitude characteristics of the original EEG signal and has two main characteristics; a lower border which gives an indication of overall cerebral activity and a width which reflects the variability of cerebral activity (figure 19).

The filter reduces the emphasises of the lower frequencies (diagram 20). This is necessary, as the electrical energy in the EEG tends to decrease with increasing frequency and weighting is required if the high frequency components are to be adequately represented on the display used.

Impedance is monitored on a separate channel and an overload network monitors the peak voltage, cutting out both channels if the system becomes overloaded. These aspects are useful for artefact detection.

THE CEREBRAL FUNCTION ANALYSING MONITOR.

The CFAM is a development from the original CFM (128). Two input channels allow the operator to alternate

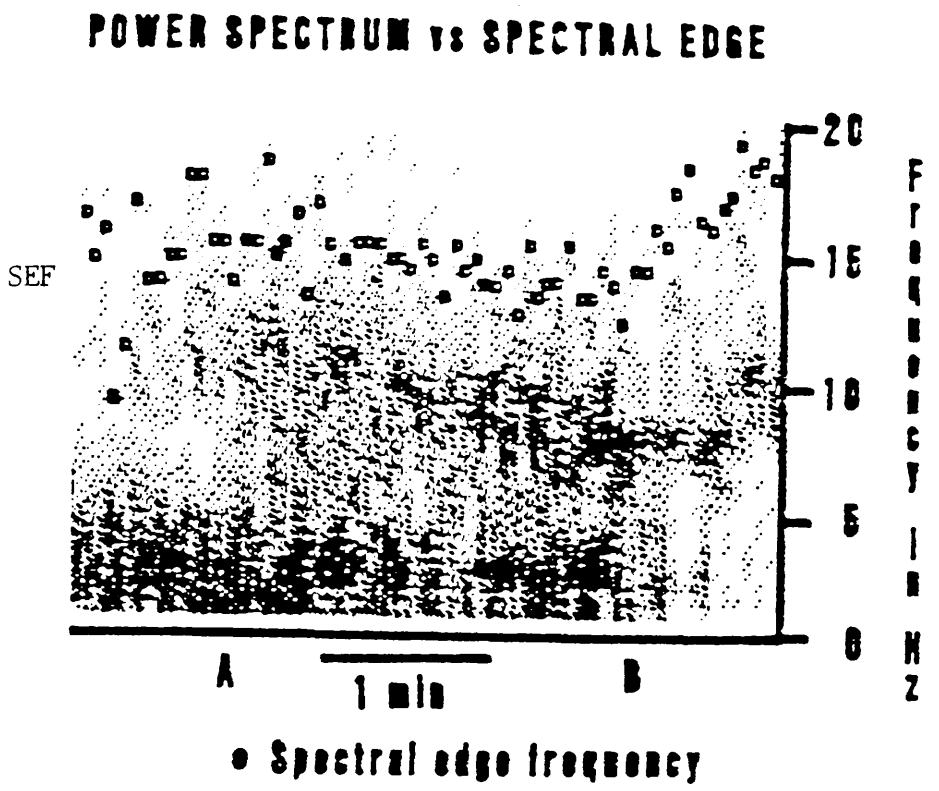


Figure 18. SEF and overall EEG activity.

A comparison of the SEF and the density modulated spectral array In this sequence a low frequency band slowly decreases in amplitude (density in the diagram) to (B) where it stops abruptly. A high frequency band gradually decreases in frequency and increases in amplitude. At (A) the SEF represents low frequency activity while after (B) the same numeric value represents high frequency activity (from ref. 127).

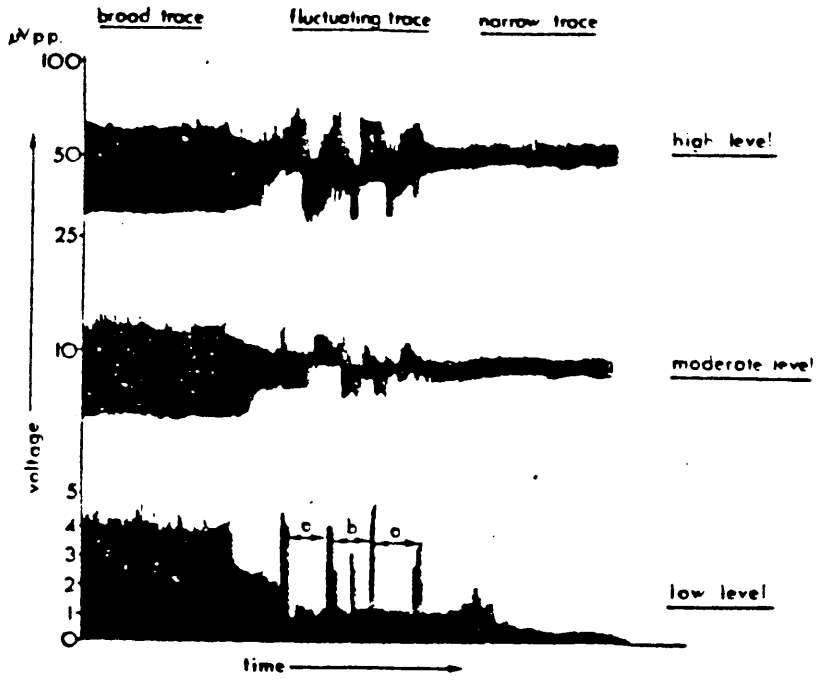


Figure 19. Diagrammatic representation of the general types of CFM activity.

These traces may be described according to the level of activity, band width and degree of fluctuation. The lower border of the trace indicates the lowest peak to peak voltage against time, the upper border the highest peak to peak voltage against time and the width the variability in signal amplitude. Note the burst suppression in the low level trace (from ref. 122).

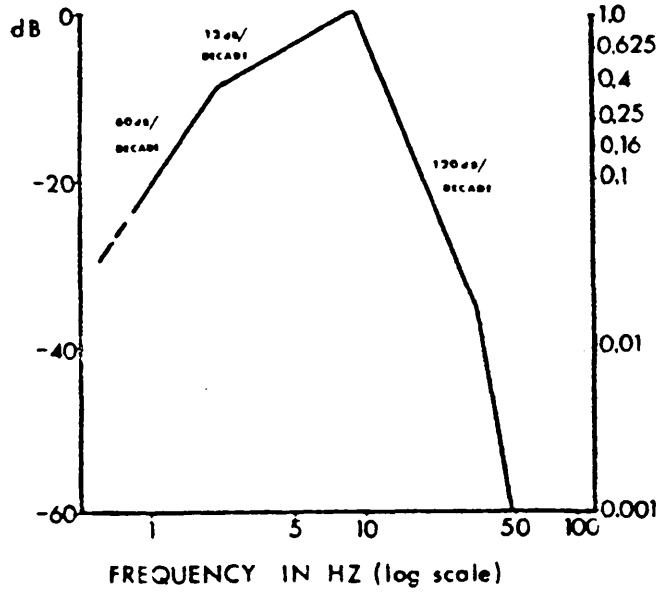


Figure 20. The frequency response of the CFM.

The filter is designed to sharply reject frequencies below 2Hz and above 20Hz. Amplification increases with frequency from 2Hz (from ref. 122).

between recording sites. The amplitude distribution is smoothed over 20 seconds and plotted on a logarithmic scale as the mean, 10th. and 90th. centiles of the derived value. Absolute maximum and minimum amplitude values are superimposed. Frequency information is displayed as the percentage of activity in each of the classic frequency bands; very low frequency waves (less than 1 Hz) being plotted separately. The percentage of time that the EEG amplitude is below a pre-set level (1 - 5 Hz), and muscle activity (in the 200 - 1000Hz band) are both indicated on separate channels (figure 21). This machine may be used to measure evoked potentials.

THE ANAESTHESIA AND BRAIN MONITOR.

The ABM selectively filters the input signal through low and high pass filters to monitor both the EEG (1.5 - 25Hz) and the EMG (65 - 300Hz). Notch filters eliminate interference from the mains source and its harmonics and an additional filter removes the DC component to prevent errors in the calculation of the zero crossing frequency (ZXF). This technique is used to calculate the frequency content of the original signal (figure 22).

The filtered potentials are full wave rectified, integrated and passed through log amplifiers i.e. amplifiers whose output is proportional to the log of the input. Both the EEG and EMG amplitude data are presented on relative linear scales of 0 - 100 EEG (or EMG) units. One hundred EEG units represent 60uV and 100 EMG units 15uV. The display is updated every 10 seconds (figure 23).

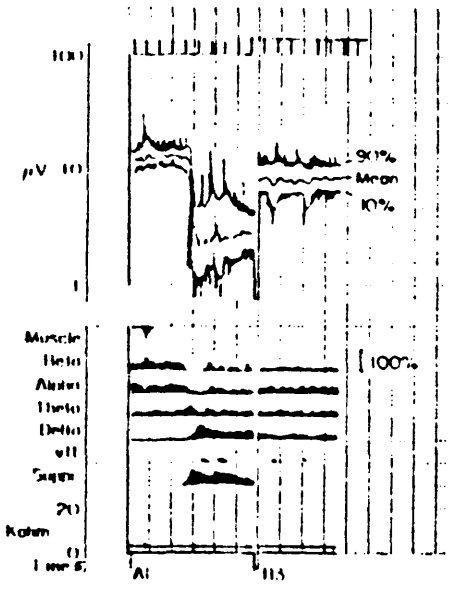


Figure 21. A simulated CFAM trace.

From top to bottom. Time marker at one minute intervals; the 90th, mean and 10th centile of the weighted amplitude; muscle activity; the percentage activity in the beta, alpha, theta and delta bands; the percentage of very low frequency activity; the suppression band; and electrode impedance (from ref. 128).

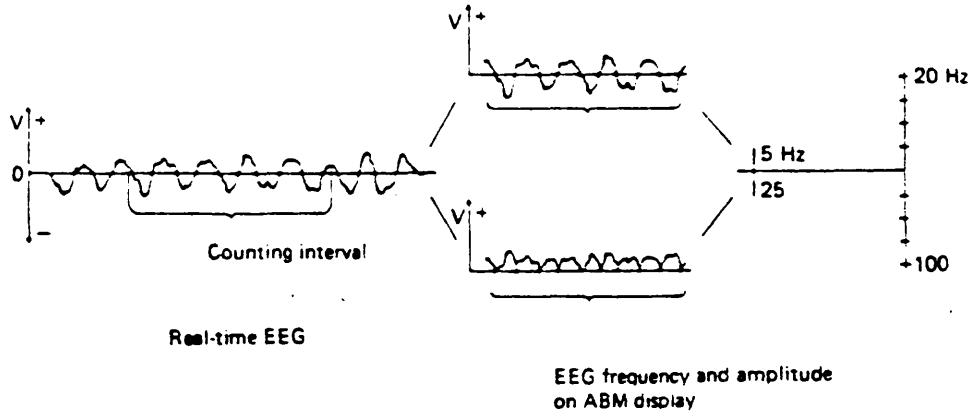


Figure 22. Calculation of the ZXF and integrated amplitude.

Each time the EEG crosses the isoelectric line an impulse is sent to the computer. The total number of pulses divided by the time epoch, expressed in seconds, is the ZXF. From the same epoch the voltage is integrated and the mean calculated, to give a value of amplitude (from ref. 129).

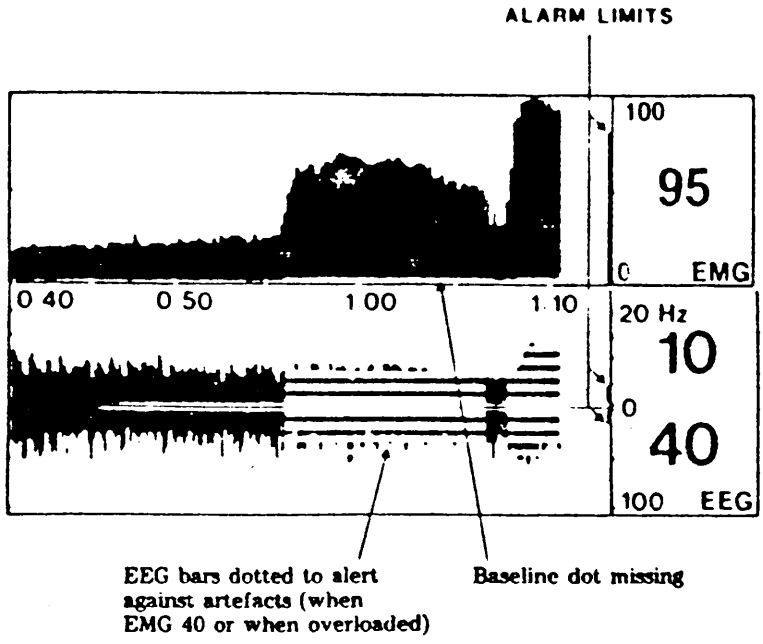


Figure 23. The ABM display.

The display shows EMG (0-100 arbitrary units) and the EEG as the ZXF (0-20Hz) and integrated amplitude (0-100 arbritary units). An elevation of the base-line dot of the EMG and dotted EEG bars indicate artefacts (from ref. 123).

THE RELATIONSHIP BETWEEN ANAESTHETIC DOSE AND THE PROCESSED EEG.

Prior (130) and her co-workers compared visually rated EEG strips with CFM and CFAM traces obtained from unstressed primates anaesthetised with althesin infusions. The six recognised EEG "depths" of anaesthesia could be distinguished by the automated methods. The combination of absolute voltage, voltage variability and frequency content gave optimal recognition of the EEG "depth".

Frank (131,132) and others (133,134,135) have shown that single amplitude, frequency and other univariate descriptors of the EEG can be correlated with the plasma levels of induction agents (thiopentone, althesin and etomidate). These simple relationships may not hold following induction, during deep anaesthesia (125) or when combinations of drugs are used (136). The effects of surgical stimulation have not been evaluated (vide infra).

USE OF THE CFM IN CLINICAL PRACTICE.

Dubois and his co-workers (137) used the CFM to monitor 121 patients undergoing a variety of surgical procedures, lasting from 5 minutes to 6 hours. Induction and maintenance of anaesthesia was achieved with one of six intravenous agents, supplemented with fentanyl (1-5ug/kg). Several effects are described:

1. Changes at Induction.
2. Changes during maintenance.
3. The effect of surgical stimulation.
4. The effect of volatile agents.

It is difficult to draw conclusions from this work.

Although a great deal of information is presented and a large number of patients were studied, the number who did (and did not) demonstrate the effects describe are not mentioned and the information given is qualitative rather than quantitative. However this work does form a base from which the processed EEG can be discussed. To prevent unnecessary repetition, information from other studies will be included in the relevant sections.

1. CHANGES AT INDUCTION.

At induction CFM activity increased to a peak, and the patients lost consciousness at this point (figure 24). This effect was independent of the induction agent used. A similar effect, which might be anticipated from the work done on the raw EEG, has been demonstrated with the CFAM (128) and the ABM (138).

2. CHANGES DURING MAINTENANCE.

Changing the infusion rate during maintenance was followed by changes in CFM activity (figure 25). A group of ("mainly") gynaecological patients under CFM control was compared to a retrospective control group and a 30% reduction in althesin requirement described. Although the authors claim that the CFM allowed better regulation of anaesthetic dose, no mention is made about the comparability of the groups with regard to age, type and duration of procedure, fentanyl dose-age, clinical state during the operation etc.

When the trace falls from above the base-line interpretation may be difficult, as this may represent lightening or deepening anaesthesia. The authors suggest

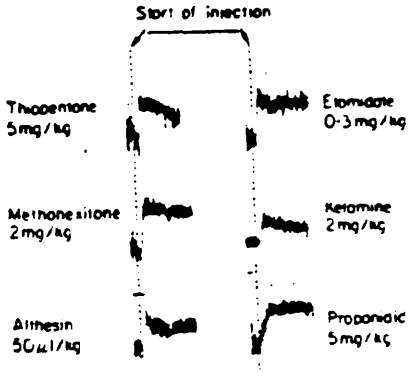


Figure 24. Induction peaks on the CFM.

Following a bolus of anaesthetic an induction peak is seen on the CFM trace (from ref. 137).

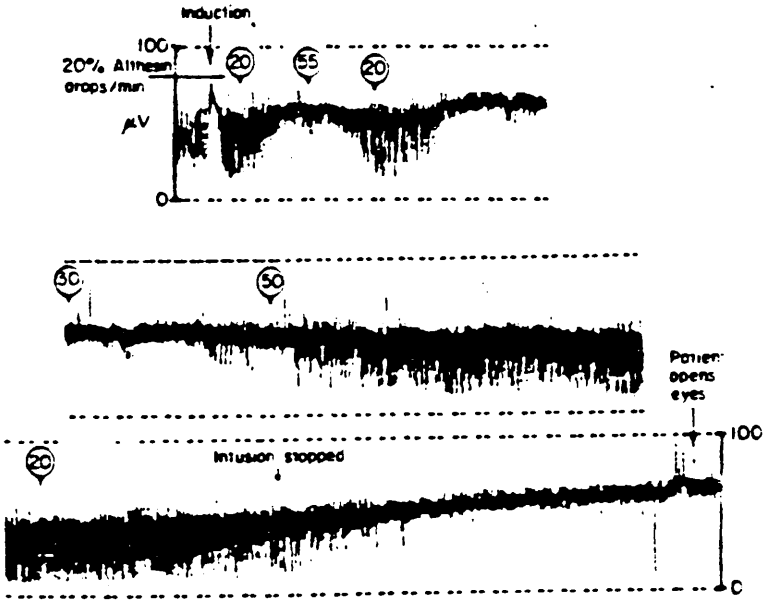


Figure 25. The effect of varying althesin infusion rates on the CFM trace.

Changes in the rate of althesin administration are associated with changes in the CFM trace (from ref. 137).

that a bolus of anaesthetic will differentiate these states, a second peak indicating re-induction (and that the patient was light) and a fall in the trace deepening anaesthesia. Although Maynard and Jenkinson describe an increase of beta activity during lightening anaesthesia (128), a high level of beta activity can occur during clinically adequate anaesthesia (139).

Sechzer and Ospina (140) assessed the CFM in 100 patients during surgery using a wide variety of anaesthetic techniques. No change in CFM voltage occurred in 80 to 100% of the trials, depending on the agent used. With some agents activity increased in some cases, but decreased or did not change in others.

Major found the CFM to give no additional information and dispensed with it the latter part of his investigation of di-isopropylphenol, relying on traditional clinical signs (141).

Edmonds (138) found that, neither alone or in combination did the frequency and amplitude parameters derived by the ABM consistently accompany clinical changes in anaesthetic depth. During recovery, the inter-patient variability was so large that emergence could not be distinguished from maintenance.

3. THE AROUSAL RESPONSE AND SURGICAL STIMULATION.

Surgical stimulation was associated with narrowing and/or upward movement of the trace, which the authors describe as "arousal" and suggest is due to inadequate analgesia. "Arousal" is not synonymous with "awareness", and describes changes in EEG activity which may be related

to an external stimulus.

The "K complex" is a diffuse wave with at least two components which spreads over the cortex following sensory stimulation in the sleeping subject (142). The response only occurs if the subject fails to awaken (101), is exaggerated in patients with abnormally functioning brains and may occur spontaneously (i.e. no with no assignable cause) (142). It is maximal following auditory stimulation and the fast component may herald a partial arousal from sleep.

Suxamethonium induces low voltage, fast wave activity in adults and high voltage, slow wave activity in children anaesthetised with halothane (143). These responses are blocked by pre-treatment with gallamine and alcuronium; are associated with an increase in heart rate; and, in 6 out of the 8 patients studied, with an increase in blood pressure. Oshima (144) studied 62 patients anaesthetised with halothane and observed these changes in 77% of cases following suxamethonium and in 88% of cases following skin incision. Increases in heart rate, blood pressure and pupillary diameter occurred in all cases. These workers concluded that the response was secondary to central nervous system activation. Infants (less than 2 months old) did not demonstrate eeg changes to either stimulus. No mention of possible artefact contamination, due to suxamethonium induced fasiculation, is made in these studies

Bimar (145) used a CSA to assess these responses in 36 patients during surgery. Characteristic (vide supra) changes occurred in 24 patients. Irregular respiration

occurred in 9 patients and cardiac arrythmias in 5. No mention is made of heart rate or blood pressure changes. These changes were usually associated with a surgical manoeuvre but this could not be quantified.

Savege and his co-workers assessed the autonomic and cerebral responses to pre-tibial pressure using the CFM (65). Light althesin and pancuronium anaesthesia was associated with continuous variability in blood pressure and heart rate. These became less variable as the dose of althesin increased. A slight reduction in the cardiovascular response to stimulation followed an increase in anaesthetic depth, as judged by the CFM. Fentanyl in small doses obtunded this response and, in larger doses (9ug/kg), had this effect despite increasing CFM activity. The authors concluded that althesin was a potent cerebral depressant which had minimal effects on the cardiovascular response to stimulation and that the dose of althesin should be limited to that required to "depress consciousness"; as larger doses delay recovery without improving the "quality" of anaesthesia.

4. VOLATILE AGENTS.

In the initial study of the CFM a small, unspecified number of patients were anaesthetised with halothane or enflurane in nitrous oxide. These agents caused a gradual increase in cerebral activity and attempts to "deepen anaesthesia and depress the trace" required concentrations of 3-5% which resulted in hypotension. The addition of halothane to a previously established intravenous anaesthetic was associated with depression of the trace.

The relationship between CFAM activity and volatile

anaesthetic agents has been assessed by several workers: Sebel (139) describes increased delta and theta activity and a fall in amplitude during deepening halothane - nitrous oxide - oxygen anaesthesia. Increased alpha and beta activity and a rise in amplitude followed discontinuation of the nitrous oxide. Discontinuing the halothane had minimal effects. In this study, minimal amplitude changes and significant beta activity were recorded from one of the five patients studied, despite clinically adequate anaesthesia.

Wark (146), used halothane as a sole agent in 8 patients. The CFAM amplitude increased at 1 MAC and decreased at 2 MAC. A progressive decreases in beta activity and increases in delta activity occurred.

Williams (147) studied the effects of 10, 30 and 50% nitrous oxide in 15 volunteers. Only 9 completed the study. Significant reductions in amplitude occurred in the 30 and 50% trials and significant increases in amplitude occurred on termination of the gas (with respect to the control values). However, the frequency changes were variable and the subjective effects of the nitrous oxide remained after the trace had returned to normal.

UNIVARIATE DESCRIPTORS OF ANAESTHETIC DEPTH.

EEG processing converts an analogue signal to a digital signal. The digitised signal may be described by a single number or a group of numbers. Some of these numbers have been used in the assessment of anaesthetic depth. On only three of these, Spectral Edge Frequency, Median Frequency and Zero Crossing Frequency, is there sufficient

data available to allow evaluation.

1. SPECTRAL EDGE FREQUENCY (SEF).

Rampil (148) defined the SEF as the "highest frequency at which a significant amount of energy is present". Hudson (133) quantified this as the frequency below which 95% of the energy in the EEG is contained. This definition is not universal. The "Neurotrac" (Interspec Ltd.), for example, uses a 97.5% energy cut-off to define the SEF.

In the original animal study (148), the SEF responded rapidly to changes in halothane and enflurane concentration and was not effected by nitrous oxide or phenylephrine induced hypertension. A large inter-animal variation in response was present although the effect was reproducible in each animal.

Hudson (133) has shown that the SEF reflects changes in thiopentone concentration at induction. Arden (134) demonstrated similar changes with etomidate but found discrepancies between drug concentration and the SEF during the the recovery (figure 26). In this study the median frequency was shown to change during both phases.

Patients with a SEF of less than 14Hz following induction with thiopentone, fentanyl and droperidol have a significantly smaller pressor response to laryngoscopy and intubation than those with a SEF greater than this value (149). No correlation was found between pre-induction blood blood pressure and the magnitude of the response. The SEF criteria described may be agent dependent and require determination for each drug and combination of drugs used.

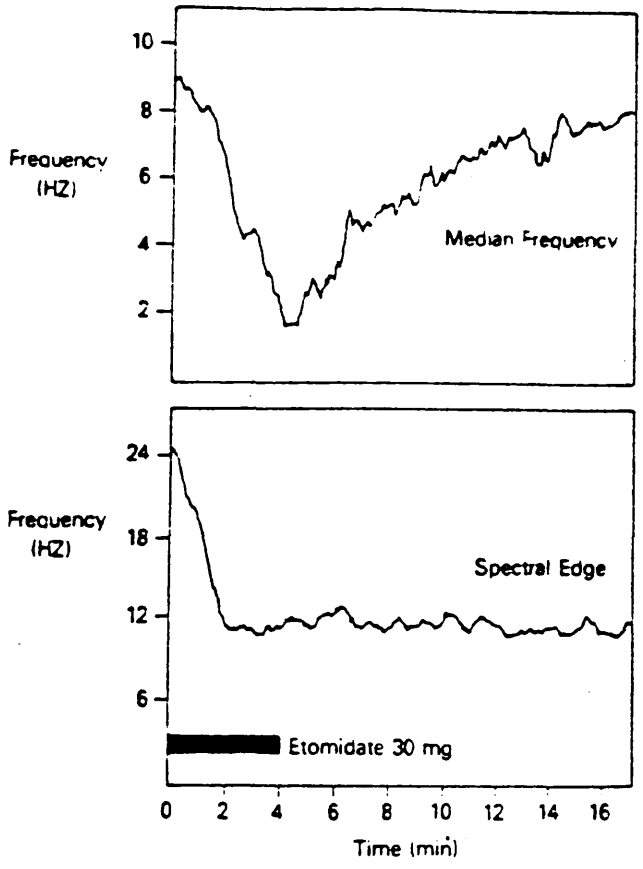


Figure 26. The effect of a bolus of etomidate on the SEF and MF.

Although the SEF reflects changes following induction with an infusion of etomidate, it does not reflect the recovery period. The median frequency reflects both phases (from ref. 134).

The SEF is insensitive to low frequency changes or when the power distribution is broad or bi-modal (127,150). Further, up to 60% of the total EEG energy may occur in the 0.5 - 2Hz band during during surgery (150). The SEF may not adequately reflect overall EEG activity in this situation while other monitors e.g. the CFM filter out these components.

2. ZERO CROSSING FREQUENCY (ZXF).

The frequency information obtained from the ABM (which uses the ZXF) is of limited use (vide supra) in this field. Klein and Davis (151) used discriminant analysis, based on derived EEG and cardiovascular parameters, to differentiate between "light", "medium" and "deeply" anaesthetised subjects, in two patient group sets. The "lightly" anaesthetised group was given 70% nitrous oxide in oxygen (and used in both patient sets); the "medium" groups received 60% nitrous oxide supplemented with 1% halothane or 1% enflurane; and the "deeply" anaesthetised received groups 60% nitrous oxide and 2% halothane or 2% enflurane. This study was carried out pre-operatively.

The best predicative accuracy for the "light", "medium" and "deep" halothane groups were 90.0, 83.3 and 86.7 percent; and for the enflurane groups 96.7, 83.3 and 90 percent. Although these results may be described as "encouraging", the patients were not operated on and the discriminator appears agent dependent.

Use of the ZXF has been criticised by Levy (125). It is sensitive to small changes in amplitude and the same

ZXF may be derived from very different EEG wave-forms (figure 27).

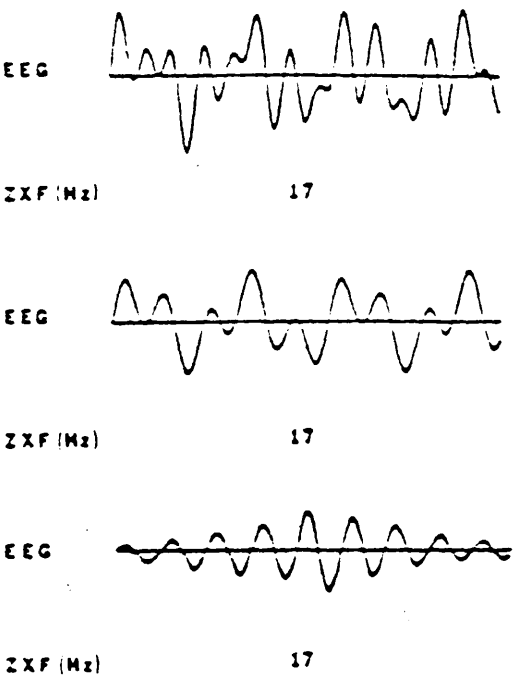
3. THE MEDIAN FREQUENCY (MF).

The MF is defined as "the median (50% quantile) of the power spectrum regarded as a distribution" (150). Schwilden and Stoekel compared several univariate EEG descriptors, in 14 patients during surgery (150). The patients were paralysed and received either 1.3 MAC or 1.5 MAC isoflurane in nitrous oxide and oxygen. Zero point six MAC was allowed for the nitrous oxide. The percentage of activity in 5 frequency bands, MF, SEF and overall amplitude were examined. None of the criteria could differentiate between the groups for any given epoch. MF was the best discriminator between the recordings during anaesthesia/ surgery and control/ recovery (figure 28). The authors concluded that MF, at a level of 5Hz signifies adequate anaesthesia as emergence occurred at frequencies greater than 5hz.

In this study periods of burst suppression (which violates the assumptions of spectral analysis) and artefact were rejected manually. If any of these techniques are to be widely applied these functions must be automated.

A study (152), in which 13 volunteers were anaesthetised with methohexitone using a feed-back control system designed to maintain the MF at 2 - 3 Hz, confirmed that the most prominent frequency shift occurred in the 0.5 - 2 Hz frequency band. However, during the recovery phase, 3 of the 13 cases opened their eyes to command when the MF was at or below 5Hz.

Figure 27.



The non-specificty of the zero crossing frequency (from ref. 125).

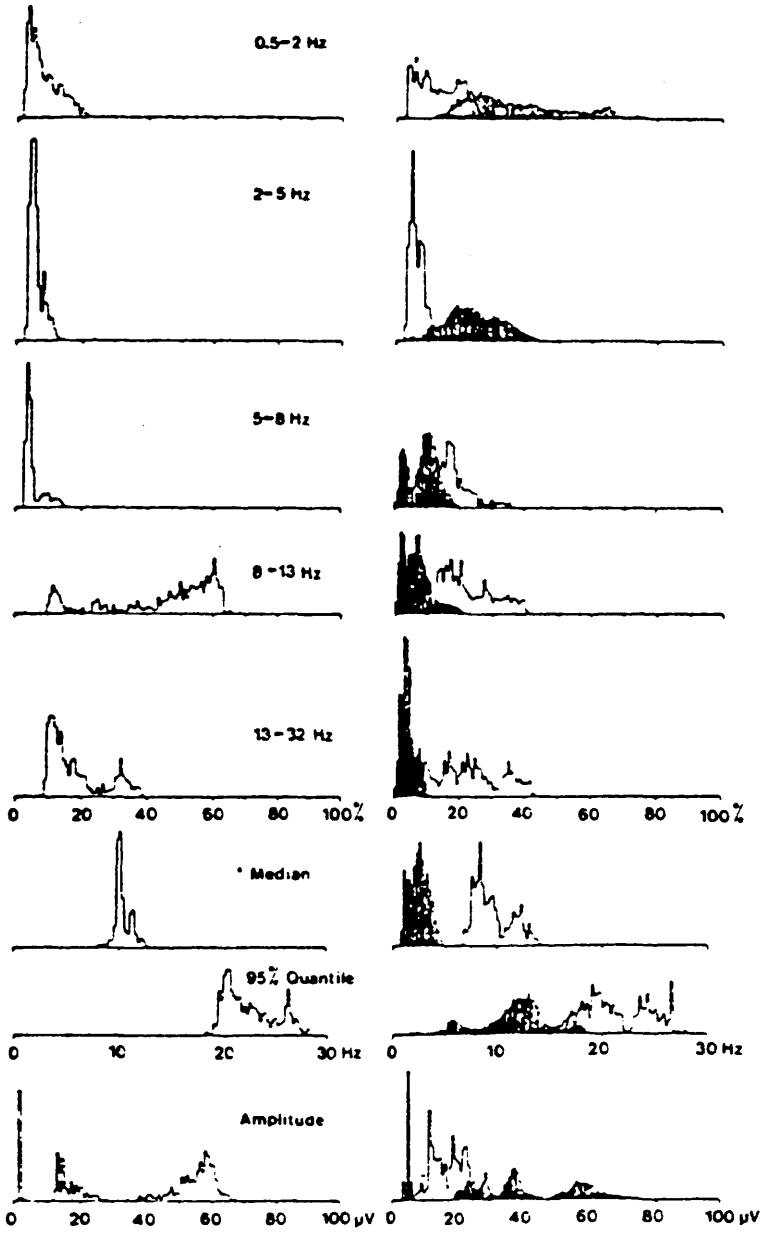


Figure 28. The distribution of EEG activity: baseline, during surgery and following recovery.

The left hand side figures depict the preoperative distribution of percentage activity in 5 frequency bands, the median frequency, the SEF (95% quantile) and overall amplitude. The right hand side figures depict these variables during surgery (shaded) and following response to command (from ref. 150).

EEG RECOGNITION OF CLINICALLY DEFINED ANAESTHETIC STATES.

Some of the techniques described have attempted to differentiate between two or more dose defined anaesthetic states. Others have attempted to use the processed EEG to differentiate between clinically identified anaesthetic states.

McEwen and his co-workers (10) defined 5 clinically significant levels of anaesthesia, based on non-EEG criteria, for patients anaesthetised with halothane and nitrous oxide:

1. Conscious
2. Light Anaesthesia; tachycardia and hypertension to surgical preparation and stimulation.
3. Light Surgical Anaesthesia; no response to preparation. Tachycardia and hypertension to surgical stimulation.
4. Surgical Anaesthesia; no response to surgery. Mild hypotension (blood pressure within 20% of normal).
5. Deep surgical Anaesthesia; bradycardia and hypotension, blood pressure less than 20% of normal.

