INDUCED HYPOTENSION WITH SODIUM NITROPRUSSIDE

Clinical studies of oxygen transport

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For Kathryn, Clare and Emma
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DECLARATION

This thesis has been composed by myself. The first two chapters are based on personal surveys of the literature and the rest of the thesis on clinical studies performed with a group of colleagues in the Department of Anaesthetics, Royal Infirmary of Edinburgh. In each case I was the principal investigator.
ABSTRACT

The history of the induction of hypotension during anaesthesia and surgery is reviewed to indicate how the problems associated with the early techniques led to a search for improved methods and in particular to the introduction of sodium nitroprusside into anaesthetic practice. Then the basic chemical and pharmacological properties of the drug are described before clinical studies of the haemodynamic, respiratory, haematological and metabolic effects of induced hypotension with nitroprusside are presented. The significance of the results is discussed.

The properties of sodium nitroprusside suggest that it might interfere with the transport of oxygen to the tissues in several ways. The studies show that sodium nitroprusside is a potent, short acting hypotensive agent without adverse effects on overall circulatory performance. Oxygen carriage by the blood may be decreased since arterial oxygen tension and haemoglobin concentration both decrease slightly. Of more significance is the metabolic consequence of high dosage. This is due to cyanide released when the agent breaks down in the body, a possibility that was thought to be of little importance when the drug was introduced into clinical practice.

Finally, various suggestions for obtaining the valuable circulatory actions and, at the same time, minimising the systemic toxicity of SNP are discussed.
CHAPTER ONE

THE HISTORY AND DEVELOPMENT OF INDUCED HYPOTENSION
CHAPTER ONE
THE HISTORY AND DEVELOPMENT OF INDUCED HYPOTENSION

The purpose of anaesthesia is to provide conditions for the patient to undergo surgery safely and successfully. For virtually a hundred years after the discoveries of Wells, Morton and Simpson all that was required was an unconscious patient who did not respond to pain, but by the nineteen forties advances in surgery were demanding more from the anaesthetist. One of the new requirements was control of bleeding, either to allow visualisation of anatomical detail, or to prevent the patient losing large amounts of blood. Chloroform had long been used to reduce bleeding, but increased understanding of the pathophysiology of deep anaesthesia, especially with an agent as potentially toxic as chloroform, stimulated a search for more specific methods (Gillies, 1954).

Apart from the development of surgical procedures requiring ischaemia there was, at the same time, an increase in the amount of operative bleeding caused by anaesthetic factors. The introduction of cyclopropane, muscle relaxants (used initially with spontaneous ventilation) and some anaesthetic apparatus with high expiratory resistance all contributed (Gillies, 1952). It was soon emphasised (Gillies, 1954) that avoidance of hypoxia, hypercapnia, straining, respiratory obstruction, excessive apparatus resistance and a light plane of anaesthesia would all help to reduce bleeding, but the effects of these factors only made the need for a method of control seem more urgent at the time.

Posture - the operation site being raised well above the level of the heart to aid venous drainage - was used (Gillies, 1951).
On its own it was a crude technique and it was realised that if the legs were dependent a major fall in venous return (and thus cardiac output) would occur (Gillies, 1954). Perhaps because of this the three specific techniques introduced in the nineteen forties were evolved for use with patients undergoing operations on the upper half of the body; arteriotomy in neurosurgery; high spinal anaesthesia for thoraco-lumbar sympathectomy; and ganglionic blockade in plastic surgery.

Arteriotomy

It is almost part of the 'apochrypha' of induced hypotension that Harvey Cushing, the great pioneer neurosurgeon, used arteriotomy before World War I. His superb monograph (Cushing, 1917) on acoustic neuroma is usually quoted in support of this. Examination of his book reveals that Cushing realised that minimising haemorrhage would benefit the patient and he described his operative techniques for achieving this, but there is no evidence of the deliberate use of arteriotomy, nor even support for the statement (Larson, 1964) that he "observed and made use of the dry operating field which followed haemorrhage".

The first report of arteriotomy (the removal of 500 to 1500ml of arterial blood with subsequent retransfusion to restore blood pressure at the end of the procedure) was made by Gardner (1946) who coined the term induced hypotension. Influenced by animal work on shock and its therapy (Kohlstaedt and Page, 1943) he employed deliberate bleeding prior to surgery for a meningioma. He felt that overall blood loss was decreased and that a "better" operative removal of the tumour was attained. He attributed the effect to vasoconstriction rather than to hypotension. Gardner described one patient in detail and mentioned six others.
Larger series were reported by Hale (1948), for middle ear, as well as neurosurgical procedures, and by Bilsland (1951), who named it controlled hypotension. An increase in pulse rate was noted and Bilsland (1951) warned that a rising respiratory rate was an urgent indication for retransfusion. Both workers attributed morbidity and mortality to the technique which was obviously a controlled form of shock.

**High Spinal Anaesthesia**

The next development was by Griffiths and Gillies (1948) working in Edinburgh. They had to devise an anaesthetic technique for the operation of thoraco-lumbar sympathectomy then in vogue for severe essential hypertension. The requirements were analgesia and muscle relaxation for thoracotomy, and a bloodless field for the detailed retropleural dissection. High spinal anaesthesia had been employed previously for surgery of the thorax, head and neck (Koster, 1923; Koster and Kasman, 1929), and hypotension and reduced bleeding observed. Griffiths and Gillies (1948) chose this technique and are notable for:

(a) their deliberate use of the hypotension;
(b) emphasising the difference between hypotension induced by vasodilation in the presence of normovolaemia, and that due to reduced blood volume;
(c) stressing the importance of the Trendelenburg position to maintain venous return;

and (d) for insistence on maintenance of oxygenation using artificial ventilation if necessary.

Deaths occurred early in the series, but the lessons were learnt and considering the poor condition of the patients, many suffering from
malignant hypertension, the later results were remarkable.

Ganglionic Blockade

The discovery of the ganglionic blocking drugs is a classic example of a major discovery made almost by accident. The polymethylene bis-quaternary ammonium salts were being investigated for curare-like activity when it was noted that C6 (hexamethonium) was a ganglionic blocking drug "offering possibilities of clinical usefulness in such fields as hypertension and vascular disease" (Paton and Zaimis, 1948). Further, when studying (in themselves) reversal of the neuromuscular effect of C10 (decamethonium) by C5 (pentamethonium), Organe, Paton and Zaimis (1949) noted postural hypotension as a side effect of the latter.

These observations led to the use of the drugs for the treatment of hypertension and, following the introduction of hypotension by vasodilation by Griffiths and Gillies (1948), encouraged others to try them for this latter purpose. Scurr was reported to have used them in 1949 (Organe, 1950) and Enderby (1950) produced his classic paper on controlled circulation with posture and ganglionic blockade, emphasising that reduction in bleeding rather than hypotension per se was the prime aim.

Immediate developments

The introduction of the ganglionic blockers produced an increase in the use of hypotensive anaesthesia which arteriotomy and high spinal anaesthesia had not. One major reason was that the ganglion blockers are technically much easier to administer. In addition, there were major objections to the wider use of the other methods. The potential of arteriotomy for causing tissue hypoxia was appreciated (Learmonth, 1953), and it fell into disuse, although it
was claimed (Brown, 1954) that it still had a place in neurosurgical practice because the absence of post-operative postural hypotension allowed nursing in the head-up position. Even the protagonists of high spinal anaesthesia felt that the technique was difficult to justify where muscle relaxation was not required (Gillies, 1952). Thus the ganglion blocking drugs assumed the dominant position (Hampton and Little, 1953).

The justification for using induced hypotension by any technique quickly became, and remains, one of the greatest causes for argument between anaesthetists. The protagonists (Wyman, Cox and Gillies, 1953) argued that, as well as improving operating conditions, induced hypotension reduced anaesthetic requirements and improved the patient's condition during and after the operative procedure. This was attributed to prevention of blood loss and protection from operative trauma.

As mentioned earlier much of the excessive bleeding encountered during surgery at this time was probably related to (although not understood as such) poorly conducted anaesthesia. Many welcomed a method of overcoming this but to superimpose a hypotensive agent on a poorly conducted anaesthetic was asking for trouble. Armstrong Davison (1953) felt that the technique was increasing mortality and attacked both the principle of induced hypotension and the methods used to produce it. He advised that hypotension should be used only as a means of saving life or of removing a symptom which made life unbearable, and where haemorrhage made the necessary operation impossible.

Early enthusiasm for induced hypotension was indicated by the replies to a questionnaire sent to anaesthetists in Great Britain.
(Hampton and Little, 1953). 178 out of a total of 289 replying said that they used controlled hypotension. The replies also added weight to Davison's fears about mortality. Major complications (from delayed recovery to major arterial thromboses and organ failure) were reported as frequently as 1 case in 38 and the death rate was 1 in 149. A postal questionnaire is a dubious method of assessment because it will tend to draw only positive replies, but such reports of major complications enabled Larson (1964) to write in his comprehensive review: "This ignited a gunpowder fuse of still fizzing denunciation, and only from the tenacity of a handful of anaesthetists and surgeons did the technique survive". As with many another therapeutic advance initial popularity was followed by a distinct swing away before the true place of the technique was established.

Apart from the complications there were other reasons for the decrease in use. Acceptance that much bleeding was caused by anaesthetic factors eventually led even enthusiasts (Gillies and Holmes, 1965) to allow that "prevention of these factors may obviate the need for special hypotensive measures". Particularly important were proper understanding of the use of neuromuscular blockers with endotracheal intubation and artificial ventilation (Gray and Feoc, 1952) and the introduction into clinical practice of halothane (Johnstone, 1956). This is a potent volatile agent which provides smooth anaesthesia with a degree of circulatory depression more than adequate enough for the majority of routine situations.

As a result of these many factors guidelines for the use of induced hypotension evolved in the nineteen fifties (Larson, 1964; Leigh, 1975). The technique was to be employed for a positive reason (to make the impossible, possible) and not as a panacea for poor anaesthesia. Both surgeon and anaesthetist should be agreed on its use.
A smooth anaesthetic, with proper positioning of the patient, was a necessary preliminary to drug injection, which should be in a dose aimed to control bleeding, not to produce a particular blood pressure as had many earlier practitioners (Hampton and Little, 1953). This was the situation in 1964 when Larson's review marked the end of the era of clinical development, and more importantly, called for more scientific investigation of all aspects.

Variations and development in basic technique

The large numbers of drugs and modifications to technique tried over the years bear witness to the fact that no method is perfect. Bromage (1951) introduced extradural spinal block as opposed to the intradural method used by Griffiths and Gillies (1943). The former is more difficult to perform but subarachnoid block was already under the cloud of neurological sequelae (Davison, 1953) when the Woolley and Roe case dealt it a body blow even though no negligence was found (Cope, 1954). Such was the effect of the case that regional anaesthesia as a whole was underutilised in Britain although there were still those prepared to use both intra- and extradural anaesthesia for hypotension (Scott, 1958).

Generally the ganglion blockers became ever more dominant in hypotensive practice, but were not without side effects (Holmes, 1956). Paralytic ileus was an occasional complication and postural hypotension could persist post-operatively. Both were probably related to the somewhat prolonged duration of action of hexamethonium.

Another problem was difficulty in achieving satisfactory operating conditions, particularly in young patients. This was first highlighted by Enderby and Pelmore (1951) who noted it in 50% of patients given pentamethonium and 15% given hexamethonium. This
Resistance was to the production of both hypotension and ischaemia and was thought to be due to tachyphylaxis. However Zaimis (1955) argued that true tachyphylaxis could not occur at ganglionic level, and that repeated doses (the usual therapeutic response) would only prolong the effect. She implied that the clinical problem was due to a reflex response of the intact organism. Enderby and Pelmore (1951) had noticed that the resistance was associated with tachycardia and it was later felt that this was the cause of bleeding (Holloway, Holmes and Hider, 1961), although with the ganglia blocked such resistance is likely to be due to myogenic recovery, not autonomic reflexes.

Two approaches to overcoming these problems were tried. Other ganglion blocking agents were developed and various methods tried to potentiate their effect. Mason and Pelmore (1953) combined procaineamide with hexamethonium to increase vasodilation and prevent tachycardia. That same year trimetaphan (Nicholson, Sarnoff and Crehan, 1953) was introduced, having a much shorter duration of effect, and a direct vasodilatory, as well as a ganglion blocking, effect. Resistance with tachycardia still occurred and large doses could lead to a prolonged effect, particularly if histamine release ensued.

Pentolinium and phenacyl homatropinium were two latterly used ganglion blockers. Enderby (1954) introduced the former, but reported it as slow in onset. Although tachycardia was not a feature, the young were still resistant. The other drug was similar in many ways to trimetaphan (Robertson and Armitage, 1959) although it did not release histamine. Pentolinium remains in use but phenacyl homatropinium has long been unavailable since it had insufficient advantage over trimetaphan to displace it.

As well as reducing the need for specific hypotensive measures in many patients, the introduction of halothane in 1956
provided an excellent anaesthetic base for a hypotensive technique (Enderby, 1960). Associated with the need for smooth anaesthesia was the avoidance of hypercarbia which stimulates the circulation. This was taken a step further when controlled ventilation was used in the management of resistant cases (Enderby, 1958) to lower carbon dioxide tension and decrease venous return.

However, many preferred spontaneous ventilation (Holmes, 1956) claiming that it acts as a monitor of medullary perfusion and that the slight elevation in carbon dioxide that occurs will maintain cerebral blood flow. Later measures tried to control the tachycardia were guanethidine (Holloway, Holmes and Hider, 1961) which was slow in onset and long in duration, and the beta-blockers which decrease cardiac output during anaesthesia (Stephen, Davie and Scott, 1971) and are said to make the assessment of depth of anaesthesia difficult (Hellewell and Potts, 1966).

Introduction of sodium nitroprusside

In spite of these many variations there was still dissatisfaction with the techniques available (Hellewell and Potts, 1966). Each anaesthetist using induced hypotension developed his own combination of the various drugs and manoeuvres to suit his own situation, patients and surgeons, presumably basing the choice on what was considered an acceptable physiological trespass (Gillies, 1952). The continuing search for a better agent led Moraca et al (1962) to try sodium nitroprusside (SHP) which had been studied (Page et al, 1955) for the therapy of essential hypertension.

Moraca et al (1962) used SHP to induce hypotension in four neurosurgical cases. During the sixties other reports of its use
appeared (Ditzler, 1964; Schiffman and Fuchs, 1966), including the earliest British report (Jones and Cole, 1968). These early reports were small scale and usually from neurosurgical units, although Schiffman and Fuchs (1966) were working with urological and orthopaedic patients. Soon Taylor et al (1970) and MacRae (1971) were able to report larger series, both from E.N.T. departments.

Recent use of induced hypotension

As has been indicated there was a marked reduction in the use of hypotensive anaesthesia following the enthusiasm of the early fifties (Little, 1964), but in the mid nineteen-sixties there was a considerable renewal of interest (Telfer and Campbell, 1966). There was no obvious reason for this and many factors were probably relevant. Little (1964) felt that the time had come to look again at the technique following good reports from those still using it. Standards of anaesthesia were improving, understanding of the physiology of induced hypotension was increasing and the proper indications and contraindications were established. Regional, particularly spinal, anaesthesia began its rehabilitation in this country following the publishing of large series without neurological sequelae and is particularly appropriate for hypotension for operations in the lower half of the body.

The introduction of SNP was also responsible for a major increase in the use of induced hypotension. Described by Moraca et al (1962) as "potent, inexpensive, quick in action, short in duration and non-toxic in clinical dosage" it seemed close to being ideal. The other early workers mentioned above confirmed these features and this resulted in a rapid increase in use. Because SNP was introduced at a time when physiological methods were becoming widely used to study
many aspects of anaesthetic practice, its detailed effects became rapidly and widely published. This thesis is based on a series of investigations of the effects of induced hypotension with SNP on oxygen transport.
CHAPTER TWO

PROPERTIES, METABOLISM, AND CLINICAL USES OF
SODIUM NITROPRUSSIDE
CHAPTER TWO

PROPERTIES, METABOLISM, AND CLINICAL USES OF

SODIUM NITROPRUSSIDE

Chemistry

\[
2\text{Na}^+ + 2\text{H}_2\text{O} \rightarrow \text{CN}^- + \text{Fe}^{++} + \text{NO}^+ + \text{CH}^- + 2\text{H}^+ \\
\]

Figure 2.1: Structure of Sodium Nitroprusside

Sodium Nitroprusside (Molecular Weight 297.97: Figure 2.1) is produced by the action of 30% nitric acid on ferrocyanide or ferricyanide and was first described by Sayfair (1849). It forms red, odourless, transparent, rhomboid crystals which dissolve in water to give a brownish solution. This slowly turns blue on exposure to light as the ferrous ion is oxidised to the ferric form. SNP reacts with small quantities of many organic compounds to produce coloured complexes. This property was the basis for its early medical use in diagnostic tests for acetone, aldehydes, alkali sulphides and sulphur dioxide. It is a particularly potent oxidiser of sulphydryl groups.

Early views of mode of action

The first record of the action of SNP was published by Hermann (1885) who noted an intense odour of cyanide in the body cavities of animals given fatal doses. Other early studies (see Johnson, 1929) confirmed the view that SNP exerted its effect by
release of cyanide, and it was occasionally used as an agent for suicide (Lazarus-Barlow and Norman, 1941; Hill, 1942).

The therapeutic potential of low dose SNP was first considered by Johnson (1929). In animal studies SNP rapidly produced hypotension by the oral, intravenous and subcutaneous routes. Limb volume increased and heart and kidney volume decreased, but the pressor responses to painful stimuli and adrenaline were not blocked. The effects were identical to those of nitrite given to the same animals, but equivalent amounts of cyanide produced hypertension. He concluded that SNP (and not a metabolic product) had a direct action on vascular smooth muscle independent of its innervation and that it was a nitrite (−NO₂) type action due to the nitroso (−NO) group. He estimated that the nitroso group was 50 to 1,000 times more potent in effect on blood pressure than the nitrite. He found that the effective subcutaneous hypotensive dose in rabbits was a tenth of the toxic one and suggested that it could be used quite safely in man. One hypertensive, and two normotensive patients were given single injections and a hypotensive response demonstrated.

Therapeutic use had to wait until the work of Page et al (1955). They studied the cardiovascular effects in animals and hypertensive man using both intravenous and oral administration and confirmed Johnson's findings. Importantly they demonstrated that the speed of action was too rapid to be due to production of cyanide or thiocyanate. The effect of other hypotensive agents was potentiated by SNP.

Metabolism

Hill (1942) demonstrated that the initial breakdown of SNP was due to a non-enzymatic reaction with a "constituent in the blood" causing slow release of cyanide. Page et al (1955) produced evidence that this reaction was with sulphydryl groups and noted that incubation
with whole blood resulted in faster release of cyanide than with plasma. They attributed this to the presence of large numbers of sulphydryl groups in red blood cells.

However, Smith and Kruszyna (1974) have shown that SNP can also react non-enzymatically with haemoglobin (Figure 2.2).

![Figure 2.2: Reaction of nitroprusside with haemoglobin.](image)

An electron is transferred from the haemoglobin (producing methaemoglobin) to the nitroprusside ion. The latter becomes unstable and breaks down releasing the five cyanide groups, one of which reacts with the methaemoglobin to form cyanomethaemoglobin. This would explain why, on a molar basis, SNP is only four times as toxic as cyanide although it contains five equivalents of cyanide (Ivankovich, Miletich and Tinker, 1978).

At present there is no evidence as to which route is the more important but Smith and Kruszyna (1974) did demonstrate that relatively high concentrations (≥8m mol/l) are necessary for SNP to penetrate red cell membranes. Such concentrations are much higher than those found clinically. They also concluded that a third theoretical pathway for the breakdown of SNP, that by the liver enzyme mixed-function oxidase, was unimportant. No matter which path is followed the end result is certainly cyanide. This then enters the body pool.

In animals over 80% of cyanide is converted to thiocyanate.
by reaction with thiosulphate (Figure 2.3). The enzyme rhodanese

\[
\text{Rhodanese} \quad \begin{array}{c}
\text{CN}^- + \text{Na}_2\text{S}_2\text{O}_3 \rightarrow \\
\text{SON}^- + \text{Na}_2\text{S}_2\text{O}_3 \\
\downarrow \\
\text{URINE}
\end{array}
\]

\[\text{Figure 2.3: Conversion of cyanide to thiocyanate.}\]

catalyses the reaction (Lang, 1933) and the thiocyanate is excreted in the urine (Lang, 1894). The presence of thiocyanate in the blood and urine of patients receiving nitroprusside (Page et al, 1955) would confirm this route in man. Saunders and Himwich (1950) demonstrated enough rhodanese in dog liver to convert over 1 gram of cyanide in fifteen minutes. The limiting factor would thus seem to be availability of thiosulphate, which is a normal metabolite of unknown formation (Williams, 1959).

There are also several minor pathways for the detoxication of cyanide (Figure 2.4). In rats up to 15% may combine with cystine

\[\text{Figure 2.4: Minor metabolic pathways for cyanide (after Williams, 1959)}\]

and the product (2-imino-thiazolidine-4-carboxylic acid) is excreted in the urine (Wood and Colley, 1956). Small amounts are exhaled unchanged or metabolised to either carbon dioxide or formate (Ivankovich, Miletich and Tinker, 1978). Cyanide also combines reversibly with both free hydroxycobalamin and methaemoglobin. These minor pathways play an unimportant part in cyanide metabolism.
When all the pathways are insufficient to prevent cyanide accumulating it will exert its toxic effect by combining (reversibly) with cytochrome oxidase. This prevents aerobic metabolism at the cellular level and histotoxic anoxia results (see Chapter 6).

The metabolic fate of the other constituents of the nitroprusside molecule has received little attention. The iron atom must enter the body pool, and presumably the nitroso group is, like aromatic nitroso groups (Williams, 1959), reduced to an amino group.

Mode of action at cellular level

More recent work has done little but confirm Johnson’s (1929) view on the mode of action of SNP and its specificity for smooth muscle. It is of interest that the nitroso group can be replaced by octylamine to yield a ferrate compound which is said to be effective in animals (Palmer and Lasseter, 1975). Other minor modifications to the molecule also produce vasoactive compounds (Kreye and Gross, 1977). This would suggest that it is the whole complex that is active, not simply the nitroso group.

Elucidation of the cellular action is hampered because of gaps in the detailed knowledge of the biochemistry of the smooth muscle cell (Bulbring and Bolton, 1979). The process of smooth muscle contraction (and relaxation) can be divided into three stages:

1. Excitation of membrane receptors (for both contraction and relaxation) by physiological agonists and antagonists,

2. Coupling of excitation to the contractile process,

and

3. The contractile process itself.
Stages 1 and 3 are relatively well understood. Various hormones and neuronal transmitters affect different types of smooth muscle in ways appropriate for their function. It is important to remember that a single agent (i.e. adrenaline) may contract one type of smooth muscle and relax another. Contraction is, as in striated muscle, due to activation of actin and myosin filaments by a rise in intracellular calcium (Perry and Grand, 1979). Whilst calcium is the link between excitation and contraction it is precise knowledge of the factors that control its intracellular level that is lacking.

The situation is complicated by the ability of smooth muscle to contract in two ways. Phasic contraction is similar to that of striated muscle and is associated with membrane depolarisation, at the time of which calcium enters through the cell membrane and is released from intracellular stores. Sustained contractions are also related to influx and release of calcium but there is little or no change in membrane potential. In both cases relaxation is due to re-uptake of calcium by intracellular stores and extrusion across the cell membrane. Nitroprusside relaxes sustained contractions but has minimal effect on phasic ones. Knowledge of the factors that control calcium levels during sustained contraction is therefore of importance.

Rasmussen and Goodman (1977) have reviewed this subject and suggested a complex scheme whereby agonists and antagonists of cell activity have direct effects on calcium entry and release, and indirect effects by activation of two nucleotides – cyclic adenosine monophosphate (cAMP) and guanosine phosphate (cGMP). Both actions are mediated via receptors in the cell membrane (Figure 2.5). An increase in cAMP favours relaxation by increasing extrusion and uptake of calcium and cGMP produces the reverse. However, an apparently
paradoxical rise in cAMP can occur during contraction because of a feed-back mechanism whereby calcium inhibits cAMP breakdown and so enhances its own re-uptake. By a reverse process an increase in cGMP may occur during relaxation. Presumably these feed-back mechanisms are responsible for the fine adjustment of intracellular calcium level. The ratio of cGMP : cAMP is probably the most important factor and is known to be elevated in hypertensive rats (Amer et al, 1974).

![Diagram of factors affecting intracellular calcium](image)

**Figure 2.5:** Factors affecting intracellular calcium (after Rasmussen and Goodman, 1977)

Against this complex background the studies of the cellular action of SNP must be set. Needleman et al (1973) proposed that each type of vasodilator reacts with its own specific receptor on the smooth muscle cell membrane, and suggested that there is a common pathway for the effect on contractile units. They considered SNP's ability to oxidise sulphydryl groups to be the mechanism by which it combines with receptors, but made no suggestions as to the nature of the final pathway.

Many vasodilators act by elevating cAMP levels (Lugnier,
Bertrand and Stoclet, 1972) but Kreye et al (1975) found them to be unaffected by SNP. These workers confirmed that it did not affect adrenergic receptors and they favoured a direct effect on the coupling of excitation to contraction by prevention of the influx and intracellular activation of calcium. Possibly an interaction with cell membrane sulphhydryl groups leads to interference with calcium movement (Miletich and Ivankovich, 1978a).

Haeusler and Thorens (1976) were unable to suggest a precise explanation for its action, raising only the possibility of an interaction with calcium or a direct affect on the contractile proteins. Verhaeghe and Shepherd (1976) felt that the action was independent of calcium influx.

Two groups of workers (Katsuki, Arnold and Murad, 1977; Schultz, Schultz and Schultz, 1977) have shown an increase in cGMP, and no change in cAMP, associated with the effect of many vasodilators including SNP. Possibly the concept of calcium control outlined above is wrong or they were noting the paradoxical rise due to decreased calcium level or their experimental model was inappropriate. Both groups used vas deferens muscle whereas all other workers used vascular muscle, and Diamond and Janis (1978) have criticised both their experimental methods and conclusions.

Finally Ito, Suzuki and Kuriyama (1978) found that SNP produced membrane hyperpolarisation as well as direct effects on both contractile units and calcium. Most interestingly they demonstrated a difference in the effect on two different types of muscle from the same animal. Thus the conflicting evidence reviewed above may simply relate to differences in experimental models. It was noted above that adrenaline contracts some smooth muscle and relaxes others;
similarly cAMP and cGMP may be agents for both contraction and relaxation depending on the tissue involved.

Following the early work (Johnson, 1929) it was thought that SNP had a specific action on vascular smooth muscle. However, more recent work has shown that other types of smooth muscle are affected, but not equally. The sensitivity of a particular type depends on the relative proportion of phasic and sustained contraction important to its physiological activity (Robinson and Collier, 1979). In the vascular system SNP is ten times more potent in its effect on peripheral veins than arteries (Robinson, Collier and Dobbs, 1979), indicating the importance of sustained contraction in the former’s capacitance function. In addition muscle from pulmonary artery (Haeusler, 1975), portal vein (Ito, Suzuki and Kuriyama, 1978), trachea (Kreye et al, 1975) and uterus (Pauli, 1975) have all been shown to be relaxed.

**Duration of action**

The mechanism of action is in doubt (Kreye, 1980). Possibly more obscure is the reason for the very brief duration of action. Hypotension produced by intravenous infusion is evanescent (Chapter 3), but in vitro it takes over an hour for whole blood to convert SNP to cyanide (Page et al, 1955) and during infusion cyanide levels take 45 minutes to become maximum (Vesey, Cole and Simpson, 1977).

Virtually no study has discussed, let alone been able to explain, the mechanism of the drug’s most valuable feature! Vesey, Cole and Simpson (1977) suggested initial combination with a plasma constituent followed by entry into red blood cells to be the explanation. However, high concentrations are required to penetrate
red cells (Smith and Kruszyna, 1971). The ability to oxidise sulphydryl groups suggests a rapid reaction with these groups in the blood to inactivate SNP which then decomposes slowly to release cyanide.

**OXYGEN TRANSPORT DURING NITROPRUSSIDE INFUSION**

Consideration of the basic properties of sodium nitroprusside outlined above suggests that there are several, at least theoretical, mechanisms by which it (or its metabolites) might interfere with that most important of physiological functions - the transport of oxygen to, and its metabolism by, the tissues. Assessment of the actual effects on oxygen transport are of obvious importance for safe clinical use, particularly since interference with this process has probably been responsible for the majority of complications of induced hypotension by all methods (Lindop, 1975; Strunin, 1975).

Oxygen transport can be divided into four stages:

1. Oxygenation of the blood by the lungs.
2. Carriage of oxygen in the blood by haemoglobin.
3. Distribution of oxygenated blood by the circulation.
4. Consumption of oxygen by the tissues.

These four correspond to the classical definition of anoxia as being anoxic, anaemic, stagnant or histotoxic in nature. As well as its vasodilator action (on pulmonary, as well as systemic vessels) SNP dilates bronchi; can undergo a reaction with haemoglobin; through that and other mechanisms may produce methaemoglobinemia; and finally releases cyanide, a cellular poison, when it breaks down.

This thesis contains studies of the actions of SNP on these
four stages to assess the actual effects of the above. It would be logical to present the studies in the order outlined above, but since interpretation of the results of the other studies requires knowledge of the cardiovascular study, that is presented first. As that study was performed first the others follow in chronological order.

**CLINICAL USE**

The first clinical use of SNP was in the therapy of essential hypertension. Page et al (1955) used intravenous SNP for up to 14 days in malignant hypertension and gave it orally for as long as 2 years. Because thiocyanate would accumulate if renal function was impaired, but more particularly because of the need for frequent doses and the development of other oral agents for hypertension, SNP was never widely used for chronic therapy. It remains, however, the most rapid and consistently effective agent for malignant hypertension (Wood, 1974).

The early use of SNP for induced hypotension has been described (Chapter One). The third, and most recent, application has been in very low dosage to produce peripheral vasodilatation without hypotension in patients with acute myocardial infarction. The resultant decrease in ventricular afterload reduces myocardial work and improves cardiac performance (Franciosa et al, 1972).

**Preparation and use in induced hypotension**

Until recently SNP was not available commercially, but had to be prepared by hospital pharmacies, and sterilised by filtration because it is heat labile. In 1977 Roche Products Ltd., who had always manufactured the chemical, introduced a pharmaceutical preparation (Nipride:Roche). Each ampoule contains 50mg of SNP powder for reconstitution with 2ml of 5% dextrose. An aliquot is
added to 500ml of 5% dextrose for infusion. Contamination should be avoided because of the risk of chemical reaction. Coloured compounds are produced with a wide range of organic and inorganic compounds and if these appear the solution should be discarded. It is recommended that the constituted solution is protected from light and discarded after four hours.

Patients vary in their requirement and a commonly used regime is that of MacRae (1971) (Table 2.1). Stable anaesthesia is established, the appropriate concentration made up and the infusion rate increased until the required conditions are produced. An infusion pump greatly simplifies administration. The studies presented in this thesis were performed using this dose schedule.

<table>
<thead>
<tr>
<th>Infusion concentration</th>
<th>50mg/500ml (0.01%)</th>
<th>25mg/500ml (0.005%)</th>
<th>10mg/500ml (0.002%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males Age (yrs)</td>
<td>&lt; 30</td>
<td>30-50</td>
<td>&gt; 50</td>
</tr>
<tr>
<td>Females yrs</td>
<td>&lt; 20</td>
<td>20-40</td>
<td>&gt; 40</td>
</tr>
</tbody>
</table>

Table 2.1: Concentrations for induced hypotension with sodium nitroprusside (MacRae, 1971)
CHAPTER THREE

CARDIOVASCULAR ACTIONS
CHAPTER THREE

CARDIOVASCULAR ACTIONS

Following the introduction of induced hypotension by vasodilation one of the major causes for controversy was the question of the adequacy of cardiovascular performance. From Griffiths and Gillies (1948) onwards the protagonists have argued that the vasodilation would not affect tissue perfusion, but there have always been those who argued that such interference with the circulation was unwarranted. Reports of major organ failure (Hampton and Little, 1953) supported the view that blood flow could be inadequate.

The resurgence of interest in the nineteen sixties based on the lessons of earlier experience (Chapter One) was associated with much more research into the effects of induced hypotension as had been suggested by Larson (1964). Around the time of the introduction of nitroprusside the cardiovascular effects of the hypotension produced by both epidural anaesthesia and trimetaphan during general anaesthesia (Stephen, Lees and Scott, 1969; Scott et al, 1972) had been studied. It was decided to study nitroprusside in the same way to confirm the features of the drug noted clinically and to compare its effects with the other methods.

METHODS

Patients and anaesthesia

Five patients (3 male, 2 female; aged 23 to 45 years), who were to undergo major otolaryngological procedures under hypotensive anaesthesia, were studied. Their general health was good and they gave informed consent for the investigation.
The patients were premedicated with oral diazepam 10mg and anaesthesia was induced with intravenous thiopentone 250-350mg. The trachea was intubated with the aid of suxamethonium 50mg and the patients then breathed spontaneously a mixture of nitrous oxide, oxygen (60%) and halothane 1.5 - 2.0% from a semi-closed circuit with carbon dioxide absorption.

Measurements and calculations

After induction of anaesthesia arterial (19G Venflon) and central venous (18G, 24in E-Z Cath) catheters were inserted percutaneously into the radial artery and median basilic vein of one arm. These lines were used to measure arterial and central venous pressures using Bell and Howell 1327-L221 transducers and matching amplifiers calibrated against a column of saline. These lines were also used in the measurement of cardiac output using the indocyanine green dye dilution method. 5mg of dye in 2ml of dilutant were injected via the central venous line using a semi-automatic injector which delivers volumes within ±2% of each other. Blood was withdrawn from the arterial line with a Harvard pump via a Waters 303 cuvette and densitometer. The E.C.G. was monitored throughout and used to derive heart rate. Recordings were made on Devices hot pen recorders. The pressure measuring systems were critically damped.

Cardiac output was subsequently calculated from the general formula:

\[
\text{Cardiac output} = \frac{60 \times \text{dose of dye injected}}{\text{Mean dye conc.} \times \text{transit time}}
\]  
(Hamilton et al, 1932)

The mean concentration was derived using a mathematical method for the area under the dye-dilution curve (Williams, O'Donovon and Wood, 1966).