A computer based EEG pattern recognition system was devised using values extracted from sets of time and frequency domain features. Statistical analysis showed the EEG criteria to correctly estimate the clinically defined anaesthetic state in 50 - 94% trials, depending on the type of analysis used.

A similar study (9) extracted features from power spectral analysis of the EEG. The performance of this system was estimated at 55 - 80%.

When the inter-rater variability in EEG interpretation is considered (121), these systems are surprisingly good. Further work is required both in the anaesthetic definition and the feature extraction systems before the usefulness of this approach can be ascertained.

CONCLUSION

If the raw EEG signal contains sufficient information, and the relevant features can be identified and extracted by EEG processors then these techniques would be useful. Although some techniques have been shown to reflect changes in both determinants of the anaesthetic state (surgical stimulation and anaesthetic dose) it is not known if these are a valid reflection of the true anaesthetic state. Further, all automated techniques depend on the data following trend rules e.g. that is is analysable as a certain number of sine waves. These rules may be violated by some waveforms e.g. burst suppression. This limitation and, the limitations of automated artefact detection techniques must be overcome.

METHODS OF ASSESSING THE ANAESTHETIC STATE

III) ELECTROENCEPHALOGRAPHY AND RELATED METHODS.

3 THE EVOKED EEG.

INTRODUCTION.

Sensory evoked potentials (SEP) are the electrophysiological response to the stimulation of peripheral or cranial nerves. They are believed to arise during the propagation of impulses centrally and demonstrate the functional integrity of the specific sensory pathway under investigation and, to an extent, the function in adjacent structures (153). These stimulus specific, event-related potentials represent only 1% of the amplitude of ongoing EEG activity (154) and can be extracted from this background "noise", which is random in nature, by averaging or summing multiple EEG segments time-locked to a repetitive sensory stimulus. This may require over 2000 separate stimuli and take over 5 minutes.

Although SEP monitoring generates numerically quantifiable data with regard to the latency and amplitude components of the evoked wave-forms, recognition of the individual waveforms may involve a degree of subjectivity (155) and care must be taken to ensure the correct identification of the specific waves (156).

Auditory, visual and somatosensory stimuli may be used. Auditory evoked potentials are the easiest to record in theatre (157). Current nomenclature defines these potentials with reference to the point of measurement (i.e. electrode position) and by description of the extracted waveform; in terms of latency (in milliseconds),

amplitude (in millivolts) and polarity. Potentials measured close to their source of generation are referred to as "near field" and those distally as "far field" (158). The latency and amplitude values are dependent on the technique used and normal values have to be defined by each laboratory (153).

With respect to anaesthetic depth, auditory evoked potential (AEP) have been have been most examined and will be described further.

The Auditory evoked responses consist of (figure 29):

1. A first section consisting of six peaks (I-VI) which can be recorded in the first 9msec^{-1} and are believed to arise from specific anatomical sites from the acoustic nerve to the medial geniculate body (brainstem component).
2. A second section consisting of five waves (No,Po,Na,Pa & Pb) recorded at 8-50msec^{-1} and are the result of neural activity between the thalamus and the cortex (early cortical or middle latency component).
3. A third section recorded at 50-500msec$_{-1}$, represents wide-spread activation of the frontal cortex (late cortical component).

The effects of anaesthetic agents, or other variables, is described with reference to the latency and amplitude of the individual components. Latencies between individual peaks (IPL) allows assessment of the conduction times between the periphery and the brainstem (IPL I - III) and through the brainstem itself (IPL III - V) (154).

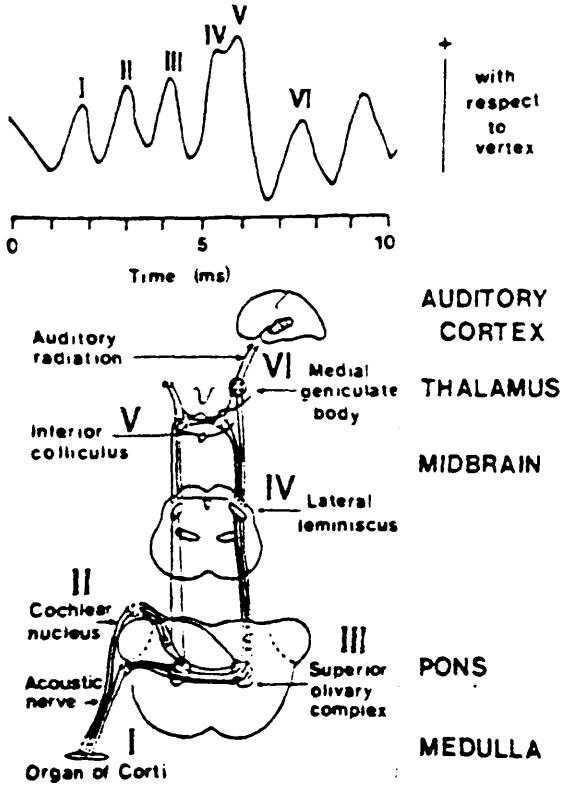


Figure 29. The auditory evoked potential.

The upper diagram illustrates the AEP waveform and the lower diagram the different auditory pathways involved (from ref. 156).

THE EFFECTS OF ANAESTHETIC AGENTS ON THE AEP.

In a series of small studies (156,159,160,161, 162,163) workers at Northwick Park found the volatile agents (isoflurane, enflurane and halothane) and the intravenous agents (althesin, etomidate and diprivan) cause dose related changes on the early cortical components of the AEP. These studies were were carried out pre-operatively. In general, the patients were induced with thiopentone, paralysed with pancuronium and ventilated to normocarbia with a mixture of nitrous oxide and oxygen.

The effects of the volatile and intravenous agents on the brain-stem components of the AEP are different.

VOLATILE AGENTS.

Although Duncan (164) and Rosenblum (165) found halothane and enflurane to have no effect on the brainstem components, other workers have described dose related changes with these (156,159,166) and other agents (163,167). The changes described by different groups are at variance. For example, Heneghan (163) found the latencies of waves III and V to increase with increasing isoflurane concentrations up to 2.85%, while Manninen (167) has described a plateau effect at isoflurane concentrations greater than 1.0%.

Comparing the effects of halothane, enflurane and isoflurane on the AEP, with respect to MAC, Heneghan (163) found quantitatively similar changes in the latencies of waves III and V and the amplitudes of the middle latency waves Pa and Nb. The latencies of waves Pa and Nb were found to differ.

In the studies done by the Northwick Park group (see above) a small number of patients (6 in total) were studied during the reversal of anaesthesia. With all agents recovery of waves Pa and Nb occured, although this was not always be associated with recovery of the brainstem components (156).

A recent cross-over comparison of nitrous oxide (60%) and isoflurane (0.6%) demonstrated a significantly lower amplitude in waves Pa and Nb in the isoflurane trials, despite similar MAC levels (168). Sebel investigated the effects of nitrous oxide on evoked potentials in 7 volunteers (169). The latencies of brainstem audio-evoked potentials were not effected, however the amplitudes of both the visual evoked potentials (VEP) and the somatosensory evoked potentials (SSEP) were significantly reduced.

The volatile agents all increase the latency and decrease the amplitude of the cortical components of the somato-sensory evoked potential (170,171). Peterson (171) found the changes to be most pronounced with enflurane and least with halothane. The effect of isoflurane was intermediate. In this study, discontinuation of nitrous oxide resulted in substantial recovery of latency and amplitude. Pathak (170) found isoflurane and enflurane to have a lesser effect on the cortical components of the SSEP than halothane. Both these studies suggest that, with respect to MAC, the three agents have different potency.

Dose related changes have been demonstrated on the cortical component of the VEP under halothane anaesthesia (172). A large inter-individual variation was present, the

latency at the highest halothane concentration (1.13%), in some subjects, was less than the awake control value of others.

INTRAVENOUS AGENTS.

Etomidate and Althesin (160,162) have no effect on the brain-stem components of the AEP, but significant, dose related effects on the middle latency components Pa and Nb. Diprivan (161) increases the latency and decreases the amplitude of the middle latency components of the AEP and increases the latency of waves III and V of the brainstem component. No increase in brainstem conduction time (IPL III-V) was apparent.

It has been suggested (162) that the lack of effect of etomidate and althesin on the brainstem components of the AEP, in conjunction with studies of regional glucose metabolism in the rat under althesin anaesthesia (173), indicate that important site of anaesthetic action is in the forebrain.

OTHER FACTORS.

Stockard has emphasised a standard protocol and demonstration of reproducibility are crucial prior to interpretation (154).

Carbon dioxide status is a variable often uncontrolled during anaesthesia. Thornton (156) found an increased end-tidal carbon dioxide tension to have no effect on the latency of wave III and only a small, but statistically significant effect, on wave V at a constant end-tidal concentrations of enflurane. Hypocapnia has been shown to significantly increase the latencies of the

brainstem components of the AEP (166). Other factors such as hypothermia may significantly increase latency (153).

THE EFFECTS OF SURGICAL STIMULATION.

In a small study of 11 patients, surgical stimulation increased the amplitudes of waves Nb and Pb/Pc in 8 and 9 cases respectfully (174). Only 3 of the patients demonstrated an increase in autonomic activity and there was no relationship between the increased activity and changes in the auditory evoked response.

SUMMARY.

Both the evoked and non-evoked, processed EEG respond to changes in anaesthetic dose and surgical stimulation. It is therefore likely that some measure of EEG activity does reflect the true anaesthetic state. However, several problems remain to be solved:

1 Artefact rejection systems must be perfected.

2 Although "arousal" responses have been demonstrated in response to surgical and other stimuli (vide supra), their relevance is unknown. Specifically, these responses have not been related to awareness (see chapter 4).

3 Many of the techniques described appear to be agent dependent or are affected by "non-anaesthetic" variables e.g. carbon dioxide status.

4 The usefulness of the various techniques proposed have not been fully assessed.

METHODS OF ASSESSING THE ANAESTHETIC STATE

IV. ELECTROMYOGRAPHY.

In 1961 Fink (175) described electromyography (EMG) as an "interesting adjunct to the close observation of surgical patients." The introduction of the ABM (vide supra), which has the facility to monitor spontaneous frontalis muscle activity (SEMG), and the suggestion that increasing SEMG activity is an early sign "of arousal and potential awareness" (176), has revived interest in this technique. This suggestion followed the observation of increasing SEMG activity during the recovery period. Since that time several observations and claims have been made about the usefulness of SEMG (177):

1 Induction of anaesthesia is associated with a fall in EMG activity.
2 EMG activity reflects the state of abdominal relaxation.
3 The frontalis muscle is resistant to neuro-muscular blocking agents.
4 Increased EMG activity indicates impending awareness.

Although EMG activity falls after induction the change cannot be quantified as the spontaneous activity in the awake subject often saturates the pre-amplifier (138). Although "adequate" anaesthesia was associated with decreased EMG activity in this study, no change in activity was found in 50 (of 58 cases studied) when "anaesthetic depth" was decreased. An abrupt increase in activity did occur during emergence but this was usually coincidental with movement.

Edmonds and his co-workers (178) found skin incision

to have no effect on SEMG activity, mean arterial pressure, heart rate or zero crossing frequency. However, auditory stimulation caused significant increases in SEMG activity although the cardiovascular parameters remained unchanged. However the mean change was only 1.9uV and changes of this magnitude are not obvious on the ABM display.

A significant correlation between log EMG activity and log pain scores was found in the post-operative period and opiates (butorphanol and morphine) were associated with significant reductions in activity. However the fall in activity was not always associated with adequate analgesia.

SUMMARY.

Although selected individual case reports suggest that the SEMG may be useful in the assessment of the anaesthetic state (138,177) and some stimuli (e.g. sound) are associated with an increase in activity, the large inter-individual variability in the mean level of activity during surgery means that the absolute value of activity cannot differentiate between the awake and anaesthetised states. Further, the SEMG may be of limited value if opiates are used as part of the anaesthetic technique and it appears insensitive when compared to standard clinical methods (138,178). And, although the frontalis muscle is resistant to neuro-muscular blocking agents, their use makes interpretation of the SEMG difficult (138).

CHAPTER 4

STATES OF AWARENESS.

Awareness is "The ability of a patient to recall, with or without prompting, any event occurring during anaesthesia" (179). This topic is well reviewed and the reader is referred to these articles (180,181). However, it is apparent that different "states" of awareness may occur.

UNCONSCIOUS PERCEPTION.

Several workers have demonstrated that "unconscious" perception of auditory material may occur during anaesthesia e.g. by post-operative hypnosis (182); by demonstrating an improved post-operative course after positive intra-operative suggestion (183); or by demonstrating a motor response postoperativly following an intra-operative suggestion (i.e. "When I come to talk with you, you will pull on your ear." 184). This work has been criticised (185,186) and some studies have failed to demonstrate unconscious perception (187).

AMNESIC WAKEFULNESS.

If a tourniquet is applied to an upper limb, prior to the administration of muscle relaxants, the anaesthetist can assess motor activity in the isolated arm, despite intense neuro-muscular blockade elsewhere. Motor function is not impaired for some twenty minutes (188). Tunstall (188) introduced this isolated fore-arm technique (IFT) and described those patients who moved their hands in response to command as wakeful. Twelve patients undergoing Caesarean section were studied. Of these 9 showed considerable movement and 4 moved their hands in direct

response to instruction. No patient recalled any intra-operative event. In a second study (189) of 32 patients undergoing Caesarean section; 23 were wakeful in the first 3 minutes following induction but prior to surgery, 31 moved their arms spontaneously in response to skin incision and 2 responded to command at this time.

Russell (190) randomly assigned 55 patients, scheduled for major gynaecological surgery, to receive either a nitrous oxide anaesthetic supplemented with fentanyl and increments of thiopentone or an etomidate based anaesthetic supplemented with fentanyl. The incidence of wakefulness was higher in the nitrous oxide group (6.7% vs. 44%). One patient in this group was aware. The incidence of wakefulness and "other signs of light anaesthesia" (e.g. sweating) was so high in the nitrous oxide group that this study was abandoned at the half-way stage. The results of the nitrous oxide group were reported in a letter (191) and "..all patients who had previous experience of general anaesthesia felt that in terms of post-operative well being this was their anaesthetic of choice."

Beckendridge and Aitkenhead (192) used the IFT in 24 patients undergoing elective intra-abdominal surgery. Surgery proved impossible while the tourniquet was inflated because of "purposeful movement of the arm". However, no patient responded to verbal instruction, recalled intra-operative events or remembered dreaming. The authors concluded that clinical signs are a more sensitive method of assessing anaesthetic adequacy.

CONCLUSIONS.

Absence of a motor response to surgical stimulation, in the absence of neuromuscular blocking drugs, does not preclude unconscious perception (182) or factual recall of intra-operative events (193); although the latter is rare. On the other hand movement (even if purposeful or in response to command) during surgery is rarely associated with awareness. Although the IFT might be used to confirm the wakeful state during anaesthesia and surgery; and therefore to determine if other techniques (e.g. the EEG) can differentiate this state from the non-wakeful state, the relationship between this state and the "aware" state is unknown. Further, clinical signs may be a better method of assessing the adequacy of anaesthesia in lightly anaesthetised patients (vide supra).

The relationships between the arousal responses described during EEG and EMG monitoring; the wakeful state; unconscious perception; and awareness are unknown. The only proven method of assessing awareness is by post-operative interview, and anaesthesia is therefore a retrospective diagnosis.

CHAPTER 5

OBJECTIVES OF THE STUDY.

The techniques proposed as monitors of the anaesthetic state have been reviewed. It is apparent, that without the description of an individually valid anaesthetic state, these techniques cannot be fully assessed. Clinical signs, despite some obvious inadequacies, are currently the only practical, universally accepted method of assessing anaesthetic adequacy. As such they form the basis for the administration of thousands of anaesthetics each day and there is therefore a large weight of evidence which suggests these signs are a valid measure of the true anaesthetic state in the vast majority of patients.

However, their interpretation is both subjective and variable. Until a reproducible, individualised description of the anaesthetic state is available the usefulness of clinical signs cannot be fully assessed nor can they be used as a standard with which other techniques may be compared.

Our overall objective was to develop a computer control system, operating from rules based on clinical signs, to produce an individually tailored anaesthetic state. In the future, this could then lead to the objective assessment of other techniques for assessing depth of anaesthesia such as the EEG or frontalis muscle activity.

The aim of the work presented in this thesis was to:

1 Develop a computer driven control system to maintain a patient's SAP at a predetermined target value by altering the inspired concentration of volatile

anaesthetic.

2 To determine if we achieved (1) would we produce a state recognisable as general anaesthesia.

The relevant aspects of control theory and the equipement used in this study are discussed in the following two chapters.

CHAPTER 6

ASPECTS OF CONTROL THEORY.

INTRODUCTION.

Control systems are designed to make the measured output from the controlled process follow a reference (or target) input (figure 30). There are two basic types of control system: open-loop control systems (OLCS) and closed-loop control system (CLCS). The terminology used in this thesis is based on that suggested by Doeblin (194).

In an OLCS the strategy is to provide a dosage regimen based on previously computed data and no provision is made to link the controlled variable to the manipulated variable (figure 31). A washing machine is an OLCS. The user selects the appropriate program depending on the type of washing (cotton, linen, coloured etc.); the control director (the program) then instructs the control effector (the washing machine) to carry out the necessary steps (wash, spin etc.). No provision is made to sample the controlled variable (i.e. the cleanliness of the wash) and to alter the program if the wash is not proceeding satisfactorily.

A CLCS incorporates a feedback path and is designed to maintain the controlled variable close to a predetermined target value in spite of variations in the disturbance input. The temperature control system of a domestic oven forms a simple CLCS (figure 32). In this system the heating element, oven space and its contents are the controlled process; the oven temperature is the controlled variable; the oven thermometer is the feedback transducer; the setting of the temperature dial is the target value; the thermostat is the control director; and

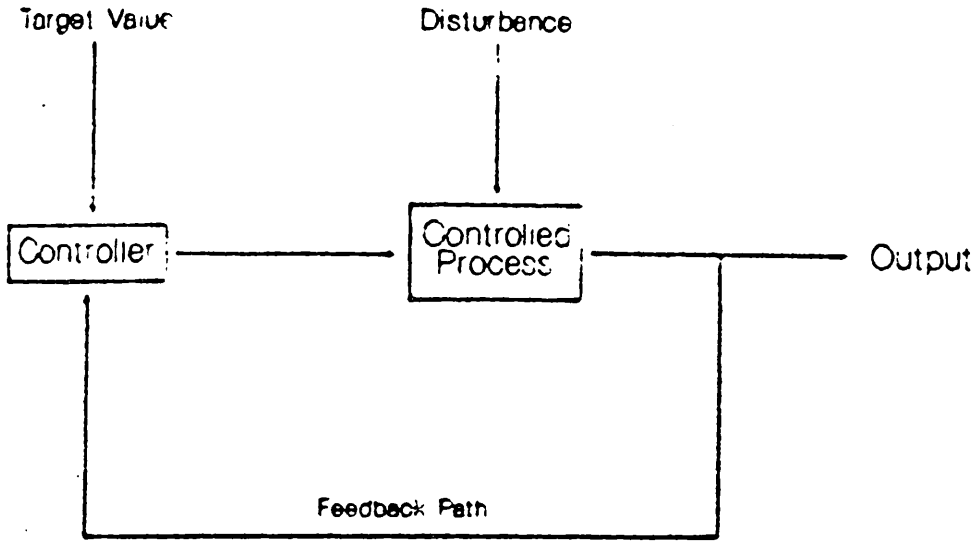


Figure 30. The configuration of a basic control system.

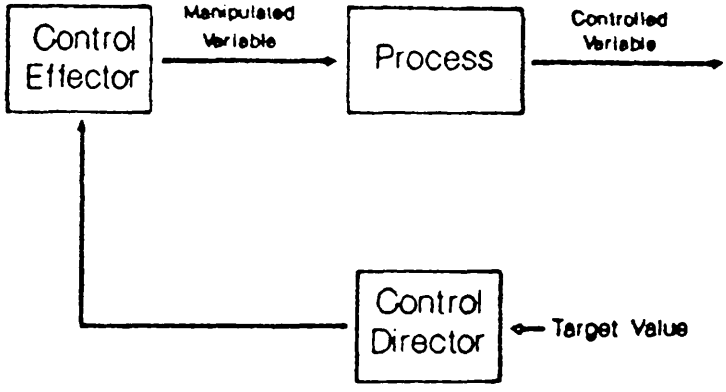


Figure 31 An open loop control system

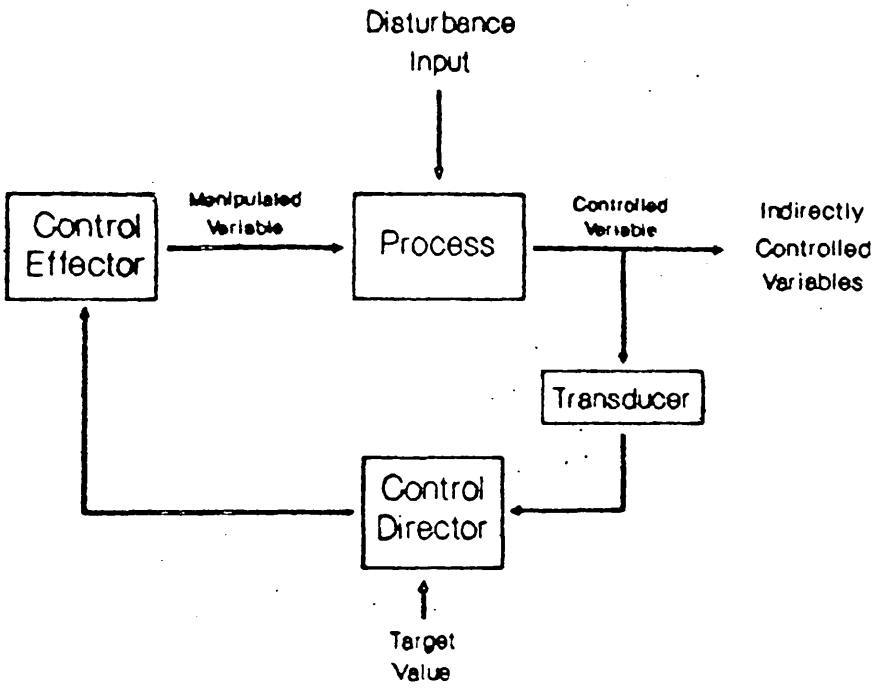


Figure 32 A closed loop control system

the energy supply is the manipulated variable. Possible disturbance inputs in this system would be opening the oven door, a change in ambient temperature etc. In a well designed system the controller will quickly re-establish the dial setting following a disturbance input. A change in dial setting is a change in the target value and not a change in the process.

Most therapeutic situations in medicine use feedback information to optimise drug dosage (e.g. a patients response to surgery is used to assess his anaesthetic requirement). This type of system will be considered further.

THE COMPONENTS OF A BIOLOGICAL CONTROL SYSTEM.

Five "components" may be identified in a biological feedback system (figure 33, ref. 195)

1. The process:

   The patient, as the central part of the control system, is the process and may be described by a model which represents the relationship between drug dose and response. Such a model is complex as it will represent the pharmacodynamic and pharmacokinetic pathways and effects within the individual.

2. The input to the controlled process:

   The dosage is the manipulated input to the process and is delivered continuously or intermittently.

3. The process response:

   The response of the process to the manipulated and disturbance inputs comprises the controlled and indirectly controlled variables. The controlled

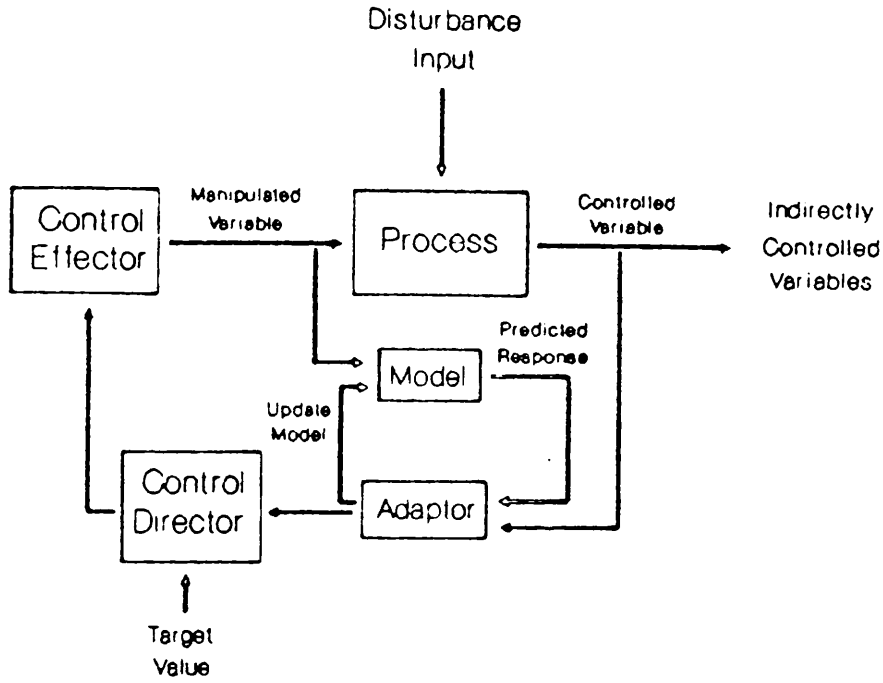


Figure 33 The components of a control system.

variable represents that part of the process response on which therapeutic decisions are made. Ideally the controlled variable should be the "true" therapeutic variable (e.g. depth of anaesthesia) but this is rarely possible and "intermediate" variables (e.g. blood pressure and heart rate) are often substituted. To be useful, an intermediate variable should have a high predictive value for the true variable, be accessible for repeated measurement and allow the investigation and assessment of the relationship between dose and response. For efficient control the time for equilibrium between dose and response should be short.

4. The adaptor:

Some systems incorporate a formal mathematical model which is presumed to represent the true process model. An adaptive algorithm updates the parameters which describe this model according to the recent behaviour of the system. Not all CLCS have an adaptive element.

5. The controller:

The controller comprises of 3 parts; a transducer, the control director and the control effector. The control director calculates the required dose by comparing data received from the transducer to the target value (reference input) and carries out any change through the control effector.

If the system is adaptive the controller also carries out the necessary steps to update the model's parameters.

A CLASSIFICATION OF CLOSED LOOP CONTROL SYSTEMS.

CLCS can be further classified into tight-loop systems which exclude the physician's interaction from the feedback loop and loose loop systems which advise the physician who makes the final decision about the dose requirement (195). These can be sub-divided into adaptive and non-adaptive types.

In non-adaptive control systems the assumption is made that the process has constant parameters which can be determined from test runs using empirical rules e.g. Zeigler-Nicholas rules (196). Efficient tuning of these systems requires knowledge of the relationship between the controlled variable and the manipulated variable so that the "average" features of the dynamic process can be determined and an appropriate controller designed.

For a control system to work well the sampling frequency must be correct, the appropriate control strategy applied and the characteristics of an individual patient not deviate significantly from those individuals from which the strategy was devised.

Adaptive control methods recognise that some features of the process can change and allowances are made for these. These features relate to inter-individual variation in drug response and intra-individual variation in drug requirement. This type of system often incorporates a formal model of the process and although it should theoretically cope more efficiently with these problems they rely on an accurate description of the process model and are therefore difficult to design. An adaptive system designed around a PID controller (vide infra) might update

the gain values during a control run.

A non-adaptive system was used in this study and these will be considered further.

THE PRINCIPLES OF NON-ADAPTIVE SYSTEMS.

The strategy in a non-adaptive CLCS is to minimise the difference between the target value and the measured output (the error signal), ideally keeping it at zero. Because the feedback signal is subtracted from the target value this type of system is often called a negative feedback system.

The response to an error signal is dependent on the control algorithm and the gain of each component in the algorithm. Gain is the magnitude of response of the controller to the error signal.

TECHNIQUES OF CONTROL AND TYPES OF ALGORITHM.

"BANG-BANG" SYSTEMS.

An on-off (bang-bang) system is the simplest type of control system. In this system the input to the process is either on or off e.g. the thermostat in the oven. Although these systems are crude and oscillation is inevitable they are simple to design, rugged and may provide adequate control in some circumstances.

P-I-D CONTROL SYSTEMS.

The most commonly used control systems incorporate one (or more) of three principle control effects (197). These are generally described as:

1. Proportional Control
2. Integral Effect
3. Derivative Effect

PROPORTIONAL CONTROL.

In this type of system the output of the controller varies linearly with the error. The response of a proportional system to a change in the error signal is dependent on its gain. If the gain is high then any tendency for the error signal to become significant will result in a rapid response and the error is reduced. With a high gain any offset will be small (the offset is the difference between the value of the controlled variable and the target value in the steady state). However, if the gain is too high the system will tend to overcorrect any error resulting in a worse error in the opposite direction, further over correction and so on i.e. the system will oscillate. Although oscillation is less likely if the gain is low the off-set tends to increase and the response to a disturbance may become inadequate.

The correct gain for a system is therefore a compromise between rapid response, off-set and the risk of oscillation.

If unacceptable oscillatory behaviour is to be avoided, the off-set reduced and an adequate response attained a simple proportional system is often found to be inadequate.

INTEGRAL EFFECT.

The integral effect is achieved by summing all the errors and applying a suitable gain. It tends to reduce the off-set towards zero and improve the steady-state accuracy of a proportional system but can cause oscillation. This detrimental effect increases as the gain

is itself increased.

DERIVATIVE FUNCTION.

This function allows the controller to respond to the rate of change in the error signal. Use of a derivative tends to stabilise a potentially unstable system and decrease the response time.

COMBINATIONS OF EFFECT.

The output from a combined P-I-D system can be calculated from a simple equation:

$$\text{Dose} = (K_p * e) + (K_i * \Sigma e) + [K_d * (e - e')]$$

where K_p, K_i and K_d are the gains for the proportional, integral and derivative components; and e, Σe, and $e - e'$ represent the error, the sum of the errors and the current error minus the previous error.

P, PI, PD and PID control systems are described (197). Figure 34 is a block diagram of the control system used in this study and it is discussed in detail later.

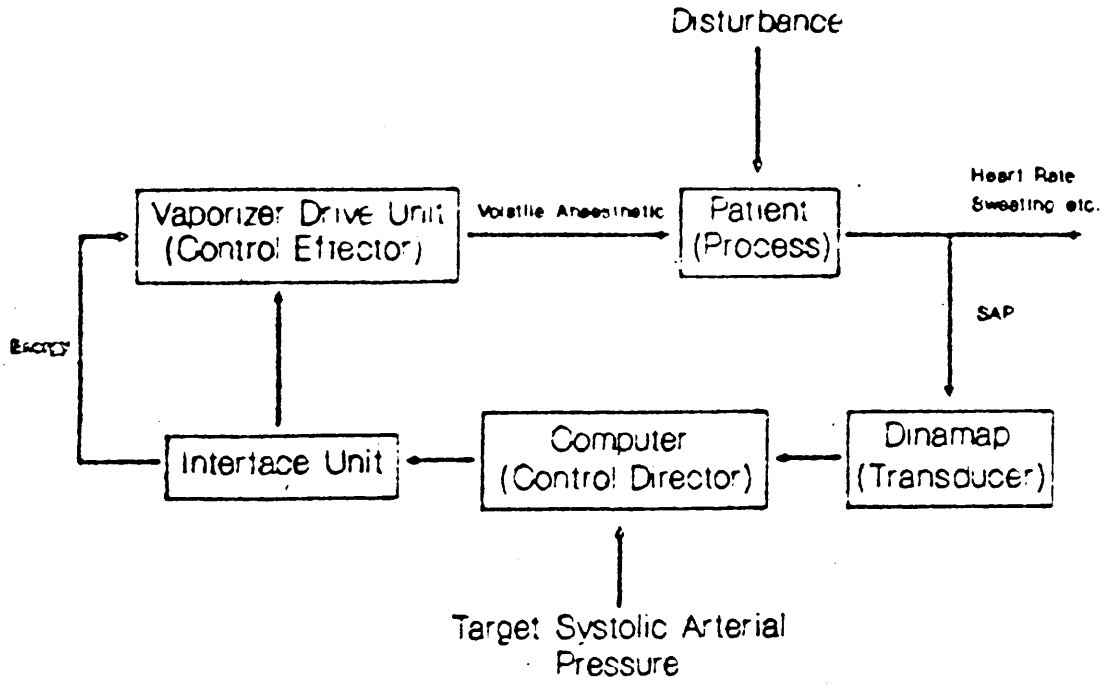


Figure 34 A block diagram of the control system used in this study.

CHAPTER 7

EQUIPMENT USED IN THE STUDY.

1. DINAMAP BLOOD PRESSURE MONITOR, MODEL 1846 (CRITIKON INC., TAMAPA, FLORIDA).

The Dinamap range of blood pressure monitors was introduced in the mid-1970s and is an acronym for "Device for Indirect Non-invasive Mean Arterial Pressure". The model used in this study (figure 35) automatically and non-invasively measures systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP) and pulse rate (PR).

GENERAL DESCRIPTION.

The machine may operate in one of three modes; manual mode (i.e. the operator initiates a single determination by pressing the start button), auto mode (i.e. the user determines a cycle time of 1-90 minutes following which the machine will automatically perform further measurements) and stat mode (i.e. the machine will do sequential determinations for a 5 minute period).