Protocol

After stable anaesthesia had been established four control
readings of mean arterial pressure, cardiac output, central venous pressure and heart rate were made at 2-minute intervals. An infusion of sodium nitroprusside was then started into a peripheral vein and adjusted to produce a systolic pressure of about 60 mm Hg. A further four readings were then obtained, again at 2-minute intervals. The infusion was stopped and a final three readings obtained.

Analysis

Subsequently stroke volume was calculated from cardiac output and heart rate, and peripheral resistance from cardiac output and mean arterial pressure. Statistical comparisons were made using a 't'-test for paired data.

RESULTS

Table 3.1 shows the mean values for mean arterial pressure, cardiac output, central venous pressure, heart rate, stroke volume and peripheral resistance before, during and after infusion of sodium nitroprusside. Mean changes occurring when hypotension was induced, and again when it was discontinued, are given in Table 3.2, together with probability values.
<table>
<thead>
<tr>
<th></th>
<th>CONTROL</th>
<th>SNP INFUSION RUNNING</th>
<th>SNP STOPPED</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-8</td>
<td>-6</td>
<td>-4</td>
</tr>
<tr>
<td>MEAN ARTERIAL PRESSURE (mm.Hg)</td>
<td>72</td>
<td>70</td>
<td>68</td>
</tr>
<tr>
<td>CARDIAC OUTPUT (litres/min.)</td>
<td>5.3</td>
<td>5.6</td>
<td>5.7</td>
</tr>
<tr>
<td>CENTRAL VENOUS PRESSURE (mm.Hg)</td>
<td>7.7</td>
<td>7.9</td>
<td>8.3</td>
</tr>
<tr>
<td>HEART RATE (beats/min.)</td>
<td>67</td>
<td>68</td>
<td>67</td>
</tr>
<tr>
<td>PERIPHERAL RESISTANCE (dynes/sec/cm²)</td>
<td>1230</td>
<td>1270</td>
<td>1140</td>
</tr>
<tr>
<td>STROKE VOLUME (mls)</td>
<td>81</td>
<td>84</td>
<td>87</td>
</tr>
</tbody>
</table>

Table 3.1: Mean values of haemodynamic parameters at 2-minute intervals of five cases before, during and after sodium nitroprusside.
<table>
<thead>
<tr>
<th></th>
<th>Control Mean</th>
<th>SNP Mean</th>
<th>Mean Difference ± SD</th>
<th>p</th>
<th>SNP Mean</th>
<th>Post-SNP Mean</th>
<th>Mean Difference ± SD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean Arterial Pressure</strong> (mm. Hg)</td>
<td>69 ± 10</td>
<td>41 ± 6</td>
<td>-28 ± 10</td>
<td>&lt;0.005</td>
<td>68 ± 8</td>
<td>-27 ± 8</td>
<td>&lt;0.005</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac Output</strong> (litres/min.)</td>
<td>5.5 ± 0.6</td>
<td>6.5 ± 0.9</td>
<td>+1.0 ± 0.6</td>
<td>&lt;0.025</td>
<td>5.7 ± 0.9</td>
<td>-0.8 ± 0.9</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td><strong>Central Venous Pressure</strong> (mm. Hg)</td>
<td>3.1 ± 2.1</td>
<td>2.8 ± 2.8</td>
<td>-5.3 ± 3.8</td>
<td>&lt;0.02</td>
<td>2.8 ± 2.8</td>
<td>+3.9 ± 2.8</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td><strong>Heart Rate</strong> (beats/min.)</td>
<td>67 ± 7</td>
<td>83 ± 5</td>
<td>+15 ± 7</td>
<td>&lt;0.01</td>
<td>83 ± 5</td>
<td>-18 ± 5</td>
<td>&lt;0.005</td>
<td></td>
</tr>
<tr>
<td><strong>Peripheral Resistance</strong> (dynes/sec/cm²)</td>
<td>1210 ± 300</td>
<td>600 ± 350</td>
<td>-610 ± 300</td>
<td>&lt;0.01</td>
<td>600 ± 350</td>
<td>+580 ± 350</td>
<td>&lt;0.025</td>
<td></td>
</tr>
<tr>
<td><strong>Stroke Volume</strong> (mls)</td>
<td>84 ± 18</td>
<td>78 ± 14</td>
<td>-6 ± 18</td>
<td>NS</td>
<td>78 ± 14</td>
<td>+11 ± 14</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

**Table 3.2:** Statistical comparison of means of haemodynamic parameters of five cases before and during, and during and after, sodium nitroprusside. Paired t-test.
Mean arterial pressure

This decreased in every case to an average value of 58% of control and quickly returned to control value on discontinuation (Figure 3.1). Both changes were significant to a high degree.

**Figure 3.1:** Mean values of arterial pressure at 2-minute intervals in five cases before, during and after sodium nitroprusside. Vertical bars represent ±1 standard error. On the right are shown the mean before, during and after nitroprusside in individual cases.
Cardiac output

The group as a whole showed a moderate and statistically significant increase in cardiac output during infusion. No patient suffered a fall in output, though in one case it remained the same (Figure 3-2). On withdrawal of nitroprusside cardiac output decreased in four patients and increased further in one.

**Figure 3-2**: Mean values of cardiac output at 2-minute intervals in five cases before, during and after sodium nitroprusside. Vertical bars represent ±1 standard error. On the right are shown the mean before, during and after nitroprusside in individual cases.
Central venous pressure

Unfortunately no record of CVP was kept in one patient because of a technical fault, and figures are for the other four only. CVP decreased markedly during infusion, and afterwards returned towards initial values (Figure 3.3).

**Figure 3.3:** Mean values of central venous pressure at 2-minute intervals in five cases before during and after sodium nitroprusside. Vertical bars represent ±1 standard error. On the right are shown the mean before, during and after nitroprusside in individual cases.
There was a consistent rise in heart rate during infusion of around 22%, which promptly reversed on discontinuation (Figure 3.4).

**Figure 3.4:** Mean values of heart rate at 2-minute intervals in five cases before, during and after sodium nitroprusside. Vertical bars represent ±1 standard error. On the right are shown the mean before, during and after nitroprusside in individual cases.
Peripheral resistance

During administration of nitroprusside there was a profound decrease in this parameter in every case. The average was 49%. On discontinuation values quickly returned to control levels (Figure 3-5).

**Figure 3-5:** Mean values of peripheral resistance at 2-minute intervals in five cases before, during and after sodium nitroprusside. Vertical bars represent ±1 standard error. On the right are shown the mean before, during and after nitroprusside in individual cases.
Stroke volume

Changes in stroke volume were small and inconsistent (Figure 3.6). During infusion it decreased in two cases and increased in three. After nitroprusside was stopped three increased and two decreased.

**Figure 3.6:** Mean values of stroke volume at 2-minute intervals in five cases before, during and after sodium nitroprusside. Vertical bars represent ±1 standard error. On the right are shown the mean before, during and after nitroprusside in individual cases.
Overall circulatory effects

These results confirm the initial clinical views (see Chapter One) on the suitability of SNP as an agent for induced hypotension. The blood pressure decreased rapidly after starting the infusion, was easily controlled at a steady level and rapidly returned to initial values when the drug was discontinued. Perhaps the most striking change that occurred was the increase in cardiac output. Hypotension was due to a decrease in peripheral resistance. There was an associated decrease in central venous pressure and an increase in heart rate.

Franciosa et al (1972) also reported an increase in cardiac output in patients receiving SNP after myocardial infarction. There was an associated reduction in left ventricular filling pressure. That study is not strictly comparable with this, but the clinical picture during controlled hypotension with SNP of a well perfused patient with an easily palpable pulse fits well with the finding of a near normal or increased cardiac output. Shortly after this work was published (Appendix 2) a comparable study appeared with similar results (Styles, Coleman and Leary, 1973).

It is quite possible for an agent which causes vasodilatation, but has no direct action on the heart (Adams et al, 1973), to increase cardiac output. The enormous reduction in peripheral resistance will speed flow through the arteriolar beds, and unless gravity is used to prevent it, venous return will also be increased. The heart rate is unaffected and can deal with this increase.
Regional blood flow

Overall circulatory performance is not impaired by hypotension with SNP, but perfusion of the vital organs could still be embarrassed. Perfusion pressure is decreased, although not as much as arterial pressure, because venous pressure is also lower. (Figure 3.3).

The possibility that hypotension might embarrass the coronary circulation seems to be outweighed by the reduction in the work load of the heart caused by the decrease in peripheral resistance. Franciosa et al (1972) reported an improved clinical state in patients infused with nitroprusside after myocardial infarction and it is still widely used in such patients (Reves et al, 1978). This suggests that the coronary circulation is not in jeopardy.

The effect of SNP on coronary blood flow has been measured in patients after myocardial infarction (Chatterjee et al, 1973) and in hypotensed animals (Wang, Liu and Katz, 1977; Rowe and Henderson, 1974) and the overall effect is that heart muscle oxygenation is improved. Such studies have not been made during anaesthesia in man but Simpson, Bellamy and Cole (1976) studied electrocardiographic recordings during clinical hypotension. Some minor changes occurred, but none were permanent.

There have been clinical studies of the effect of induced hypotension with SNP on cerebral, renal and liver blood flow. Cerebral (Griffiths et al, 1974) and liver (Abdel Salem et al, 1976) blood flows were unaffected, but renal blood flow decreased (Birch and Boyce, 1977). This may be related to generation of the potent renal vessel constrictor, angiotensin, by renin which is released.
from the kidney during hypotension with SNP (Kaneko et al., 1967). Souren et al. (1973) found that urine production ceased during SNP hypotension, but that renal function recovered completely after anaesthesia.

It is interesting to speculate that the activation of the renin/angiotensin system referred to above may at least contribute to the rapid return of blood pressure at the end of infusion. As mentioned in Chapter Two no clear explanation for this exists.

Animal studies

The majority of the studies reviewed in the above two sections has been performed in anaesthetised patients undergoing induced hypotension. The last decade or so has seen a wealth of material published on SNP and the circulation based on work in animals and patients in intensive care. This has been reviewed (Miletich and Ivankovich, 1978a) and in general is in accord with the above. That review also included the results of an animal study in which flow to all organs was studied simultaneously. The vital organs were all shown to take a small share of the increase in cardiac output.

Comparison with other techniques of hypotension

No other method of inducing hypotension has been subject to anything like the same scrutiny as SNP. Epidural and spinal anaesthesia produce sympathetic blockade, so the circulatory effect depends on the upper level of the block (Bonica, 1969; Akamatsu, 1969). The tendency is for both heart rate and output to decrease although the effects may be modified if local anaesthetic solutions with adrenaline are used. Organ blood flow has been little studied but
there is general agreement that liver blood flow will fall (Kennedy, 1969).

Comparison of the effects of these techniques with SNP is however not very valid since the clinical indications are different. Prior to the introduction of SNP the standard short acting intravenous agent was trimetaphan. Its effects were studied (Scott et al, 1972) in similar circumstances to those described here. SNP produces a more rapid induction of hypotension, and certainly a more rapid recovery of pressure than trimetaphan. The latter also produces less of a tachycardia and a slight decrease in cardiac output. Thus SNP would seem to have considerable advantages over trimetaphan. Trimetaphan is also said to be unpredictable and relatively uncontrollable (Miletich and Ivankovich, 1978b).

A comparison of nitroprusside and trimetaphan in anaesthetised dogs (Wang, Liu and Katz, 1972) showed similar differences to those found clinically. Those workers also looked at organ blood flow and felt that an undesirable feature of trimetaphan was to redistribute cardiac output to skin and muscle.

It must be emphasised that the study described in this chapter was performed during halothane anaesthesia using spontaneous ventilation and with the patients level. In other clinical situations circulatory changes may be different (Palmer and Lasseter, 1975). Many anaesthetists employ artificial ventilation and or a head-up tilt during induced hypotension and these manoeuvres may modify the circulatory effects by their adverse effect on venous return.
CHAPTER FOUR

RESPIRATORY EFFECTS
Another major controversy surrounding induced hypotension has concerned the method of ventilation to be employed. Eckenhoff and colleagues (1963) found a large increase in physiological deadspace with a concomitant increase in $P_aCO_2$ in patients undergoing ganglionic blockade. They recommended that respiration should be controlled with high tidal volume and high inspired oxygen concentration. Others (Holmes, 1956) believe that the pattern of spontaneous breathing is a useful monitor of cerebral perfusion, and has no adverse effect on venous return.

In common with most other hypotensive techniques there has been, relative to circulatory studies, little work on the effect of SNP on respiration. In addition, arterial blood sampling during nitroprusside infusion revealed oxygen tensions which were less than expected. Therefore it was decided to study blood gas tensions during sodium nitroprusside infusion and to assess the influence of artificial ventilation on these.

**METHODS**

**Patients and anaesthesia**

Twenty-six patients undergoing major otolaryngological surgery were studied. The nature of the study was explained to the patient at the visit before operation, and consent was obtained. Premedication was with oral diazepam 10mg. Anaesthesia was induced with thiopentone 250-400mg. Endotracheal intubation was performed with the aid of suxamethonium 75-100mg in the first 14 patients (Group I)
and tubocurarine 30-45 mg in the next 12 patients (Group II).
Anaesthesia was maintained with 50% nitrous oxide in oxygen
supplemented with halothane 1-2%.

After recovery from suxamethonium, Group I patients breathed
spontaneously from a non-return circuit (Figure 4.1 - S.V.) which
allowed inspired gas sampling and collection of mixed expired gas.

**Figure 4.1:** Gas circuits used in respiratory studies.

In Group II artificial ventilation was performed at 15 breaths/min.
with a Cape-Waine anaesthetic ventilator (Cape Engineering Ltd.)
using a pressure-operated valve (Sykes, 1969) to allow collection of
expired gas into a Douglas bag (Figure 4.1 - I.P.P.V.). The
ventilator was adjusted so that the expired volume, measured with a
Wright's respirometer (British Oxygen Company Ltd.), was that predicted by the Radford (1955) nomogram. All patients were maintained in a 5° head-up position.

Protocol

An arterial blood sample was taken before operation. After anaesthesia had been induced, a percutaneous 21G scalp vein needle (Abbot Laboratories Ltd.) was inserted into a radial artery for direct arterial pressure measurement and used for further arterial sampling.

When the heart rate and arterial pressure had become stable inspired gas, mixed expired gas and arterial blood were sampled. An infusion of SNP into a peripheral vein was then commenced and adjusted to give a systolic pressure of 50-60mm Hg. After 15 minutes at this pressure another set of samples was taken. Hypotension was maintained until surgery was complete, when the infusion was discontinued. After the arterial pressure had returned to the pre-infusion value, a third set of samples was taken. The duration of the operation was between 1 and 3 hours.

Measurements

Standard micro-electrode units (Radiometer Ltd.) were used to measure \( P_{aO_2} \) and \( P_{aCO_2} \). Calibration was with two gas mixtures for carbon dioxide, and nitrogen and water equilibrated with air at 37°C for oxygen. The same apparatus was used to analyse the gas mixtures, but the span of the oxygen electrode was now calibrated with air. For blood the laboratory work to ± 0.27 kPa (2mmHg) for duplicate estimations.

Calculations

Ideal alveolar oxygen tension \( (P_{A\,O_2}) \) was calculated as
follows:

\[
P_{A_2} = P_{I_2} - P_{a^2} \left( \frac{P_{I_2} - P_{E_2}}{P_{E^2}} \right)
\]

where \(P_{I_2}\) and \(P_{E_2}\) are the inspired and mixed expired \(P_2\) values; and the ratio of physiological deadspace to tidal volume \((V_d/V_t)\) was derived from:

\[
V_d/V_t = (P_{a^2} - P_{E^2}) / P_{a^2}
\]

No correction was made for apparatus deadspace.

Statistical comparisons were made using Student's t tests for paired or unpaired data as appropriate, and linear regression analysis.

**RESULTS**

Details of the patients studied are shown in Table 4.1. Patient 12 was omitted because of technical problems with the collection of gas samples. The preoperative sample in patient 3 would seem to have been from a vein. There was a statistically significant difference \((P<0.025)\) between the groups in respect of mean \(P_{a^2}\) \((42\text{mm Hg in group I and } 30\text{mm Hg in group II})\). The mean age in group II was 41 years and that in group I was 35 years, but this difference was not statistically significant.

Tables 4.2 and 4.3 and Figure 4.2 show the measured and derived data of the two groups before, during and after the administration of SNP. \(P_{I_2}\) and \(P_{A_2}\) values were similar in the two groups and changed little throughout. In both groups there was a marked decrease in \(P_{a^2}\) when nitroprusside was administered \((\text{group I, } 190 - 154\text{ mm Hg; group II, } 180 - 133\text{ mm Hg; } P<0.005 \text{ in both groups})\).
### Table 4.1: Details of the two groups of patients

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Spontaneous ventilation</th>
<th>Artificial ventilation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age (yr)</td>
<td>Height (cm)</td>
</tr>
<tr>
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<td>2</td>
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<td>3</td>
<td>15 41</td>
<td>15 16 17 18 19 20 21 22 23 24 25 26</td>
</tr>
<tr>
<td>4</td>
<td>M M M M M M M M M F F F F</td>
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<td>M F M F M F M M M M F M</td>
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<td>3 38</td>
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<td>33 36 39 43 42 38 35 41 36 37 36 40</td>
</tr>
</tbody>
</table>

- **Spontaneous ventilation**
- **Artificial ventilation**

**Note:** The data includes age, sex, height, weight, tobacco use, and arterial pressures for different patients.
Table 4.2: Lung and blood-gas data (mm Hg) in group I (spontaneous ventilation) patients before, during and after the administration of sodium nitroprusside.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Before SNP</th>
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<td>P_aO2</td>
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<tr>
<td>Mean</td>
<td>367</td>
<td>319</td>
<td>190</td>
</tr>
<tr>
<td>SD</td>
<td>27</td>
<td>26</td>
<td>59</td>
</tr>
</tbody>
</table>
Table 4-3: Lung and blood-gas data (mm Hg) in group II (I.P.P.V.) patients before, during and after the administration of sodium nitroprusside.
When the infusion of SNP was stopped, and arterial pressure had increased, $P_{a}O_2$ returned to previous values.

During anaesthesia, $P_{a}CO_2$ was greater in group I than in group II, but the administration of SNP had little effect on either this measurement or on $V_D/V_T$ in either group, although the small increase in mean $V_D/V_T$ in group II was statistically significant ($P<0.05$).

**DISCUSSION**

If alveolar ventilation and inspired $O_2$ remain constant, there are three possible explanations for the reduction in $P_{a}O_2$ during
the administration of SNP. Firstly, cardiac output may have decreased, causing a reduction in mixed venous oxygen content and thus increasing the effect of intrapulmonary shunting. However, it has been shown that cardiac output increases when nitroprusside is administered during anaesthesia (Styles, Coleman and Leary, 1973; Chapter Three). Those studies were performed on supine patients, whereas these patients had a 5° head-up tilt, but changes in $P_{aO_2}$ similar to those described here, have also been observed in supine patients by Griffiths et al (1974). Secondly, there may have been an increase in whole body oxygen consumption, but this seems unlikely. Finally there is the possibility of an increase in the scatter of ventilation/perfusion ratios throughout the lung or an increase in the proportion of blood not being exposed to ventilation, or both.
A major factor affecting the distribution of ventilation/perfusion ratios is the age of the patient (West, 1974). Figure 4-3 shows the values of $P_aO_2$ of all patients studied, both before and during nitroprusside infusion, plotted against age. There is a good correlation for the relationship under both conditions: the older patients had the greatest reduction in $P_O_2$ when SNP was given. Figure 4-4 shows the change in $P_aO_2$ plotted against age.

![Graph showing relationship between age and $P_aO_2$ during anaesthesia, before and during infusion of nitroprusside. $P_O_2$ before nitroprusside = $301 - 3.1 \times \text{age(yr)}$ ($r = 0.73$); $P_aO_2$ during nitroprusside = $301 - 4.3 \times \text{age(yr)}$ ($r = 0.82$).]

Figure 4-3: Relationship between age and $P_aO_2$ during anaesthesia, before and during infusion of nitroprusside. $P_O_2$ before nitroprusside = $301 - 3.1 \times \text{age(yr)}$ ($r = 0.73$); $P_aO_2$ during nitroprusside = $301 - 4.3 \times \text{age(yr)}$ ($r = 0.82$).
West (1969) predicted the effects of worsening the distribution of ventilation and perfusion within the lung, using a mathematical model in which the ventilation/perfusion ratios were distributed in a log-normal fashion. He pointed out that, with such a model, maldistribution could lead to large alveolar-arterial oxygen tension differences at high \( P_{aO_2} \) values. Recent experimental work in the conscious human subject and anaesthetised dogs (Wagner et al, 1974; Wagner, Saltzman and West, 1974; West, 1974) has substantiated the assumptions used in these theoretical predictions.

If those patients whose \( P_{aO_2} \) was low before operation are considered to have increased V/Q scatter, then, according to these predictions, the \( P_{aO_2} \) response to an increase in inspired oxygen concentration to 50% could be less than in those patients with higher
$P_aO_2$ values before operation. This is what has been found (Figure 4·5, pre-SNP), and is similar to the findings in a study of oxygen therapy in chronic bronchitis (Mithoefer, Keighley and Keretzky, 1971). If nitroprusside caused a further increase in $V/Q$ scatter, $P_aO_2$ would decrease. At this inspired oxygen concentration the reduction would be more evident in those in whom $P_aO_2$ was already reduced. This seems to have happened (SNP data, Figure 4·5). If the reductions in $P_aO_2$ were caused by an increase in blood passing through unventilated areas, it is difficult to explain the more marked effect in these patients.

Figure 4·5: Relationship between preoperative $P_aO_2$ and $P_aO_2$ during anesthesia, before and during the infusion of sodium nitroprusside. $P_aO_2$ before nitroprusside = $a_4 \times$ preop. $P_aO_2 = 138 (r = 0.78)$; $P_aO_2$ during nitroprusside = $a_4 \times$ preop. $P_aO_2 = 288 (r = 0.81)$. 
At the time that this work was published (Appendix Two) there was little evidence to suggest how such a change in V/Q scatter might occur. However, as indicated in Chapter Two recent work has shown that SNP can relax smooth muscle from both the tracheo-bronchial tree and the pulmonary vessels; and the hypoxic pulmonary vasoconstrictor response, which maintains ventilation-perfusion ratios, has been shown to be depressed by SNP (Hill et al, 1978). It is perhaps surprising that the fall in arterial oxygen tension was not greater.

One feature of the results of this study would appear inconsistent with the above. If nitroprusside relaxes bronchial smooth muscle, an increase in deadspace would be expected when the drug is administered. This did occur in the artificially ventilated patients (Table 4.3) but not in those breathing spontaneously (Table 4.2). The explanation would seem to be related to the difference in $P_{aCO_2}$ between the groups. In the artificially ventilated patients $P_{aCO_2}$ was in the range 35 - 42 mm Hg and 42 - 59 mm Hg in the others. An increase in $P_{aCO_2}$ is associated with an increase in $V_D/V_T$ (Trimble et al, 1971), possibly because of dilatation of the bronchial tree (Widdicombe, 1966). $V_D/V_T$ was greater in the spontaneously ventilating patients and it could be that bronchial dilatation was already maximal before SNP was administered.

This more recent work on the inter-relationship between $CO_2$ and $V_D/V_T$ may also be relevant to the work of Eckenhoff et al (1963) referred to earlier. They assumed that $P_{aCO_2}$ increased as a result of an increase in physiological dead space and therefore advised artificial ventilation. However it could equally be that some other factor increased $P_{aCO_2}$ and that $V_D/V_T$ increased as a result of this.
Additional support for the view that the decrease in $P_{aO_2}$ was due to increased $V/Q$ scatter is provided if the Bohr equation for $V_D/V_T$ ratio is solved for $O_2$, rather than $CO_2$.

Thus $V_D/V_T = \frac{P_{F_2O_2} - P_{aO_2}}{P_{I_2O_2} - P_{aO_2}}$

A statistically significant increase in mean $V_D/V_T$ ratio is now found in both groups (Table 4.4). Change in "$V_D/V_T$ ratio" thus calculated includes any alteration in physiological shunting, as well as in dead space. If the decrease in $P_{aO_2}$ was due to increased perfusion of non-ventilated areas of lung such a change would not have occurred.

<table>
<thead>
<tr>
<th>$V_D/V_T$</th>
<th>Pre SNP</th>
<th>Per SNP</th>
<th>Post SNP</th>
</tr>
</thead>
<tbody>
<tr>
<td>S.V.</td>
<td>0.88(0.06)</td>
<td>0.92(0.04)</td>
<td>0.86(0.07)</td>
</tr>
<tr>
<td>I.P.P.V.</td>
<td>0.89(0.09)</td>
<td>0.92(0.08)</td>
<td>0.88(0.11)</td>
</tr>
</tbody>
</table>

To show $V_D/V_T$ (Mean and S.D.) solved from the Bohr equation for oxygen. For all within group changes 'p'<0.05.

Table 4.4: Sodium nitroprusside has many features that make it attractive as a hypotensive agent but these results suggest that it should be used in the presence of a high inspired $P_{O_2}$, especially in older patients. None of the patients described here had a reduction in $P_{aO_2}$ to dangerous values, but Campkin and colleagues (1974) have reported a patient of 58 years whose $P_{aO_2}$ decreased to 48 mm Hg during SNP hypotension while breathing 50% oxygen.

Since artificial ventilation did not prevent a decrease in $P_{aO_2}$ other factors may govern the choice of ventilation. Spontaneous ventilation allows use of the pattern of ventilation as a monitor of cerebral perfusion, does not impede venous return and may even increase cerebral perfusion because of the associated increase in carbon dioxide tension. Respiratory compensation may prevent a disastrous acidosis and aid diagnosis if overdosage should occur (see Chapter Six).
CHAPTER FIVE

HAEMATOLOGICAL EFFECTS
An interesting minor finding of the earliest study of the effect of induced hypotension with SNP on cerebral blood flow and oxygenation (Griffiths et al, 1971) was a small, but statistically significant, decrease in haemoglobin concentration. Because their patients were undergoing major neurosurgery those workers were unable to exclude the possibility that it was due to blood loss. An investigation was therefore performed in patients undergoing induced hypotension for operative procedures where blood loss is minimal.

**METHODS**

Two studies were made in adult patients undergoing middle ear surgery. They gave informed consent for the withdrawal of blood samples from arterial lines inserted for routine blood pressure measurement. Anaesthetic technique was exactly the same as in group I in Chapter Four.

In the first study ten patients, in whom hypotension was induced with SNP, had samples taken after induction of anaesthesia, after 15 minutes of hypotension and at the end of the period of hypotension. In the second study twenty patients were randomly allocated to receive either SNP or trimetaphan. Blood samples were taken after induction of anaesthesia, at the end of the period of hypotension and one hour after the procedure.

Blood samples were taken into tubes containing ethylenedimine tetra-acetic acid as anticoagulant. They were analysed for haemoglobin concentration (Hb), red blood cell count (RBC), haematocrit (Hct),
mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH) and mean corpuscular haemoglobin concentration (MCHC) on a Coulter counter, which has a coefficient of variation of <1% for these parameters.

Statistical analyses were performed using t tests for paired or unpaired data as appropriate.

RESULTS

<table>
<thead>
<tr>
<th>Control Hb (g/dl)</th>
<th>15 minutes</th>
<th></th>
<th>End of procedure</th>
<th></th>
<th>Duration (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Volume (ml)</td>
<td>Hb (g/dl)</td>
<td>Volume (ml)</td>
<td>Hb (g/dl)</td>
<td></td>
</tr>
<tr>
<td>14.2</td>
<td>225</td>
<td>13.8</td>
<td>500</td>
<td>13.4</td>
<td>79</td>
</tr>
<tr>
<td>11.7</td>
<td>50</td>
<td>11.4</td>
<td>110</td>
<td>11.6</td>
<td>55</td>
</tr>
<tr>
<td>13.3</td>
<td>75</td>
<td>13.0</td>
<td>225</td>
<td>12.8</td>
<td>70</td>
</tr>
<tr>
<td>16.0</td>
<td>225</td>
<td>15.2</td>
<td>700</td>
<td>15.3</td>
<td>40</td>
</tr>
<tr>
<td>13.4</td>
<td>20</td>
<td>12.8</td>
<td>250</td>
<td>13.7</td>
<td>43</td>
</tr>
<tr>
<td>12.2</td>
<td>50</td>
<td>11.9</td>
<td>200</td>
<td>11.5</td>
<td>49</td>
</tr>
<tr>
<td>14.2</td>
<td>100</td>
<td>13.6</td>
<td>175</td>
<td>13.2</td>
<td>30</td>
</tr>
<tr>
<td>14.2</td>
<td>140</td>
<td>14.0</td>
<td>480</td>
<td>13.4</td>
<td>40</td>
</tr>
<tr>
<td>16.1</td>
<td>75</td>
<td>15.6</td>
<td>400</td>
<td>15.3</td>
<td>74</td>
</tr>
<tr>
<td>14.6</td>
<td>140</td>
<td>14.2</td>
<td>480</td>
<td>13.7</td>
<td>45</td>
</tr>
<tr>
<td>Mean</td>
<td>14.0</td>
<td>13.6</td>
<td>355</td>
<td>13.4</td>
<td>51</td>
</tr>
<tr>
<td>SD</td>
<td>1.4</td>
<td>1.3</td>
<td>184</td>
<td>1.3</td>
<td>18</td>
</tr>
</tbody>
</table>

Table 5.1: To show individual haemoglobin concentrations in 10 patients before, after 15 minutes of, and at the end of induced hypotension with SNP, together with the volumes of fluid infused and the durations of the procedures.

Table 5.1 gives the individual haemoglobin concentrations from the first ten patients together with the volumes of fluid containing SNP infused at the time of taking each sample and the durations of the procedures. There was no correlation between the volume of fluid infused and the change in haemoglobin at either time interval.
Table 5.2: Means (and SD) of data in first study, together with probability values for changes between control and 15 minutes, and 15 minutes and the end of the procedure.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>P</th>
<th>15 minutes</th>
<th>P</th>
<th>End of procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (g/dl)</td>
<td>14.0(1.4)</td>
<td>&lt;0.0005</td>
<td>13.6(1.3)</td>
<td>NS</td>
<td>13.4(1.3)</td>
</tr>
<tr>
<td>RBC (x10^{12}/l)</td>
<td>4.70(0.37)</td>
<td>&lt;0.0005</td>
<td>4.56(0.34)</td>
<td>NS</td>
<td>4.50(0.34)</td>
</tr>
<tr>
<td>Hot</td>
<td>12.5(1.1)</td>
<td>&lt;0.0005</td>
<td>11.2(3.6)</td>
<td>NS</td>
<td>10.6(3.5)</td>
</tr>
<tr>
<td>MCV (fl)</td>
<td>90(3)</td>
<td>NS</td>
<td>90(4)</td>
<td>NS</td>
<td>90(3)</td>
</tr>
<tr>
<td>MCH (pg)</td>
<td>30.2(1.0)</td>
<td>NS</td>
<td>30.1(1.0)</td>
<td>NS</td>
<td>30.2(1.1)</td>
</tr>
<tr>
<td>MCHC (g/dl)</td>
<td>33.1(0.7)</td>
<td>NS</td>
<td>33.0(0.7)</td>
<td>NS</td>
<td>33.1(0.6)</td>
</tr>
</tbody>
</table>

Table 5.2 summarises the results of all six measurements in those ten patients. Mean haemoglobin concentration fell from 14.0 to 13.6 g/dl in 15 minutes and to 13.4 by the end of the operations. There were parallel changes in RBC and Hot and all these decreases were statistically significant.

Table 5.3 shows the results of the study where the two hypotensive agents were compared. Similar decreases in Hb, RBC and Hot occurred with both agents. The changes were comparable to those in the first study and one hour after anaesthesia the figures had returned to control. The only difference between the agents was in the volume of fluid infused.

In neither study were there any changes in MCV, MCH or MCHC.
<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>P</th>
<th>End of procedure</th>
<th>P</th>
<th>One hour after procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (g/dl)</td>
<td>SNP</td>
<td>14.3(1.3)</td>
<td>&lt;0.005</td>
<td>13.5(0.9)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td></td>
<td>ARF</td>
<td>14.4(1.3)</td>
<td>&lt;0.005</td>
<td>13.7(1.6)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>RBC (x10^{12}/l)</td>
<td>SNP</td>
<td>4.73(0.42)</td>
<td>&lt;0.005</td>
<td>4.66(0.35)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td></td>
<td>ARF</td>
<td>4.65(0.39)</td>
<td>&lt;0.005</td>
<td>4.62(0.49)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Hot</td>
<td>SNP</td>
<td>41(4)</td>
<td>&lt;0.005</td>
<td>39(3)</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td></td>
<td>ARF</td>
<td>41(3)</td>
<td>&lt;0.005</td>
<td>39(4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>MCV (fl)</td>
<td>SNP</td>
<td>88(4)</td>
<td>NS</td>
<td>89(4)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>ARF</td>
<td>89(5)</td>
<td>NS</td>
<td>89(4)</td>
<td>NS</td>
</tr>
<tr>
<td>MCH (pg)</td>
<td>SNP</td>
<td>30.5(1.7)</td>
<td>NS</td>
<td>30.6(1.7)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>ARF</td>
<td>31.2(1.8)</td>
<td>NS</td>
<td>31.3(1.9)</td>
<td>NS</td>
</tr>
<tr>
<td>MCHC (g/dl)</td>
<td>SNP</td>
<td>34.6(1.5)</td>
<td>NS</td>
<td>34.5(1.3)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>ARF</td>
<td>34.8(0.7)</td>
<td>NS</td>
<td>35.0(0.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Volume infused (ml)</td>
<td>SNP</td>
<td>488(215)</td>
<td>274(176)</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ARF</td>
<td>488(215)</td>
<td>274(176)</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Time (min)</td>
<td>SNP</td>
<td>65(23)</td>
<td>NS</td>
<td>57(40)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>ARF</td>
<td>65(23)</td>
<td>NS</td>
<td>57(40)</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Table 5.3:** Means (and SD) of data in comparative study together with probability values for changes within, and differences between, groups.
DISCUSSION

These results confirm that haemoglobin concentration decreases during infusion of SNP even when blood loss is minimal. A similar change occurred with trimetaphan and has been demonstrated when hypotension is produced by halothane and epidural anaesthesia (Bond, 1969). This suggests that it is an effect of hypotension rather than of a specific drug. Since the parameters of red cell integrity (MCV, MCH and MCHC) were unaffected and the changes in Hb, HBC and Hct had returned to control level an hour after the procedure the effect might seem to be due to plasma expansion. Measurements during induced hypotension with hexamethonium (Morris et al., 1953) have shown that plasma volume does increase. The explanation would be that during hypotension the normal pressure gradient at the capillary is reversed and fluid moves from the interstitial space back into the circulation. However, the major part of the change in haematocrit is apparent after 15 minutes of hypotension (Tables 5.1 and 5.2) which seems rapid for such a process and there is relatively little change thereafter. In addition, two other possible explanations exist.