FUNCTIONAL DESCRIPTION

The operating cycle consists of 4 parts, the inflation time, the deflation time, the evaluation time and the wait time (figure 36). At the start of a determination sequence the cuff is inflated to a pressure 30 mmHg above the previous systolic reading or, if no previous systolic pressure is stored, to a pressure of 178 mmHg. If this pressure is lower than the patient's systolic pressure the Dinamap automatically re-inflates the cuff to a higher value, to a maximum of 250mmHg.

[vaporizer drive unit]

[monitor]

[keyboard]

[printer]

[computer]

[interface unit]

[dinamap]

Figure 35 The equipment for use in theatre.

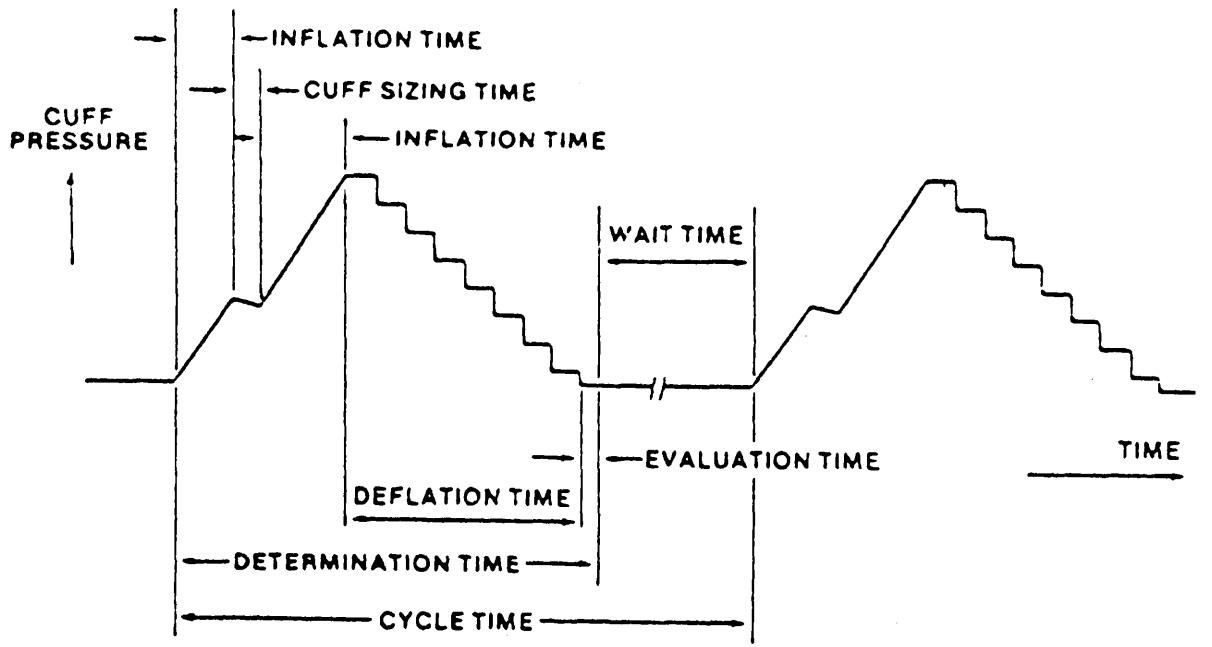


Figure 36 The operational cycle of the Dinamap (from ref. 198)

Inflation is followed by a stepped deflation sequence, with each step occurring when 2 pulsations of relatively equal amplitude are encountered. This process rejects artefact due to patient movement and greatly enhances the accuracy of the machine.

A microprocessor, linked to a sensitive pressure transducer, calculates SAP, MAP, DAP and PR during the deflation sequence. Following determination the cuff is deflated to zero pressure. A residual pressure of greater than 20mmHg during the wait period causes the machine to alarm. The performance specifications of this machine are listed in table 7 and figure 37 illustrates the determination sequence.

In some circumstances e.g. shock the systolic and diastolic pressures may not be accurately determined and in these cases only the MAP is displayed.

THE HOST-SERIAL COMMUNICATIONS PORT.

This is an RS-232 compatible serial interface and is set up to transmit and receive ASCII characters asynchronously in an 8 bit format at a fixed baud rate of 600. This facility allows the Dinamap's memory to be polled. The serial output to the host is shared with serial output to the printer and a delay (usually 0.5 - 1 sec.) occurs before transmission following a request. The Dinamap automatically goes into the receive mode when switched on and will not transmit until a valid request is received from the host. A valid request for transmission is a 4 character string of the format "BBA-carriage return." The response is a 30 character string. The port connections and content of the 30 character string are

Table 7. The performance specifications of the Dinamap (model 1846).

Specification	Compliance
Cuff pressure range	0 - 250 mmHg
Initial cuff inflation	178 +/- 15 mmHg
SAP determination	30 - 245 mmHg
MAP determination	20 - 225 mmHg
DAP determination	10 - 210 mmHg
Pulse Rate	40 - 200 bpm (+/- 3.5%)
Determination time	20 - 45 sec., max 120sec.*

* the determination time is dependent on the pulse rate of the patient (adapted from ref. 198).

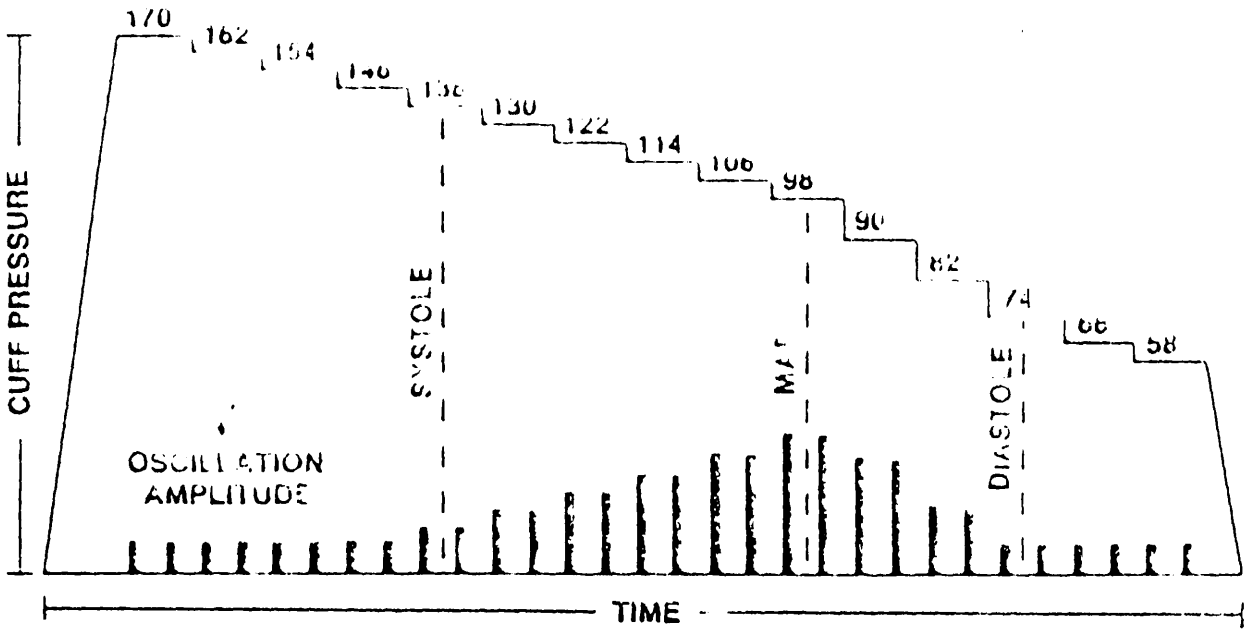


Figure 37 The determination sequence of the Dinamap (from ref. 198).

detailed in Appendix I.

ACCURACY OF THE THE DINAMAP.

With any device utilising a blood pressure cuff it is important to use the correct size of cuff (relative to the limb circumference) and to apply the cuff correctly. We used a "normal" size cuff and all patients with an arm circumference greater than that for which it is designed (43 cm) were excluded from the study.

In a study (199) comparing the 845 model to intra-arterial pressure the Dinamap was shown to produce reliable trend information during anaesthesia. These workers calculated a correlation coefficient of 0.96% and 95% confidence limits of +/- 16.4 mmHg for SAP. The authors suggest that, as the confidence limits for the mean lie closer to the regression line precipitous action should not be taken on unexpected individual readings unless it is supported by other clinical observations. The machine failed to follow large, rapid changes in blood pressure due to the determination time of 20 - 45 sec. and tended to under-read at high pressures and over-read at low pressures. The Dinamap may not function on patients with dysrhythmia.

Since this study both the pneumatic and microprocessor components of the Dinamap have been improved. A study by Critikon (200), comparing direct central aortic pressure measured during cardiac catheterization to that measured by the Dinamap described a mean difference (from 473 recordings) of 2.80 mmHg and a standard deviation of 5.22 mmHg for SAP. The results from

this study are listed in table 8.

SAFETY.

There is a risk of ulnar palsy when the cuff is incorrectly positioned (201) and frequent readings over prolonged periods may increase this. Both an electronic malfunction and contamination of the air release valve have been associated with factitiously low blood pressures (202). In each case the heart rate, as recorded by the Dinamap was significantly lower than that derived from the ECG.

We followed the manufacturers directions and took added precautions in light of the above.

2. THE RML COMPUTER.

The RML 380Z-D computer (figure 35) used in this study is a robust, stand-alone, 32k, 8 bit machine which uses the CP/M operating system. All programs used in this study were written in BASIC (RML version 6.0G). The input-output (I/O) ports used in the control system and the software are described in Appendix I. The integration of the various components in the control system is discussed below.

3. THE VAPORIZER CONTROLLER AND VAPORIZER DRIVER UNITS.

The vaporizer controller was developed and built at the Department of Clinical Physics and Bio-Engineering in Glasgow. It comprises a drive unit and an interface unit (203).

THE DRIVE UNIT.

The drive unit (figures 35 and 38) incorporates a

Table 8. The accuracy of the Dinamap 1846 compared to central aortic pressure.

	SAP	DAP	MAP	HR
Mean difference	2.80	2.91	2.13	-1.17
SD.	5.22	4.79	5.15	2.68
No. of records	473	473	461	486

These data were obtained from adult male patients undergoing cardiac catheterization (from ref. 200).

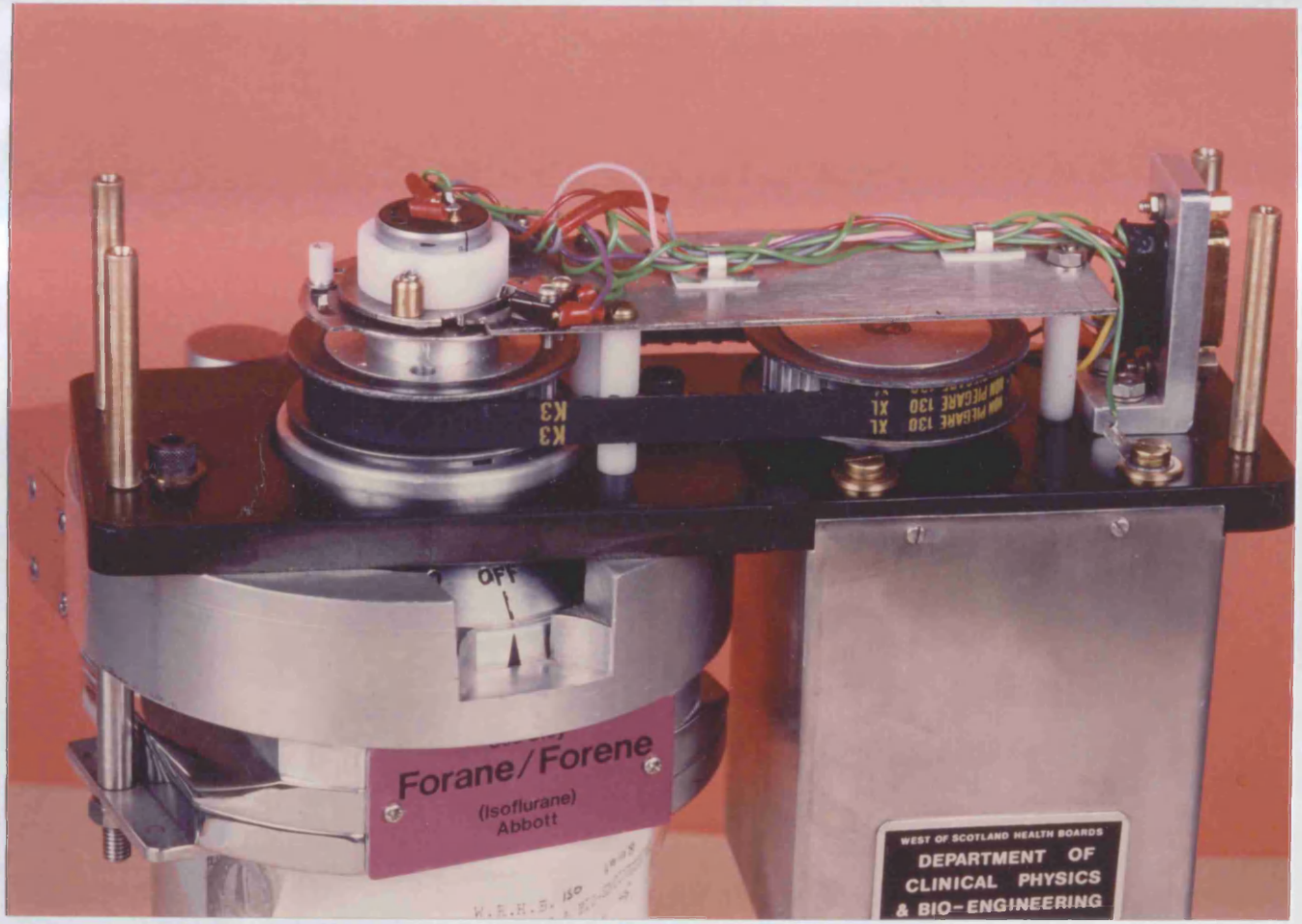


Figure 38 The vaporizer drive unit. (see figure 38B overleaf for description).

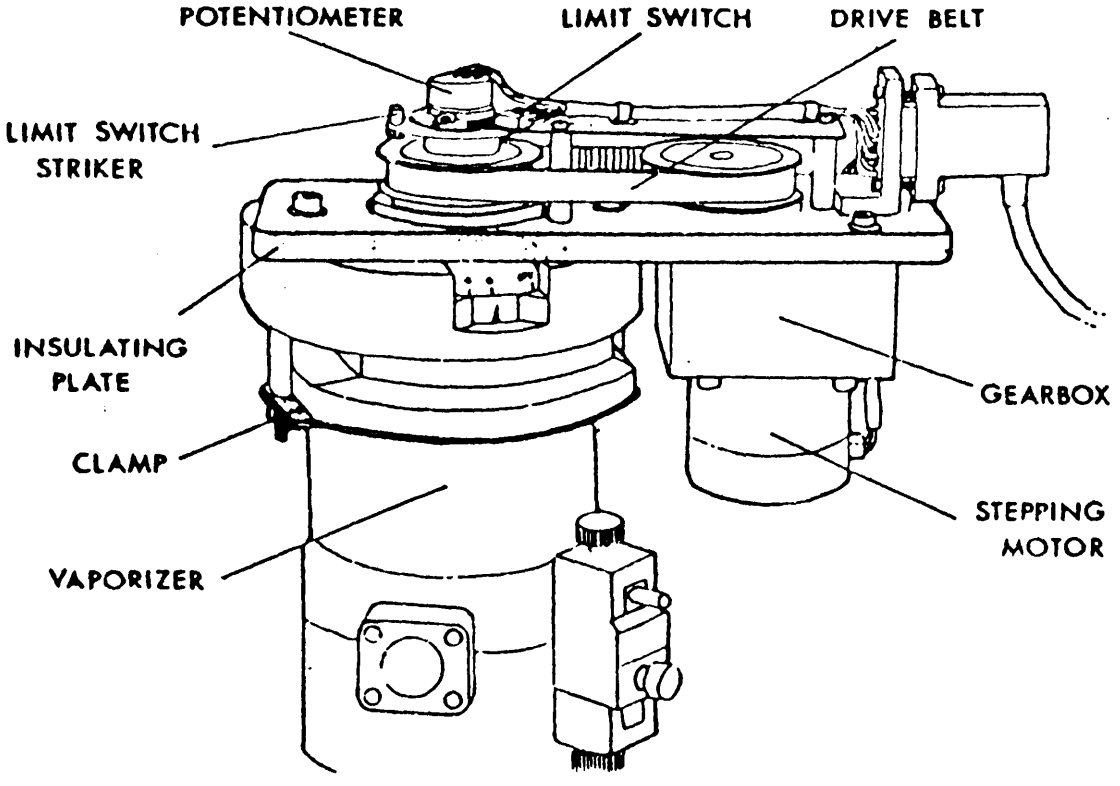


Figure 38B A line drawing of the vaporizer drive unit (from ref. 203).

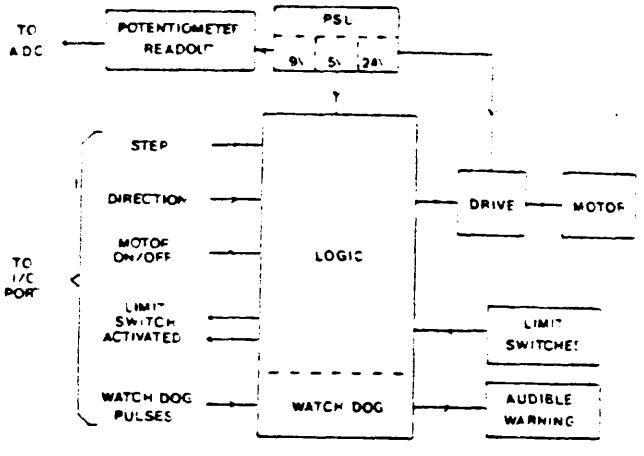
stepping motor, gear box, toothed belt transmission, upper and lower limit switches, and a "position" checking potentiometer. The gear box provides a 50 : 1 reduction and gives increased resolution for each step of the motor. Approximately 3200 pulses drive the vaporizer from the 'OFF' position to the 5% setting. Limit switches at these settings allow initialisation and prevent damage to the drive unit. Initialisation involves driving the unit until the lower limit switch is activated i.e. the vaporizer is driven to a known setting, the 'OFF' position. The number of pulses required to drive the vaporizer to any marked setting from the 'OFF' position is determined in the laboratory and the current 'position' of the vaporizer (relative to the 'OFF' position) is then determined by keeping a count of the number of pulses used, and the direction of travel taken each time the vaporizer is driven to a new setting. A small backlash of approximately 50 pulses occurs with each change of direction and this is allowed for in the computer program.

The output voltage of a potentiometer coupled to the rotatory drive of the vaporizer is used to check the vaporizer setting via the analogue to digital converter in the computer. The output voltage changes by some 3 volts over the full vaporizer range and the output at each marked vaporizer setting is determined in the laboratory.

THE INTERFACE UNIT.

Figure 39 is a block diagram of this unit (see also figure 35). The unit, under instruction from the computer drives the vaporizer via the drive unit to the correct

Figure 39.



A block diagram of the interface unit for the vaporizer controller (from ref. 203).

setting. Activation of a limit switch disables the stepping motor, permitting movement only in the opposite direction. When this occurs a signal is sent to the computer indicating that the state of the switch has changed. The interface unit can also be instructed to switch off the motor to prevent power dissipation.

SAFETY FEATURES.

The position of the vaporizer is determined by keeping account of the number and direction of driving pulses from the 'OFF' position (vide supra). Each new vaporizer setting is compared to the expected potentiometric output voltage at that setting and any significant discrepancy from the expected value results in a warning being given to the operator by the computer. The program then re-initialises the vaporizer unit and drives the vaporizer back to the desired setting. The original dial of the vaporizer is visible and can be used as a further check.

The watch-dog is a retriggerable monostable in the interface and is connected to a visual alarm and an audible warning. If a signal is not received from the computer by the monostable in any 9 second period an alarm is sounded. The audible warning may be disabled.

The vaporizer and drive unit fit on a standard Ohmeda Selectatec back bar and can be quickly removed and replaced with a standard vaporizer if necessary.

Electrically the controller and drive unit meet all the requirements of class I type B equipment. The unit is not designed for use with inflammable agents.

PERFORMANCE.

An attached vaporizer can be driven from the 0 to 5% positions in 15 sec., when driven by a BASIC program.

As the vaporizer scale is non-linear and the resolution of the system is one step of the stepping motor the accuracy of the unit is dependent on the setting. At 0% one step corresponds to 0.0006% and at 5% to 0.003%. When the backlash is considered the accuracy in terms of concentration is better than +/-0.01% at 0% and +/-0.05% at 5%.

Prolonged testing before its use in theatre and during the study have demonstrated no shift in the settings.

CHANGING THE VAPORIZER.

Although the unit is designed to drive any Cyprane Tec III vaporizer, the attachment to the drive unit is not straight-forward and was done by the Engineering Department. Following this, the unit was recalibrated for the new vaporizer i.e. the number of steps to and potentiometric output at each marked setting, as well as the backlash correction factor, determined. These changes were incorporated in the control program and the system tested prior to its use in theatre. The whole procedure takes 2 - 3 days.

4. PUPILLOMETER.

A purpose built pupillometer (84) was used to measure pupil diameter. This device (figure 40) consists of a welder's goggle through which passes a fixed length focal microscope. A graticule scale, graduated to 0.1 mm, comes

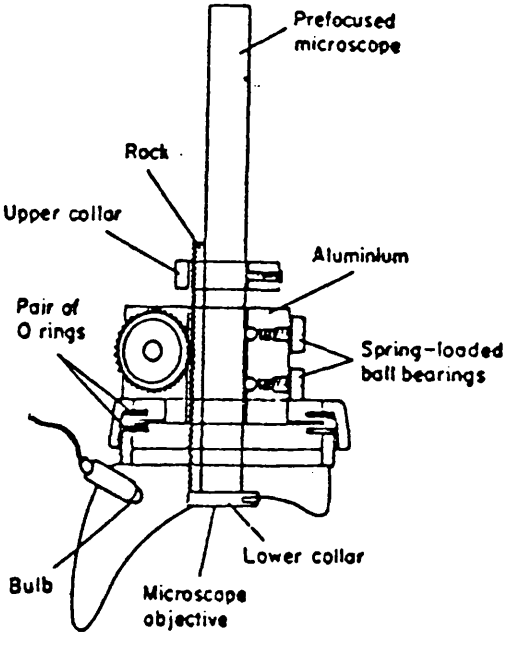


Figure 40.

A drawing of the pupillometer (from ref. 84)

A drawing of the pupillometer showing its construction. The pinion engaging the rack sllows controlled verticle movement of the microscope. The 0 rings permit lateral movement. The spring loaded ball bearings keep the rack and pinion engaged. The welder's goggle fits closely the patient's eye and the pupil is illuminted from the side by laryngoscope bulbs (only one shown).

into focus when the pupil itself is in focus (figure 41). The aluminium block which supports the microscope allows both lateral and vertical movement of the microscope. Vertical travel is limited by a stop to prevent damage to the cornea.

Oblique lighting is supplied by 2 laryngoscope bulbs connected to a constant voltage battery box. A third bulb can be flashed directly at the pupil to assess the light response.

A correlation coefficient of 0.985 has been described for sequential measurements made by two observers (84). The device is therefore both a safe and reliable method of assessing pupillary changes during anaesthesia.

5. THE NEUROTRAC ELECTROENCEPHALOGRAPHIC ANALYSER (INTERSPEC, CONSHOHOCKEN, USA.).

During the latter part of the study this monitor became available on loan and was used on a small number of cases.

GENERAL DESCRIPTION.

The Neurotrac is a two channel EEG monitor designed to collect analyse and display the EEG signal (figure 42). A facility for measuring evoked potentials is also available. The system consists of a main unit which comprises a control panel and display unit, and an optional printer unit. An RS232 interface is available to transfer either the raw EEG or spectral data to an external computer. Unfortunately we did not have the facilities to utilise this option.

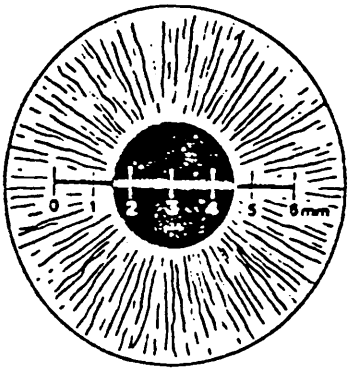


Figure 41.

A view of the pupil seen when making a measurement with the pupilometer (from ref. 84).

Figure 42 The Neurotrac monitor.

OPERATIONAL CHARACTERISTICS.

The operational cycle has 3 stages:

a) Signal collection, amplification and conversion.

b) Data analysis

c) Formatting and Display

A) SIGNAL COLLECTION, AMPLIFICATION AND CONVERSION.

i) The Electrodes.

Paediatric ECG electrodes are suitable; the positive electrodes are attached close to the hair-line on each side of the forehead, the negative electrodes behind the ear on the mastoid process and the reference electrode to the middle of the forehead.

Electrode impedance is checked during the "start-up" procedure and if the impedance of any active lead is over 10 Kohms use of the channel involved is prohibited. During operation the impedance is checked every 2 minutes, if an impedance test failure occurs the monitor "beeps" and the letter "I" is printed on the screen.

ii) Amplification.

The gain of the internal amplifiers is automatically set during the start-up. During operation the gain can be reset if required. The amplified signal is filtered with a pass band of 4 - 30Hz. The signals from the two channels are multiplexed, passed to an analogue to digital converter and sampled at 128 Hz per channel.

iii) Artefact Detection.

A 3 part algorithm is used to detect artefact. If the incoming signal to the ADC, the power contribution of the 30.5 - 63.5 Hz band (muscle activity) or the 49.5 -50.5 Hz

band (mains activity) exceed their pre-set limits then an artefact is noted on the screen. The raw EEG signal can be displayed on the monitor and visually checked.

B) DATA ANALYSIS.

A Fast Fourier Transformation algorithm is used to calculate the spectral values of each 2 second EEG epoch (256 data points) for each channel. Power bands are calculated for each 0.5 frequency bin over the range 0 - 63.5 Hz. Only the lower half of these values (0 - 30 Hz) is subsequently displayed. The power in each band is derived mathematically from the peak voltage in the raw EEG signal at that frequency.

C) DATA FORMATTING AND DISPLAY.

One of four formats may be used; the raw EEG, the compressed spectral array (CSA), the spectral histogram and the power band display.

1 The raw EEG is displayed in two second strips on the screen. A hard copy may be made of any strip.

2 A general description of the CSA has already been given (figure 17). The Neurotrac allows the use of two scales (1 to 15 and 1 to 30 Hz). The spectral edge frequency may be superimposed and a density modulated display is available.

3 The Spectral Histogram displays each 0.5 Hz power value over the range 1 - 30 Hz, a new histogram is placed on the screen at the selected up-date interval.

4 The Power Band Display displays four user defined power bands as a bar graph, again these are replaced

on screen at the selected up-date time. The default settings select the classical alpha, beta, delta and theta bands.

The update time may be set from 2 seconds to 4 minutes. Exponential weighting is used to calculate the values fro up-date rates of more than 2 seconds.

6) OTHER EQUIPMENT.

A) VENTILATOR AND ACCESSORIES.

All the patients studied were ventilated with a Bain circuit, driven by an OAV ventilator.

With this system, providing the minute volume of ventilation is greater than the fresh gas flow (FGF), the patients arterial $PaCO_2$ will depend on the FGF and is "highly predictable" (204). Henville and Adams, using a FGF of 100 mls/kg, a respiratory rate of 12 breaths per minute and a tidal volume of 10 mls/kg, describe a mean $PaCO_2$ of 34.3 mmHg and standard deviation of 4.5 mmHg (204).

B) OTHER EQUIPMENT.

All patients were attached to an ECG monitor (Datascope 2000) during surgery and a Normac, anaesthetic agent monitor (Datex Instrumentarium Corporation, Helsinki) was used to check the function of the vaporizer. A capnograph was not available.

THE SOFTWARE.

The software (computer program) is central to any

computer driven control system. The program used was designed to interpret the input from the Dinamap, determine the required output following each valid input and make any necessary change through the vaporizer control unit. The program relies on the Dinamap to cycle automatically at 1 minute intervals. A hard copy of cardiovascular and other data is made and stored to disk at the end of the control run. A full description of the program is given in Appendix I. Figure 34 is a flow diagram showing how the various components of the control system are integrated. Figure 43 shows the equipement in use in theatre.

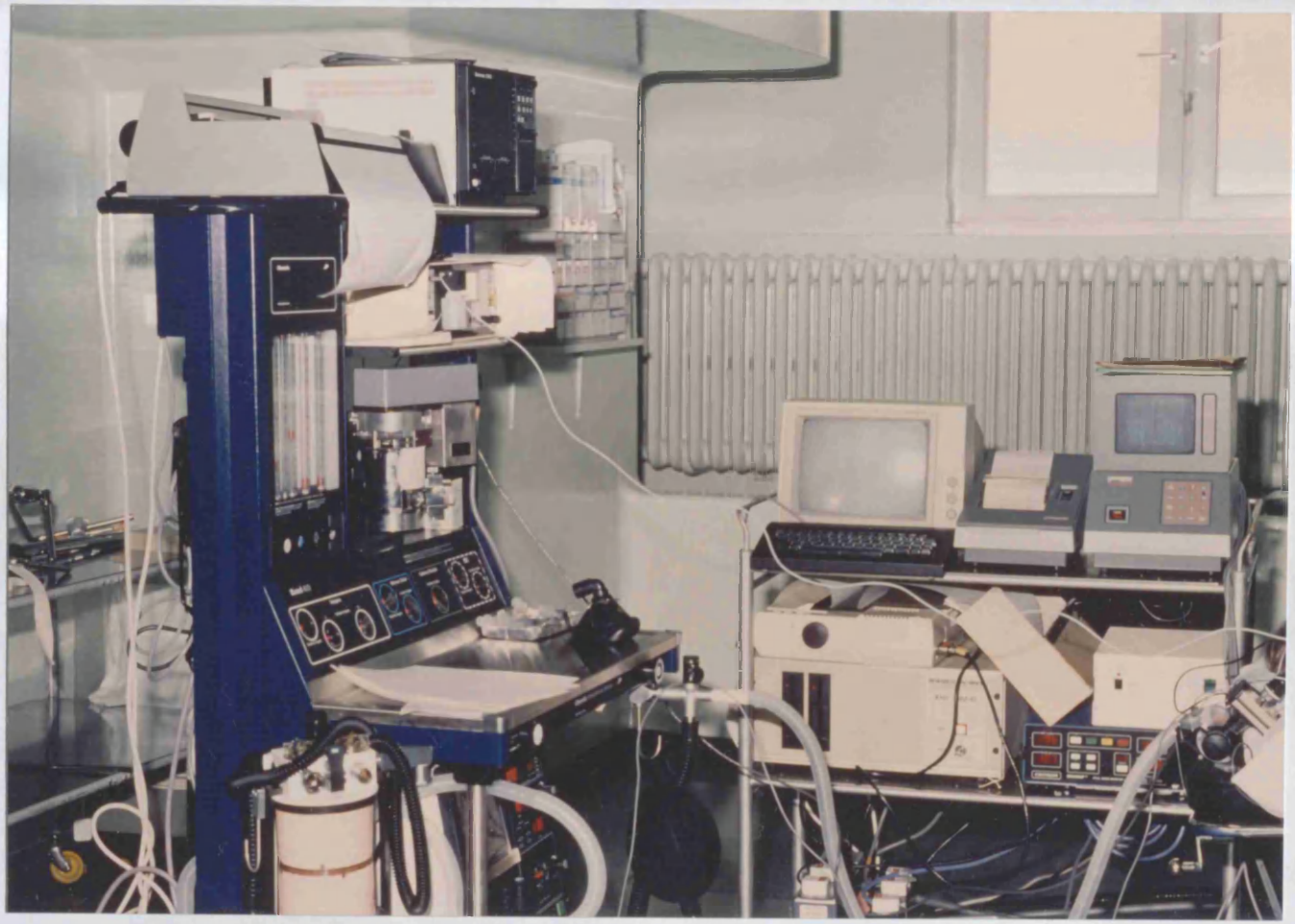


Figure 43 The equipment being used in theatre.

CHAPTER 8

DEVELOPMENT OF THE CONTROL SYSTEM.

GENERAL REMARKS.

A standard anaesthetic technique was used:

1 All the patients studied were ASA grade I - II and any patient with a disease state or on medication known to effect the cardiovascular or central nervous system was excluded. The only exception was patients prescribed "sleeping" tablets.

2 Anaesthesia was induced in the anaesthetic room and the controller not activated until the patient had been transferred to theatre.

3 All patients were paralysed and received a 'basal' anaesthetic of nitrous oxide (70%) in oxygen. Supplementary enflurane requirement was determined, and automatically delivered, by the controller.

4 All patient's received 0.5 - 1 litre of crystalloid per hour to cover insensible fluid losses. Blood loss was replaced as clinically indicated.

No attempt was made to standardise other aspects of the anaesthetic (induction agent, premedicant etc.), except that opiates were not given until the controller was discontinued.

DETERMINING THE TSAP.

Defining a patients 'normal' blood pressure is difficult. However, if arterial pressure is to be used as the controlled variable an individually valid target value must be available.

Using age-sex related SAP data in the Geigy tables (205) regression lines of SAP against age were calculated

for both sexes and used to predicted SAP for individual patients. The relationship is described by the equations:

Pred = 108 + (0.75 * age) for males and

Pred = 98.5 + (0.5 * age) for females.

Where Pred is the predicted systolic arterial pressure in mmHg and age is in years.

Using this as a baseline the TSAP was defined as 90% of the predicted value during the development of the system and in main study. To 'check' this value three patients were studied with a TSAP representing 85% of PRED after the algorithm used in the main study had been determined (vide infra). Achieving and maintaining the TSAP in these cases required a high inspired concentration of enflurane and an unacceptably long recovery time ensued, suggesting that these patients were "over-anaesthetised".

DETERMINING THE CONTROL ALGORITHM.

Step-tests (i.e. measuring the response of the controlled process to changes in input) are often used by engineers to to determine the gain settings when a control system is being developed. In this situation the effects of surgical stimulation are continually changing the process and it is not possible to use this method. Instead knowledge of dose - response - disturbance relationships, gained through clinical experience, was used to design the initial control algorithm which was refined experimentally.

A PROPORTIONAL CONTROL SYSTEM.

Initially a proportional control system with a gain of 0.1 was set up i.e. 0.1% enflurane was delivered by the controller for every mmHg the SAP was above the TSAP. This system was studied in 4 patients and a mean off-set from the TSAP of 13.7 mmHg occurred (range 13.1 - 20.4). The stability of control about this mean off-set value was good and is reflected by a mean standard deviation of 5.7mmHg. Figure 44 shows a typical example with this control system.

A PROPORTIONAL - INTEGRAL CONTROL SYSTEM.

To reduce this off-set an integral component was added to the algorithm. The gain for this component was initially set at 0.05, the gain of the proportional component being left at 0.1. Although this corrected the off-set the rapid cumulation in integral value following SAP increases led to the patient receiving excess enflurane when the TSAP was again reached. In the case illustrated (figure 45) the integral value increases by a further 37% following the initial peak in SAP and before the TSAP is acheived. This results in the patient receiving 5% enflurane at the TSAP. The integral was therefore reduced to 0.01.

In a small series of runs with the P - I gains set at 0.1 and 0.01 control of SAP during surgery was generally good (figures 46 and 47). However, some problems had now become apparent:

1 As discussed above the Dinamap may only register the mean pressure in some situations, returning "0" readings for SAP and DAP. The original program

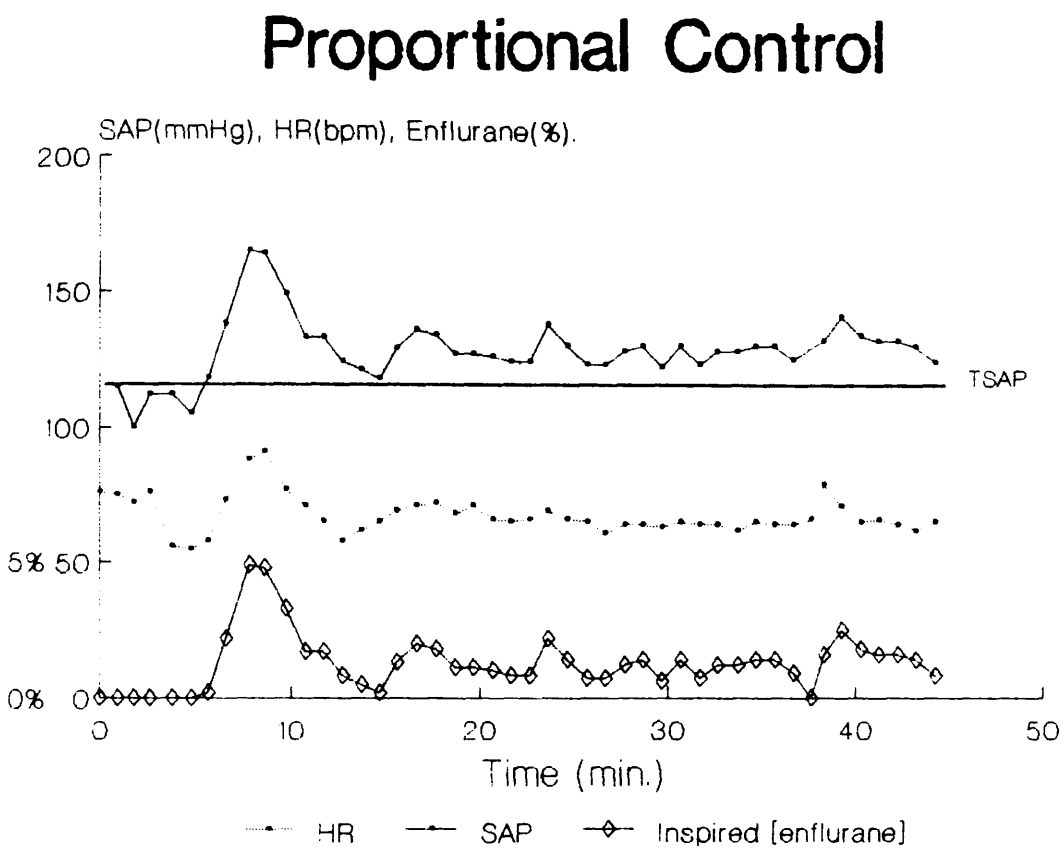


Figure 44. An example of proportional control.

Note the offset from the target value and that no enflurane was delivered for the first 6 minutes. The latter effect results in an SAP "peak" following the start of surgery (at seven minutes in the figure).

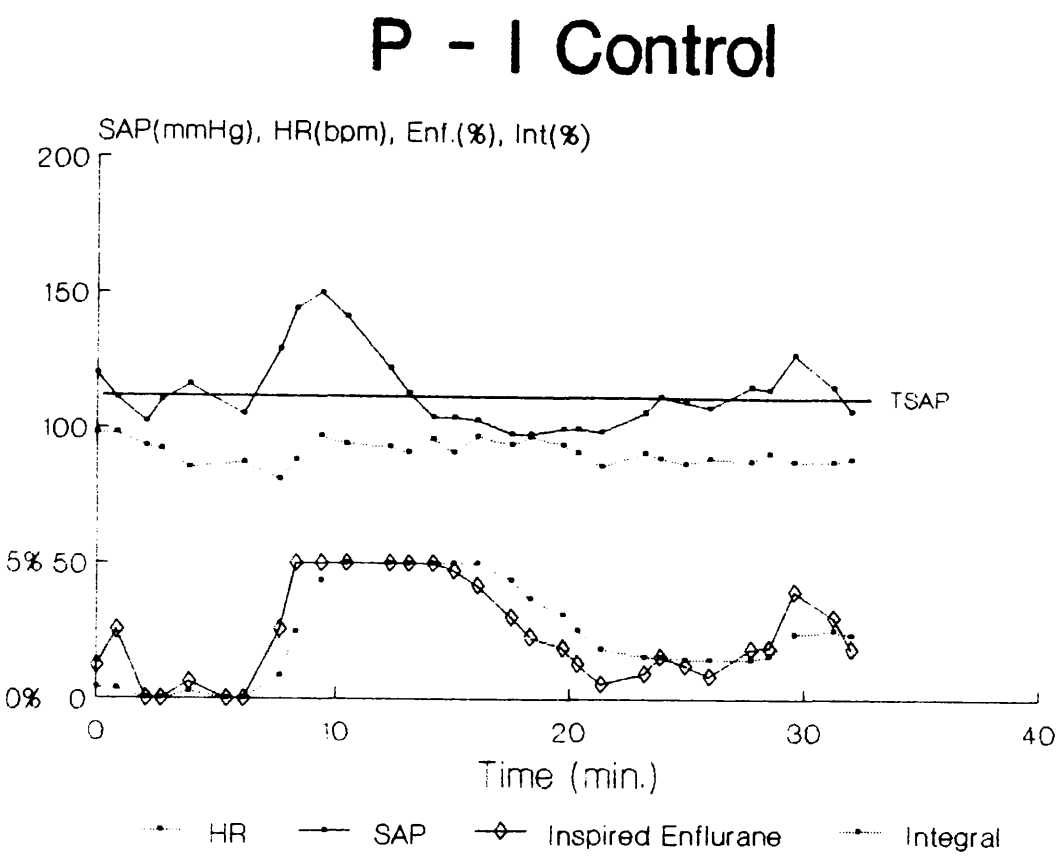


Figure 45.

An example of P - I control with the gains set at 0.1 and 0.05.

In this figure, and all subsequent figures in which the integral is plotted; the integral is expressed as the dose of enflurane (0-5%) which would result from the integral term alone i.e. if the proportional component was ignored.

Note that the rapid cumulation of the integral results in this patient receiving an excessive dose (5%) when TSAP is acheived following a peak in SAP at 10 minutes.

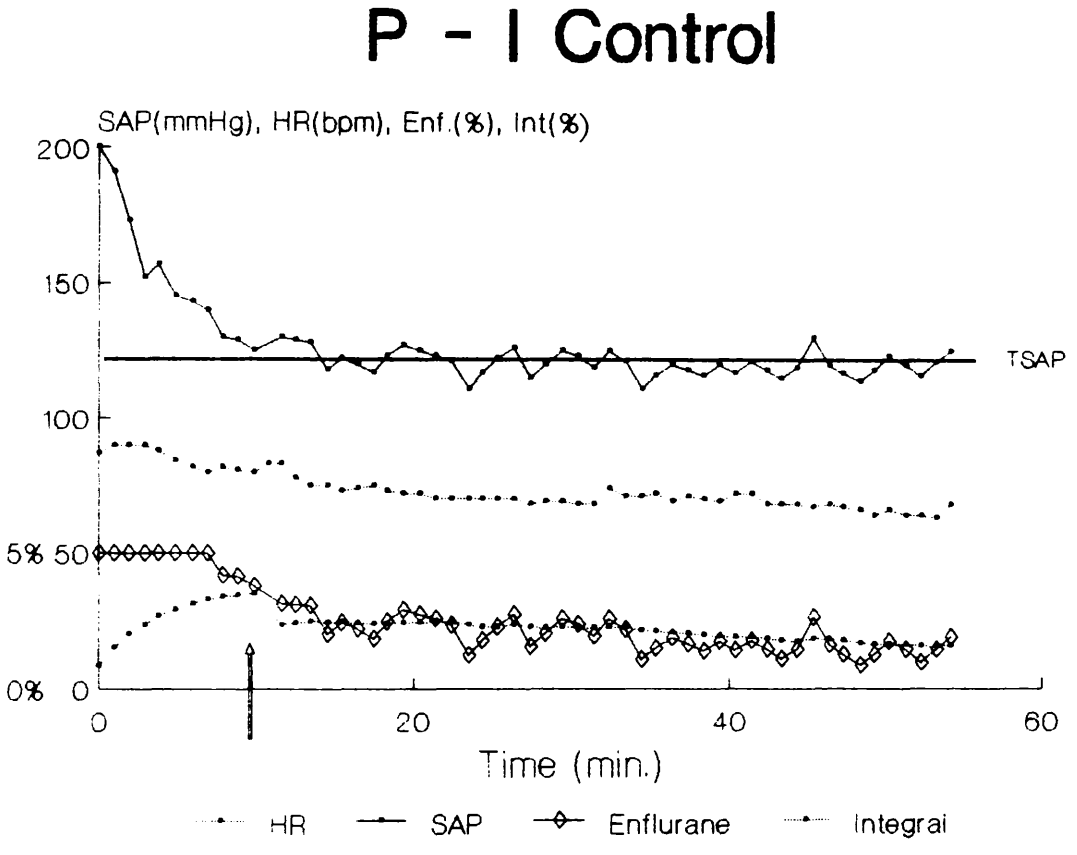


Figure 46.

An example of P-I control with the gains set at 0.1 and 0.01.

This patient was hypertensive relative to the TSAP following transfer to theatre. Control of SAP in this case is good. The arrow indicates a "0" SAP measurement (not marked) which the controller treated as a valid input, reducing the integral by 127 (the value of the TSAP). In this case control was probably improved as an overshoot, which can be anticipated, does not occur.

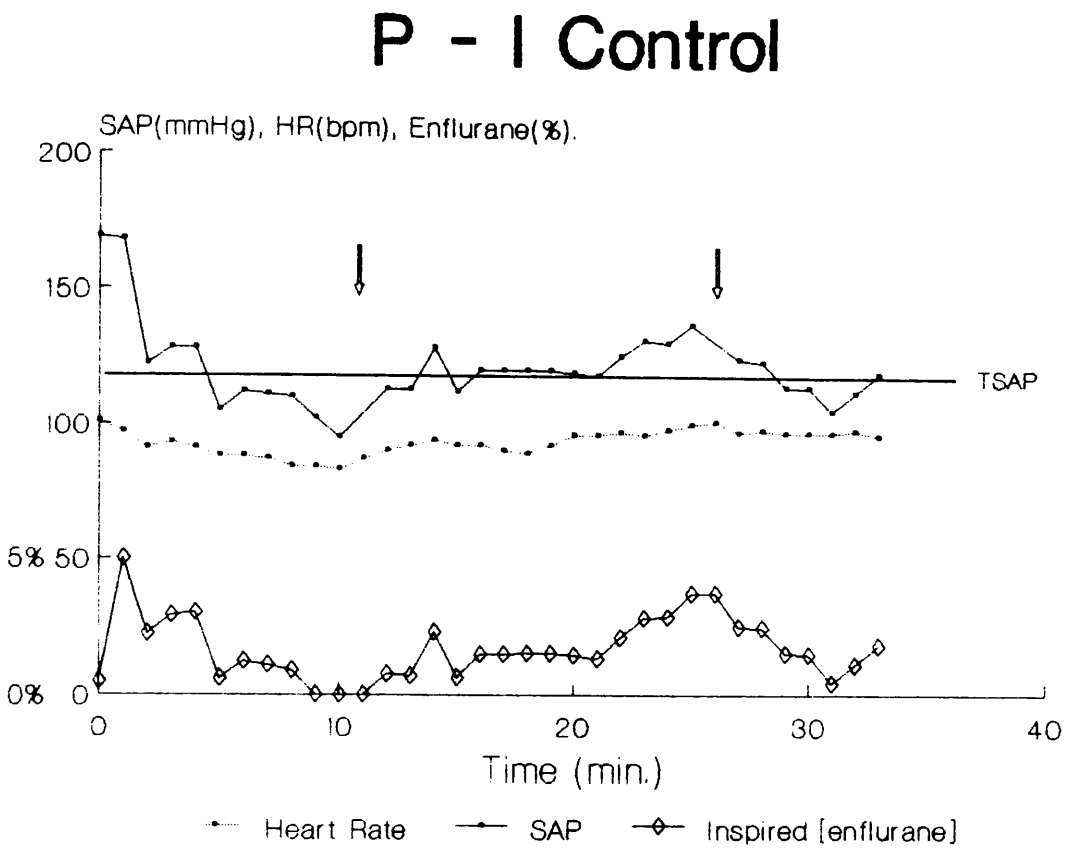


Figure 47.

An example of P-I control with the gains set at 0.1 and 0.01.

The arrows indicate "0" SAP measurements (not plotted) which the controller is instructed to ignore and to leave the inspired enflurane concentration unchanged.

treated a zero systolic pressure as a valid input and acted accordingly i.e. the vaporizer was driven to the "0" position and the integral was reduced by the value of the TSAP (figure 46). As this occurrence represents an error signal the program was altered so that zero readings were ignored and the vaporiser setting was left unchanged until the next valid SAP input (figure 47).

2 As the integral value is accumulated gradually, SAP readings of less than the target value at the start of the control period may result in the patient receiving no or minimal concentrations of volatile anaesthetic when surgery commences, with the risk of the patient being "inadequately" anaesthetised at this point. Further, those patients who received limited amounts of volatile initially appeared to have a larger pressor response to surgical stimulation (compare figures 44 and 45 to figures 46 and 47). This can be expected to increase the time taken to achieve adequate control of SAP. In general, the longer the period between induction and incision the more likely a patient is to be hypotensive relative to their TSAP at the start of surgery. As this delay is unpredictable it was decided that a minimum dose of 0.6% enflurane should be delivered for the first 10 minutes in an attempt to limit the effect of this occurrence (figure 48).

3 On the other hand some patients were relatively hypertensive on arrival in theatre (figure 46). A pre-loaded integral was incorporated to decrease the

Rule 1 - Minimum Concentration

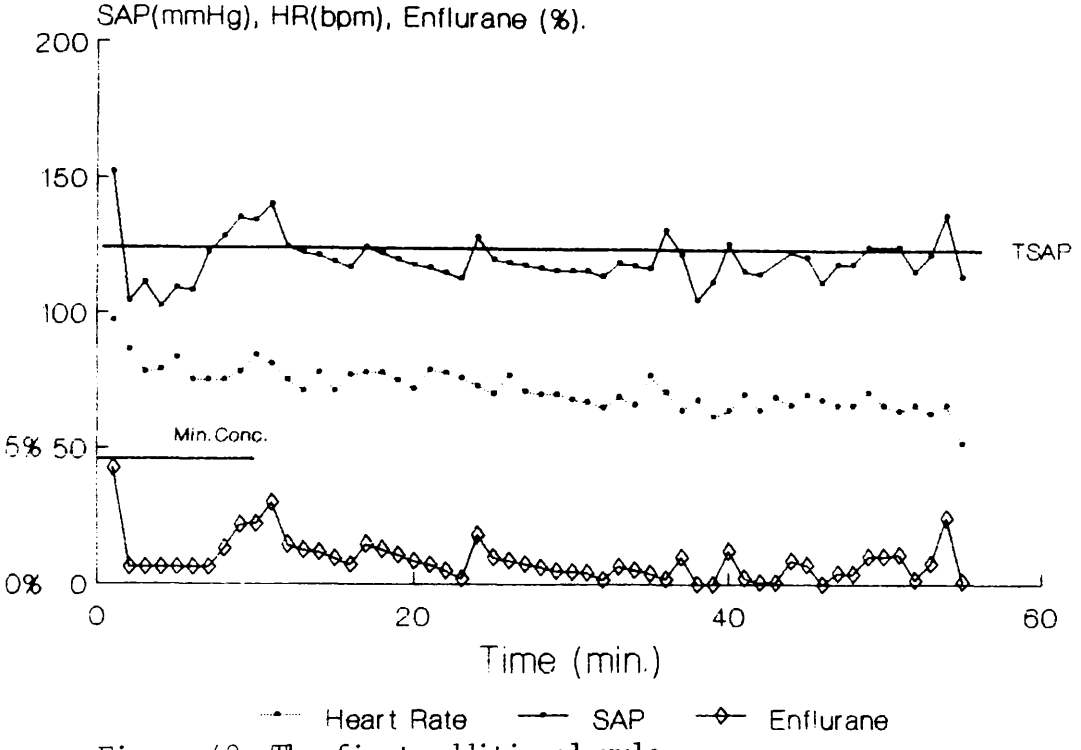


Figure 48. The first additional rule.

Although the patient is hypotensive relative to the TSAP, the controller delivers a minimum concentration of 0.6% for the first 10 SAP measurements . There is a limited pressor response to the initial surgical stimulus (at seven min).

time the system took to gain control of these cases. This value was based on age and determined as:

INL = 20 + (100 - Age)

Where INL is the pre-load for the integral and age is in years. The value was chose to both improve the response in those hypertensive (with respect to the TSAP) but to have little effect in patients who were relatively hypotensive.

THE PILOT STUDY.

The system was now felt to be ready for formal testing. A small pilot was carried out to determine:

1 Any additional features for the protocol to be used in the main study.

2 The adequacy of the control system with regard to:

a) The initial response to surgery (i.e. to assess the effects of the modifications).

b) The degree of control exerted on the SAP.

3 If the anaesthetic state produced by the system was clinically acceptable.

The protocol used in the pilot study was similar to that used in the main study and is detailed in the following chapter. No patient in the pilot study received an opiate prior to induction and the TSAP was defined as 90% of that predicted by age and sex (vide supra).

Seven patients aged 28 - 61 (mean 41.9) years, scheduled for abdominal hysterectomy, were studied and results are listed in table 9.

The results from the first four cases, in terms of control, were encouraging. In all cases the mean off-set

Table 9. Results of the pilot study.

Case No.	TSAP	ATPR	SAP	TSAP-SAP	RMSD	HR	VAP
1	119	8	120.2	1.2	6.06	87.2	1.9
2	108	23	111.9	3.9	6.02	92.8	3.4
3	109	22	112.6	3.6	7.24	86.4	3.3
4	120	4	119.8	-0.2	6.24	70.1	0.8
5	121	4	119.9	-1.1	9.91	67.1	1.8
6	131	9	139.9	8.9	17.15	71.2	1.9
7	114	14	118.6	4.6	7.16	85.6	2.0

TSAP = target systolic arterial pressure (mmHg)

ATPR = anaesthetic termination patient response time (min)

SAP = systolic arterial pressure (mmHg)

TSAP-SAP = the difference between the TSAP and the SAP.

RMSD = root mean square deviation

VAP = the inspired enflurane requirement

HR = heart rate.

note: the RMSD is the root mean square deviation and is analagous to the standard deviation but uses the TSAP in place of the mean SAP. This term reflects the goodness of control about the TSAP.

was less than 4 mmHg and the RMSD values (table 9) ranged from 6.02 to 7.24 i.e. SAP was successfully controlled with respect to the TSAP. However the second and third cases took an excessively long time to recover, as determined by the time taken to respond to command.

These cases had developed integral values of over 350 by the time the controller was discontinued i.e. an enflurane concentration of over 3.5% was required to maintain the SAP at the target level and the patients were excessively anaesthetised (figure 49).

In an attempt to improve the recovery time without changing the target value the following modification was made to the controller:

> If the inspired enflurane concentration exceeded 15% over 5 consecutive vaporizer settings and each individual setting exceeded 2.5% then the controller instructed the operator to give a bolus of morphine (0.05mg/kg) and to reset the integral to its pre-load value. This was done by pressing a key on the keyboard. This rule could only be executed once in any 15 minute period. In practice the loop remained "tight" i.e. all decisions were made by the controller, the operator having a passive role.

This new rule was tested in 3 cases (cases 5 to 7), and was used twice (cases 6 & 7). The rule appeared to have the desired effect of limiting the integral value which appeared to stabilise at a lower level following the morphine bolus (figure 50). The recovery time in both these cases was acceptable (i.e. less than 15 minutes).

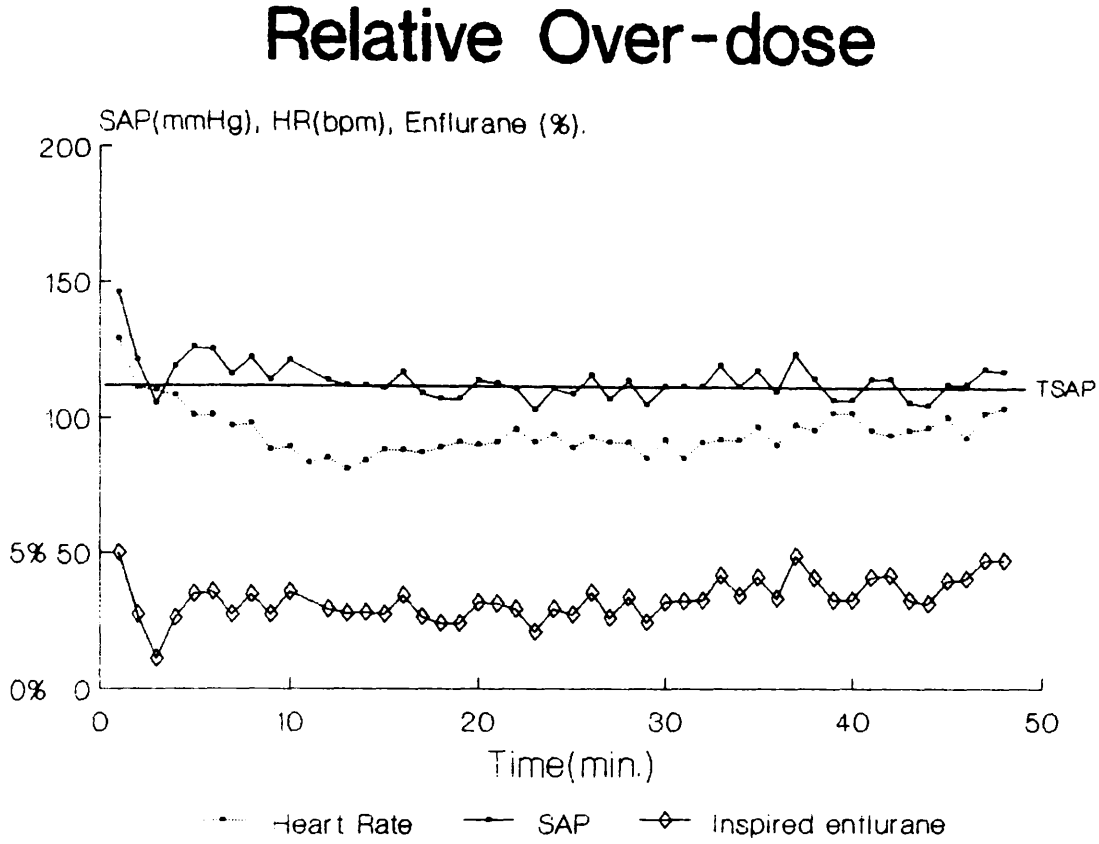


Figure 49. An example of a case who received a relative overdose of anaesthetic.

Although control of SAP is good, this patient took an excessive time to recover.

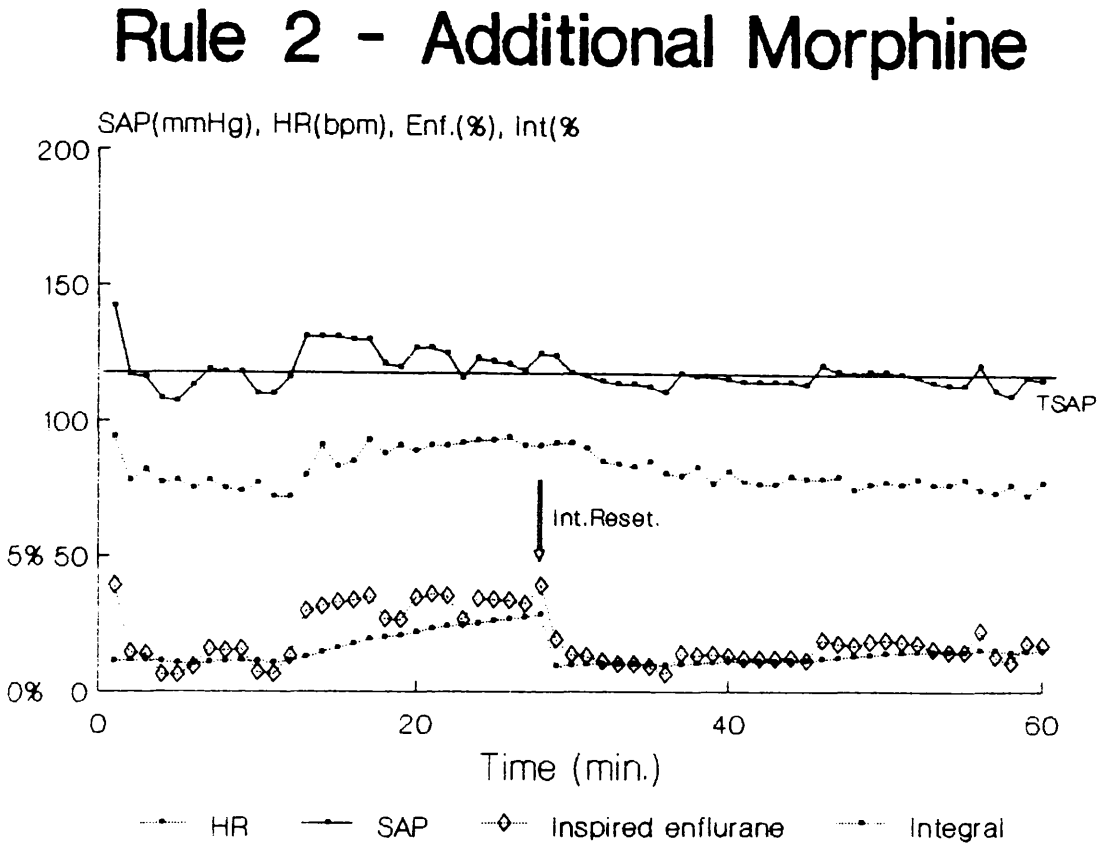


Figure 50. The second additional rule.

As this patient was receiving an excessive dose of enflurane the computer instructed the anaesthetist to give a bolus of morphine and to reset the integral (arrow in the diagram). This results in a lower enflurane requirement. Resetting the integral prevents further overdose. Note the rising integral value prior to the bolus, and that the integral stabalises after this event.

In the initial part of the control period only one patient had a pressure response to surgical stimulation of more than 25mmHg (with respect to the TSAP). Supplying a minimum dose of 0.6% enflurane over the first ten minutes appeared to have had the desired effect. The rule was used in five of the seven cases.

As the P - I system with the additional rules produced an acceptable anaesthetic state and adequate control in the majority of patients studied it was decided to proceed with the main study.

CHAPTER 9

THE MAIN STUDY.

Local Hospital Ethical Committee approval was obtained and all participating patients gave informed, written consent to the study.

DETAILS OF THE CONTROL SYSTEM.

The P-I control system gains were set at 0.1 and 0.01. A pre-loaded integral and two additional rules were incorporated (vide supra):

1 All patients received a minimum inspired volatile concentration of 0.6%

2 If the inspired concentration exceed a pre-set limit then the controller instructed the operator to give a bolus of morphine (0.05mg/kg) and to reset the integral to the pre-loaded value.

PATIENTS AND METHODS.

INCLUSION CRITERIA.

1 Age 17 - 70 years of age.

2 Health status - ASA Grade I or II

3 Any patient who satisfied the above criteria in whom the anaesthetic technique (see below) was deemed appropriate, with the following exclusions:

a) History of cardio-vascular disease. Specifically those patients suffering from or treated for hypertension, arrythmias or cardiac failure.

b) Patients with psychiatric or other CNS disease.

c) Patients on CNS "active" drugs except sleeping tablets.

d) Patients in whom the anaesthetic technique was felt inappropriate e.g. epileptics.

e) Patients with an arm circumference of more than 43cm.

As a simple "change" of vaporizer is not possible (vide supra) patients could not be randomly allocated to receive enflurane or isoflurane. Therefore the first group of patients studied received enflurane (n = 22) and the second group isoflurane (n = 35).

Only those changes necessary to adjust the controller to the isoflurane vaporizer were made following the enflurane study. The PI gains, initial minimum inspired concentration and dose limit that determined the requirement of additional morphine were left unchanged.

PRE-OPERATIVE VISIT.

All patients were visited pre-operatively and the nature and relevant details of the study explained. Written consent was obtained and all patients weighed.

PRE-MEDICATION.

1 Ranitidine (150mg) at 06.00 on the day of the operation.

2 Temazepam (10-20 mg) 1-2 hours pre-operatively.

INDUCTION SEQUENCE IN THE ANAESTHETIC ROOM.

1 Measurement of SAP (Dinamap 845)

2 Placement of intra-venous cannula (14 or 16 gauge) under local anaesthetic in the left arm or hand.

3 Induction, morphine 0.1mg/kg followed by thiopentone (2.5mg/kg) and, if the eyelid reflex was still present after 30 seconds, an additional 1mg/kg of thiopentone was given. The second part of this

sequence was repeated as necessary.

4 Following loss of the eyelid reflex Vecuronium (0.1 mg/kg) followed by:

5 Manual ventilation with a facemask (and airway if required) for 90 seconds with a mixture of nitrous oxide (70%) in oxygen supplemented with 1% enflurane (or 1% isoflurane).

6 Intubation and following fixation of the endotracheal tube transfer to theatre.

MAINTENANCE OF ANAESTHESIA.

1 Ventilation on a Bain circuit supplied with a fresh gas flow of 100mls/kg (nitrous oxide 70% in oxygen) and driven by an OAV ventilator at a rate of 12 breaths per minute and a tidal volume of 10 mls/kg.

2 Enflurane (or isoflurane) was delivered by the controller and additional morphine on instruction from the controller.

3 Relaxation was maintained with timed boluses of vecuronium (30% of induction dose) given every 25 minutes.

4 All patients received 10 - 15 mls/kg Ringer Lactate over the first hour and 5 - 10 mls/kg over subsequent hours to cover basal fluid requirements. Blood loss was replaced with crystalloid, colloid or blood products as clinically indicated.

5 Minor interventions e.g. alteration of the table slope, passing of a naso-gastric tube, re-siting of peripheral cannulae etc. were noted. Major interventions in particular the administration of

other drugs (unless on instruction from the controller) constituted a breach of protocol and depending on the situation the use of the control system might be abandoned. These cases are not included in the analysis.

MONITORING.

1 All patients had their ECG (lead II) continually monitored.

2 Blood pressure was recorded every minute by the Dinamap (model 1845) interfaced to the controller. The integral alarms in the controller and Dinamap were used.

3 If the Normac analyser was available then end-tidal enflurane (or isoflurane) concentration was measured and recorded graphically.

4 Tidal volume, respiratory rate and peak airway pressure were monitored and appropriate alarm values selected.

5 If a neuromuscular function monitor was available then the train of four was maintained at 2 or less.

6 A clinical assessment of anaesthetic adequacy was made every 5 minutes. This consisted of:

a) PRST score (91)

b) Capillary Refill

c) Venous Tone

b) Pupil diameter and light reflex using the pupillometer.

END OF SURGERY.