Firstly haematocrit varies in different parts of the circulation because of the phenomena of plasma skimming. Whole-body haematocrit is lower than that of blood from a large artery or vein (Kelman, 1971). It may be that the vasodilation produced by hypotensive agents leads to better "mixing" of blood from different parts of the body and the measured haematocrit becomes nearer to the true whole-body figure. This phenomenon might also explain the "increase" in plasma volume observed by Morris et al (1953).

Secondly the hypotensive agents were given in diluted form
by infusion. It is possible that plasma expansion might be due simply to the volume of this fluid. The mean haemoglobin concentration of the patients in the first study prior to hypotension was 14 g/dl. If a blood volume of 5 litres is assumed the addition of 110mls of fluid (the mean volume infused in the first 15 minutes) will result in a haemoglobin of 15.7 g/dl. The measured figure was 13.6. However, against this as a possibility is that individual patients' change in haemoglobin did not correlate with the fluid volume they received, and in the comparative study those who received trimetaphan had very similar changes to those who received nitroprusside although the volumes infused were much less (Table 5.3). Further, a dilutional explanation assumes that none of the infused fluid moves from intravascular to extravascular space. However, it is possible that red cell sequestration by the spleen is increased by SNP.

Other haematological effects

An early topic of concern regarding a possibly toxic effect of SNP was related to the finding of a decrease in plasma levels of vitamin B12 (Vesey et al, 1974). It was thought that this was of some major significance to B12 metabolism. However, combination of cyanide with hydroxycobalamin is one of the minor pathways that the former may follow (Chapter Two). This decrease in B12 was just the earliest indication that the metabolic effects of nitroprusside were not as benign as had been believed (see Chapter Six).

Finally, concern was expressed that SNP would give rise to significant methaemoglobinaemia. Bower and Peterson (1975) described a patient who developed cyanosis after four days of nitroprusside therapy following myocardial infarction. The methaemoglobin concentration was found to be 2 g/dl. However, it was pointed out that no evidence was presented that the patient did not have congenital
methaemoglobinaemia (Gabel, 1976) and that that degree of methaemoglobinaemia is of questionable significance (Posner, 1976). Smith and Carleton (1976) examined 4 similar patients and found no evidence of accumulation of methaemoglobin above physiological levels nor did du Cailar et al (1978) in 42 hypotensed patients. Thus although methaemoglobin may be formed by the metabolism of nitroprusside (Chapter Two) it would seem to be of more theoretical than practical interest. This would suggest that the reaction with haemoglobin outlined in Chapter Two is not a major pathway for nitroprusside breakdown.
CHAPTER SIX

METABOLIC EFFECTS
CHAPTER SIX

METABOLIC EFFECTS

When SNP was first introduced into clinical practice it was, as a result of the work of Johnson (1929) and Page et al (1955), believed that the risk of cyanide toxicity was minimal, if not non-existent, at pharmacological doses. However, occasional case reports appeared in the literature describing severe metabolic acidosis associated with high dosage requirement to overcome "resistance" to the hypotensive action of SNP. Usually these cases were fatal, but in at least one case respiratory compensation in a spontaneously ventilating patient was thought to have contributed to survival (MacRae and Owen, 1974). In addition McDowall et al (1974) described animal studies where their experimental subjects frequently developed a fatal metabolic acidosis.

This was circumstantial evidence that cyanide toxicity could occur. Then Vesey, Cole and Simpson (1976) reviewed the case reports of presumed cyanide toxicity and published measurements of cyanide concentrations in plasma and red blood cells made during and after infusion of SNP in anaesthetised man. They found that significant amounts of cyanide were being released and made recommendations regarding the safe maximum dose based on these measurements. However, cyanide measurements were questioned as suitable indicators of exposure to cyanide after nitroprusside (Smith and Kruszyna, 1976), and the significance of the findings of Vesey, Cole and Simpson (1976) questioned.

Cyanide blocks oxidative phosphorylation by the cytochromes. Some energy is produced anaerobically by glycolysis with production of
lactate from pyruvate which is unable to enter the Kreb's cycle. It was decided to study blood lactate and pyruvate concentrations as indicators of this effect of cyanide release in patients receiving nitroprusside during anaesthesia. Patients who received trimetaphan were studied as controls so that any effect of hypotension itself on perfusion (and therefore on oxygenation) could be assessed separately from that due to any metabolic consequence of SNP breakdown.

METHODS

Patients and Anaesthesia

Twenty patients undergoing middle ear surgery for which hypotensive anaesthesia was indicated were studied. The nature of the study was explained to the patient and consent obtained. Premedication was with oral diazepam 10mg. Anaesthesia was induced with thiopentone 250-400mg and endotracheal intubation performed with the aid of pancuronium 6-8mg. Anaesthesia was maintained with 50% nitrous oxide in oxygen with halothane 1-2%. The lungs were ventilated artificially at 15 breaths/min. using a Cape-Waine anaesthetic ventilator (Cape Engineering Ltd.) with tidal volume set so that expired volume, measured with a Wright respirometer (British Oxygen Company Ltd.) equalled that indicated by the Radford (1955) nomogram.

Protocol

After induction of anaesthesia a 19G Verflon cannula (Everett Medical Products Ltd.) was inserted percutaneously into a radial artery to allow measurement of arterial pressure and sampling of arterial blood. After 15 minutes of stable anaesthesia samples of arterial blood were collected for estimation of lactate, pyruvate
and haemoglobin concentrations and for blood-gas analysis. An infusion of 0.9% saline containing either SNP or trimetaphan (Arfonad, Roche) was started. Allocation to either drug was on a random basis and infusion rates were adjusted to produce a systolic arterial pressure of 60mm Hg. The infusion was continued until the end of surgery, when a second set of samples was taken. Pancuronium was antagonised with neostigmine, the tracheal tube removed, and the patient breathed 35% oxygen from a Ventimask (Vickers Medical Ltd.) until a third set of samples was taken one hour after the second. The arterial cannula was then removed.

**Measurements**

Blood samples for lactate and pyruvate and blood-gas estimation were drawn into two heparinised iced glass syringes. One was sealed and placed in an ice-water mixture for transport to the laboratory where analysis for $H^+$, $P_{a}O_2$ and $P_{a}CO_2$ were performed using an IL 213 microelectrode system. Standard bicarbonate was derived from $H^+$ and $P_{a}CO_2$ using the Signar-Anderon alignment nomogram. The lactate-pyruvate sample was immediately decanted into an iced glass tube. An aliquot was aspirated to an iced glass pipette, placed in an equal volume of iced perchloric acid, the mixture centrifuged, and the supernatant liquid assayed for lactate and pyruvate using an enzymatic method (The Boehringer Corporation (London) Ltd.).

**Analysis**

Following the comparative study another six patients who received SNP were studied to provide more data for analysis of the dose-effect relationship on lactate-pyruvate changes.

Differences between the two randomised groups were compared
using a t-test for two means, and changes within groups compared with a paired t test.

RESULTS

Table 6.1 shows the details of the two groups of patients in the comparative study. Those who received trimetaphan were younger, heavier and underwent procedures of shorter duration than those who received SNP, but none of the differences were statistically significant. The results from one patient in each group were incomplete and have been omitted.

<table>
<thead>
<tr>
<th></th>
<th>Nitroprusside</th>
<th>Trimetaphan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>36 ± 18</td>
<td>29 ± 10</td>
</tr>
<tr>
<td>Sex</td>
<td>5M 4F</td>
<td>6M 3F</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>62 ± 7</td>
<td>65 ± 15</td>
</tr>
<tr>
<td>Duration of surgery (mins)</td>
<td>62 ± 24</td>
<td>48 ± 29</td>
</tr>
</tbody>
</table>

Table 6.1: Ages, sex, weight and duration of surgery in two groups of nine patients who received nitroprusside or trimetaphan. (Means ± SD).
Table 6.2 summarises the blood-gas data. The patients in both groups were well oxygenated and there were minimal changes in mean $P_aCO_2$.

<table>
<thead>
<tr>
<th></th>
<th>Nitroprusside</th>
<th>Trimetaphan</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$P_aO_2$ (mm Hg)</td>
<td>$P_aCO_2$ (mm Hg)</td>
</tr>
<tr>
<td>One (IPFV: F$O_2$ 0.5)</td>
<td>203 ± 38</td>
<td>38 ± 5</td>
</tr>
<tr>
<td>Two (IPFV: F$O_2$ 0.5)</td>
<td>189 ± 45</td>
<td>39 ± 5</td>
</tr>
<tr>
<td>Three (SV: F$O_2$ 0.35)</td>
<td>143 ± 23</td>
<td>42 ± 5</td>
</tr>
</tbody>
</table>

Table 6.2: Summary of blood-gas data (mean ± SD) in the two groups of patients. Samples taken at the start (One) and finish (Two) of hypotension, and one hour after (Three) the procedure.

Table 6.3 summarises the lactate, pyruvate and standard bicarbonate concentrations and the lactate/pyruvate ratios of the 18 patients in the comparative study. Changes in the measurements were generally small and inconsistent. There was a small progressive decrease in mean lactate concentration in those who received trimetaphan whereas there was a small increase in the SNP group between the second and third samples. In none of these measurements were within-group changes or between-group differences statistically significant.
<table>
<thead>
<tr>
<th>Group Measurement</th>
<th>Nitroprusside (n=9)</th>
<th>Trimetaphan (n=9)</th>
<th>Nitroprusside (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactate mmol/l</td>
<td>0.85 (0.30)</td>
<td>0.87 (0.22)</td>
<td>1.05 (0.44)</td>
</tr>
<tr>
<td></td>
<td>0.85 (0.31)</td>
<td>0.85 (0.28)</td>
<td>0.95 (0.32)</td>
</tr>
<tr>
<td></td>
<td>0.89 (0.61)</td>
<td>0.73 (0.29)</td>
<td>0.80 (0.32)</td>
</tr>
<tr>
<td>Pyruvate mmol/l</td>
<td>0.050 (0.019)</td>
<td>0.043 (0.018)</td>
<td>0.064 (0.024)</td>
</tr>
<tr>
<td></td>
<td>0.053 (0.012)</td>
<td>0.043 (0.014)</td>
<td>0.058 (0.013)</td>
</tr>
<tr>
<td></td>
<td>0.051 (0.033)</td>
<td>0.042 (0.04)</td>
<td>0.050 (0.014)</td>
</tr>
<tr>
<td>L/P Ratio</td>
<td>17.5 (5.9)</td>
<td>26.4 (17.5)</td>
<td>16.8 (5.7)</td>
</tr>
<tr>
<td></td>
<td>16.3 (1.8)</td>
<td>18.0 (7.3)</td>
<td>16.2 (4.5)</td>
</tr>
<tr>
<td></td>
<td>16.1 (10.6)</td>
<td>19.3 (9.9)</td>
<td>16.9 (8.1)</td>
</tr>
<tr>
<td>Bicarbonate mmol/l</td>
<td>22.2 (2.0)</td>
<td>22.3 (1.8)</td>
<td>21.2 (2.3)</td>
</tr>
<tr>
<td></td>
<td>22.9 (2.3)</td>
<td>22.4 (1.8)</td>
<td>20.8 (2.6)</td>
</tr>
<tr>
<td></td>
<td>22.2 (1.5)</td>
<td>21.6 (1.3)</td>
<td>20.8 (1.7)</td>
</tr>
<tr>
<td>Dose Rate (\mu g/kg/min)</td>
<td>12.1 (9.9)</td>
<td>-</td>
<td>12.6 (15)</td>
</tr>
<tr>
<td>Total Dose (mg/kg)</td>
<td>0.68 (0.5)</td>
<td>-</td>
<td>0.38 (0.3)</td>
</tr>
</tbody>
</table>

Table 6.3: To summarise (means ± SD) the lactate, pyruvate, lactate-pyruvate ratio and bicarbonate results of patients studied. (n=9) are groups in comparative study and (n=6), the additional group who received nitroprusside. 1 = samples at start of procedure, 2 = samples at end of procedure and 3 = samples one hour after the procedure.
Table 6.3 also summarises the data for the additional six patients studied with SNP infusion and Figure 6.1 illustrates the changes in lactate concentration that occurred in all 15 patients who received SNP. These changes were analysed in respect of both total dose and dose rate and no obvious relationships were apparent; neither were changes in lactate concentration related to duration of hypotension.

![Plot of change in lactate concentration with dose of SNP](image)

**Figure 6.1:** Relationship between dose of nitroprusside and change in lactate concentration between the start of hypotension and one hour after the operation.

Lactate concentration decreased in the majority of patients who received nitroprusside (Figure 6.1) and the slight increase in mean lactate concentration in the original SNP group was caused almost entirely by one patient whose arterial pressure was resistant to the effect of SNP from the outset. The results for this patient are shown in Table 6.4, with some subsequent blood-gas values: the lactate concentration increased and there was a decrease in standard bicarbonate; the lactate/pyruvate ratio decreased and the excess
<table>
<thead>
<tr>
<th>Sample No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactate (mmol/l)</td>
<td>1.12</td>
<td>1.45</td>
<td>2.39</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pyruvate (mmol/l)</td>
<td>0.04</td>
<td>0.08</td>
<td>0.13</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>L/P ratio</td>
<td>28</td>
<td>18.5</td>
<td>18</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Excess Lactate (mmol/l)</td>
<td>-</td>
<td>-0.76</td>
<td>-0.75</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hydrogen ion (mmol/l)</td>
<td>34</td>
<td>42</td>
<td>39</td>
<td>41</td>
<td>38</td>
</tr>
<tr>
<td>$\text{P}_a\text{CO}_2$ (mm Hg)</td>
<td>44</td>
<td>49</td>
<td>42</td>
<td>36</td>
<td>40</td>
</tr>
<tr>
<td>Bicarbonate (mmol/l)</td>
<td>25.5</td>
<td>22</td>
<td>21.5</td>
<td>22.5</td>
<td>26</td>
</tr>
<tr>
<td>$\text{P}_a\text{O}_2$ (mm mm Hg)</td>
<td>146</td>
<td>195</td>
<td>134</td>
<td>84</td>
<td>99</td>
</tr>
<tr>
<td>$\text{F}_1\text{O}_2$</td>
<td>0.5</td>
<td>0.5</td>
<td>0.35</td>
<td>0.21</td>
<td>0.21</td>
</tr>
</tbody>
</table>

Table 6.1: Results from patient 2: 28-year old, 54 kg female. Non-smoker. Received 86mg of sodium nitroprusside in 42 mins. 1 = start of hypotension: 2 = end of operation: 3 = one hour after procedure: 4 = three hours after procedure: 5 = one day after procedure.
lactate value (Huckabee, 1958) was negative. At the end of the procedure the patient's condition was clinically unremarkable and within 3 hours standard bicarbonate had increased spontaneously.

**DISCUSSION**

Certain physiological and other safeguards are necessary to allow blood lactate concentrations to be used to assess intracellular acidosis. Although it is an indirect method it is the best available (Cohen and Simpson, 1975). Oxygen delivery to the tissues must be adequate; the patients in the present study were all well oxygenated and cardiac output is known to be normal or slightly increased during induced hypotension with nitroprusside (Chapter Three; Styles, Coleman and Leary, 1973). Changes in $P_{\text{CO}_2}$, particularly hypocapnia, affect lactate concentration (Cohen and Woods, 1976), and for that reason normocapnia was maintained. Infusion of glucose can increase blood lactate (Cohen and Woods, 1976); the drugs were given in saline. Blood was withdrawn from an arterial cannula to avoid stasis. All glassware was iced and the specimen for lactate decanted into perchloric acid as soon as possible so that the effect of red cell glycolysis after withdrawal was minimal.

Lactate and pyruvate data are often expressed as the ratio of the two, but this does not seem to be of use in this situation. In the one patient with clear changes, this ratio decreased when it would have been expected to increase. This was because there was a greater proportional increase in pyruvate than in lactate. Excess lactate has also been used to indicate changes in lactate concentration independent of alterations in pyruvate (Huckabee, 1958). Mathematically, however, this figure is not independent of pyruvate (Cohen and Woods, 1976) and in the same patient the change was the
reverse of that which would be expected.

The results show that hypotensive anaesthesia with trimetaphan is not associated with any evidence of cellular hypoxia. Mean lactate concentration decreased slightly with this agent, presumably because peripheral perfusion was improved by vasodilatation. Increased oxygen tension during anaesthesia or simple physical inactivity could also have been responsible, but normotensive halothane anaesthesia produces a slight increase in lactate concentration (Chamberlain and Lis, 1968; Yamazaki et al, 1975). SNP in low doses also decreased lactate concentrations and it has been used (Taradash and Jacobsen, 1973) to treat idiopathic lactic acidosis associated with poor peripheral perfusion.

With larger doses, the lactate concentration may increase, presumably as the toxic effect begins to counter the effect on perfusion. The patient who showed resistance to the hypotensive effect of SNP required 1.6mg/kg and had the greatest increase in lactate concentration (Figure 6.1). Although the increase was small and recovery uneventful, this case shows the need to limit total dosage in acute administration, and these results would support the suggested maximum dose of 1.5mg/kg based on cyanide studies (Vesey, Cole and Simpson, 1976). Suggestions have also been made regarding the maximum safe rate (Editorial, 1978) - a dose of 10μg/kg/min being quoted. While this may apply to administration over a period of days, these results indicate little relationship to dose rate during hypotensive anaesthesia.