Five minutes from the end of surgery as judged by the

anaesthetist the controller was discontinued i.e. the volatile agent was switched off. Following the last skin suture or staple the nitrous oxide was discontinued and the patient ventilated with 5% carbon dioxide in oxygen. The relaxant was antagonised at this point with neostigmine (2.5mg) and glycopyrollate (0.6mg).

Following the return of spontaneous ventilation (defined as a tidal volume of over 5 mls/kg) all patients who did not receive an additional bolus of narcotic were given morphine (0.05mg/kg).

The patients were then extubated.

RECOVERY.

Recovery was deemed complete (for the purposes of the study) following purposeful response to command i.e. sticking out the tongue or opening their eyes when requested.

POST-OPERATIVE DETAILS AND VISITS.

The patients were kept in theatre until they became responsive. Following this they were transferred to a recovery area where they stayed for 4 - 8 hours. Routine post-operative care was undertaken i.e. oxygen 35% was given by facemask, intravenous fluids continued as necessary and analgesia given on demand. Combinations of papaveretum and prochlorperazine or morphine and cyclizine were used but no attempt was made to standardise these.

All patients were visited in recovery and the following day. At the second interview they were asked:

1 Last event recalled prior to induction

2 First event recalled after the termination of

anaesthesia.

3 If they recalled any event between these i.e. suffered from awareness.

DATA AND STATISTICAL METHODS.

1. PATIENT GROUPS.

Two groups of patients were studied, an enflurane group and an isoflurane group. These groups were in effect subdivided by the controller into those who required extra morphine during the procedure and those who did not.

In the initial part of the isoflurane study three patients suffered a severe bradycardia (heart rate less than 20). These were effectively treated by stopping surgery and giving atropine (0.6 mg). In view of this all subsequent patients with heart rates of less than 50 bpm were given glycopyrollate, 0.2 mg every 2 minutes, until the rate was greater than 55 bpm. The observer determined this requirement from the ECG rate. As no patient in this group required an additional bolus of morphine five patients groups resulted:

1 Group E; ethrane, morphine bolus at induction, no additional morphine.

2 Group EM; ethrane, morphine bolus at induction and additional bolus(es) of morphine during the control run.

3 Group I; isoflurane, morphine bolus at induction, no additional morphine.

4 Group IM; isoflurane, morphine bolus at induction and an additional bolus of morphine during the control run.

5 Group IA; isoflurane, morphine bolus at induction and an anticholinergic agent during the control run.

The groups are therefore identified by one or two letters. The first letter (E or I) identifies the volatile anaesthetic agent the patients received; the second letter, if present, identifies those patients who required additional morphine (M), or an anticholinergic agent (A), during the proceedure.

Group M is used to describe all the patients who received additional morphine, irrespective of the volatile agent used, and Group NO all the patients who did not require additional morphine. The latter group includes those patients who received an anticholinergic drug.

2. TIMES.

Time was measured from induction and the following determined:

1 Total Anaesthetic Time (TAT), time from induction to termination of the anaesthetic (i.e. the discontinuation of the nitrous oxide).

2 Total System Time (TST), time from starting the controller to its discontinuation.

3 System Termination Patient Response Time (STPR), the time taken to respond to command after the controller was switched off.

4 Anaesthetic Termination Patient Response Time (ATPR), the time to response to command from the termination of the anaesthetic (i.e. the discontinuation of the nitrous oxide).

5 The period over which the cardiovascular, SAP control

and inspired volatile requirements were calculated is designated the control period (CP). The CP includes all valid records from the 11th. to the end of the control period. The first 10 records are excluded to allow the controller to achieve a degree of stabilisation. A recording was considered invalid if the SAP measured was "0" mmHg and all data determined at that record was discarded. All cases with a CP of less than 15 minutes were excluded from the study.

2. CARDIOVASCULAR DATA AND VOLATILE REQUIREMENTS.

The HR, SAP, MAP, DAP were measured by the Dinamap each minute and the RPP and required volatile concentration determined by the computer. This data was stored to disc at the end of a control run.

A program was written to read the data from disc and calculate the criteria used to assess the adequacy of control (vide infra). A utility program was used to convert the data to the format used by Statmode 1 (SM1), a well known commercial statistical package. The mean and standard deviations for the cardiovascular and inspired volatile data were calculated for each patient with this program.

3. PRST SCORES.

The mean PRST score was calculated for each group by summing all P, R, S, and T values and dividing the total by the number of PRST records. The percentage contribution of each component to the total group score was also calculated.

4. PUPILLARY DIAMETER (PD).

PD measurements were made at the start of a Dinamap inflation sequence. The correlation between SAP and PD was claculated using Statmode 2 (SM2).

5. ASSESSMENT OF SAP CONTROL.

The control of SAP is assessed by three criteria (see Appendix II for details):

1 The root mean square deviation (RMSD). The RMSD is analogous to the standard deviation but uses the TSAP value in place of the mean in its calculation. This parameter gives an idea of the spread of SAP about the target value.

2 The point ratio (PR). The PR is the ratio of the percentage of SAP points falling above the TSAP to the percentage of points falling below the TSAP.

3 The mean deviation from the TSAP (MD_{TSAP}). This reflects the difference between the mean measured SAP and the TSAP.

These three indices should be considered together, control of SAP is considered "good" if:

1 The RMSD is less than 10mmHg.

2 The PR lies between 0.4 and 2.3

3 The MD_{TSAP} is less than 5 mmHg.

6. THE ANAESTHETIC STATE PRODUCED.

The anaesthetic state was considered acceptable if:

1. Physiological variables were maintained within acceptable limits:

a. The SAP control was adequate (vide supra).

b. The mean HR ranged from 50 to 100 beats per minute.

c. The mean RPP was less than 12000.

d. The PRST scores were less than 4.

Other physiological variables e.g. ventilation and neuromuscular blockade are assumed to be within normal limits.

2. Recovery was achieved within 15 minutes of the discontinuation of the nitrous oxide. However, a difference of more than 5 minutes between the STPR and ATPR indicates that the controller was switched off too soon and that the ATPR may be misrepresentative of the recovery period. To allow for this a corrected ATPR (cATPR) was calculated:

   cATPR = ATPR + (STPR - ATPR) - 5 min.

   For each minute the difference between the STPR and ATPR exceeds 5 minutes one minute is added to the cATPR. The cATPR is therefore a better reflection of recovery if the controller was switched off "early".

3. If direct questioning established no recall of events between induction and extubation.

STATISTICAL METHODS.

The calculation of mean and standard deviation values for the cardiovascular and related data has been explained (vide supra).

A two-tailed Mann-Whitney U test was used for all inter-group comparisons. Probability values were calculated with SM2. A probability value of 0.05 or less is considered significant.

The values calculated by SM1 and SM2 were checked

manually for three patients selected at random.

SPECTRAL EDGE FREQUENCY.

The neurotrac was used to record the SEF in 8 patients in the isoflurane group during surgery. As we did not have the facilities to record the EEG data on disc the neurotrac printer was set to record the CSA with the SEF superimposed. The control program was modified to allow the operator to "mark" the data print-out by pressing "E" on the keyboard. As the neurotrac incorporates an event marker the operator can then "mark" both print-outs simultaneously so that the two records can be related later.

To determine if a relationship between SEF and SAP exists two "numbers" are required, a single SEF frequency and the corresponding SAP measurement. The SEF frequency was determined by measuring the distance from the 0 Hz baseline to the start of the SEF "box" and applying the appropriate correction factor (figure 51).

Although a series of SAP measurements and SEF frequencies are available and these series can be related in time, it is not possible to relate any single Dinamap reading to a specific SEF because the Dinamap takes a variable, unknown time to check any single reading and the neurotrac always gives a time weighted average.

When these are considered it is apparent that statistical analysis would be of limited value. We decided to take a period during each run over which the SAP was relatively stable and to plot SAP, SEF and HR against time to determine if any visual relationship was apparent. It

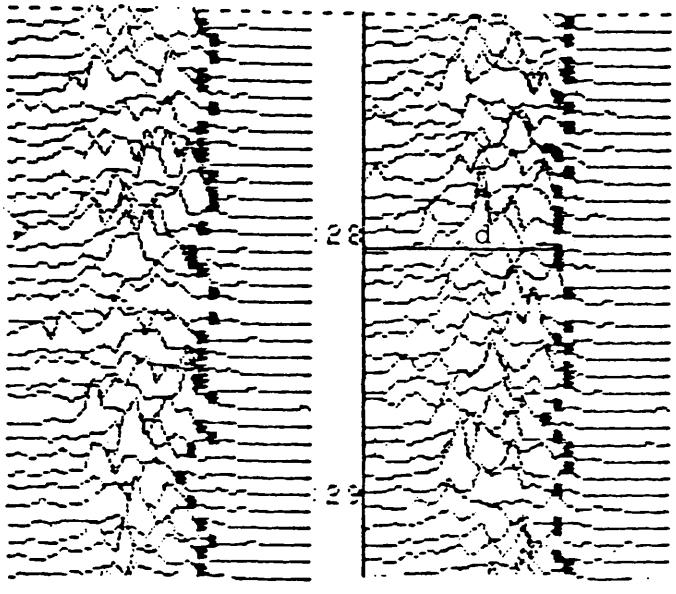


Figure 51 Measuring the SEF.

The distance from this baseline is measured in mm. (d in the example). This distance is then converted to Hertz, ie.

frequency (Hz) = d * (42/30)

Note the tracing from the left hemisphere is ignored.

must be accepted that the SEF and SAP may be out of phase by up to one minute.

CHAPTER 10

RESULTS

GROUPS.

Fifty seven patients consented to the study, 22 received enflurane and 35 isoflurane. Adequate control of SAP was not acheived in two patients and they received an excessive dose despite additional morphine. These cases were abandoned. A breach of protocol occured in three of the isoflurane cases:

1 One patient was not given a bolus of morpine at the correct time.

2 One patient suffered a blood-loss of 3.5 liters and was hypotensive with respect to the TSAP for some 50 minutes.

3 One patient gave a history of her heart "slowing down and stopping" during a previous laparoscopy. This patient was admitted to the study but received glycopyrollate at induction.

The latter 2 cases are considered seperatly.

Fifty two patients are therefore included in the inter-group comparisons. The generation of the five groups has been discussed and is summarised in table 10.

The details of the patients and their operations are listed in tables 11 and 12. There was no statistical diference between the groups with respect to age, weight, pre-operative and pre-induction blood pressures, total anaesthetic time or total system running time.

CONTROL OF SAP.

Figures 52 to 56 are examples of the control of SAP acheived during individual runs. These examples are

Table 10. The five patient groups.

GROUP	CHARACTERISTICS
E	Received morphine at induction and were controlled with enflurane alone.
EM	Received morphine at induction and enflurane for maintenance but required additional morphine during the proceedure. This requirement was determined by the controller.
I	Received morphine at induction and were controlled with isoflurane alone.
IM	Received morphine at induction and isoflurane for maintenace but required additional morphine during the proceedure. This requirement was determined by the controller.
IA	Received morphine at induction and were controlled with isoflurane alone. These patients were given an anticholinergic agent because of a bradycardia.

Note, all patients were ventilated and received 66% nitrous oxide in oxygen.

Table 11. Group details (1), the surgery performed.

	Group				
Operation	E	EM	I	IA	IM
Hysterectomy (+/- BSO)	9	7	13	8	3
Ovarian Cystectomy	1	-	2	1	-
Uterine Myomectomy	1	-	-	-	-
Vaginal Hysterectomy and P.F.R.	2	-	1	1	-
Reversal of Sterilisation	1	-	-	-	1
BSO	-	-	-	-	1

BSO = Bilateral Salpingo-oopherectomy
P.F.R = Pelvic Floor Repair

Table 12 - Group details (2), general information.

	Age			Weight		
Group	Mean	SD	Range	Mean	SD	Range
E	41.8	9.87	24 - 57	60.8	11.97	45 - 83
EM	37.6	10.47	25 - 54	60.7	11.88	45 - 80
I	43.1	9.07	32 - 65	60.1	8.97	48 - 82
IA	42.2	7.27	33 - 62	64.3	10.13	53 - 82
IM	37.6	7.27	26 - 73	64.6	16.56	45 - 91

	Pre-induction BP			Total Anaesthetic Time		
Group	Mean	SD	Range	Mean	SD	Range
E	129.2	10.52	118 - 151	67.2	23.14	47 - 135
EM	128.9	8.21	120 - 140	74.9	17.27	45 - 100
I	128.6	13.99	110 - 151	65.0	20.05	34 - 106
IA	128.9	10.21	109 - 142	62.3	22.32	58 - 96
IM	129.8	4.99	123 - 135	69.8	13.24	58 - 92

	Total System Time		
Group	Mean	SD	Range
E	55.8	23.42	35.9 - 123.7
EM	62.7	16.97	35.8 - 86.6
I	54.3	18.31	29.0 - 85.2
IA	51.0	20.99	24.1 - 85.2
IM	56.5	14.76	43.8 - 81.7

Example from Group E.

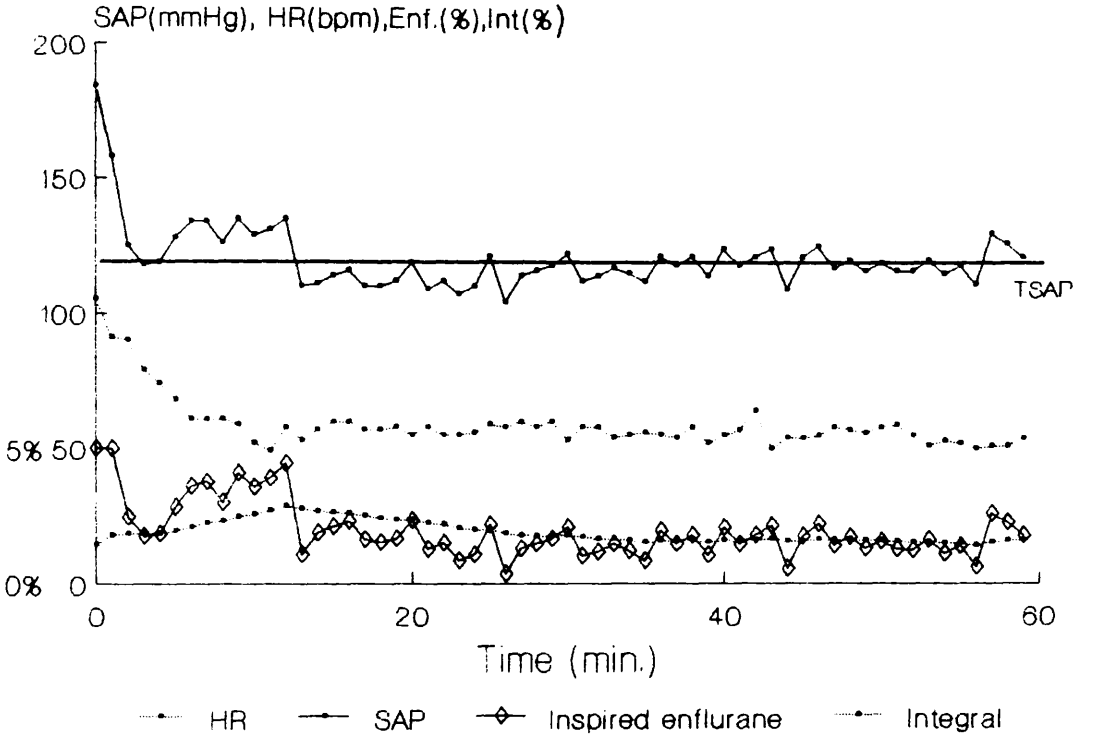


Figure 52. An example from group E.

The RMSD in this case was 6.6.

Example from Group EM.

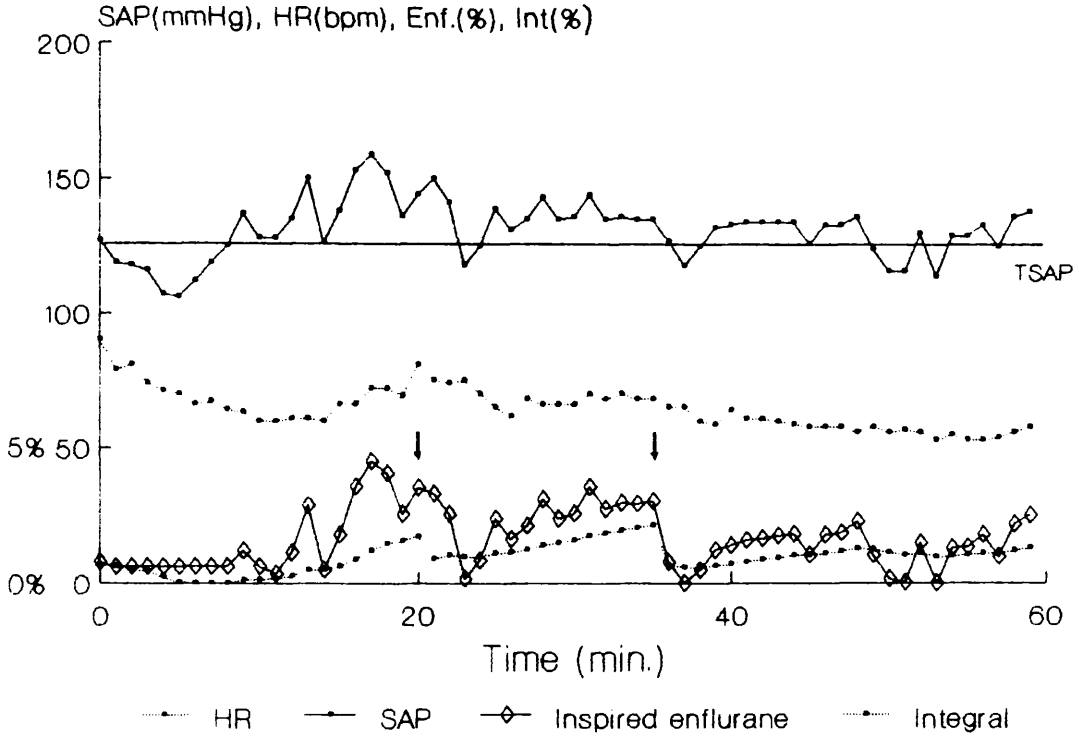


Figure 53. An example from group EM.

The RMSD in this case was 11.47. This patient required two boluses of morphine (arrowed). Following the second bolus the inegral stabilised.

Example from Group I

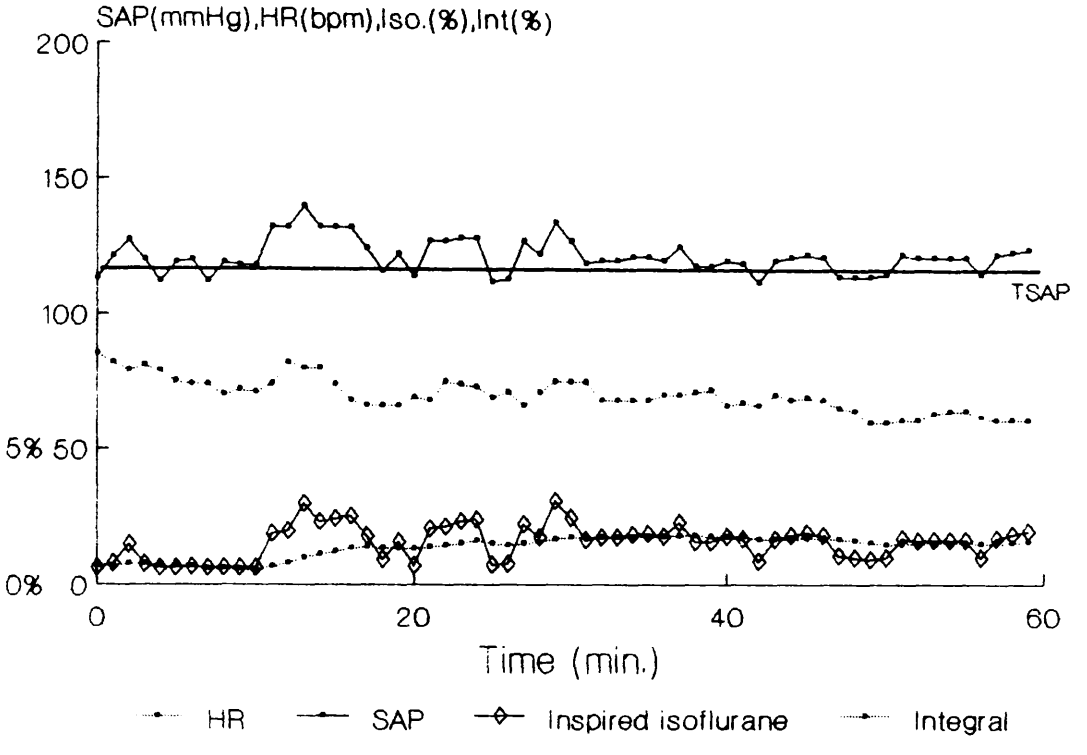


Figure 54. An example from group I.

The RMSD in this case was 6.64.

Example from Group IA

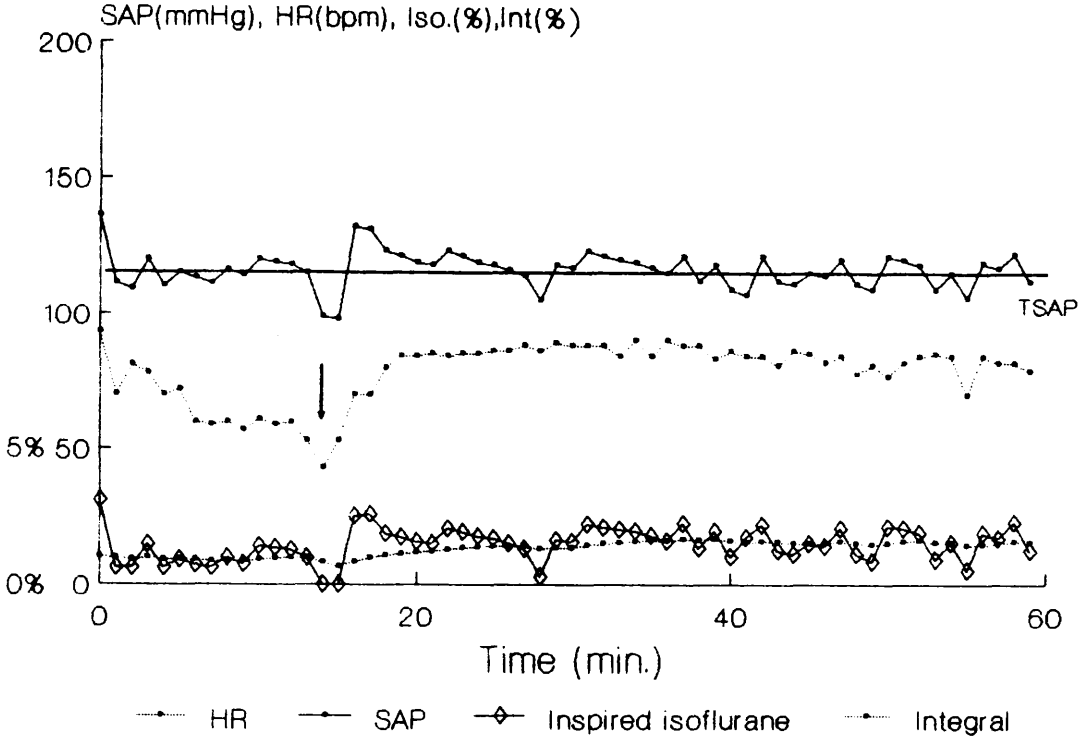


Figure 55. An example from group IA.

The RMSD in this case was 6.03. This patient received atropine 0.3mg for a bradycardia of 30 bpm (arrowed). This event was not recorded by the Dinamap.

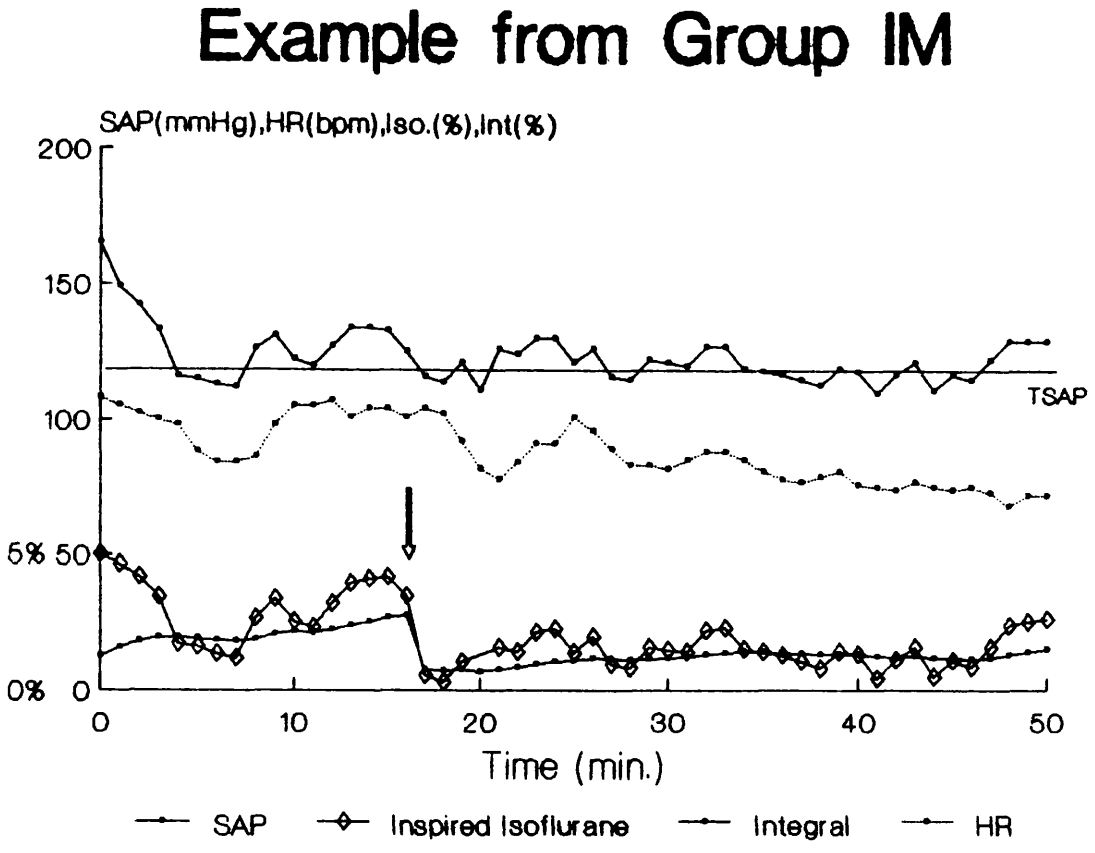


Figure 56. An example from group IM.

The RMSD in this case was 7.46. This patient received a single additional bolus of morphine (arrowed).

selected to be representative of the group from which the patients were chosen, the RMSD values in each case being close to the mean value for the group.

The mean and standard deviations for TSAP, measured SAP, MD_{TSAP}, RMSD and PR for each of the five groups are listed in table 13. There was no diference between the groups with respect to the TSAP or mean SAP values.

Control of SAP, as reflected by the RMSD was poorer in group EM when compared to the other groups (table 14). However, when the PR and MD_{TSAP} are also considered control was significantly better in the groups which did not require additional morphine.

Overall, control of SAP was "inadequate" (vide supra) in 19 patients i.e. 36.5% of the total (see Appendix III for details). Of these, 10 patients were in the two groups who required additional morphine i.e. all the criteria were not fulfilled in 83.3% of these patients, compared to 22.5% of patients in the other groups. Two or more of the three control criteria were acheived in 37 of the 40 patients in the three groups of patients in whom additional morphine was not required i.e. 92.5%.

The overall control of SAP is illustrated graphically in figure 57. This figure illustrates the main diference between the patients who required additional morphine and those who did not i.e. those patients who did require additional morphine appear to be controlled about a higher TSAP.

THE ADEQUACY OF THE ANAESTHETIC STATE.

A. PRST SCORES.

At no time did any of the anaesthetists involved,

Table 13. Group details (3), SAP control data.

	TSAP			SAP		
Group	Mean	SD	Range	Mean	SD	Range
E	117.4	6.85	105-128	116.9	6.27	105.7-126.8
EM	114.4	7.25	106-126	120.8	8.60	111.2-132.8
I	118.0	6.38	110-133	118.4	7.53	109.1-133.6
IA	117.3	5.29	111-131	117.6	5.62	111.7-132.5
IM	114.4	5.13	106-118	119.0	6.15	109.6-124.3

	MDTASP			RMSD		
Group	Mean	SD	Range	Mean	SD	Range
E	-0.52	1.85	-3.03- 2.16	7.27	2.34	4.81-13.37
EM	6.33	3.11	3.38-13.00	10.60	3.45	6.73-17.60
I	0.38	3.09	-7.40- 7.74	7.00	2.17	4.20-11.70
IA	0.28	1.77	-4.48- 1.6	7.66	1.66	5.77-10.60
IM	4.65	1.55	3.20- 6.4	8.48	2.49	4.81-10.82

(continued)

Table 13. Group details (3), SAP control data (continued).

Group	Point Ratio	% SAP at TSAP.
E	1.25 (+/- 1.69)	8.0
EM	3.41 (+/- 2.28)	6.2
I	2.64 (+/- 5.98)*	5.6
IA	1.08 (+/- 0.34)	5.1
IM	3.24 (+/- 1.14)	5.7

* A ratio of 24.81 in one patient in this group greatly effects this value. If the patient is excluded a mean of 1.16 (+/- 0.93) results.

Table 14. Inter-group comparisons (1), control of SAP.

	Group.				
	E-EM	E-I	E-IA	E-IM	EM-I
MD_{TSAP}	0.0001	ns	ns	0.001	0.0002
RMSD	0.007	ns	ns	ns	0.008
PR	0.0008	ns	ns	0.003	0.004

	Group.				
	EM-IA	EM-IM	I-IA	I-IM	IA-IM
MD_{TSAP}	0.0001	ns	ns	0.0007	0.002
RMSD	0.03	ns	ns	ns	ns
PR	0.0002	ns	ns	0.009	0.0007

ns = not significant ($P > 0.05$)

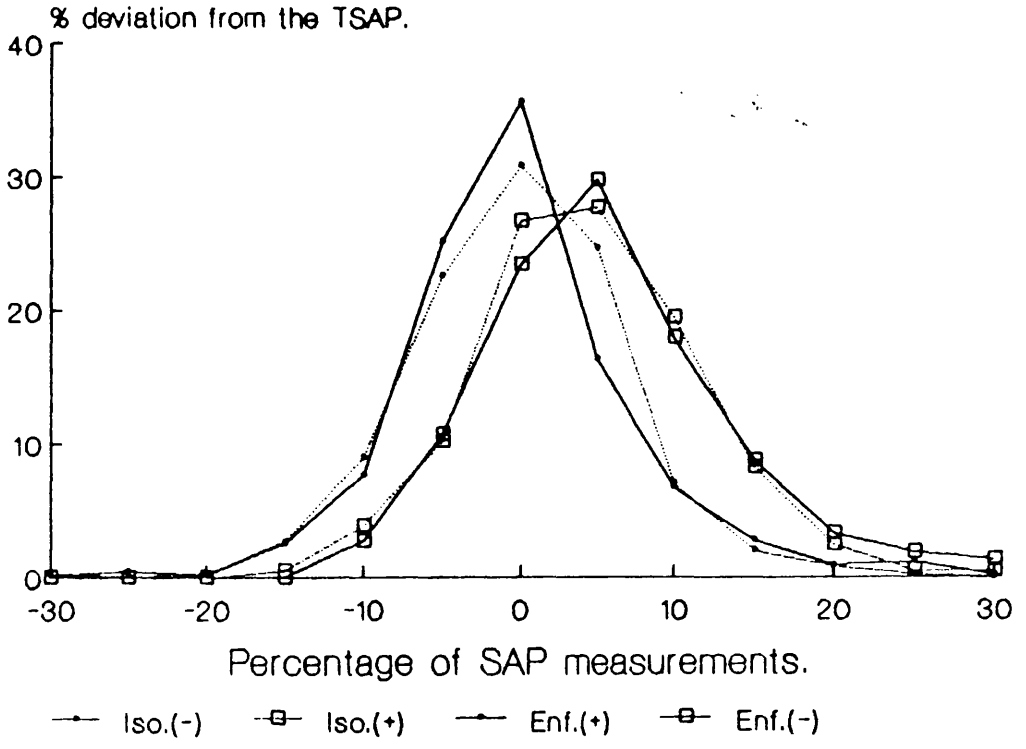


Figure 57 A diagram to show the spread of SAP about the TSAP.

A utility program was used to calculate the number of records in each control run falling in 5% brackets about the TSAP, ie. -27.5% to + 27.5%. Points + or - 30% were considered to fall at 30%. The number of measurements in each bracket are plotted as the percentage of the total number of records in each group. The minus and plus signs designate those patients who received additional morphine (+), and those who did not (-). Enf. and Iso. refer to the volatile anaesthetic agent the patients received, enflurane or isoflurane.

Note that there is a greater percentage of measurements in all brackets over +12.5% in the enflurane (+) group when compared to the isoflurane (+) group.

including independant anaesthetists, feel that a patient was too "lightly" anaesthetised. The mean PRST scores were all less than 2 and was lowest in Group E (table 15). The higher values in the other groups reflect the higher heart rates in these patients.

B. PHYSIOLOGICAL STATE.

The control of SAP has been considered in detail. The HR, RPP and inspired volatile requirement in each group is listed in table 16 and the inter-group comparisons in table 17. In two patients in group EM and one in group IM the RPP exceeded 12000. The mean heart rate was greater than 100 in only one case (group EM). The physiological state, with respect to HR and RPP was therefore acceptable in all but 3 patients. All of these cases were in the two groups which required additional morphine. The heart rate was generally lower in those cases who did not require additional morphine or an anticholinergic agent.