The increase in blood lactate concentration in the resistant patient could have been caused by a reduction in hepatic clearance.
because of a reduction in liver blood flow, rather than by increased production of lactate. Clearance of indocyanine green has been used as an indicator of liver blood flow and is not influenced by infusion of SNP during halothane anaesthesia (Abdel Salam et al, 1976).

This study investigated the effects of clinical use of SNP on metabolism. Instead of measuring cyanide concentrations, and attempting to deduce toxicity indirectly, alterations in the metabolic state were sought. When it is used within its known toxic concentrations, there is no metabolic upset. This means that for practical purposes the drug can be administered in normal doses without fear of producing metabolic acidosis, except in patients with known contraindications (Cole, 1978).

Unfortunately, this does not mean that the problem of metabolic acidosis as a potential complication can be ignored. There is no means of predicting how much drug will be needed for any particular patient. Most require only small amounts, but occasionally doses approaching 1.5mg/kg are needed. It has been argued that safe use of nitroprusside requires ready access to lactate estimation (Editorial, 1978), but those results confirm animal studies which suggested that changes in lactate are mirrored by changes in bicarbonate concentration (Simpson et al, 1977). Blood-gas analysis is easier, quicker and cheaper to perform and far more readily available. It is suggested that this estimation is adequate for assessing toxicity following acute administration during anaesthesia, and should be performed when the total dose is likely to exceed 1.5mg/kg.
CHAPTER SEVEN

CONCLUSIONS AND SUGGESTIONS FOR MINIMISING ADVERSE EFFECTS
Sodium nitroprusside has many features that make it suitable for use as a hypotensive agent during anaesthesia and surgery. It produces a rapid decrease in blood pressure that is readily controllable, and the blood pressure returns to control levels equally rapidly on discontinuation of infusion. During the hypotension overall circulatory performance is unaffected so that, with the exception of the kidney, organ blood flow is preserved. The safe use of such a potent agent during surgery does of course require a high standard of anaesthesia with careful monitoring of the patient's condition and the drug's effect.

Oxygen carriage by the blood is impaired by the decreases that occur in both arterial oxygen tension and haematocrit. A high inspired oxygen tension during administration is therefore essential to ensure maximum haemoglobin saturation. Affinity of oxygen for haemoglobin is not affected by SNP in vivo (Vesey, Krapes and Cole, 1980). The decrease in haematocrit is common to the use of other hypotensive drugs, and could be looked upon as an advantage since blood viscosity will also be decreased. This may aid maintenance of blood flow and ensure oxygenation.

Of greater significance for patient safety is the risk of cyanide toxicity when high doses are required. The majority of cases can be managed without approaching these doses, but in a proportion of patients they will be exceeded. Several options are open to the anaesthetist who values the circulatory advantages of SNP, but who is concerned about toxicity.
When the dose level approaches that likely to produce acidosis the patient's acid-base status should be monitored and if an acidosis is developing a change can be made to another agent. However, this can produce difficulties of pressure control at the time of change-over and is a policy that involves the deliberate courting of disaster.

One possibility might be to give sodium thiosulphate. As outlined in Chapter Two cyanide is detoxified by a reaction with thiosulphate. As the liver contains large amounts of the necessary enzyme, rhodanese, the availability of thiosulphate is the limiting factor. Thiosulphate therapy will increase the safe maximum dosage in animals (Michtenfelder and Tinker, 1977) but increases the SNP dose requirement (Ivankovich et al, 1980). It has not yet been tried in man.

A more practical approach is to try and reduce the amount of SNP required. The effect of SNP is potentiated by other vasodilators (Page et al, 1955) suggesting that combining it with another might achieve a reduction in dosage. Dinmore (1977) combined SNP with trimetaphan, using two separate infusions. This is difficult to control and has never found favour. Recently this combination, but with both drugs in the same infusion has been tried (MacRae, Wildsmith and Dale, 1981). 12.5mg of SNP and 125mg of trimetaphan were added to 500ml of 5% dextrose and administered in much the same way as SNP alone.

The assessment of this technique is at an early stage, but blood pressure changes were almost as rapid and as controllable as with nitroprusside alone, and a significant decrease in dosage of
the latter was achieved (Table 7.1). An associated benefit was that

<table>
<thead>
<tr>
<th>Total dose</th>
<th>Used alone</th>
<th>Mixture</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNP</td>
<td>0.68</td>
<td>0.095</td>
</tr>
<tr>
<td>ARF</td>
<td>6.7</td>
<td>0.95</td>
</tr>
</tbody>
</table>

Table 7.1: Total dose (mg/kg) of sodium nitroprusside and trimetaphan when used alone (data from patients described in Chapter Five) or in combination (data from MacRae, Wildsmith and Dale, 1981).

it was felt that better operating conditions were obtained than with SNP alone. This may relate to trimetaphan tending to decrease cardiac output (Scott et al, 1972) whereas SNP tends to increase it (Chapter Three) and raises the interesting topic of whether it is a reduction in flow or blood pressure to an operative area that is responsible for ischaemia. The implication of the experience with the mixture of nitroprusside and trimetaphan is that it may be better to avoid the increase of output that may occur with SNP alone.

Beta-blocking drugs have also been used to potentiate the effect of SNP and reduce its dosage (Bedford, Berry and Longnecker, 1979). One reason for the use of these drugs is to prevent the reflex tachycardia produced by SNP, but they have been shown to have a more interesting action -- the reduction of renin release (Pettinger and Keeton, 1975). SNP hypotension stimulates renin release (Kaneko et al, 1967), presumably by reflex mechanisms. Renin activates angiotensin, a directly acting vasoconstrictor, and thus antagonises SNP. Greater amounts have to be given to maintain hypotension and the risk of toxicity is increased.
Little is known about renin release in other forms of pharmacological hypotension, but it may be that the dose reduction produced by combination of SNP with trimetaphan is due to blockage of the reflex arc by trimetaphan at the ganglionic level. SNP mediated renin release is certainly decreased in conscious hypertensive patients by pretreatment with ganglionic blocking drugs (Kaneko et al, 1970). That study also showed that the decrease in renal blood flow associated with SNP is abolished by the combination of the two drugs. This opens the possibility of SNP dose reduction in the future by its combination with one of the renin antagonists currently being investigated (Editorial, 1980).

This search for methods for increasing the safety of SNP is not dissimilar to the pattern outlined in Chapter One for improving the early methods of induced hypotension - history repeating itself to some extent. The introduction of sodium nitroprusside into anaesthetic practice represented a major advance, but its ideal circulatory effects are offset by the risk of cyanide toxicity. The search now is for a technique that has one but not the other. The combination with trimetaphan has given good clinical results, and has opened up several avenues for further research.
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Several colleagues (named in the papers in Appendix Two) helped in the performance of the studies. In particular I would like to thank Dr. W.R. MacRae, without whose continued light-hearted support and encouragement little might have been achieved. Our many discussions during the preparation of this thesis made its completion so much easier.

Ever since the pioneer work of Griffiths and Gillies the Department of Anaesthetics, Royal Infirmary of Edinburgh has been involved in the practice and study of induced hypotension. A large number of the papers referred to here are by past and present members of the department. The close contact I have had with those authors over the years has been of great benefit. To have received my early clinical training in induced hypotension with Dr. H.W.C. Griffiths was an irreplaceable experience.

My interest in Sodium Nitroprusside began when I was in receipt of a Graduate Research Fellowship from the Faculty of Medicine, University of Edinburgh, and the haemodynamic study was supported in part by the British Heart Foundation. Gas and blood gas analyses were performed by the Respiratory Function Laboratory, City Hospital, Edinburgh; Lactate and Pyruvate estimations by the Department of
Medicine at the Royal Infirmary, University of Edinburgh; and the haematology measurements by the Department at the Royal Infirmary of Edinburgh.

The preparation of a thesis requires considerable library support. Some of the important work on nitroprusside is not readily available and I am very grateful to the staff of the Central (now Erskine) Medical Library, University of Edinburgh and to Roche Products Ltd. (particularly their hospital representative, Mr. R. Laird) for their help in obtaining the relevant publications.

My adviser, Dr. A.H.B. Kasson, has given continued support and advice, and I would like to thank my wife for her assistance and understanding of the time I have committed to this project. She, with Miss Dorothy Taylor, also undertook possibly the most difficult task of all — turning my handwritten script into the first typed draft! Finally my thanks to Mrs. Frances Turnbull for producing the script.
APPENDIX ONE

ABBREVIATIONS
## ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARF</td>
<td>Trimetaphan camsylate (Arfonad: Roche)</td>
</tr>
<tr>
<td>B₁₂</td>
<td>Vitamin B₁₂</td>
</tr>
<tr>
<td>°C</td>
<td>Degrees centigrade</td>
</tr>
<tr>
<td>cAMP</td>
<td>Cyclic adenosine monophosphate</td>
</tr>
<tr>
<td>cGMP</td>
<td>Guanosine phosphate</td>
</tr>
<tr>
<td>cm</td>
<td>Centimetre</td>
</tr>
<tr>
<td>CN⁻</td>
<td>Cyanide ion</td>
</tr>
<tr>
<td>CNB₁₂</td>
<td>Cyanocobalamin</td>
</tr>
<tr>
<td>CNmetHb</td>
<td>Cyanomethaemoglobin</td>
</tr>
<tr>
<td>CO₂</td>
<td>Carbon dioxide</td>
</tr>
<tr>
<td>conc.</td>
<td>Concentration</td>
</tr>
<tr>
<td>COOH⁻</td>
<td>Formate ion</td>
</tr>
<tr>
<td>CVP</td>
<td>Central venous pressure</td>
</tr>
<tr>
<td>dl</td>
<td>Decilitre</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiograph</td>
</tr>
<tr>
<td>F</td>
<td>Female</td>
</tr>
<tr>
<td>F₂O₂</td>
<td>Fraction of inspired oxygen</td>
</tr>
<tr>
<td>fl</td>
<td>Femtolitre</td>
</tr>
<tr>
<td>g</td>
<td>Gramme</td>
</tr>
<tr>
<td>Hb</td>
<td>Haemoglobin</td>
</tr>
<tr>
<td>Hct</td>
<td>Haematocrit</td>
</tr>
<tr>
<td>in</td>
<td>Inch</td>
</tr>
<tr>
<td>IPFV</td>
<td>Intermittent positive pressure ventilation</td>
</tr>
<tr>
<td>kg</td>
<td>Kilogramme</td>
</tr>
<tr>
<td>l (or L)</td>
<td>Litre</td>
</tr>
<tr>
<td>L/P</td>
<td>Ratio of concentrations of Lactate and Pyruvate</td>
</tr>
<tr>
<td>M</td>
<td>Male</td>
</tr>
<tr>
<td>MCH</td>
<td>Mean corpuscular haemoglobin</td>
</tr>
<tr>
<td>MCHC</td>
<td>Mean corpuscular haemoglobin concentration</td>
</tr>
<tr>
<td>MCV</td>
<td>Mean corpuscular volume</td>
</tr>
<tr>
<td>methHb</td>
<td>Methaemoglobin</td>
</tr>
<tr>
<td>mg</td>
<td>Milligramme</td>
</tr>
<tr>
<td>min</td>
<td>Minute</td>
</tr>
<tr>
<td>ml</td>
<td>Millilitre</td>
</tr>
<tr>
<td>mmHg</td>
<td>Millimetre of mercury</td>
</tr>
<tr>
<td>mmol</td>
<td>Millimole</td>
</tr>
</tbody>
</table>
n
Number in a group

Na$_2$SO$_3$
Sodium sulphite

Na$_2$S$_2$O$_3$
Sodium thiosulphate

mmol
Nanomole

NP
Nitroprusside ion

NS
Not significant at 1 in 20 level

P
Probability

P$_a$CO$_2$
Tension of carbon dioxide in arterial blood

P$_A$O$_2$
Tension of oxygen in alveolar gas

P$_a$O$_2$
Tension of oxygen in arterial blood

P$_E$CO$_2$
Tension of carbon dioxide in mixed expired gas

P$_E$O$_2$
Tension of oxygen in mixed expired gas

per
During

pg
Picogramme

P$_I$O$_2$
Tension of oxygen in inspired gas

post
After

pre
Before

preop
Before the operation

r
Regression coefficient

RBC
Red blood cell count

SCN$^-$
Thiocyanate ion

SD
Standard deviation

sec
Second

SNP
Sodium Nitroprusside (Nipride: Roche)

SV
Spontaneous ventilation

V$_D$/V$_T$
The ratio of physiological deadspace to tidal volume

V/Q
The ratio of pulmonary ventilation to perfusion

yr
Years

µg
Microgramme

Δ
Change in

<
Less than

>
Greater than
APPENDIX TWO

PUBLISHED PAPERS
PUBLISHED PAPERS


(Copies of each of the above are bound in overleaf)
HAEMODYNAMIC EFFECTS OF SODIUM NITROPRUSSIDE DURING NITROUS OXIDE/HALOTHANE ANAESTHESIA

J. A. W. WILDSMITH, R. L. MARSHALL, J. L. JENKINSON, W. R. MACRAE AND D. B. SCOTT

Brit. J. Anaesth. (1973), 45, 71
HAEMODYNAMIC EFFECTS OF SODIUM NITROPRUSSIDE DURING NITROUS OXIDE/HALOTHANE ANAESTHESIA


SUMMARY

Haemodynamic studies were made in five patients receiving sodium nitroprusside by intravenous infusion for controlled hypotension during nitrous oxide/halothane anaesthesia. There were marked falls in arterial pressure, peripheral resistance and central venous pressure. Heart rate and cardiac output rose while stroke volume was little changed. All parameters returned quickly to control values on discontinuation of sodium nitroprusside administration.

In recent years there has been renewed interest in sodium nitroprusside as a hypotensive agent, particularly for use during surgery, to provide a bloodless field. Its very evanescent effect, which made it difficult to use in the medical treatment of hypertension, is ideal for this purpose (Jones and Cole, 1968; Taylor, Styles and Lamming, 1970; Siegel, Moraca and Green, 1971; MacRae, 1971).

It was decided to measure its effects on the circulation so that comparison could be made with trimetaphan camysylate, the haemodynamic effects of which we recently reported (Scott et al., 1972).

METHODS

A study was made of five patients, three male and two female, undergoing anaesthesia with induced arterial hypotension for middle ear surgery. They were aged between 23 and 45 years and their general health was good. Consent for the investigation was obtained from each patient after explanation of the procedure.

The patients were premedicated with diazepam 10 mg orally and anaesthesia induced with thiopentone 250–350 mg intravenously. All were intubated with a cuffed oral tube with the aid of suxamethonium 50 mg. Thereafter they were allowed to breathe spontaneously a mixture of nitrous oxide (2 l/min) and oxygen (3 l/min) containing 1.5–2% halothane, from a semiclosed circuit with carbon dioxide absorption.

Haemodynamic studies were made in exactly the same way as in the trimetaphan series (Scott et al., 1972). Arterial and central venous pressures were measured directly and cardiac output by the indicator dye dilution technique using indocyanine green. The electrocardiogram was monitored throughout and used to obtain heart rate.

Stable anaesthesia having been achieved, four control readings of mean arterial pressure, cardiac output, central venous pressure and heart rate were made at 2-min intervals. An intravenous infusion of sodium nitroprusside 0.005% was then started, and adjusted to produce a fall in systolic arterial pressure to about 60 mm Hg. A further four readings of the above parameters were then obtained, again at 2-min intervals. The infusion was then stopped and a final three readings made. The patients were kept horizontal throughout and surgery was not started until all recordings were completed in order to avoid interference with measurements by surgical stimuli.

Subsequently stroke volume was calculated from cardiac output and heart rate, and peripheral resistance from cardiac output and mean arterial pressure. Statistical analysis of the changes in the six parameters was carried out using the paired $t$-test.

RESULTS

Table I shows the mean values for mean arterial pressure, cardiac output, central venous pressure, heart rate, stroke volume and peripheral resistance before, during and after infusion of sodium nitroprusside. Mean changes occurring when hypotension was induced, and again when it was discontinued, are given in table II, together with $t$ and probability values.
**TABLE I.** Mean values of haemodynamic parameters at 2-min intervals of five cases before, during and after sodium nitroprusside (SNP).

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>SNP infusion running</th>
<th>SNP stopped</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td><strong>Mean arterial pressure</strong></td>
<td>72 ± 69</td>
<td>40 ± 42</td>
<td>65 ± 68</td>
</tr>
<tr>
<td>(mm Hg)</td>
<td></td>
<td>±13</td>
<td>±12</td>
</tr>
<tr>
<td><strong>Cardiac output (l/min)</strong></td>
<td>5.5 ± 5.5</td>
<td>6.8 ± 6.7</td>
<td>5.8 ± 6.0</td>
</tr>
<tr>
<td><strong>Central venous pressure</strong></td>
<td>7.7 ± 8.1</td>
<td>2.3 ± 2.8</td>
<td>5.9 ± 7.3</td>
</tr>
<tr>
<td>(mm Hg)</td>
<td></td>
<td>±3.0</td>
<td>±2.9</td>
</tr>
<tr>
<td><strong>Heart rate (beats/min)</strong></td>
<td>67 ± 67</td>
<td>82 ± 83</td>
<td>67 ± 65</td>
</tr>
<tr>
<td><strong>Peripheral resistance</strong></td>
<td>1230 ± 780</td>
<td>580 ± 600</td>
<td>1110 ± 780</td>
</tr>
<tr>
<td>(dyn/sec/cm²)</td>
<td></td>
<td>±11</td>
<td>±13</td>
</tr>
<tr>
<td><strong>Stroke volume (ml)</strong></td>
<td>81 ± 84</td>
<td>83 ± 75</td>
<td>88 ± 83</td>
</tr>
<tr>
<td></td>
<td>±12</td>
<td>±14</td>
<td>±18</td>
</tr>
</tbody>
</table>

**Mean arterial pressure.** This fell in every case to an average value of 58% of control and quickly returned to control value on discontinuation (fig. 1). Both changes were significant to a high degree.

**Cardiac output.** The group as a whole showed a moderate and statistically significant rise in cardiac output during infusion. No patient suffered a fall in output, though in one case it remained the same (fig. 2). On withdrawal of nitroprusside all patients exhibited a slight fall, which did not reach the level of statistical significance.

**TABLE II.** Statistical comparison of means of haemodynamic parameters of five cases before and during and after sodium nitroprusside (SNP). Paired t-test used.

<table>
<thead>
<tr>
<th></th>
<th>Control mean</th>
<th>SNP mean</th>
<th>Mean diff. ± SD</th>
<th>t</th>
<th>SNP mean</th>
<th>Post-SNP mean</th>
<th>Mean diff. ± SD</th>
<th>t</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean arterial pressure</strong></td>
<td>69 ± 10</td>
<td>41 ± 10</td>
<td>-28 ± 10</td>
<td>6.84</td>
<td>41 ± 6.5</td>
<td>68 ± 27</td>
<td>7.97 ± 0.005</td>
<td></td>
</tr>
<tr>
<td>(mm Hg)</td>
<td></td>
<td>±1.0</td>
<td>±0.6</td>
<td>3.61</td>
<td>6.5 ± 5.7</td>
<td>-0.8 ± 0.07</td>
<td>&lt;0.05 ± 0.05</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac output</strong></td>
<td>5.5 ± 5.5</td>
<td>6.5 ± 1.0</td>
<td>+1.0 ± 0.6</td>
<td>5.13</td>
<td>2.8 ± 6.7</td>
<td>+3.9 ± 2.8</td>
<td>&lt;0.05 ± 0.05</td>
<td></td>
</tr>
<tr>
<td>(l/min)</td>
<td></td>
<td>±0.6</td>
<td>±2.1</td>
<td>4.9 ± 8.3</td>
<td>65 ± 18</td>
<td>-18 ± 7.65</td>
<td>1.69 ± 1.69</td>
<td></td>
</tr>
<tr>
<td><strong>Central venous pressure</strong></td>
<td>8.1 ± 3.8</td>
<td>2.8 ± 2.1</td>
<td>-5.3 ± 2.1</td>
<td>4.57</td>
<td>600 ± 1180</td>
<td>580 ± 360</td>
<td>3.69 ± 0.025</td>
<td></td>
</tr>
<tr>
<td>(mm Hg)</td>
<td></td>
<td>±2.0</td>
<td>±15 ± 7</td>
<td>4.9 ± 83</td>
<td>65 ± 5</td>
<td>5 ± 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heart rate</strong></td>
<td>67 ± 83</td>
<td>84 ± 7</td>
<td>+6 ± 18</td>
<td>0.70</td>
<td>78 ± 11</td>
<td>89 ± 14</td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td>(beats/min)</td>
<td></td>
<td>±7</td>
<td>±18</td>
<td>±0.7</td>
<td>±18</td>
<td>±18</td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td><strong>Peripheral resistance</strong></td>
<td>1210 ± 610</td>
<td>4.57 ± 300</td>
<td>-610 ± 0.01</td>
<td>4.57</td>
<td>600 ± 1180</td>
<td>580 ± 360</td>
<td>3.69 ± 0.025</td>
<td></td>
</tr>
<tr>
<td>(dyn/sec/cm²)</td>
<td></td>
<td>±300</td>
<td>±300</td>
<td>±0.7</td>
<td>±300</td>
<td>±300</td>
<td>&lt;0.025</td>
<td></td>
</tr>
<tr>
<td><strong>Stroke volume</strong></td>
<td>84 ± 78</td>
<td>84 ± 6</td>
<td>-6 ± 11</td>
<td>0.70</td>
<td>78 ± 11</td>
<td>89 ± 14</td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td>(ml)</td>
<td></td>
<td>±7</td>
<td>±18</td>
<td>±0.7</td>
<td>±18</td>
<td>±18</td>
<td>n.s.</td>
<td></td>
</tr>
</tbody>
</table>

**Fig. 1.** Mean values of arterial pressure at 2-min intervals in five cases before, during and after sodium nitroprusside (SNP). Vertical bars represent ±1 standard error. On the right are shown the mean before, during and after nitroprusside in individual cases.

**Fig. 2.** Mean values of cardiac output at 2-min intervals in five cases before, during and after sodium nitroprusside. Vertical bars represent ±1 standard error. On the right are shown the mean before, during and after nitroprusside in individual cases.
EFFECTS ON NITROUS OXIDE/HALOTHANE ANAESTHESIA

Fig. 3. Mean values of central venous pressure at 2-min intervals in five cases before, during and after sodium nitroprusside. Vertical bars represent ±1 standard error. On the right are shown the mean before, during and after nitroprusside in individual cases.

Fig. 4. Mean values of heart rate at 2-min intervals in five cases before, during and after sodium nitroprusside. Vertical bars represent ±1 standard error. On the right are shown the mean before, during and after nitroprusside in individual cases.

Fig. 5. Mean values of peripheral resistance at 2-min intervals in five cases before, during and after sodium nitroprusside. Vertical bars represent ±1 standard error. On the right are shown the mean before, during and after nitroprusside in individual cases.

Fig. 6. Mean values of stroke volume at 2-min intervals in five cases before, during, and after sodium nitroprusside. Vertical bars represent ±1 standard error. On the right are shown the mean before, during and after nitroprusside in individual cases.

Central venous pressure. Unfortunately no record of c.v.p. was kept in one patient because of a technical fault, and figures are for the other four only. C.v.p. fell markedly during infusion, and then returned towards initial values (fig. 3). However, as with cardiac output, this second change did not reach statistical significance.

Heart rate. There was a consistent rise in heart rate during infusion of around 22%, which promptly reversed on discontinuation (fig. 4).

Peripheral resistance. During administration of nitroprusside there was a profound fall in this parameter in every case. The average fall was 49%. On discontinuation values quickly returned to control levels (fig. 5).

Stroke volume. Changes in stroke volume were small and inconsistent (fig. 6). During infusion it fell in two cases and rose in three. After nitroprusside was stopped three rose and two fell.

DISCUSSION

The most striking circulatory change that occurred during the hypotension produced by sodium nitroprusside infusion was an increase in cardiac output. As stroke volume remained much the same this was attributable to the tachycardia produced and there was an associated fall in central venous pressure, which is a feature of many forms of hypotension including trimetaphan infusion (Scott et al., 1972) and epidural block (Stephen, Lees and Scott, 1969).

Franciosa and associates (1972) also reported an increase in cardiac output in patients being infused with sodium nitroprusside, this increase being associated with a marked reduction in left ventricular filling pressure. Though their series is not strictly comparable with ours since they were studying patients with myocardial infarction and were producing only a minor degree of hypotension, the
It is quite possible for an agent which causes vasodilation without any direct action on the heart to increase cardiac output. The enormous reduction of the peripheral resistance which occurs will speed flow through the arteriolar beds and, unless gravity is used to prevent venous return, this will also be increased. The heart, being unaffected, will easily deal with this increase. It is often assumed that the relaxation of the venous tone leads to "pooling" of blood but this can only occur if gravity is used to prevent blood returning to the heart.

The possibility that hypotension could embarrass the coronary circulation seems to be outweighed by the reduction in the work load of the heart caused by the decreased peripheral resistance. The improved clinical state of patients with acute myocardial infarction reported by Franciosa and associates (1972) suggests that the coronary circulation is not in jeopardy.

Sodium nitroprusside differs from trimetaphan in two important respects. First, its action ceases much more quickly on discontinuation of infusion, all parameters in our cases returning to the control levels within 6 min, even after marked hypotension. Secondly, trimetaphan causes, if anything, a slight (though possibly unimportant) reduction in cardiac output (Scott et al., 1972). This may well be due to the fact that, being a ganglionic blocking drug, its effects on the heart cannot be completely ignored. The interruption of sympathetic innervation to the heart may have a similar negatively inotropic effect during halothane anaesthesia to the administration of beta-blocking drugs (Stephen, Davie and Scott, 1971).

Sodium nitroprusside then is a potent, short-acting, specific vasodilator whose effects on the circulation are probably superior to those of trimetaphan. It is now, in our opinion, the drug of choice in those situations requiring controlled hypotension for which trimetaphan has been indicated in the past.

ACKNOWLEDGMENTS

We wish to thank Dr B. Dale and Dr K. McLay for permission to study patients under their care, and also the nursing staff of the ENT theatre, City Hospital, Edinburgh, for their co-operation. This work was supported in part by a grant from the British Heart Foundation.

REFERENCES


EFFETS HEMODYNAMICIQUES DU NITROPRUSSID SODIQUE DURANT L'ANESTHESIE AU PROTOXYDE D'AZOTE/ HALOTHANE

SOMMAIRE

Des études hemodynamiques ont été faites chez cinq patients recevant du nitroprusside sodique en infusion intra- veineuse pour hypotension contrôlée durant l'anesthésie au protoxyde d'azote/halothane. On remarqua des chutes prononcées de la pression artérielle, résistance périphérique et pression veineuse centrale. La fréquence cardiaque et le débit cardiaque augmentèrent tandis que le volume pul- satoire ne se modifia que peu. Tous les paramètres retom- bèrent rapidement aux valeurs de contrôle, lorsqu'on arrêta l'administration du nitroprusside sodique.

HAEMODYNAMISCHE WIRKUNGEN VON NITROPRUSSIDNATRIUM WAHRDEN DER ANAESTHESIE MIT LACHGAS/HALOTHAN

ZUSAMMENFASSUNG


EFECTOS HEMODINAMICOS DEL NITROCIANURO SODICO DURANTE LA ANESTESIA CON OXIDO NITROSO/HALOTANO

RESUMEN

Fueron efectuados estudios hemodinámicos en cinco paci- entes que estaban recibiendo nitrociánuro por infusión intravenosa para una hipotensión controlada durante la anestesia con oxido nitroso/halotano. Hubo marcadas reducciones en la presión arterial, resistencia periférica y presión venosa central. La frecuencia cardíaca y gasto cardíaco aumentaron en tanto que el volumen sistólico fue poco modificado. Todos los parámetros retornaron rápidamente a los valores de control al discontinuar la administración de nitrociánuro sódico.
BLOOD-GAS CHANGES DURING INDUCED HYPOTENSION WITH SODIUM NITROPRUSSIDE

J. A. W. Wildsmith, G. B. Drummond and W. R. MacRae

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BLOOD-GAS CHANGES DURING INDUCED HYPOTENSION WITH SODIUM NITROPRUSSIDE

J. A. W. Wildsmith, G. B. Drummond and W. R. MacRae

SUMMARY

A blood-gas study of the respiratory effects of sodium nitroprusside during anaesthesia has shown a marked reduction in $P_{A O_2}$ when the drug was administered. After nitroprusside $P_{A O_2}$ returned to the previous values. It is suggested that the reduction in $P_{A O_2}$ is a result of an increased scatter of ventilation/perfusion relationships in the lung. The reduction in $P_{A O_2}$ was evident during both spontaneous and artificial ventilation. Nitroprusside was associated with a small decrease in actual bicarbonate.

Induced hypotension during anaesthesia is a technique which has produced many controversies since its introduction by Griffiths and Gillies (1948). These include the decision on whether the patients should be allowed to breathe spontaneously. Eckenhoff and colleagues (1963) found a large increase in physiological deadspace with a concomitant increase in $P_{A CO_2}$, in patients under ganglion blockade, and recommended that respiration be controlled with high tidal volumes and high inspired oxygen concentration. Others believe that the pattern of spontaneous breathing is a useful monitor of cerebral perfusion, and has no adverse effect on venous return (Holmes, 1956).

The cardiovascular effects of sodium nitroprusside have been investigated extensively (Page et al., 1955; Franciosa et al., 1972; Styles, Coleman and Leary, 1973; Wildsmith et al., 1973), but, in common with most other hypotensive techniques, little has been published about its effects on lung function. Arterial blood sampling, by us, during nitroprusside infusion had revealed oxygen tensions which were less than expected. This is a study of blood-gas tensions during sodium nitroprusside infusion with an assessment of the influence of artificial ventilation.

There has been recent concern about the acid-base states of patients receiving nitroprusside (McDowall et al., 1974; MacRae and Owen, 1974), and this aspect has been studied also.

METHODS

Patients and anaesthesia

Twenty-six patients undergoing major otolaryngological surgery, for which hypotensive anaesthesia is routine in our hospital, were studied. The nature of the study was explained to the patient at the visit before operation, and consent was obtained. Pre-medication was with oral diazepam 10 mg. Anaesthesia was induced with thiopentone 250–400 mg. Endotracheal intubation was performed with the aid of suxamethonium 75–100 mg in the first 14 patients (group I), and tubocurarine (30–45 mg) in the next 12 (group II). Anaesthesia was maintained with 50% nitrous oxide in oxygen supplemented with halothane 1–2%.

After recovery from suxamethonium, group I patients breathed spontaneously from a non-return circuit which allowed inspired gas sampling and collection of mixed expired gas. In group II artificial ventilation was performed at 15 b.p.m. with a Cape-Waine anaesthetic ventilator (Cape Engineering Ltd), using a pressure-operated valve to allow collection of expired gas (Sykes, 1969). The ventilator was adjusted so that the expired volume, measured with a Wright’s respirometer (British Oxygen Company Ltd), was that predicted by the Radford (1955) nomogram. All patients were maintained in a 5° head-up position.

Protocol

An arterial blood sample was taken before operation. After anaesthesia had been induced, a percutaneous 21G scalp vein needle (Abbott Laboratories Ltd) was inserted into a radial artery for direct arterial pressure measurement, and further arterial sampling.

When the heart rate and arterial pressure had become stable inspired gas, mixed expired gas and arterial blood were sampled and analysed as in a previous study (Wildsmith and Masson, 1974). An infusion of sodium nitroprusside into a peripheral vein was commenced. The dose regimen was that
described by MacRae (1971) and the infusion was adjusted to give a systolic arterial pressure of 50–60 mm Hg. After 15 min at this pressure another set of samples was taken. Hypotension was maintained until surgery was complete, when the infusion was discontinued. When the arterial pressure had returned to the pre-infusion value, a third set of samples was taken. The duration of the operations was between 1 and 3 hr. No patient received more than 150 mg of sodium nitroprusside.

**Calculations**

Ideal alveolar PO2 (PAO2) was calculated as follows:

\[ \text{PAO}_2 = \text{PVO}_2 - \text{PAO}_2 \left( \frac{\left(\text{PVO}_2 - \text{PE}_\text{O}_2\right)}{\text{PE}_\text{CO}_2} \right) \]

where PVO2 and PE02 are the inspired and mixed expired PO2 values, and the ratio of physiological deadspace to tidal volume (VD/VT) was derived from:

\[ \frac{\text{VD}}{\text{VT}} = \frac{\left(\text{PAO}_2 - \text{PE}_\text{CO}_2\right)}{\text{PAO}_2} \]

No correction was made for apparatus deadspace.

Actual bicarbonate was determined from pH and PAO2, using the Siggaard–Andersen alignment nomogram.

Statistical comparisons were made using Student's t tests for paired or unpaired data as appropriate, and linear regression analysis.

**RESULTS**

Details of the patients studied are shown in table I. Patient 12 was omitted because of technical problems with the collection of gas samples. The preoperative sample in patient 3 would seem to have been from a vein. There was a statistically significant difference (P<0.025) between the groups in respect of mean PAO2 (42 mm Hg in group I and 38 mm Hg in group II). The mean age in group II was 41 yr and that in group I was 35 yr, but this difference was not statistically significant.

Tables II and III and figure 1 show the measured and derived data of the two groups before, during and after the administration of nitroprusside. PVO2 and PAO2 values were similar in the two groups and either constant or little changed throughout. In both groups there was a marked decrease in PAO2 when nitroprusside was administered (group I 190–154 mm Hg; group II 180–133 mm Hg; P<0.005 in both groups). When the infusion of nitroprusside was stopped, and the arterial pressure returned to its previous value, PAO2 returned to the previous values.

During anaesthesia, PACO2 was greater in group I than in group II, but the administration of nitroprusside had little effect on either this measurement or on VD/VT in either group, although the small increase in mean VD/VT in group II was statistically significant (P<0.05).

The mean values for bicarbonate, with standard deviations and levels of significance, are shown in table IV. There was a tendency for bicarbonate to decrease slightly in all patients. The mean value before operation was 24 m-equiv/litre decreasing to 22.5 m-equiv/litre by the end of the procedure.