The inspired volatile requirements were significantly lower in groups NO when compared to groups M. There was no statistical diference between the inspired isoflurane and inspired enflurane requirements in otherwise comparable groups. Specifically, the inspired volatile requirement in group IA was similiar to that in groups I and E, the other two groups who did not require additional morphine.

As the end-tidal concentrations during the control period were not stable long enough for equilibration between the alveolar and brain concentrations to take place analysis of this data was not undertaken.

Table 15. Group details (4), mean PRST scores.

Group	Observ-ations	Total Variable Score P	R	S	T	Mean PRST
E	145	3 (4.5)	10 (14.9)	4 (6.0)	50 (74.6)*	0.46
EM	80	13 (19.7)	45 (68.2)	1 (1.5)	7 (10.6)	0.82
I	187	13 (8.5)	81 (52.9)	11 (7.2)	48 (31.4)	0.82
IA	82	4 (5.1)	55 (70.5)	0 (0.0)	19 (24.4)	0.95
IM	46	8 (10.5)	49 (64.5)	5 (6.6)	14 (18.4)	1.10

The observations are the number of PRST measurements made in each group and the total variable score the summed total P, R, S and T values for all the observations in that group. The figures in brackets are the percentage contribution of the individual components to the total score.

Table 16. Group details (5), cardiovascular and vaporizer data.

	Heart Rate.			Vaporizer Output.		
Group	Mean	SD	Range	Mean	SD	Range
E	66.9	8.15	55.6- 83.5	1.0	0.66	0.11 - 1.80
EM	83.1	16.66	61.7-109.6	2.2	0.45	1.83 - 3.13
I	73.6	8.06	62.7- 87.3	1.0	0.54	0.25 - 2.00
IA	80.3	10.28	63.5- 99.1	0.8	0.46	0.12 - 1.68
IM	89.4	9.78	77.0- 99.4	2.1	0.36	1.76 - 2.52

Rate Pressure Product.

Group	Mean	SD	Range
E	7821.9	1059.9	6518.7 - 10606.8
EM	10105.4	2384.0	8225.4 - 14214.8
I	8677.4	1144.5	7191.6 - 11100.6
IA	9462.6	1230.3	4788.7 - 11452.1
IM	10634.0	1030.4	9603.6 - 12248.7

Table 17. Intergroup comparisons (2), cardiovascular and inspired volatile requirements.

	Group				
	E-EM	E-I	E-IA	E-IM	EM-I
HR	0.02	ns	0.004	0.0007	ns
VAP	0.0001	ns	ns	0.002	0.0001
RPP	0.02	0.04	0.002	0.001	ns

	Group				
	EM-IA	EM-IM	I-IA	I-IM	IA-IM
HR	ns	ns	ns	0.009	ns
VAP	0.0001	ns	ns	0.002	0.0007
RPP	ns	ns	ns	0.009	ns

C. RECOVERY TIMES.

A relative anaesthetic overdose, defined as an ATPR time of more than 15, minutes occured in 6 isoflurane cases and half of these occured in group IM. The ATPR times were acceptable in all the ethrane patients. As the ATPR may be misrepresentative (vide supra) a cATPR was calculated for each patient (table 18). The recovery assessed by the cATPR is excellent in groups E and I, in more than 70% of cases in groups EM and IA but poor in group IM. The differences between the groups are listed in table 19.

D. OVERALL INTER-GROUP COMPARISONS.

The criteria defining adequate control and an adequate anaesthetic state were acheived in the majority (70%) of patients in groups NO. These were acheived in only 1 patient in groups M (table 20). Seven point five percent of patients in groups NO failed two or more of the criteria compared to 83.3% of patients who required additional morphine.

"INTERESTING CASES" AND THOSE EXCLUDED FROM THE STUDY.

1. EXCLUSIONS.

In these two cases the TSAP was reset to higher value during the proceedure because the patients were receiving an excessive doseage of volatile despite additional morphine (vide supra). In both cases the pre-operative blood pressure, as recorded by the nursing staff, was 160/90 mmHg and these patients were not considered as "hypertensive". In the patient who received enflurane further questioning post-operativly revealed a history of

Table 18. Group details (6), recovery times.

	ATPR Time			
	Mean	SD	Range	No. of Cases with a cATPR > 15 minutes.
E	4.9	1.93	2 - 9	0 (0%)
EM	10.0	3.74	5 - 15	2 (28.6%)
I	7.1	5.31	1 - 21	1 (6.3%)
IA	8.5	6.62	2 - 22	2 (20%)
IM	20.4	9.34	13 - 36	3 (60%)

The cATPR is the corrected ATPR and is calculated:

cATPR = ATPR + (STPR - ATPR) - 5.

Any significant (more than 5 minute) prolongation of the STPR - ATPR time is reflected by an increase in this value.

	STPR TIME			STPR - ATPR TIME		
Group	Mean	SD	Range	Mean	SD	Range
E	9.6	3.55	5 - 17	4.7	2.75	1 - 10
EM	17.3	5.67	8 - 26	7.3	5.88	3 - 20
I	11.9	5.84	2 - 25	4.8	2.32	1 - 10
IA	12.7	8.82	3 - 29	4.2	2.90	0 - 7
IM	24.8	6.63	17 - 40	4.4	1.67	2 - 6

Table 19. Intergroup comparisons (3), recovery times.

	E-EM	E-I	E-IA	E-IM	EM-I
ATPR	0.004	ns	ns	0.0002	ns
STPR	0.004	ns	ns	0.0003	0.05

	EM-IA	EM-IM	I-IA	I-IM	IA-IM
ATPR	ns	0.02	ns	0.0007	0.03
STPR	ns	0.0003	ns	0.002	ns

Table 20. Group details (7), the patients in whom the control of SAP or the anaesthetic state produced was inadequate.

The number of patients in each group in whom the criteria for adequate control or an acceptable anaesthetic state were not acheived. See text for the definition of these criteria and Appendix III for details of the inadequacies.

	Group				
No. of Criteria not acheived.	E	EM	I	IA	IM
1	2	1	4	4	-
2	1	5	1	0	2
3 or more.	0	1	1	0	2
Total:	3	7	6	4	4
% of group:	21.4	100	37.5	40.0	80.0

"previous" hypertension despite a denial of problems with a "raised blood pressure" pre-operativly. In both cases the preinduction blood pressure was within acceptable limits.

Like the patients in group M, control of SAP was not acheived with clinically acceptable volatile doseage and the controller instructed the operator to give additional morphine. However, the effect of the morphine boluses in these cases was minimal and the integral continued to rise (compared figure 58 to figures 50, 53 and 56). The controller did not acheive control of SAP in these cases, despite high doses of volatile anaesthetic, and the TSAP was reset to prevent over-dose.

2. THE EFFECT OF HAEMORRHAGE.

In one patient the surgeon had to go "through" the uterus to gain access to the uterine vessels. This resulted in a large blood loss (over 3.5 liters), a SAP below the TSAP and the patient receiving no isoflurane for approximatly 20 minutes. At no point during this period did either of the two anaesthetists invlolved feel that anaesthesia was inadequate or that the action taken by the controller was inappropriate. Following restoration of the blood volume the SAP gradually rose towards the TSAP and the integral was reset to the pre-loaded value by the operator. Control of SAP from this time (see figure 59) was good.

3. THE EFFECT OF GLYCOPYROLLATE AT INDUCTION.

One patient received glycopyrollate at induction (0.6mg). The control of SAP and anaesthetic state acheived

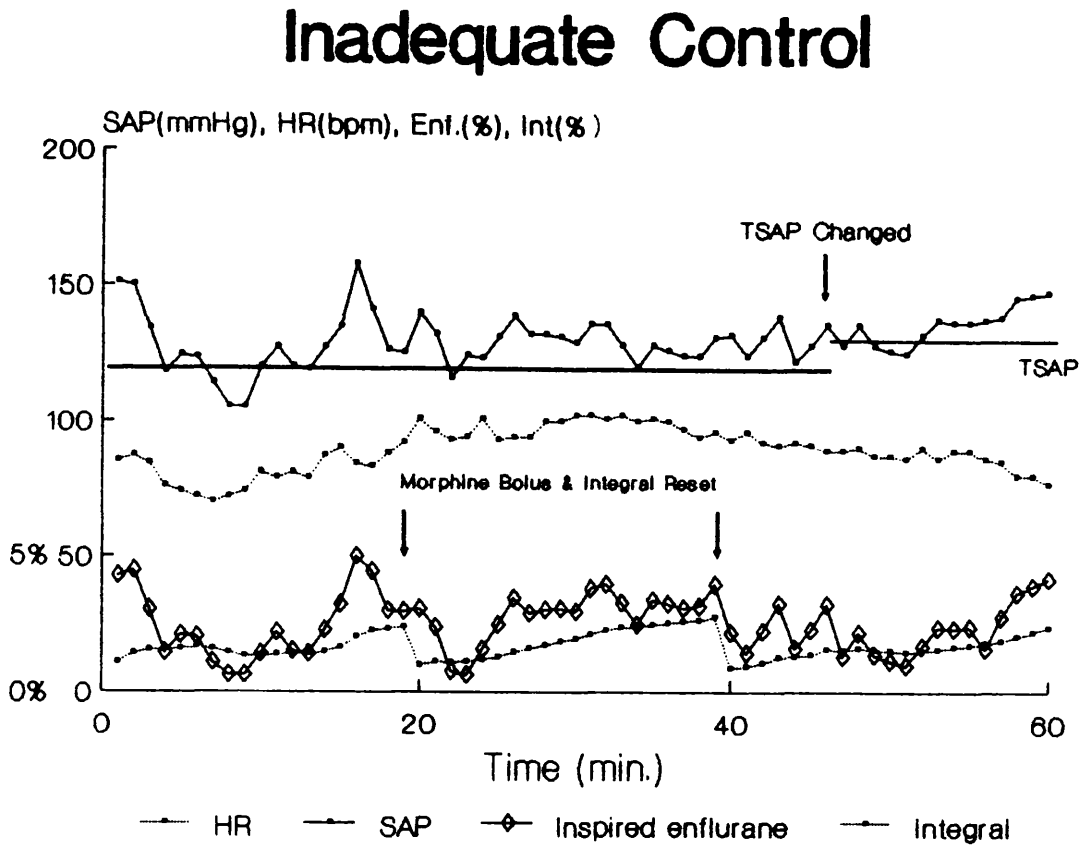


Figure 58 An example of inadequate control.

This patient received a relative overdose of enflurane despite two additional boluses of morphine (lower arrows) and the TSAP was changed (upper arrow). The integral did not stabilise after either bolus of morphine but continued to accumulate.

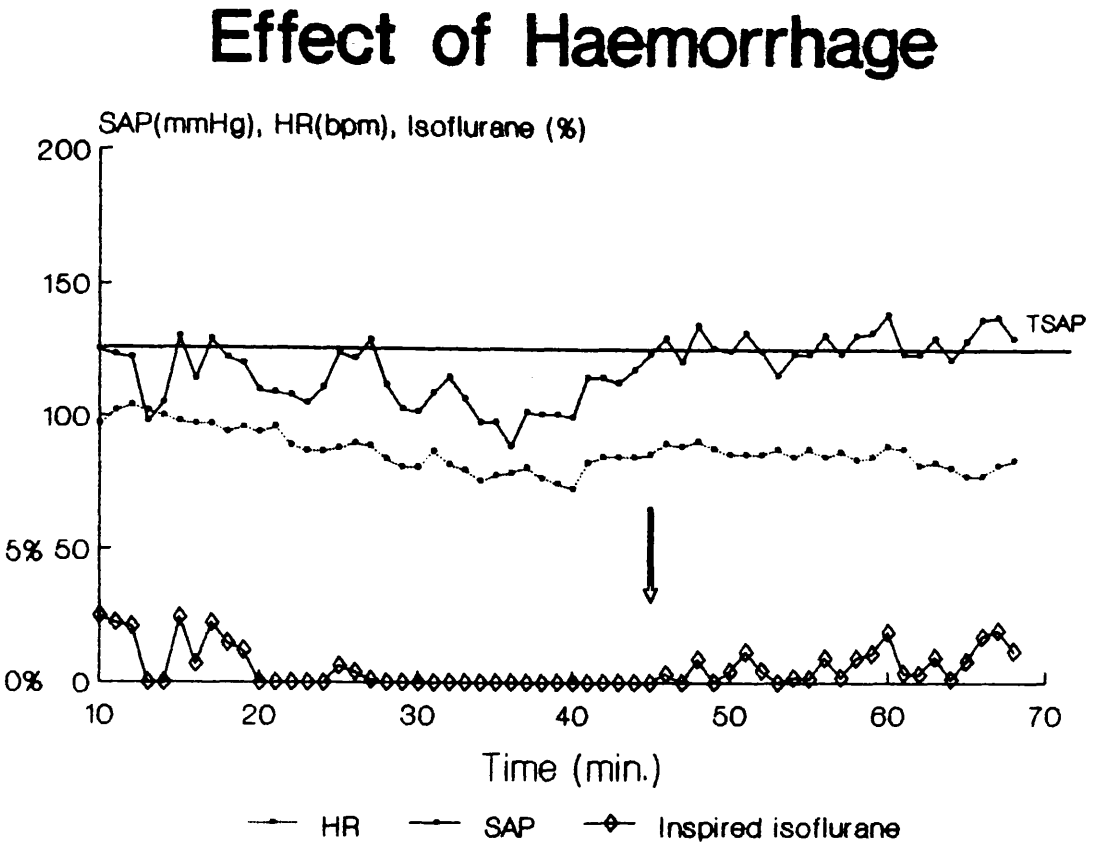


Figure 59. The effect of haemorrhage.

This patient lost over 3.5 litres of blood during the procedure and was hypotensive, relative to the TSAP, for most of the control run. When the TSAP was achieved the integral was reset (arrow) and from this point control of SAP was acceptable.

in this patient were acceptable in all respects (table 21).

4. THE PATIENT WHO RECEIVED ENFLURANE AND ISOFLURANE.

A 26 year old patient, admitted for abdominal hysterectomy for severe dysfunctional bleeding, was admitted to the latter part of the enflurane study. This patient required two additional boluses of morphine during the proceedure at which an "abnormal" right ovary was biopsied. Histological examination later confirmed an abnormality which was suggestive of carcinoma in-situ and the patient was re-admitted for a **bilateral** oopherectomy. By this time we were studying isoflurane and the patient consented to the use of the controller for her second operation. At this operation the patient required a single additional bolus of morphine. The data from the two operations is listed in table 22.

Apart from a higher heart rate during the second proceedure the results appear comparable although control was marginally better during the second proceedure. Statistical comparison of two data sets would be of limited use and was not undertaken.

PUPIL DIAMETER.

Pupil diameter was measured in 34 patients. A significant correlation was found in 5 cases. The correlation coefficients and P values for these cases are listed in table 23. These patients are derived from 4 of the 5 groups and, when considered as a group in their own right, there is no single outstanding feature which suggests that the anaesthetic state in these cases difered

Table 21. Data from the patient who received glycopyrollate at induction.

TSAP = 116 mmHg	HR = 96.7 bpm
SAP = 118.6 mmHg	RPP = 11470.4
MD_{TSAP} = 2.6 mmHg	ATPR = 11 min.
RMSD = 8.5 mmHg	cATPR = 12 min.
PR = 1.5	

Table 22. Data from the patient who received enflurane and isoflurane.

	Enflurane	Isoflurane
TSAP	106	106
SAP	111.2	109.6
MD_{TSAP}	5.2	3.6
RMSD	9.24	8.62
PR	2.9	2.7
HR	78.0	99.4
RPP	8725.7	10891.0
VAP	2.21	1.76
cATPR	17	23

Table 23. Correlation between pupil diameter and SAP.

Group	No. of Records	Correlation	P Value
EM	14	0.62	0.02
I	7	0.83	0.05
I	9	0.69	0.05
IA	16	0.63	0.02
IM	14	0.62	0.02

significantly in any other way from the rest of patients studied (table 24).

SPECTRAL EDGE FREQUENCY.

The Neurotrac was used to measure the SEF in 8 patients who received isoflurane. Of these, 4 came from group IA, 3 from group I and one from group IM. Figures 60 and 61 show the relationship between SEF and SAP for the patients in groups I and IA. In four of these cases there appears to be a relationship between the SAP and SEF, which is most apparent in diagrams (a) and (b) in figure 60. In three cases no relationship was apparent (figure 61).

If these 7 cases are divided into two groups; Group A (n = 4), those who appear to display a relationship between SEF and SAP, and Group B (n = 3), those who do not; these groups are found to be comparable (table 25).

Insufficient markers where put on the trace from the patient who required morphine to allow the relationship between SEF and SAP to be determined. The trace recorded from this patient is itself interesting (figure 62). At the time the controller instructed the operator to give a bolus of morphine burst suppresion was apparent and the CSA became isoelectric shortly after this. This continued for some 8 minutes before burst suppresion occured and continual activity resumed. The control of SAP in this case is displayed in figure 56.

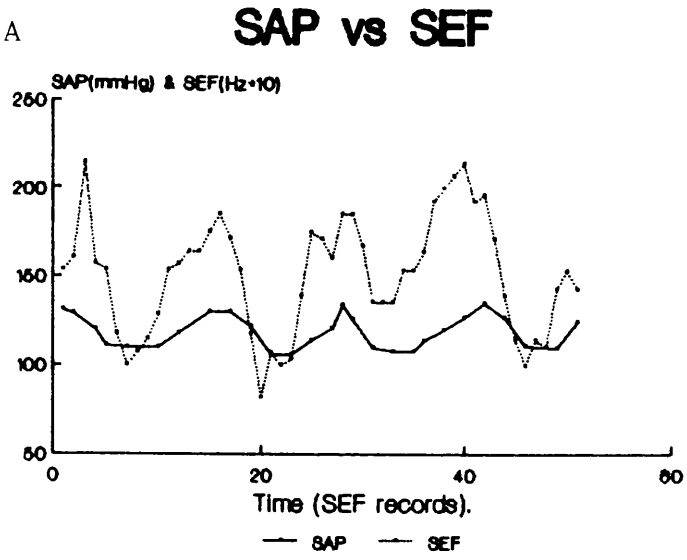
Table 24 - Data from the 5 patients with a significant correlation between PD and SAP.

Variable	Mean	SD	Range
ATPR	9	7.52	4 - 22
TSAP	117.2	6.72	106 - 124
SAP	120.3	8.14	109.6 - 131.7
MD_{TSAP}	3.1	3.82	-1.4 - 7.74
RMSD	8.7	1.32	6.7 - 10.0
HR	80.4	15.21	63.5 - 99.3
VAP	1.5	0.65	0.7 - 2.0

Table 25. A comparison of the 4 cases who display a visual relationship between SAP and SEF and the three patients who do not.

	Visual Relationship		No Visual Relationship	
Variable	Mean	S.D.	Mean	S.D.
ATPR	12.3	8.3	6.3	3.1
TSAP	117.8	1.7	110.7	0.6
SAP	118.2	1.2	113.8	2.8
MD_{TSAP}	0.4	1.5	1.4	1.0
RMSD	8.7	1.7	6.4	3.3
HR	77.5	12.1	75.8	5.6
VAP	0.9	0.1	1.0	0.1

A



B

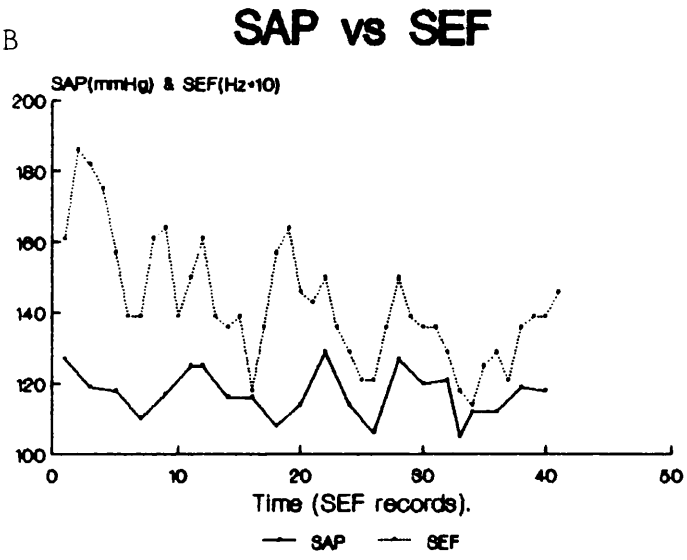
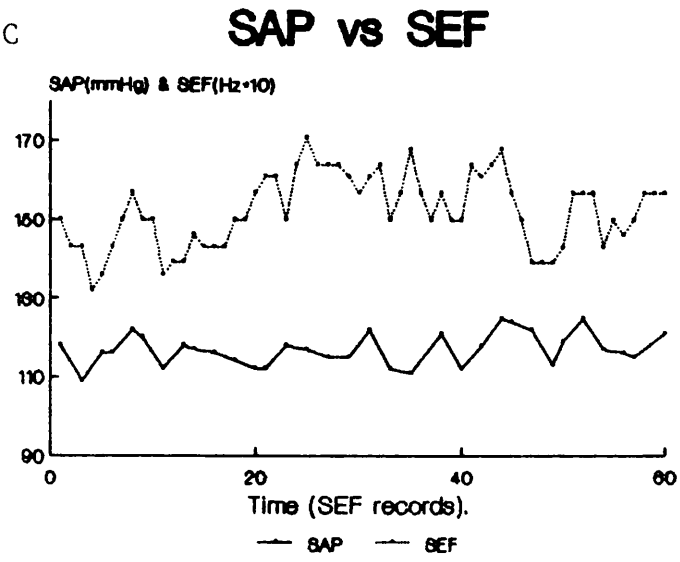


Figure 60. The 4 cases in whom a visual relationship between SAP and SEF was apparent.

(continued)

C



D

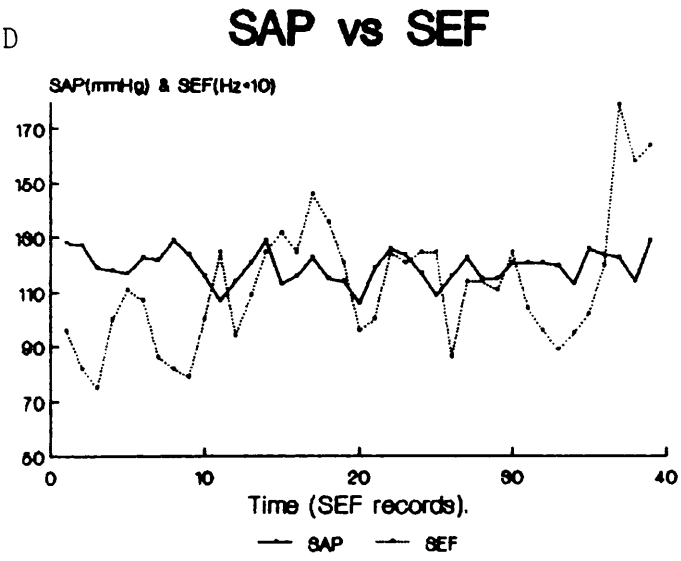


Figure 60 (continued).

The 4 cases in whom a visual relationship between SAP and SEF was apparent.

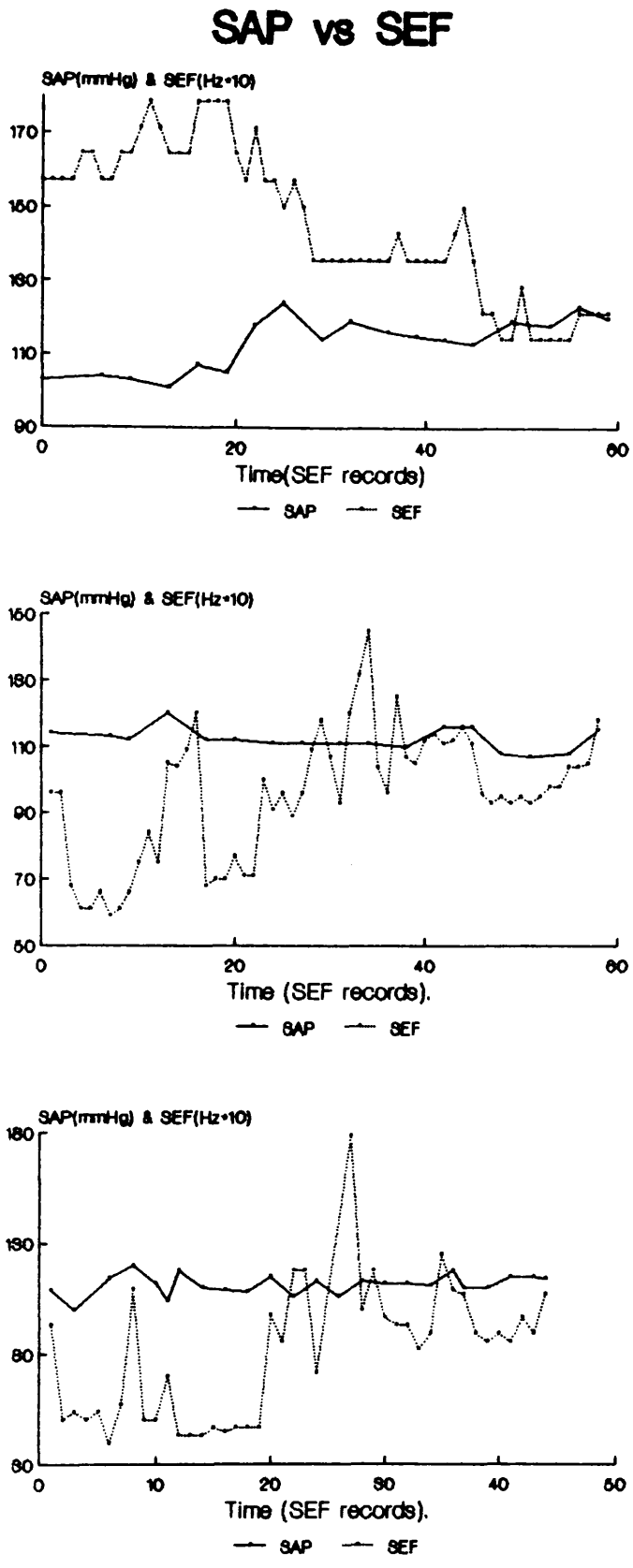


Figure 61. The 3 cases in whom a visual relationship between SAP and SEF was not apparent.

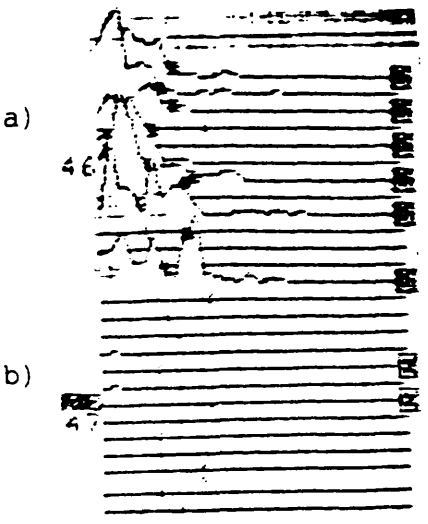
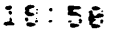


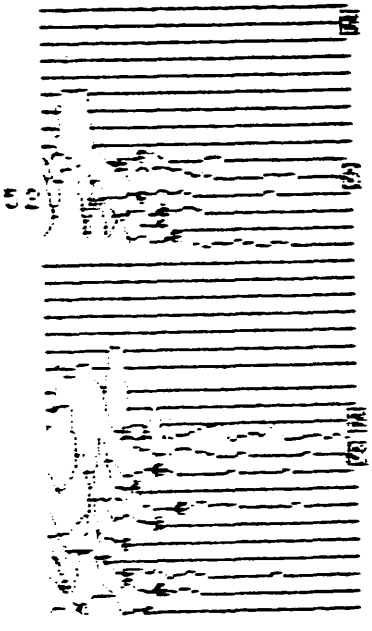
Figure 62 The single case in group IM in whom the SEF was monitored.

At the time the computer instructed the operator to give an additional bolus of morphine burst suppresion was apparent on the CSA trace (a). The trace became isoelectric shortly after this (b).



An EEG trace was taken to confirm this (c).

The only visible activity on this trace is ECG contamination. After 8 minutes EEG activity returned (d) and became continuous after 30 seconds (e).



The figures show the activity in the right hemisphere, the left trace was identical. The missing segment is isoelectric.

CHAPTER 11

DISCUSSION

A RESUME:- DIFFICULTIES IN ASSESSING TECHNIQUES PROPOSED AS MONITORS OF THE ANAESTHETIC STATE.

If it is accepted that the anaesthetic state results from the balance between the effects of anaesthetic dose and the effects of surgical stimulation on the CNS, then it is reasonable to assume that any variable which reflects changes in these determinants may "measure" this state. However, the validity of such variables, as measures of the true anaesthetic state, is unknown. This is because:

1 Surgical stimulation cannot be quantified. And, although it may be described qualitatively as a graded sequence of responses, the validity of these responses as a measure of the true anaesthetic state is unknown.

2 The wide variation in anaesthetic requirement means that anaesthetic dose per se cannot be used as a measure of the anaesthetic state. The limitations of indices, such as MAC, have been discussed (chapter 2).

Therefore, if the various techniques proposed as monitors of the anaesthetic state (see chapter 3) are to be fully assessed, an individually valid anaesthetic state must be available for reference.

THE USE OF CLINICAL SIGNS AS A STANDARD OF ANAESTHETIC ADEQUACY.

Clinical signs are currently the only practical,

universally accepted method of assessing anaesthetic adequacy and are used to guide the administration of thousands of successful anaesthetics each day. Individual anaesthetists must therefore be able to identify the zone of surgical anaesthesia, for individual patients, with the techniques he uses (see introduction). However the exact location and best definitions for the boundaries of this zone are unknown. The current definition of what constitutes an adequate clinical anaesthetic state is therefore, both subjective and variable.

If a computer control system, operating from rules based on clinical signs, produces an individually tailored anaesthetic state that achieves the goals of anaesthesia, a clinically standardised anaesthetic state would be available. The use of a computer control system would ensure that the description of the state is objective and not subjective, eliminating the individual variation caused by the different ways anaesthetists work.

There are obvious limitations to the use of clinical signs i.e. they cannot be expected to give reliable information during some types of surgery (e.g. cardio-pulmonary bypass surgery) and, in some situations, the validity of individual signs may be reduced e.g. heart rate changes will have less importance following atropine. However, within these limitations, the controller could be used to evaluate other techniques in circumstances where the validity of these signs is clinically established and complicating factors e.g. atropine and beta blockers are excluded.

Such a control system would therefore allow the

various techniques proposed as monitors of anaesthetic adequacy to be more fully assessed. Further, the degree of effect variables, which are known to detract from the usefulness of clinical signs, have on the validity of these signs as an index of anaesthetic adequacy, could be more fully assessed.

It should be noted that although clinical signs may not contain sufficient information to determine whether a patient is "aware", there is currently no proven method of assessing "awareness" intraoperativly. The absence of intraoperative recall must therefore be determined postoperativly. The difference between amnesic wakefulness and awareness has been discussed.

SAP AS AN INDICATOR OF THE ANAESTHETIC STATE.

The use of SAP as the sole variable to control the delivery of anaesthetic agents can be criticised on several grounds. Anaesthetists use combinations of clinical signs to determine the anaesthetic state and SAP alone cannot be expected to give reliable information in all cases, hypovolaemic and hypertensive patients being obvious examples. In this study we have attempted to limit the effects of these factors by careful patient selection.

However, SAP is one of the few quantifiable clinical indices of anaesthetic adequacy and the author's consider that a SAP within the range expected for normal sleep is one of the many clinical requirements of a good anaesthetic and, in routine anaesthetic practice, increases in SAP are often treated with anaesthetic drugs.

CONTROLLING SAP.

Systems, designed to control arterial pressure, have been described (206,207,208).

Suppan (206) described a system in which the operator selected SAP limits, determined after a clinically satisfactory anaesthetic state was achieved. The controller maintained SAP within these limits by delivering one of three, preselected, halothane concentrations. This system is crude and requires careful supervision by the anaesthetist.

A self-tuning control system has been used to control MAP during hypotensive anaesthesia with both isoflurane and nitroprusside (207,209). And a "discrete digital control system" , which uses a combination of MAP and recent drug requirement to determine the dose requirement, has been used to control MAP with both halothane (208) and nitroprusside (210). This system has only been used in laboratory animals. A PID controller has been used to control SAP following cardiac surgery (211).

In our study SAP was controlled with doses of anaesthetic used in routine practice and SAP was controlled at normal, not hypotensive, levels. We chose to select the simplest system which would achieve control of SAP because the pharmacological situation is complex and simple systems gives the best understanding of the process with the maximum safety. Control of SAP with such a system has many limitations e.g. it cannot anticipate drug demand and cannot be expected to produce optimal control in all patients. Improvement may be difficult as more complex systems e.g. self tuning systems which might have the

flexibility to cope with the inevitable non-linearities which exist, when one is trying to suppress the SAP response to surgery, might require more data than SAP sampled once a minute.

Most workers e.g. Woodcock and his co-workers (207) have assessed control by the time taken to achieve the target and the goodness of control about the target once it is reached. We chose to assess SAP control over most of the control run, excluding only the initial ten records, so that the overall quality of the anaesthetic (in terms of SAP) and the controller could both be assessed. A direct comparison of our results to those of other workers is therefore not appropriate.

THE TARGET SAP.

Choice of a TSAP corresponding to a reasonable anaesthetic state is difficult. Spot measurements in the ward or in the anaesthetic room are likely to be unrepresentative due to anxiety or sedation. For this reason we used age and sex related values from tables. A TSAP of 90% of this value was chosen after initial trials suggested that a TSAP of 85% of this value overdosed the patients.

This method of selecting the TSAP is crude. The standard deviations of the mean SAP in females, quoted in the tables we used (205) range from 11.8mmHg, in the 20-24 year age group; to 29.0mmHg, in the 65-69 year age group. It is possible that those patients who required additional morphine reflect those in whom the TSAP is too low.

Berger monitored arterial pressure directly in 34 female patients for a 36 hour period over the peri-

operative period (212). These workers determined a preoperative baseline (POB), the average value recorded in the second hour of monitoring; and a preanaesthetic standard (PAS), the average value of 15 consecutive measurements made at 1 minute intervals prior to induction. The mean POB was 130.8mmHg and the standard deviation 26mmHg. The PAS (in the 26 patients receiving general anaesthesia) was 150.1mmHg. These workers concluded that "... continuous or at least repeated measurements of blood pressure and heart rate obtained while the patient is not under the influence of drugs should be the most appropriate baseline". The direct measurement of blood pressure preoperatively is not appropriate in general anaesthetic practice. Repeated preoperative measurements in a "relaxed" setting, with a Dinamap or similar machine to prevent observer bias and "white coat" hypertension (213), may give a more valid reference value.

THE ADDITIONAL RULES.

In the preliminary work, carried out before the additional rules were introduced, some limitations of the control system became apparent. The additional rules were introduced in light of these findings.

A major limitation of the control system is that it cannot anticipate "predictable" changes in the level of surgical stimulation and therefore anaesthetic requirement e.g. following skin incision. In anaesthetic practice, some stimuli can be anticipated and the anaesthetic dose increased. We attempted to imitate this

practice by delivering a minimum concentration for the first 10 minutes to "cover" the effects of skin incision.

A second problem is that the system delivered a relative overdose of anaesthetic to some patients. In anaesthetic practice it is common to give a bolus of narcotic to limit the requirement of volatile anaesthetic. The second rule, which required additional morphine if the dose of volatile agent became excessive, was an attempt to imitate this practice. The resetting of the integral prevented overdose in these patients. This rule was based on anaesthetic requirement i.e. over-dose was defined in terms of anaesthetic dose. This is not ideal.

The dose limit i.e. a total inspired concentration of 15% over 5 consecutive vaporizer settings with each individual setting exceeding 2.5%, was left the same following the change to isoflurane. If the 5 groups are ranked by the percentage of patients in each group, in whom the criteria defining an adequate anaesthetic state were achieved (see table 20 for details), it is found that:

E > I > IA >>> EM > IM

(the groups are ranked from left to right)

That an acceptable anaesthetic state was achieved in a slightly higher percentage of patients in group I when compared to group IA suggests that small doses of anticholinergic agents detract from the usefulness of SAP as an indicator of anaesthetic adequacy (vide infra). The differences between otherwise comparable isoflurane and enflurane groups (i.e. groups I and E; and groups IM and

EM) may reflect the limitation of the second rule.

In terms of MAC, isoflurane is more potent than enflurane. If this relationship is true, with respect to the SAP response to surgical stimulation then, on a population basis, the "split" between those patients who required additional morphine and those who did not will have occurred at a "lighter" level of anaesthesia in the enflurane group. There is some evidence to suggest this is true:

1. Only 16% of the isoflurane patients required additional morphine compared to 33% of the enflurane patients.
2. No patient in group IM required more than 1 additional bolus of morphine while 3 of the 7 enflurane patients in group EM required 2 boluses and one patient required 3.
3. Although there is no statistical difference in recovery times between comparable groups the percentage of cases in whom the cATPR was over 15 minutes rises from 0% in group E to 60% in group I (table 18).

If this explanation is correct and a more representative TSAP cannot be defined (vide supra), then an individually valid method of determining when anaesthesia is excessive is required

In the single isoflurane patient who had SEF measured and required additional morphine, the requirement of morphine might have been determined by EEG changes i.e. burst suppression. The processed EEG might therefore be used, with isoflurane, to determine the requirement of

morphine. However, the automated recognition of this EEG pattern is not easy (150) and burst suppression does not always indicate that the clinical state is adequate, far less excessive (117,119,120).

A bang-bang control system using two feedback variables, MAP and SEF, has been developed (214). The on/off MAP and EEG systems were tested separately in 4 experiments and the combined system in one dog. Although the results suggest the system may be useful in the future, the animal was not undergoing surgery and several step tests were required to determine the MAP and SEF thresholds before the loop could be closed.

DOES THE CONTROLLER ACHIEVE THE GOALS OF ANAESTHESIA.

No patient showed clinical signs that suggested anaesthesia was inadequate and no patient complained of awareness post-operativly.

Although clinical scoring systems have severe limitations, the PRST score is a simple method of summating the significance of clinical signs and was used in this study as a general measure of anaesthetic adequacy. The highest score recorded was 4 and the mean values suggest that anaesthesia was adequate. However, the lowest mean value occurred in Group E which, in terms of recovery, was the most lightly anaesthetised group and the highest score in group IM which, by the same criteria, was the most deeply anaesthetised group.

In group E only 14.9% of the total PRST score is attributable to heart rate but in the other groups the heart rate contribution exceeds 50% of the total score.

The higher heart rates in these groups is probably drug related and not attributable to increased autonomic activity.

The PRST score cannot therefore differentiate between adequate and excessive anaesthesia as low scores occurred in all groups. However, as the clinical assessment of the anaesthetic state is largely successful, it is likely that clinical signs are a sensitive measure of insufficient anaesthesia. The PRST score will reflect this occurrence.

THE EFFECT OF ANTICHOLINERGIC AGENTS.

There are no statistically significant differences between groups I and IA. However, an acceptable anaesthetic state was achieved in only 40% of patients in group IA compared to 31.2% in group I. Small doses of anticholinergic agents may therefore detract from the use of SAP as an indicator of anaesthetic adequacy. This effect appears to be limited as the goals of anaesthesia were achieved by the controller in the patient who received a bolus of glycopyrollate at induction.

THE RELATIONSHIP BETWEEN PUPIL DIAMETER AND THE ANAESTHETIC STATE.

We believe that eye signs have limited value during anaesthesia and surgery and were surprised to find a correlation between PD and SAP in several cases. However, there appears to be no relationship between the clinical anaesthetic state (as defined by SAP) and pupil diameter.

THE RELATIONSHIP BETWEEN SEF AND SAP.

The visual relationship between SAP and SEF is apparent during relatively small fluctuations in SAP (approximately 10 to 20mmHg). If fluctuations in SAP of this size reflect changes in the true anaesthetic state, then SAP may be a more sensitive indicator of the anaesthetic state than previously accepted e.g. one of the criteria Thornton and his co-workers used to define a "marked" autonomic response was an increase in SAP of 20mmHg or more (174).

However, our method of determining a relationship between SEF and SAP is crude; we only compared SEF and SAP during a short period in a small number of patients; we did not find a relationship in all cases; and it is not known if SEF is related to the true anaesthetic state. Further, we did not demonstrate any significant difference between those patients in whom a relationship was apparent and those in whom it was not. Therefore, it cannot currently be proven that SAP is a sensitive measure of the anaesthetic state.

CONCLUSIONS.

In conclusion, the controller achieved the immediate aim of controlling SAP and also produced a pattern of clinical signs recognisable as general anaesthesia, thereby approaching a standardised anaesthetic state. Although further work is required to determine a more valid TSAP and a method of determining a relative anaesthetic overdose, this technique could ultimately be used in developing new anaesthesia monitoring methods.

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APPENDIX I

APPENDIX I.

THE SOFTWARE

GENERAL REMARKS.

The control program is written in BASIC and designed to:

1 Read HR, SAP, MAP and DAP from the Dinamap's memory.

2 Determine the required dose from the control algorithm and the additional rules after each SAP determination.

3 Drive the vaporizer to the required setting.

Additional facilities allow a hardcopy of the control data to be printed, and stored to floppy disk; and SAP and the inspired volatile concentrations to be plotted on the screen.

In the following discussion the numbers in square brackets ("[ ]") refer to lines in the program. The description of the program assumes the reader has a working knowledge of BASIC and has read the sections on "Equipment" and "Development of the Control System".

Before discussing the program the output from the Dinamap; the input output (I/O) chip and the analogue board in the computer; and the commands used to control the printer and Dinamap are considered.

THE DINAMAP'S RESPONSE TO THE STATUS REQUEST "BBA <cr>".

Host Signal	Dinamap Response
BBA<cr>	BBAhhmmssMDhhmmssSAPBPMSAPDAP<cr>

(Character No. 1----------30)

The transmitted string of 30 characters can be separated into the following components:

Section of String	Meaning
1-3	Message type, echo of host request
4-9	Current 1846 time of day (hours-min-sec)
10	Operational status:- "0" if manual mode
	"1" if auto mode
	"2" if stat mode
11	Functional status:- "0" if active
	"1" if idle
12-17	Time of determination (hours-min-sec)
18-20	MAP in mmHg
21-23	Pulse rate in bpm
24-26	SAP in mmHg
27-29	DAP in mmHg
30	Terminating carriage return (Hex 0D)

Notes.

As the host communication port is multiplexed with the printer output a delay of around 1 sec occurs prior to the transmission of the string following a request. At the set baud rate of 600, 0.5 sec is required to transmit the full string. NULs and control characters (except the carriage return) are ignored. Some alarms are 'fatal' and preclude any response to a host request e.g. the over-pressure alarm. Other valid request strings initiate different responses which may be active (e.g. an instruction to make a determination).

THE I/O CONNECTIONS USED.

The input - output (I/0) ports interface the computer to peripheral equipment. In the control system the computer is interface to the following :

1. Dinamap
2. Controller a)via the A-D converter
   b)via the PIO chip
3. Printer

THE PIO CHIP.

This chip is specifically designed to connect directly to the Z80 processor and provides the user with two 8 bit parallel ports (Ports A and B). The 16 peripheral data lines from this chip are designated PA0 - PA7 and PB0 - PB7, for ports A and B. In addition to these lines each port has a pair of handshaking lines. Handshaking is a technique used to control the rate and timing of data flow between two devices and need not be considered further. The PIO ports are used to drive the vaporizer (via the controller) to the desired setting. They are also used to send the watch-dog signal to the controller. In BASIC the commands "OUT" and "INP", in association with the correct address are used to send information to and receive information from the PIO chip (and analogue board).

THE ANALOGUE BOARD.

This board provides 2 digital to analogue converters (DAC) and one analogue to digital converter (ADC), each with a 10-bit resolution. The ADC has a 16 channel input multiplexer so any of 16 input signals can be selected and converted. This board is used to check the position of the vaporizer via its integral potentiometer.

THE DINAMAP AND PRINTER: CONNECTIONS AND COMMANDS.

The printer is connected to the parallel user port and the Dinamap to the serial port. In BASIC the command "PRINTER A,B" is used to address these. The first argument "A" is used to select the printer type, 3 selects the parallel port and 4 the serial port. The second argument "B" is used to set the baud rate and is necessary for serial devices. The code "2" selects a baud rate of 600 which is compatible with the Dinamap.

A DESCRIPTION OF "LETHE."

Figure 63 is a flow diagram of "Lethe". The program comprises:

INITIALISATION (10-1740).

The main variables are listed and set, the controller initialised (vide infra) and data requested from the operator. Some of this information is used to construct the filename. The filename (F$ at line 1230) is an 8 character string and is constructed from the patients initials, age and sex; a series number and a software code [200]. Other data; date, type of operation and whether a narcotic was given at induction is used as part of the hardcopy heading [1410-1510] but not stored to disc.

The predicted arterial pressure is calculated from the age and sex data [1280]. Both this value, and 90% of this value [1290] are printed on the screen. The operator is instructed to input the desired target systolic arterial pressure (90 - 150 mmHg, at lines 1330-1340). The pre-loaded value for the integral component of the P - I control algorithm is determined at line 1350.

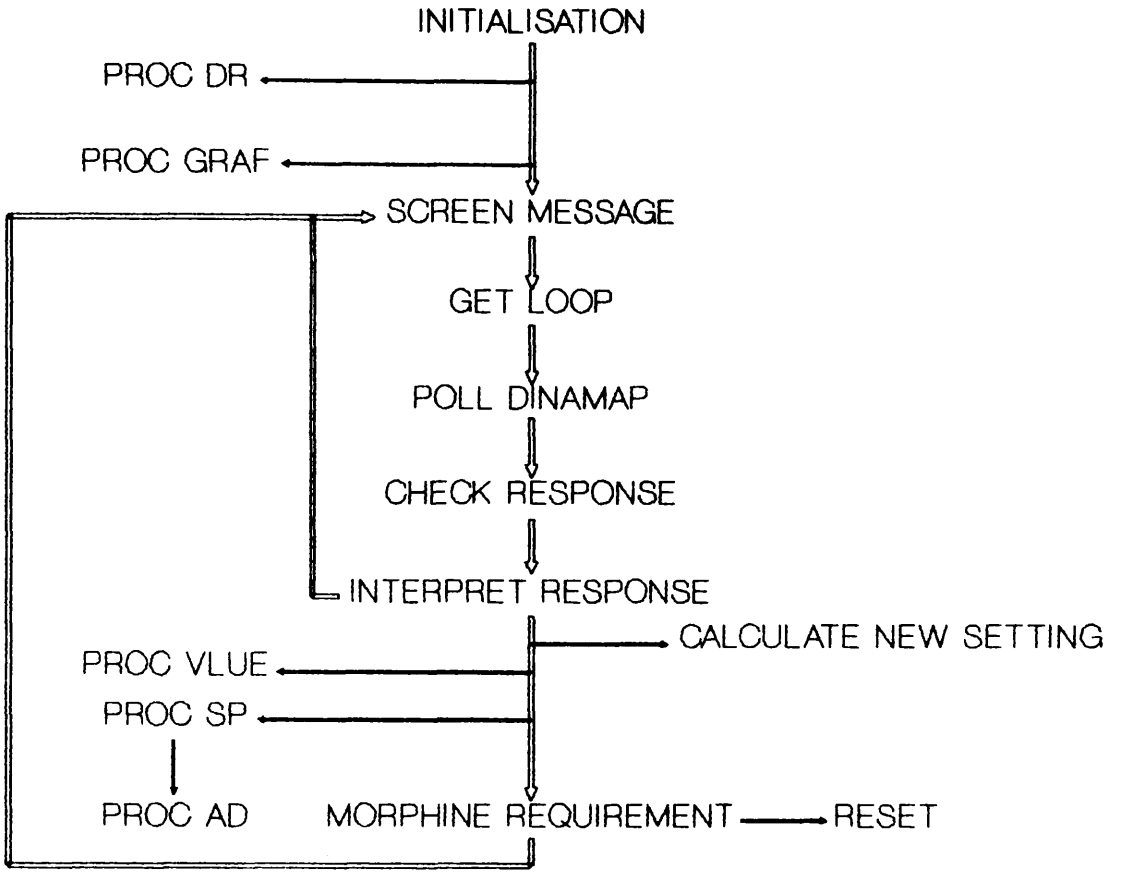

Figure 63.

A flow diagram of the control program "LETHE".

Array D [1640], dimension (6, size) is used to store the cardio-vascular and inspired volatile data. "Size" is the variable which defines the number of records which can be stored and is set at 240 [210]. Each record comprises the time (from starting the controller), HR, SAP, MAP, DAP, RPP, and inspired concentration. "C" is the counter for the Dinamap cycle [220]. "TS" is the first time read from the Dinamap's memory [230 & 2230]; "T" is the current time in the Dinamap's memory [240, 2260]; "T1" is the elapsed time i.e. T1 = T - TS [2230-2240]; and "BD" is the previous value of "T" [250 & 2190]. Three arrays designated PU, CO and VO are created and filled [530-770]. These arrays hold data which relates the marked vaporizer settings (array CO, in which 'OFF' is designated -0.2); to the number of pulses required to drive the vaporizer to that setting from the 'OFF' position (array PU) and the read-out voltage from the potentiometer at that setting (array VO). The data for the arrays PU and VO were determined in the laboratory as was the back-lash correction factor (NB, line 460) which is required when the vaporizer is driven in the opposite direction to the previous motion. The peripheral input output ports, analogue to digital converter ports and multiplexer channel are also selected and addressed [790-930].

PROC DR [3750-4050] is used to initialise the vaporizer and is called at line 980. This procedure drives the vaporizer to the 'OFF' setting, which corresponds to -0.2 in array CO. The motor in the drive unit is switched on, the vaporizer driven 3500 pulses in an anti-clockwise direction and the motor then switched off. During the

driving sequence a signal is sent to the watchdog. With this number of pulses the vaporizer will be "over-driven" to the 'OFF' position from any previous setting and the lower limit switch activated. The status of the limit switches [3920] is checked; if correct i.e. lower-limit switch active and upper-limit switch inactive the program proceeds, if incorrect a warning is displayed and the program halts [3930-4030]. Before returning to the main program PROC AD is called [4230-4310]. This procedure determines the potentiometer voltage. If the measured voltage is outwith 0.02 volts of the expected voltage (in array VO) then a warning is printed and the program halts.

After the vaporizer has been initialised and the requested data received the operator is instructed to set the Dinamap to cycle at one minute intervals and then press "R". PROC GRAF [4360-4620] is called to set up the screen graphics, a signal sent to the watchdog [1680-1690] and the operator instructed to press "R" to close the control loop [1730-1740].

THE MAIN PART OF THE PROGRAM.

The main section of the program comprises a loop (see figure 63). A print out of the program is included at the end of this appendix.

1. SCREEN MESSAGE [1840-1860]: The current SAP, vaporizer setting and time followed by the 5 options available to the operator (see GET loop) are printed on the screen.
2. GET LOOP (1870-1920): This loop is a timed, single character input routine which gives the operator 5

options:

a. "E" to end the control run (2590-2810): "End of Run" is printed on the hardcopy, the vaporizer driven to "OFF" [with PROC DR], the data stored to disc [2640-2700] and the option of a screen dump given [2720-2790].

b. "O" to open the control loop: the vaporizer is driven to off but the computer continues to collect data.

c. "C" to close the loop if opened. These two inputs ("O" and "C") have their effect at lines 2440 and 2450.

d. "N" initiates a subroutine at 4810. This subroutine resets the integral and the bolus counter (vide infra); and prints this event.

e. "S" to reset the TSAP. The TSAP may be reset to any value between 90 and 150mmHg (1930-2000). The graphic display is updated.

If no input is made the program continues.

3. POLL DINAMAP [2040-2130]; the Dinamap is polled [2050-2080] and "T" determined [2160].

4. CHECK RESPONSE (2160-2190): If "T" does not equal "BD" then a further determination of SAP has occurred; "BD" is updated [2190] and the program proceeds. If not, the program loops back to "SCREEN MESSAGE".

5. INTERPRET RESPONSE [2210-2320]: The rest of the Dinamap string is interpreted and array D incremented.

6. CALCULATE NEW SETTING: a subroutine [2860-3030] is called at line 2360. The error signal [2900] is determined, the integral calculated [2930-2940] and the required dose ("SP") determined [2960]. If the required setting is less than 0.6% (the value of "MC" set at line 470) and less than 10 SAP readings have been made then 0.6% is delivered [2970-2980]. These steps constitute the first additional rule (see "Development of the Control System"). Lines 2990 and 3000 prevent the computer attempting to drive the vaporizer to less than 0% or more than 5%. The data in array D corresponding to the current Dinamap input is printed [3020].

7. SCREEN UPDATE: PROC VLUE [4650-4780] is called [2400]. This procedure updates the screen graphics.

8. DRIVING THE VAPORIZER to the required setting; PROC VAP [3080-3700], is called at line 2400. The number of pulses (N1), required to drive the vaporizer from its current position to the new position equals the difference between the number of pulses required to drive the vaporizer to its new position from "OFF" (P1) and the number of pulses required to drive the vaporizer to its current position (P0) i.e.

    N1 = P1 - P0 [3270]

The value P1 is determined by linear interpolation between the elements in array PU which bracket the required concentration. P0 is updated to P1 after the vaporizer has been driven to its new position. P0 is initially set at "0" [4040]. If the vaporizer is to be driven in the opposite direction from its previous

motion then an allowance must be made for the backlash. The direction of travel (relative to the previous direction) is determined by multiplying the number of pulses used previously (N0, which includes sign) by N1 [3300]. If the product is less than zero then a change of direction is involved and backlash correction is necessary [3310]. After the vaporizer has been driven to the new setting N0 is updated [i.e. N0=N1, at line 3500]. The actual number of pulse used (N2) is the absolute value of N1 (+ an allowance for backlash if necessary, lines 3290 and 3310).

After N2 and the direction of travel have been determined the motor is switched on, the direction set [3430], a signal sent to the watchdog [3440-3450], the vaporizer driven the necessary number of steps [3460-3490], N0 and P0 updated and the motor switched off [3520].

6 CHECKING THE POTENTIOMETER VOLTAGE: PROC AD is called [3580] to determine the potentiometer voltage (vide supra). The concentration corresponding to the measured voltage is determined by linear interpolation between the elements of C0 that bracket the voltage. If the measured voltage is within 0.02 volts of the expected voltage [3590-3604] then the program continues [3640]. If the voltage is outwith these limits a warning is given and the vaporizer re-initialised.

9. MORPHINE REQUIREMENT: If the time since the last bolus of morphine or start of the control run is less

than 15 minutes [2460] the computer determines the total dose over the previous 5 settings [2470-2480] and, if more than 15% [2510], initiates the subroutine at 4730. This subroutine plots a "*" on the screen and prints "Bolus of Morphine Required". The operator then gives the morphine and presses "N" to record the event, reset the integral and reset the timer.

10. The program then loops back to "Screen Messages".

LETHE

```
10 REM PROGRAM LETH.BAS [WG : 29-JUN-87; LAST UPDATE :
   06-AUG-87]
20 REM UPDATE BY HMR 11-NOV-87
30 '
40 ' PROGRAM TO CONTROL FORTEC
50 '
60 CLEAR 150 ' CLEAR SOME SPACE FOR STRINGS
70 '
80 ' INITIALISATION & DESCRIPTION OF VARIABLES
90 '
100 PB=0 ' BASE ADDRESS FOR PIO PORTS
110 AB=&20 ' BASE ADDRESS FOR A/D PORTS
120 DA$ = " "' DATE. NOT STORED ON FILE BUT PRINTED OUT
130 NA$=""'NARCOTIC GIVEN, NOT STORED ON FILE BUT PRINTED
    OUT
140 OP$ = " "'OPERATION. NOT STORED ON FILE BUT PRINTED
    OUT
150 N$=""'PATIENTS INITIALS
160 A$=""'PATIENTS AGE
170 S$=""'SEX OF PATIENT
180 SE$=""'THE SERIAL NUMBER WHEN THERE ARE >1 RUNS ON ONE
    PATIENT
190 F$=""'THE FULLY ASSEMBLED FILENAME OF THE PATIENT DATA
    FILE
200 V$="I" ' IDENTIFIER FOR SOFTWARE VERSION
210 SIZE=240'THE NUMBER OF SEQUENTIAL RECORDS
220 C=0'THE COUNTER OF THE DINAMAP CYCLES
230 TS=0' THE STARTING VALUE TIME SO THAT T-TS=ELAPSED
    TIME
240 T=0'TIMER FOR CHECKING FOR A NEW RESPONSE  WITH BD
250 BD=0'PREVIOUS TIMING FROM DINAMAP TO IDENTIFY A NEW
    READING
260 H=0'THE NUMBER OF HOURS
270 M=0'THE NUMBER OF MINUTES
280 S=0'THE NUMBER OF SECONDS
290 MAP=0' MEAN ARTERIAL PRESSURE
300 SAP=0' SYSTOLIC ARTERIAL PRESSURE
310 DAP=0'  DIASTOLIC ARTERIAL PRESSURE
```

```
320 DSAP=120'DESIRED SYSTOLIC PRESSURE IN mm Hg
330 ESAP=0'THE SAP ERROR
340 RP=10 '% REDUCTION OF PREDICTED PRESSURE
350 'CP= CALCULATED DSAP
360 G=0.1 ' THE GAIN OF THE PROPORTIONAL COMPONENT
370 LOOP$="CLOSED"'FLAG FOR THE LOOP CONDITION
380 LOOP=ASC("C")'FLAG TO CONTROL LOOP ie OPEN CLOSED OR
    END
390 WMEAN=0'EXPONENTIALLY SMOOTHED MEAN
400 WT=1.0' THE WEIGHTING FACTOR FOR THE CURRENT VALUE IN
    WMEAN
410 PRED=120' THE BP PREDICTED FROM AGE AND SEX
420 INL=0'THE RUNNING INTEGRAL
430 IG=0.01 'THE GAIN OF THE INTEGRAL COMPONENT
440 SP=0 ' CALCULATED SETTING FOR VAPORIZER
450 SP$="OFF" 'STRING FOR VAPORIZER SETTING ("OFF" WHEN
    LOOP OPEN)
460 NB=50 'NO. OF PULSES FOR BACKLASH CORRECTION
470 MC=0.6 'SETS MINIMUM CONCENTRATION GIVEN FOR PERIOD IP
480 IP=10 ' PERIOD MEASURED IN "COUNTS"
490 REM ZZ$ = INPUT FOR DUMP
500 TD=0 'TD = TOTAL DOSE
510 IB=0 'IB IS INTRA BOLUS PERIOD MARKER
520 'A$=AG$=AGE  AG$ USED TO RESET INL IF NARCOTIC GIVEN
530 '
540 CALL "RESOLUTION",0,2 ' CLEAR THE SCREEN OF GRAPHICS
550 '
560 PUT 31,21 ' CLEAR SCREEN & SET CURSOR TO TOP LEFT; SET
    UP FLASHING CURSOR
570 '
580 ' INITIALISATION OF VAPORIZER CONTROLLER
590 '
600 ' SET UP ARRAYS
610 '
620 ' PU( ), CO( ) & VO( ) HOLD CORRESPONDING VALUES OF NO
      OF PULSES,
630 ' CONCENTRATION & POSITION READOUT VOLTAGE
      RESPECTIVELY.
640 '
650 DIM PU(11), CO(11), VO(11)
660 DATA 0,615,1040,1495,1775,2075,2255,2485,2650,2845,
    3040,3230
670 DATA -0.2,0.0,0.5,1.0,1.5,2.0,2.5,3.0,3.5,4.0,4.5,5.0
680 DATA 0.430,1.036,1.447,1.885,2.146,2.436,2.608,2.834,
    2.993,3.183,3.372,3.548
690 FOR I=0 TO 11
700 READ PULSE(I)
710 NEXT I
720 FOR I=0 TO 11
730 READ CO(I)
740 NEXT I
750 FOR I=0 TO 11
760 READ VO(I)
770 NEXT I
780 '
790 ' SET UP ADDRESSES FOR A/D PORTS
800 '
810 A1 = AB + 1 ' ADDRESS FOR PORT 1 OF A/D CONVERTER
820 A2 = AB + 2 ' ADDRESS FOR PORT 2 OF A/D CONVERTER
830 A3 = AB + 3 ' ADDRESS FOR PORT 3 OF A/D CONVERTER
```

```
840 '
850 ' SET UP PIO PORTS
860 '
870 OUT PB+2,127 'SET PIO7A TO INPUT
880 OUT PB+3,15 ' SET PIO7B TO OUTPUT
890 PA=PB+1 ' PORT ADDRESS FOR OUTPUT DATA WORD TO PIO7B
900 '
910 ' SELECT MULTIPLEXER CHANNEL 1 FOR A/D CONVERTER
920 '
930 OUT AB,1
940 '
950 '
960 ' DRIVE VAPORIZER TO "OFF"
970 '
980 PROC DR
990 '
1000 '
1010 'DEFINE THE FUNCTION TO TRIM OFF EXCESS DECIMAL
      PLACES"
1020 '
1030 DEF FNTR(X)=(INT(X*100))/100
1040 '
1050 '
1060 INPUT "DATE ";DA$
1070 INPUT "OPERATION ";OP$
1080 INPUT "HAS A NARCOTIC BEEN GIVEN";NA$
1090 REM TAKE IN BASIC IDENTIFICATION DATA FOR FILENAME
     CONSTRUCTION
1100 INPUT  "TYPE IN THE PATIENTS THREE INITIALS"; N$
1110 IF LEN(N$)> 3 OR LEN(N$)=0  THEN PRINT "INCORRECT
     INITIALS - RETYPE" :GOTO 1100
1120 PUT 31
1130 INPUT "TYPE IN THE PATIENTS AGE IN WHOLE YEARS ";A$
1140 IF  LEN(A$) > 2 THEN PRINT"AGE RANGE BETWEEN 10 AND
     99 ONLY PLEASE":GOTO 1130
1150 AG$=A$
1160 PUT 31
1170 INPUT "TYPE IN THE PATIENTS SEX M OR F "; S$
1180 IF LEFT$(S$,1)="M" OR LEFT$(S$,1)="F" THEN GOTO 1190
     ELSE PRINT"ONLY M OR F ALLOWED": GOTO 1170
1190 PUT 31
1200 INPUT"TYPE IN THE SERIES NO FOR THAT PATIENT 0 - 9
     ONLY"; SE$
1210 IF LEN(SE$)>1 THEN PRINT " ONE DIGIT ONLY O - 9
     PLEASE ": GOTO 1200
1220 PUT 31
1230 F$="B:"+N$+A$+S$+SE$+V$+".DAT"
1240 IF LOOKUP(F$)<>0 THEN PUT 31: PRINT"YOUR FILENAME
     ALREADY EXISTS - CHANGE THE SERIES NO" : DIR"B:*.*":
     GOTO
1100
1250 '
1260 'THE FILE WILL NOW BE OK TO GO ON THE DISC
1270 PUT 31
1280 IF S$="M" THEN PRED = 108+0.5*VAL(A$) ELSE PRED=
     98.6+0.76*VAL(A$)
1290 CP=PRED-(PRED*RP/100)
1300 PRINT"SAP PREDICTED FROM AGE AND SEX IN A FIT PERSON
     = ";PRED
1310 PRINT;RP;"% REDUCTION OF PREDICTED PRESSURE="CP
```

```
1320 WMEAN=PRED
1330 INPUT"TYPE IN THE DESIRED SYSTOLIC PRESSURE IN mm
     Hg"; DSAP
1340 IF DSAP <90 OR DSAP>150 THEN PRINT " OUT OF RANGE !
     90-150 PLEASE ": GOTO 1330
1350 INL=20+(100-VAL(A$)) ' PRELOADED VALUE FOR INTEGRAL
1360 PUT 31
1370 PRINTER 3
1380 LPRINT CHR$(27);"C";CHR$(70); ' SET PAPER LENGTH TO
     70 LINES
1390 LPRINT CHR$(27);"N";CHR$(4); ' SET PRINTER TO SKIP 4
     LINES AT FOOT OF PAGE
1400 LPRINT CHR$(18) ' CANCEL CONDENSED PRINTING MODE
1410 LPRINT CHR$(14);"FEEDBACK CONTROL OF SAP ": LPRINT
1420 LPRINT "DISC FILENAME = ";F$: LPRINT
1430 LPRINT "DATE = ";DA$:LPRINT
1440 LPRINT "OPERATION = ";OP$:LPRINT
1450 LPRINT "NARCOTIC GIVEN = ";NA$:LPRINT
1460 LPRINT"PREDICTED SAP = "; PRED;" mm Hg","DESIRED SAP
     = ";DSAP;" mm Hg"
1470 LPRINT: LPRINT"PROPORTIONAL GAIN      = ";G,"INTEGRAL
     GAIN      = ";IG
1480 LPRINT: LPRINT "EXPONENTIAL WEIGHTING FACTOR = ";WT
1490 LPRINT: LPRINT "INITIAL INTEGRAL TERM = ";INL:LPRINT
1500 LPRINT "MINIMUM CONCENTRATION OF ";MC;" GIVEN FOR
     ";IP;"COUNTS":LPRINT
1510 LPRINT CHR$(15);"TIME"," HEART RATE"," SAP"," MAP","
     DAP"," RRP","LOOP STATE"," OUTPUT"," WMEAN", "INT":
     LPRINT
1520 PRINT "FILENAME ALLOCATED TO THIS RUN IS ";F$
1530 PRINT:PRINT"ENSURE THAT THE DINAMAP IS CONNECTED AND
     THAT IT IS SET TO
1540 PRINT"CYCLE AT ONE MINUTE INTERVALS IN AUTO MODE -
     NOT STAT MODE"
1550 PRINT"DINAMAP MUST  HAVE TAKEN ONE CYCLE BEFORE THE
     COMPUTER IS STARTED
1560 PRINT: PRINT "PRESS <R> TO START THE COMPUTER SYSTEM"
1570 IF GET(0)<>82 THEN GOTO 1570
1580 '
1590 'SET UP THE GRAPHICS DISPLAY
1600 PROC GRAF (DSAP)
1610 '
1620 '
1630 'SET UP DATA ARRAY D
1640 DIM D(6,SIZE)
1650 '
1660 '
1670 ' SWITCH ON WATCHDOG
1680 OUT PA,4 ' WATCHDOG PULSE ON
1690 OUT PA,0 ' WATCHDOG PULSE OFF
1700 '
1710 '
1720 PUT 31: PRINT "SWITCH ON 'AUDIBLE WARNING' ALARM ON
     CONTROLLER"
1730 PRINT "PRESS <R> WHEN READY"
1740 IF GET(0)<>82 THEN 1740
1750 OUT PA,4 ' WATCHDOG PULSE ON
1760 OUT PA,0 ' WATCHDOG PULSE OFF
1770 '
1780 '
```

```
1790 ' DINAMAP POLLING ROUTINE
1800 '
1810 '
1820 PRINTER 4,2 'SELECT DINAMAP SERIAL INTERFACE AS
     'PRINTER'
1830 PUT 31
1840 PRINT "SYSTOLIC PRESSURE = ";SAP;" MM HG; VAPORIZER
     SETTING = ";SP$;"; TIME = ";TI
1850 PRINT "TO TERMINATE THE PROGRAM AND STORE THE DATA
     PRESS <E>"
1860 PRINT "TO CLOSE/OPEN/RESET FEEDBACK LOOP OR REGISTRER
     NARCOTIC PRESS (C)/(O)/(S)/(N)"
1870 LOOP=GET (300)
1880 IF LOOP=ASC("E") THEN GOTO 2590
1890 IF LOOP=ASC("O") THEN LOOP$="OPEN":PROC VAP(-0.2)
1900 IF LOOP=ASC("C") THEN LOOP$="CLOSED": PROC VAP(SP)
1910 IF LOOP=ASC("N") THEN GOSUB 4810
1920 IF LOOP <>ASC("S") THEN 2020
1930 CALL "PLOT",C*2+40,DSAP,0
1940 CALL "LINE",310,DSAP,0
1950 INPUT "NEW TARGET SAP IS";DSAP
1960 IF DSAP <90 OR DSAP >150 THEN PRINT "OUT OF RANGE !
     90-150 PLEASE":GOTO 1950
1970 CALL "PLOT",C*2+40,DSAP,1
1980 CALL "LINE",310,DSAP,2
1990 PRINTER 3
2000 LPRINT:LPRINT "THE NEW DESIRED SAP IS";DSAP:LPRINT
2010 PRINTER 4,2
2020 PUT 31
2030 PRINT "SYSTOLIC PRESSURE = ";SAP;" MM HG; VAPORIZER
     SETTING = ";SP$;"; TIME = ";TI
2040 PRINT:PRINT"POLLING DINAMAP "
2050 LPRINT "BBA"
2060 OPEN #10,"RDR:"
2070 INPUT #10,A$
2080 CLOSE #10
2090 '
2100 '
2110 H = VAL(MID$(A$,12,2))
2120 M = VAL(MID$(A$,14,2))
2130 S = VAL(MID$(A$,16,2))
2140 '
2150 ' CHECK FOR NEW DINAMAP RESULT - RECYCLE TILL FOUND
2160 T=(((H*60)+M)*60+S)
2170 OUT PA,4 ' WATCHDOG PULSE ON
2180 OUT PA,0 ' WATCHDOG PULSE OFF
2190 IF BD=T THEN GOTO 1840 ELSE BD=T
2200 '
2210 ' INTERPRET REST OF DINAMAP RESPONSE AND INCREMENT
     COUNTER TO FILL D
2220 D(3,C) = VAL(MID$(A$,18,3))
2230 IF C=0 THEN D(0,0)=0 :TS=T ELSE D(0,C)=(T-TS)/60
2240 TI=D(0,C)
2250 D(1,C)  = VAL(MID$(A$,21,3))
2260 D(2,C) = VAL(MID$(A$,24,3))
2270 D(4,C) = VAL(MID$(A$,27,3))
2280 D(5,C)= D(1,C)*D(2,C)
2290 SAP=D(2,C)
2300 '
2310 PRINTER 3
```

```
2320 IF C=SIZE THEN  2590
2330 '
2340 ' CALCULATE NEW VAPORIZER SETTING
2350 '
2360 GOSUB 2860
2370 '
2380 ' PLOT SAP & VAPORIZER SETTING ON SCREEN
2390 '
2400 PROC VLUE (C, D(2,C), SP)
2410 '
2420 SP$=STR$(SP)+"%"
2430 C=C+1
2440 IF LOOP$="CLOSED" THEN PROC VAP(SP)
2450 IF LOOP$="OPEN" THEN PROC VAP(-0.2):GOTO 1820
2460 IF C < IB+15 THEN GOTO 1820
2470 FOR J=(C-5) TO (C-1)
2480 TD=D(6,J)+TD
2490 IF D(6,J) < 2.5 THEN 1820
2500 NEXT J
2510 IF TD > 15 THEN GOSUB 4730
2520 TD=0
2530 GOTO 1820
2540 '
2550 PRINTER 3
2560 CALL "PRINTER",1 'DEFINES PRINTER TYPE
2570 CALL "DUMP",0,0,319,191,1
2580 ' STORE RESULTS
2590 PRINTER 3:LPRINT:LPRINT CHR$(14);"END OF
     RUN";CHR$(12);CHR$(15)
2600 PUT 31
2610 PRINT "SWITCH 'AUDIBLE ALARM' OFF"
2620 PROC DR ' DRIVE VAPORIZER TO 'OFF'
2630 PUT 31
2640 PRINT "DATA BEING WRITTEN TO DISC"
2650 CREATE#10,F$
2660 QUOTE #10,34
2670 FOR J=0 TO C-1
2680 PRINT#10, D(0,J),D(1,J),D(2,J),D(3,J),D(4,J),D(5,J),
     D(6,J)
2690 NEXT J
2700 CLOSE #10
2710 PUT 31
2720 INPUT "DO YOU WANT A SCREEN DUMP";ZZ$
2730 IF LEFT$(ZZ$,1)="Y" OR LEFT$(ZZ$,1)="N" GOTO 2740
     ELSE 2720
2740 IF LEFT$(ZZ$,1)="N" GOTO 2790
2750 LPRINT:LPRINT "DISK FILENAME = ";F$:LPRINT
2760 CALL "PRINTER",1,1 'DEFINE PRINTER TYPE AND SET DUAL
     DENSITY
2770 CALL "DUMP",0,0,319,241,1
2780 LPRINT CHR$(12)
2790 CALL "CLEAR":TEXT
2800 PUT 31
2810 END
2820 '
2830 '
2840 'SUBROUTINE TO CALCULATE THE OUTPUT
2850 'EXP SMOOTHED MEAN
2860 IF D(2,C)=0 THEN D(6,C)=SP : GOTO 3020 ' IF SAP
     READING = 0, KEEP VAPORIZER SETTING AS BEFORE
```

```
2870 IF C=0 THEN WMEAN=D(2,0) ELSE
     WMEAN=D(2,C)*WT+WMEAN*(1.0-WT)
2880 '
2890 'SAP ERROR IS :
2900 ESAP=WMEAN-DSAP
2910 '
2920 'ACCUMULATE THE INTEGRAL OF ERROR IN INL
2930 INL=INL+ESAP
2940 IF INL<0 THEN INL=0
2950 '
2960 SP=G*ESAP +IG*INL
2970 IF C>IP GOTO 2990 'ALLOWS MINIMUM CONC FOR INITIAL
     PERIOD
2980 IF SP<MC THEN SP=MC:GOTO 3000
2990 IF SP<0 THEN SP=0
3000 IF SP>5 THEN SP=5
3010 D(6,C)=SP
3020 LPRINT FNTR(D(0,C)),D(1,C),D(2,C),D(3,C),D(4,C),
     D(5,C),LOOP$,FNTR(D(6,C)),FNTR(WMEAN);TAB(124);
     FNTR(INL)
3030 RETURN
3040 '
3050 '
3060 ' PROCEDURE TO DRIVE VAPORIZER TO REQUIRED
     CONCENTRATION C & CHECK POSITION READOUT VOLTAGE
3070 '
3080 DEF PROC VA(C)
3090 '
3100 IF C=-0.2 THEN SP$="OFF" ELSE SP$=STR$(C)+"%"
3110 PUT 31
3120 PRINT "SYSTOLIC PRESSURE = ";SAP;" MM HG; VAPORIZER
     BEING SET TO ";SP$;"; TIME = ";TI
3130 ' FIND APPROPRIATE VALUE FOR TOTAL NUMBER OF PULSES
     (P1) BY LINEAR
3140 ' INTERPOLATION BETWEEN ELEMENTS OF PULSE( ) THAT
     BRACKET P1.
3150 '
3160 FOR I=1 TO 11
3170 IF CO(I)<C GOTO 3200
3180 P1=PU(I-1) + (PU(I)-PU(I-1))*(C-CO(I-1))/(CO(I)-CO(I-
     1))
3190 GOTO 3270
3200 NEXT I
3210 '
3220 ' DRIVE VAPORIZER REQUIRED NO OF PULSES (N2). N1 IS
     NO OF PULSES
3230 ' (INCLUDING SIGN)M FOR PRESENT MOTION. N0 IS NO OF
     PULSES (INCLUDING
3240 ' SIGN) FOR PRECEDING MOTION. IF N0*N1 < 0, CHANGE OF
     DIRECTION IS INVOLVED
3250 ' & BACKLASH CORRECTION IS REQUIRED.
3260 '
3270 N1=P1-P0
3280 IF N1=0 THEN PROC RETURN
3290 N2=ABS(N1)
3300 IF N1*N0>=0 GOTO 3320
3310 N2=N2+NB 'BACKLASH CORRECTION
3320 IF N1<0 THEN 3390
3330 '
3340 ' ID IS CONTRIBUTION OF DIRECTION BIT (BIT 1) TO DATA
```

```
     WORD (0 FOR +VE
3350 ' MOTION, 2 FOR -VE MOTION)
3360 '
3370 ID=0
3380 GOTO 3430
3390 ID=2
3400 '
3410 ' SWITCH MOTOR ON & SET DIRECTION
3420 '
3430 OUT PA,ID
3440 I1=ID+5 ' DATA WORD TO TURN STEP & WATCHDOG SIGNALS
     "ON"
3450 I2=ID ' DATA WORD TO TURN STEP & WATCHDOG SIGNALS
     "OFF"
3460 FOR I=1 TO N2
3470 OUT PA,I1
3480 OUT PA,I2
3490 NEXT I
3500 N0=N1
3510 P0=P1
3520 OUT PA,8 ' MOTOR OFF
3530 '
3540 ' CALCULATE VOLTAGE VR CORRESPONDING TO REQUIRED
     CONCENTRATION C BY LINEAR INTERPOLATION BETWEEN
     ELEMENTS OF VO( )
3550 ' THAT BRACKET VR. COMPARE VR WITH POSITION READOUT
     VOLTAGE V2. IF DIFFERENCE > 0.02 V, ISSUE WARNING,
3560 ' RESET VAPORIZER TO OFF & TRY AGAIN.
3570 '
3580 PROC AD
3590 FOR I = 1 TO 11
3600 IF CO(I)<C GOTO 3630
3610 VR = VO(I-1) + (C-CO(I-1))/(CO(I)-CO(I-1))*(VO(I)-
     VO(I-1))
3620 GOTO 3640
3630 NEXT I
3640 IF V2>VR-0.02 AND V2<VR+0.02 THEN PROC RETURN
3650 PRINT "POSITION READOUT VOLTAGE OUTSIDE ACCEPTABLE
     LIMITS."
3660 PRINT " VAPORIZER WILL BE DRIVEN TO 'OFF' & RESET"
3670 LPRINT :LPRINT "POSITION READOUT VOLTAGE
     IS";V2;"VOLTS INSTEAD OF";VR;"VOLTS":LPRINT
3680 PROC DR
3690 GOTO 3110
3700 PROC END
3710 '
3720 '
3730 ' PROCEDURE TO DRIVE VAPORIZER TO 'OFF' & CHECK
     CONTROLLER FUNCTION
3740 '
3750 DEF PROC DR
3760 '
3770 PRINT "VAPORIZER BEING DRIVEN TO 'OFF'"
3780 OUT PA,2 ' SWITCH MOTOR ON AND SET DIRECTION -VE
     (TOWARDS "OFF")
3790 FOR I=1 TO 3500
3800 OUT PA,7 ' STEP & WATCHDOG "ON"
3810 OUT PA,2 ' STEP & WATCHDOG "OFF"
3820 NEXT I
3830 OUT PA,8 ' MOTOR OFF
```

```
3840 '
3850 ' CHECK VALUE OF DATA WORD ON PIO7A. TOP 6 BITS ARE
     ALWAYS HIGH.
3860 ' FOR VAPORIZER AT 'OFF', BIT 0 SHOULD BE ZERO,
     INDICATING THAT
3870 ' CLOCKWISE LIMIT SWITCH IS ACTIVATED, & BIT 1 SHOULD
     BE 1, INDICATING
3880 ' THAT ANTICLOCKWISE LIMIT SWITCH IS NOT ACTIVATED.
     THUS, THE CORRECT
3890 ' DATA WORD IS 253. THIS VALUE IS NOT OBTAINED UNDER
     ANY COMBINATION
3900 ' OF FAULT CONDITIONS.
3910 '
3920 IF INP(PB) = 253 THEN 4040
3930 TEXT: PUT 31
3940 PRINT "***WARNING***"
3950 PRINT "WRONG SIGNALS RECEIVED FROM  LIMIT SWITCHES
     WHEN PROGRAM"
3960 PRINT "ATTEMPTED TO DRIVE VAPORIZER TO 'OFF'. CHECK
     THE FOLLOWING :"
3970 PRINT "  (1) VAPORIZER CONTROLLER IS SWITCHED ON"
3980 PRINT "  (2) CABLE BETWEEN VAPORIZER AND CONTROLLER
     IS SECURE AT EACH END"
3990 PRINT "  (3) RIBBON CABLE BETWEEN CONTROLLER AND
     COMPUTER IS SECURE"
4000 PRINT
4010 PRINT "IF FAULT FOUND, RECTIFY IT AND RESTART
     PROGRAM"
4020 PRINT "OTHERWISE, DO NOT USE CONTROLLER; REPORT
     PROBLEM TO PHYSICIST"
4030 GOTO 4810
4040 P0=0 'P0 IS PULSE NO FOR PRESENT SETTING OF VAPORIZER
4050 N0=-1 ' N0 IS NO OF PULSES FOR PREVIOUS MOVEMENT.
     SIGN IS ALL THAT MATTERS.
4060 '
4070 ' CHECK ANALOG INPUT VOLTAGE
4080 PROC AD
4090 IF V2 > VO(0)-0.02 AND V2 < VO(0)+0.02 THEN 4180
4100 PRINT
4110 PRINT "***WARNING***"
4120 PRINT "NO VOLTAGE ON ANALOG INPUT TO COMPUTER"
4130 PRINT "CHECK ANALOG SIGNAL CABLEBETWEEN CONTROLLER
     AND COMPUTER"
4140 PRINT "IF FAULT FOUND, RECTIFY IT AND RESTART
     PROGRAM"
4150 PRINT "OTHERWISE, DO NOT USE CONTROLLER. REPORT FAULT
     TO PHYSICIST"
4160 GOTO 4450
4170 '
4180 PROC END
4190 '
4200 '
4210 ' PROCEDURE TO PERFORM AND AVERAGE 10 A/D CONVERSIONS
     ON CHANNEL 1
4220 '
4230 DEF PROC AD
4240 V2=0
4250 FOR I=1 TO 10
4260 OUT A1,1 ' START A/D CONVERSION
4270 WAIT A2,128,0 ' WAIT UNTIL CONVERSION BIT (BIT 7 OF
```

```
     HIGH BYTE) = 1
4280 V2 = V2 + INP(A3) + 256*(INP(A2)MOD4)
4290 NEXT I
4300 V2 = V2/2046
4310 PROC END
4320 '
4330 '
4340 'SET UP THE GRAPHICS SYSTEM
4350 '
4360 DEF PROC GRAF(DSAP)
4370 GRAPH 1
4380 CALL "RESOLUTION",0,2
4390 CALL "OFFSET",0,50
4400 CALL "PLOT",40,70,3
4410 CALL"LINE",310,70,3
4420 CALL"LINE",310,241,3
4430 CALL"LINE",40,241,3
4440 CALL "LINE",40,70,3
4450 '
4460 'SET VERTICAL SCALE
4470 CALL "CHARSIZE", 1,1
4480 FOR VERT= 70 TO 170 STEP 20: VERT$=FIX$(STR$(VERT),4)
     +" "
4490 CALL "STPLOT",0, VERT,VARADR(VERT$),3
4500 NEXT VERT
4510 '
4520 'SET HORIZONTAL SCALE
4530 FOR HIZ= 0 TO 240 STEP 30
4540 HIZ$=FIX$(STR$(HIZ/2),4): Q$="^" 'HIZ/2 CHANGES TIME
     BASE TO 0-120
4550 CALL "STPLOT",HIZ+30,55,VARADR(HIZ$),3
4560 CALL "STPLOT", HIZ+40,63,VARADR(Q$),3
4570 NEXT HIZ
4580 '
4590 ' SET THE DESIRED LEVEL FOR THE SAP
4600 CALL"PLOT", 40, DSAP,1
4610 CALL "LINE",310,DSAP,2
4620 PROC END
4630 '
4640 '
4650 DEF PROC VLUE (CZ,QSAP,QP)
4660 CALL "PLOT",CZ*2+40,QSAP,3
4670 CALL "PLOT",CZ*2+40,170,2
4680 CALL "LINE",CZ*2+40,170+20*QP,2
4690 CALL "PLOT",CZ*2+41,170,2
4700 CALL "LINE",CZ*2+41,170+20*QP,2
4710 PROC END
4720 'SUBROUTINE TO PLOT OVERDOSE
4730 DP$="*"
4740 CALL "STPLOT",C*2+40,80,VARADR(DP$),3
4750 PRINTER 3
4760 LPRINT:LPRINT "BOLUS OF NARCOTIC REQUIRED AT ";C
4770 PRINTER 4,2
4780 RETURN
4790 '
4800 'SUBROUTINE TO RESET INL AND IB AND LPRINT BOLUS
4810 PRINTER 3
4820 INL=20+(100-VAL(AG$))
4830 LPRINT : LPRINT "BOLUS OF NARCOTIC GIVEN AT ";C;"AND
     INTEGRAL RESET TO ";INL:LPRINT
```

```
4840 PRINTER 4,2
4850 IB=C
4860 RETURN
4870 END
```

APPENDIX II

APPENDIX II.

CONTROL EQUATIONS.

The equations used to determine the criteria on which the goodness of SAP control was determined.

1. The RMSD is calculated as:

   $$RMSD = \sqrt{E(SAP-TSAP)^2 / (n - 1)}$$

   Where n = the number of SAP measurements.

2. The PR is calculated as:

   PR = % of records above TSAP / % of records below TSAP

3. The MD_{TSAP} is calculated as:

   $$MD_{TSAP} = E(SAP - TSAP) / n$$

   Where n = the number of SAP measurements.

APPENDIX III

APPENDIX III.

PATIENTS IN WHOM CONTROL WAS INADEQUATE.

A detailed breakdown of the cases in whom adequate control of SAP or of the anaesthetic goals were not acheived. See chapter 9 for the criteria defining these parameters and for the derivation of the five groups of patients. A " - " indicates that the variable was within acceptable limits.

GROUP		RMSD	MD_{TSAP}	PR	HR	RPP	cATPR.
E	a	13.37	-	-	-	-	-
	b	-	5.35	7	-	-	-
	c	-	-	0.34	-	-	-
EM	a	-	5.63	2.72	-	-	-
	b	17.60	13.00	8.23	109.6	14214	-
	c	11.47	6.80	-	-	-	-
	d	-	5.18	2.94	-	-	17
	e	-	5.48	4.21	-	-	-
	f	10.70	-	-	-	12127	-
	h	-	-	-	-	-	21
I	a	11.70	-7.40	0.21	-	-	-
	b	10.12	-	-	-	-	-
	c	-	7.74	24.81	-	-	-
	d	-	-	0.37	-	-	-
	e	-	-	-	-	-	20

(continued)

GROUP		RMSD	MD_{TSAP}	PR	HR	RPP	cATPR
IA	a	-	-	-	-	-	19
	b	-	-	-	-	-	24
	c	10.22	-	-	-	-	-
	d	10.60	-	-	-	-	-
IM	a	10.82	6.27	4.00	-	-	17
	b	10.66	6.40	2.67	-	12248	-
	c	-	-	4.83	-	-	35
	d	-	-	2.72	-	-	23

APPENDIX IV

Appendix IV.

PUBLISHED ABSTRACTS

1. Robb HM, Asbury AJ, Gray WM and Linkens DA. Towards automatic control of general anaesthesia with enflurane. Br J Anaesth 1988; 61: 109P-110P.

Clinical signs are used as guidelines for the administration of anaesthetic drugs. Our ultimate objective is to devise a computer control system, operating from rules based on clinical signs, to produce an individually tailored anaesthetic state. The aim of this study was to assess the usefulness of systolic arterial pressure (SAP) as an index of anaesthetic depth for such a system.

A proportional integral control system was set up with an RML 380Z-D computer interfaced to a Dinamap and an enflurane vaporizer controller [1]. A program was designed to maintain the patient's SAP at 90% of that predicted by age and sex. A minimum dose of 0.6% enflurane was given for the first 10 min and the user instructed to give morphine 0.05mg kg^{-1} if the delivered dose of enflurane exceeded a preset limit. This rule could only be activated once in 15 min.

Following Ethical Committee approval, 21 patients (ASA I or II) were studied. After premedication with temazepam 10 -20mg and ranitidine 150mg, anaesthesia was induced with thiopentone 3-5 mg kg^{-1} and morphine 0.1 mg kg^{-1}. Neuromuscular blockade was maintained with vecuronium. The patients were ventilated with 66% nitrous oxide in oxygen. Enflurane and additional morphine were administered by, on or on instruction from, the controller. Nine clinical signs were recorded every 5 min as PRST score [2].

No patient complained of awareness. For statistical analysis the patients were divided into those who required extra morphine (group B) and those who did not (group A). There was no intergroup statistical difference in age, weight or duration of operation. Results are shown in table 1.

Table 1. Results. TSAP = Target SAP; TPR = time to patient response; VAP = inspired concentration; RMSD = root mean square deviation about TSAP; PRST = PRST score. (Mean values +/- SD). * $P<0.05$ by Wilcoxon's sum of ranks test.

	Group A (n=14)	Group B (n=7)	
TSAP (mmHg)	118.8 (7.7)	114.4 (7.2)	
TPR (min)	4.8 (1.9)	10.0 (3.7)	*
HR (bpm)	67.3 (7.8)	82.9 (16.6)	*
SAP (mmHg)	118.1 (8.1)	119.9 (8.4)	
VAP (%)	1.1 (0.7)	9.4 (0.5)	*
RMSD	7.0 (2.8)	9.4 (2.3)	*
PRST	0.46	0.96	

In conclusion, it seems that, within the limits of the study the rules applied, which technically control SAP, produce a pattern of clinical signs recognisable as general anaesthesia.

1. Nieman M, Richardson W, Gray WM, Asbury AJ. Journal of Medical Engineering Technology 1987; 11: 34-36.
2. Evans JM, Bithell JF, Vlachonikolis IG. British Journal of Anaesthesia 1987; 59: 1346-1355.

2. Robb HM, Asbury AJ, Gray WM, Linkens DA. Towards automatic control of general anaesthesia. Accepted for publication in the proceedings of the Medical Informatics International Conference on Computers in Clinical Medicine, to be held on 13-15th September 1988 at Nottingham University.

INTRODUCTION

Clinical signs of anaesthesia are a result of a balance between the effects of surgical stimulation and the suppression caused by anaesthetic drugs. There are many factors which prevent a tight definition of the intraoperative anaesthetic state, these include: the immeasurability of surgical stimulation, widely varying and multiple drug actions, interpatient variation, the varying strategies used by anaesthetists, and disease effects themselves.
Without a "gold" standard, many techniques for monitoring the anaesthetic state (e.g. the EEG) cannot be fully assessed. Clinical signs, despite some obvious inadequacies [1,2], are currently the only universally accepted indicators of anaesthetic adequacy, and form the basis for the administration of thousands of successful anaesthetics each day. However, their interpretation is subjective and variable.

OBJECTIVES

Our ultimate objective is to develop a computer control system, operating from rules based on clinical and other indices, to produce an individually tailored anaesthetic state. The objective of the current study was investigate whether a clinically acceptable anaesthetic state could be produced by using a control system to maintain the patient's Systolic Arterial Pressure (SAP) at a predetermined target value by altering the inspired concentration of enflurane. Such a control system, though limited in that it uses only one clinical sign, would help to standardise management of the anaesthetic state.

METHODS

A proportional integral (PI) control system was set up with an RML 380Z-D computer interfaced to a Critikon Dinamap 1846 automatic blood pressure monitor and an enflurane vaporizer controller [3]. A program, written in BASIC, was designed to maintain the patient's SAP at 90% of that predicted from age and sex standardised tables [4]. The program took data from the Dinamap's memory at one minute intervals, and changed the inspired enflurane concentration via the vaporizer controller. The system was designed to be supervised by the anaesthetist and allowed intervention at any time to open or close the control loop. The integral alarms on the Dinamap and vaporizer drive unit were used.
The proportional and integral gains for the PI program were determined from preliminary trials and set at 0.1 and 0.01 respectively. The integral term was preloaded with

the value 20 + (100 - age). Two additional rules were used. The first provided a 0.6% enflurane for the first ten minutes. The second instructed the operator to give a bolus of morphine (0.05mg/kg) and to re-set the integral to the preload value if the inspired enflurane concentration exceeded a preset limit. This limit was defined as a total inspired concentration of more than 15% over five consecutive vaporizer settings with each setting exceeding 2.5%. This rule could only be activated once every fifteen minutes.

The study was carried out in 22 ASA I and II female patients, aged 24-57 years, admitted for routine gynaecological surgery. Ethical Committee approval was obtained and all patients gave written consent to the study.

After routine premedication, anaesthesia was induced with morphine 0.1 mg/kg and thiopentone 3-5 mg/kg. Relaxation was achieved with vecuronium 0.1 mg/kg, which permitted endotracheal intubation.

In theatre all patients were artificially ventilated using a Bain circuit with a fresh gas flow of 100 ml/kg of nitrous oxide (66%) in oxygen. Enflurane and supplementary morphine were delivered by or on instruction from the controller. Although the operator gave the morphine and reset the integral this was on instruction from the controller and the loop remained tightly closed. Muscle relaxation was maintained by timed boluses of vecuronium (one third of the initial dose every 25 minutes). Intravenous fluids were provided as clinically indicated. Additional clinical signs (sweating and tears) were recorded every five minutes and the PRST score calculated [5].

The controller was switched off five minutes before the end of surgery and the nitrous oxide discontinued following the last skin suture or staple. At this point the muscle relaxant was antagonised with neostigmine 2.5mg and glycopyrrolate 0.6mg.

Recovery was deemed complete (for the purposes of the study) when the patient made purposeful responses to command. All patients were questioned 24 hours postoperativly, to discover whether they had been aware during anaesthesia.

When analysing the results, we wanted to consider the behaviour of the controller after the initial stabilization period, and so excluded the first ten SAP recordings in each patient. The Mann-Whitney U test was used for all the intergroup comparisons. A two-tailed probability less than 0.05 was considered significant.

RESULTS

The results are shown in the table. The controller effectively divided the patients into two groups: Group A of fourteen patients who only received the initial bolus of morphine and Group B of seven patients who required additional boluses. The controller was discontinued in one patient who received excessive enflurane despite additional morphine. This patient had an acceptable preoperative blood pressure of 160/90 mmHg but postoperative questioning revealed a history of "previous"

hypertension despite a denial of problems with "raised blood pressure" preoperatively. This patient is excluded from the analysis.
There was no statistical difference between the two groups with regard to age, weight, target systolic arterial pressure (TSAP), total anaesthetic time (from induction to discontinuation of the nitrous oxide) (TAT) or total system running time (TST).
In general the system produced a clinically acceptable anaesthetic state, and a rapid recovery in all patients. This is reflected in the PRST scores, and in the mean SAP, HR and rate pressure product. Group B however, took significantly longer to recover from anaesthesia than group A. No patient recalled any event between induction and recovery and all patient's said they would accept the same anaesthetic again.
The RMSD is the root mean square deviation about the TSAP. This term is analogous to the standard deviation but uses the TSAP in place of the mean in its calculation, and indicates the dispersion of SAP about the target value. In both groups the mean SAP is close to the mean TSAP, and mean RMSD values of 7.3 and 10.6 confirm that control was satisfactory.
Although there was no significant difference between the mean SAP and TSAP between the groups, the mean deviation from the target value was significantly lower in group A, indicating that control was better in this group. Eighty seven percent of the SAP records in Group A and 79% of those in Group B were within 10% of the TSAP. Only 0.3% of the SAP records in Group A and 1.3% of the recorded in Group B where outside 30% of the TSAP. The mean heart rates, rate pressure products and inspired enflurane requirements were lower in Group A when compared to Group B.

DISCUSSION

If a control system produces an individually standardised anaesthetic state that achieves the goals of general anaesthesia, adequate general anaesthesia can itself be partially defined in terms of the reference values on which the system is based.
The use of systolic arterial pressure as a variable to control the delivery of anaesthetic agents can be criticised on several grounds. Anaesthetists use combinations of clinical signs to determine the anaesthetic state and SAP alone cannot be expected to give reliable information in all cases, hypertensive and hypovolaemic patients being obvious examples. However SAP is one of the few quantifiable indices and increases in SAP are commonly treated with anaesthetic drugs.
We consider that a SAP within the range excepted for normal sleep is one of the many clinical requirements of a good anaesthetic, and in this study factors known to detract from the usefulness of this variable were limited by careful patient selection and aggressive fluid management. Unfortunately SAP cannot be measured more frequently than once a minute without resorting to invasive monitoring, as the arm becomes swollen.

The Target SAP

Choice of a target SAP is difficult, as spot measurements in the ward or prior to induction are likely to be unrepresentative due to anxiety or sedation. For this reason we used an age and sex related value from tables. A TSAP of 90% of the predicted value was chosen after initial trials that suggested that a TSAP of 85% overdosed the patients.
Our method of selecting the TSAP, using tables, is crude. Group B may reflect those patients in whom the calculated TSAP is too low and further work is required to determine a better method of assessing this value.

Does the Controller Achieve the "Goals" of Anaesthesia?

No patient showed clinical signs that suggested that anaesthesia was inadequate. Although clinical scoring systems have severe limitations, the PRST score represents a simple method of "summating the significance of these widely recognised clinical signs" [5]. In this study no patient had a score greater than 4, and the mean values suggest that anaesthesia was adequate. The recovery times suggest that anaesthesia was not excessive. The higher PRST score in Group B is mainly attributable to the increased heart rate in this group and probably reflects a drug effect rather than increased autonomic activity.

The Additional Rules

In the preliminary studies carried out before the additional rules were introduced, several patients after induction had SAPs below the target value prior to the start of surgery. These patients were therefore receiving minimal concentrations of enflurane at incision and there was a risk that they might be aware at this point. As the delay between starting the controller and the start of surgery is unpredictable we delivered a minimum dose of 0.6% in the main study to prevent this occurrence.
In the preliminary study the simple PI system gave a relative overdose of anaesthetic to some patients. In anaesthetic practice it is common to give a bolus of narcotic to limit the requirement of volatile agent. We attempted to imitate this practice by incorporating the second rule, which required additional boluses of morphine as the enflurane requirement became excessive. The resetting of the integral prevented overdose in these patients.

Control

As the pharmacological system is complex we chose a simple system to give the best understanding of the process with the maximum safety. This system has many limitations but improvement may be difficult. More complex systems e.g. self-tuning systems might have the flexibility to cope with the inevitable non linearities which exist when one is trying to suppress the SAP response to surgery, but might require more data than SAP sampled once a minute.

CONCLUSION

The controller achieved the immediate aim of controlling SAP and also produced a pattern of clinical signs recognisable as general anaesthesia.

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4. Diem K. and Lenter C. (1970). Documenta Geigy. Scientific Tables 7th edn. 553-554. Macclesfield: Geigy Pharmaceutical.
5. Evans J. M. Bithell J. F. and Vlachonikolas I.G. (1987) Relationship between lower oesophageal contractility, clinical signs and halothane concentration during general anaesthesia in man. British Journal of Anaesthesia **59**, 1346-1355.

TABLE

	Group A		Group B		
	Mean	SD	Mean	SD	prob.
Age (years)	41.6	9.5	37.6	10.5	ns
Weight (kg)	60.4	11.7	60.7	11.9	ns
TAT (min)	65.7	22.9	74.9	17.3	ns
TST (min)	54.0	23.4	62.7	16.9	ns
ATPR (min)	5.1	1.9	10.0	3.7	sig.
STPR (min)	9.6	3.4	17.3	5.7	sig.
TSAP (mmHg)	117.2	6.6	114.4	7.2	ns
SAP (mmHg)	117.1	6.1	120.8	8.6	ns
MD_{TSAP}	0.1	2.4	6.4	3.1	sig.
RMSD (mmHg)	7.3	2.2	10.6	3.4	sig.
HR (bpm)	67.5	8.1	83.1	16.7	sig.
Insp. Enf(%)	1.1	0.7	2.2	0.4	sig.
RPP	7909.8	1070.8	10105.4	2384.0	sig.
PRST	0.46		0.82		

TAT = Total Anaesthetic Time
TST = Total System Running Time
ATPR = Anaesthetic to Patient Response Time
STPR = System Termination to Patient Response Time
TSAP = Target Systolic Arterial Pressure
SAP = Mean Measured Systolic Arterial Pressure
MD_{TSAP} = Mean Deviation of SAP from the TSAP
RMSD = Root Mean Square Deviation
HR = Mean Heart Rate
Insp. Enf. = Mean Inspired Enflurane Concentration.
RPP = Rate Pressure Product
PRST = The mean PRST Score