**DISCUSSION**

If alveolar ventilation and inspired PO2 remain constant, there are three possible explanations for the reduction in PAO2 during the administration of nitroprusside. First, cardiac output may have decreased, causing a reduction in mixed venous oxygen content and so increasing the effect of intrapulmonary shunting. However, it has been shown previously that cardiac output increases when nitroprusside is administered during anaesthesia (Styles, Coleman and Leary, 1973; Wildsmith et al., 1973). These studies were performed on supine patients, whereas our patients had a 5° head-up tilt, but changes in PAO2 similar to those reported here, have also been observed in supine patients by Griffiths and colleagues (1974). Second, there may have been an increase in whole body oxygen consumption, but this seems unlikely. There is the possibility of an increase in the scatter of ventilation/perfusion ratios throughout the lung or an increase in the proportion of blood not being exposed to ventilation, or both.
### Table I. Details of the two groups of patients

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Spontaneous ventilation</th>
<th>IPPV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>F</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>37</td>
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</tr>
<tr>
<td>Height (cm)</td>
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<tr>
<td>Weight (kg)</td>
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<tr>
<td>Sex</td>
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<td>M</td>
</tr>
<tr>
<td>Tobacco</td>
<td>—</td>
<td>yes</td>
</tr>
<tr>
<td>PaO₂ (mm Hg)</td>
<td>73</td>
<td>86</td>
</tr>
<tr>
<td>PaCO₂ (mm Hg)</td>
<td>38</td>
<td>42</td>
</tr>
</tbody>
</table>

P = significance of difference.

### Table II. Lung and blood-gas data (mm Hg) in group I (spontaneous ventilation) patients before, during and after the administration of sodium nitroprusside (SNP); the Vd/Vt ratio is given in the last column

<table>
<thead>
<tr>
<th>Patient</th>
<th>Before SNP</th>
<th>SNP</th>
<th>After SNP</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1O₂</td>
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</tr>
<tr>
<td>PaO₂</td>
<td>PaCO₂</td>
<td>Vd/Vt</td>
<td>P1O₂</td>
</tr>
<tr>
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Mean and SD:

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<tr>
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</tr>
<tr>
<td>P2O₂</td>
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<td>P3O₂</td>
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<tr>
<td>P4O₂</td>
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</tr>
<tr>
<td>Vd/Vt</td>
<td>0.59</td>
<td>0.09</td>
</tr>
</tbody>
</table>

SNP: Sodium Nitroprusside
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Table III. Lung and blood-gas data (mm Hg) in group II (IPPV) patients before, during and after the administration of sodium nitroprusside (SNP); the Vd/Vt ratio is given in the last column

<table>
<thead>
<tr>
<th></th>
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<th>SNP</th>
<th>After SNP</th>
</tr>
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<tbody>
<tr>
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<td>PtO&lt;sub&gt;2&lt;/sub&gt;</td>
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<tr>
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<tr>
<td>21</td>
<td>320</td>
<td>298</td>
<td>112</td>
</tr>
<tr>
<td>22</td>
<td>355</td>
<td>332</td>
<td>142</td>
</tr>
<tr>
<td>23</td>
<td>350</td>
<td>341</td>
<td>230</td>
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<tr>
<td>24</td>
<td>355</td>
<td>291</td>
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<tr>
<td>25</td>
<td>366</td>
<td>314</td>
<td>265</td>
</tr>
<tr>
<td>26</td>
<td>350</td>
<td>322</td>
<td>240</td>
</tr>
<tr>
<td>Mean</td>
<td>348</td>
<td>314</td>
<td>180</td>
</tr>
<tr>
<td>SD</td>
<td>14</td>
<td>16</td>
<td>59</td>
</tr>
</tbody>
</table>

Table IV. Bicarbonate concentrations (mean ± SD) for all the patients who received nitroprusside; P values given in brackets

<table>
<thead>
<tr>
<th></th>
<th>Before operation</th>
<th>Before SNP</th>
<th>SNP</th>
<th>After SNP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P&lt;sub&gt;co&lt;/sub&gt;2</td>
<td>24 ± 2</td>
<td>23 ± 2</td>
<td>22.5 ± 2 (0.25) (0.005) (0.01)</td>
</tr>
</tbody>
</table>

A major factor affecting the distribution of ventilation/perfusion ratios is the age of the patient (West, 1974). Figure 2 shows the values of Pa<sub>O</sub>2 of all patients studied, both before and during nitroprusside infusion, plotted against age. There is a good correlation for the relationship under both conditions: the older patients had the greatest reduction in Po<sub>2</sub> when nitroprusside was given. Figure 3 shows the change in Pa<sub>O</sub>2 plotted against age.

West (1969) predicted the effects of worsening the distribution of ventilation and perfusion within the lung, using a mathematical model in which the ventilation/perfusion ratios were distributed in a log-normal fashion. He pointed out that, with such a model, maldistribution could lead to large alveolar-arterial Po<sub>2</sub> differences at high inspired Po<sub>2</sub> values. Recent experimental work has substantiated the assumptions, used in these theoretical predictions, for the conscious human subject and anaesthetized dogs (Wagner et al., 1974; Wagner, Saltzhan and West, 1974; West, 1974).

If those patients whose Pa<sub>O</sub>2 was low before operation are considered to have increased V/Q scatter, then, according to these predictions, the Pa<sub>O</sub>2 response...
to an increase in inspired oxygen concentration to 50% could be less than in those patients with higher \( \text{Pa}_0 \) values before operation. This is what has been found (fig. 4, pre-SNP), and is similar to the findings in a study of oxygen therapy in chronic bronchitis (Mithoefer, Keighley and Keretzky, 1971). If nitroprusside caused a further increase in \( V/Q \) scatter, \( \text{Pa}_0 \) would decrease. At this inspired oxygen concentration the reduction would be more evident in those in whom \( \text{Pa}_0 \) was already reduced. This seems to have happened (SNP data, fig. 4). If the reductions in \( \text{Pa}_0 \) were caused by an increase in blood passing through unventilated areas, it is difficult to explain the more marked effect in these patients. We do not know how such a change in \( V/Q \) scatter might occur, but sodium nitroprusside is a highly vasoactive compound and there may be an effect on the pulmonary circulation.

The method of ventilation had no effect on the changes in arterial oxygenation. However, those patients who breathed spontaneously had \( \text{Pa}_{CO_2} \) values in the range 42–59 mm Hg during SNP infusion, compared with 35–42 mm Hg in the patients who were ventilated artificially.

The \( V/D/V_t \) ratios are unusual in one respect. Artificial ventilation is considered to increase physiological deadspace (Lee and Atkinson, 1973), but, in this study, the patients who breathed spontaneously had the greater ratios (tables II and III), which were in excess of those predicted on the basis of age (Cooper, 1967). The reason for this is the relationship between \( V/D/V_t \) and \( \text{Pa}_{CO_2} \). It has been shown that an increase in \( \text{Pa}_{CO_2} \) is associated with an increase in \( V/D/V_t \) (Trimble et al., 1971), possibly by dilatation of the bronchial tree (Widdicombe, 1966). Figure 5 shows the \( V/D/V_t \) ratios before nitroprusside was administered plotted against \( \text{Pa}_{CO_2} \). It is clear that at a particular value of \( \text{Pa}_{CO_2} \), \( V/D/V_t \) ratio is higher in patients being ventilated artificially. Since mean \( \text{Pa}_{CO_2} \) was higher in group I, it is not surprising that mean \( V/D/V_t \) ratio was also higher. The relationship between \( V/D/V_t \) ratio and age described by Cooper (1967) was based on artificially ventilated patients, and should only be applied to that situation.

The reductions in bicarbonate were small, and it is not certain that nitroprusside was responsible. They
commenced before nitroprusside was administered (table IV) and the effect of anaesthesia, with or without other hypotensive agents, has not been assessed. However, the finding of even a small decrease is disturbing, and is to be the subject of further study.

Sodium nitroprusside has many features that make it attractive as a hypotensive agent (MacRae, 1971), but this study suggests that it should be used in the presence of a high inspired PO2, especially in older patients. None of our patients had a reduction in PaO2 to dangerous values, but Campkin and colleagues (1974) have reported a patient of 58 yr whose PaO2 decreased to 48 mm Hg during nitroprusside hypotension while breathing 50% oxygen.

A mild metabolic acidosis may develop. This may be an argument in favour of spontaneous ventilation, since, if the metabolic acidosis becomes severe, respiratory compensation may prevent a disastrous reduction in pH as well as aiding the diagnosis (MacRae and Owen, 1974).

ACKNOWLEDGEMENTS
We would like to thank Drs G. D. McDowall, B. A. B. Dale and K. McLay, for allowing us to study their patients, and the Respiratory Function Laboratory, City Hospital, Edinburgh, for performing the blood and gas measurements.

REFERENCES


VARIATIONS DES GAZ CONTENUS DANS LE SANG PENDANT L'HYPOTENSION PROVOQUEE PAR LE NITROPRUSSIATE DE SODIUM

RESUME
Une étude des effets respiratoires du nitroprussiate de sodium sur les gaz contenus dans le sang pendant une anesthésie a montré une réduction marquée du PaO2 (tension de l'oxygène artériel) lorsque la drogue a été administrée. Après le nitroprussiate le PaO2 est retourné à sa valeur antérieure. On suggère que la réduction dans le PaO2 est le résultat d'une augmentation dans la dispersion des relations ventilation/perfusion dans les poumons. La réduction dans le PaO2 a été évidente aussi bien dans la respiration spontanée que dans la ventilation artificielle. Le nitroprussiate a été associé à une légère diminution dans le teneur en bicarbonate.

Un estudio sobre el contenido de gas en la sangre respecto a los efectos respiratorios del nitroprúsido de sodio durante la anestesia ha demostrado una notable reducción de PaO₂ cuando se administró la droga. Después del nitroprúsido, la tensión del oxígeno en las arterias (PaO₂) volvió a su valor anterior. Se sugiere que la reducción de PaO₂ es el resultado de un aumento de dispersión en la relación ventilación/perfusión en el pulmón. Se hizo evidente la reducción de PaO₂ durante la ventilación espontánea y artificial. Se relaciona el nitroprúsido con un pequeño descenso en el bicarbonato efectivo.
METABOLIC EFFECTS OF INDUCED HYPOTENSION WITH TRIMETAPHAN AND SODIUM NITROPRUSSIDE

J. A. W. Wildsmith, G. B. Drummond and W. R. MacRae

Br. J. Anaesth. (1979), 51, 875
METABOLIC EFFECTS OF INDUCED HYPOTENSION WITH TRIMETAPHAN AND SODIUM NITROPRUSSIDE

J. A. W. Wildsmith, G. B. Drummond and W. R. MacRae

SUMMARY

In two groups of patients undergoing induced hypotension with sodium nitroprusside or trimetaphan blood concentrations of lactate, pyruvate and standard bicarbonate did not differ significantly between the groups. In the nine patients who received trimetaphan there was a progressive, but statistically non-significant, decrease in mean lactate. Nitroprusside (15 patients) was associated with a small increase in mean lactate, but at low dosage there was a small decrease. No relationship to dose rate of nitroprusside was found with these short-term infusions. It is concluded that sodium nitroprusside can be used safely for induced hypotension at doses less than 1.5 mg kg⁻¹ and that simple blood-gas analysis is adequate for the assessment of toxic effects when greater doses are given.

Since its introduction for inducing hypotension during anaesthesia (Jones and Cole, 1968) sodium nitroprusside has become widely used because its brief duration of action allows accurate control of hypotension and rapid restoration of arterial pressure at the end of the procedure, although there has always been concern about toxicity because metabolism of sodium nitroprusside results in formation of cyanide. Vesey, Cole and Simpson (1976), having reviewed case reports of presumed cyanide poisoning after nitroprusside and having measured cyanide concentrations in plasma and red blood cells during and after its infusion in man, made recommendations regarding the safe maximum dose. However, cyanide measurements have been questioned as suitable indicators of exposure to cyanide after nitroprusside (Smith and Kruszyna, 1976).

Cyanide blocks oxidative phosphorylation by the cytochromes. Some energy is produced anaerobically by glycolysis with production of lactate when pyruvate cannot enter the Kreb’s cycle. We have studied blood lactate and pyruvate concentrations as indicators of this effect of cyanide release in patients receiving nitroprusside to induce hypotension during anaesthesia. Patients who received trimetaphan were studied as controls.

METHODS

Twenty patients undergoing middle ear surgery for which hypotensive anaesthesia was indicated were studied. The nature of the study was explained to the patient and consent obtained. Premedication was with oral diazepam 10 mg. Anaesthesia was induced with thiopentone 250–400 mg and endotracheal intubation performed with the aid of pancuronium 6–8 mg. Anaesthesia was maintained with 50% nitrous oxide in oxygen with halothane 1–2%. The lungs were ventilated artificially at 15 b.p.m. using a Cape–Waine anaesthetic ventilator (Cape Engineering Ltd) with tidal volume set so that expired volume, measured with a Wright respirometer (British Oxygen Company Ltd), equalled that indicated by the Radford (1955) nomogram.

After induction of anaesthesia a 19-gauge Venflon cannula (Everett Medical Products Ltd) was inserted percutaneously into a radial artery to allow measurement of arterial pressure and sampling of arterial blood. After 15 min of stable anaesthesia samples of arterial blood were collected for estimation of lactate, pyruvate and haemoglobin concentrations and for blood-gas analysis. An infusion of 0.9% saline containing either sodium nitroprusside (prepared by the hospital pharmacy) or trimetaphan (Arfonad, Roche) was started. Allocation to either drug was on a random basis and infusion rates were adjusted to produce a systolic arterial pressure of 60 mm Hg. The infusion was continued until the end of surgery, when a second set of samples was taken. Pancuronium was antagonized with neostigmine, the tracheal tube removed, and the patient breathed 35% oxygen from a Ventimask (Vickers Medical Ltd) until a third set of samples was taken 1 h after the second. The arterial cannula was then removed.

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Blood samples for lactate and pyruvate and blood-gas estimation were drawn into two heparinized iced glass syringes. One was sealed and placed in an ice-water mixture for transport to the laboratory where analyses for H⁺, PaO₂, and PaCO₂ were performed using an IL 213 microelectrode system. Standard bicarbonate was derived from H⁺ and PaCO₂ using the Sigggaard-Andersen alignment nomogram. The lactate–pyruvate sample was immediately decanted into an iced glass tube. An aliquot was aspirated to an iced glass pipette, placed in an equal volume of iced perchloric acid, the mixture centrifuged, and the supernatant liquid assayed for lactate and pyruvate using an enzymatic method (The Boehringer Corporation (London) Ltd).

Following the comparative study another six patients who received nitroprusside were studied to provide more data for analysis of the dose–effect relationship on lactate–pyruvate changes.

Differences between the two randomized groups were compared using a t test for two means, and differences within groups compared with a paired t test.

RESULTS

Table I shows the details of the two groups of patients in the comparative study. Those who received trimetaphan were younger, heavier and underwent procedures of shorter duration than those who received nitroprusside, but none of the differences was statistically significant. The results from one patient in each group were incomplete and have been omitted.

Table II summarizes the blood-gas data. The patients in both groups were well oxygenated and there were minimal changes in mean PaCO₂.

Table III summarizes the lactate, pyruvate and standard bicarbonate concentrations and the lactate/pyruvate ratios of the 18 patients in the comparative study. Changes in the measurements were generally small and inconsistent. There was a small progressive decrease in mean lactate concentration in those who received trimetaphan whereas there was a small increase in the nitroprusside group between the second and third samples. In none of these measurements were within-group changes or between-group differences statistically significant.

Table III also summarizes the data for the additional six patients studied with nitroprusside infusion. Changes in lactate concentration in all 15 patients receiving nitroprusside were analysed in respect of both total dose and dose rate and no obvious relationships were apparent; neither were changes in lactate concentration related to duration of hypotension.

Lactate concentration decreased in the majority of patients (fig. 1) and the slight increase in mean lactate concentration in the original nitroprusside group was caused almost entirely by one patient whose arterial pressure was resistant to the effect of nitroprusside from the outset. The results for this patient are shown in Table IV, with some subsequent blood-gas values and vitamin B₁₂ concentrations: the lactate concentration increased and there was a decrease in standard bicarbonate; the lactate/pyruvate ratio decreased and the excess lactate value (Huckabee, 1958) was negative. At the end of the procedure the patient's condition was clinically un-

<table>
<thead>
<tr>
<th>Sample</th>
<th>Nitroprusside</th>
<th>Trimetaphan</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>PaO₂ (mmHg)</td>
<td>PaCO₂ (mmHg)</td>
</tr>
<tr>
<td>I (IPPV: FiO₂ 0.5)</td>
<td>27 ± 5</td>
<td>5.0 ± 0.6</td>
</tr>
<tr>
<td>II (IPPV: FiO₂ 0.5)</td>
<td>25 ± 6</td>
<td>5.2 ± 0.7</td>
</tr>
<tr>
<td>III (SV: FiO₂ 0.35)</td>
<td>19 ± 3</td>
<td>5.6 ± 0.6</td>
</tr>
</tbody>
</table>
remarkable and within 3 h standard bicarbonate had increased spontaneously.

![Graph](image)

**Fig. 1.** Relationship between dose of nitroprusside (SNP) and change in lactate concentration between the start of hypotension and 1 h after the operation.

**DISCUSSION**

Certain physiological and other safeguards are necessary to allow blood lactate concentrations to be used to assess intracellular acidosis. Although it is an indirect method it is the best available (Cohen and Simpson, 1975). Oxygen delivery to the tissues must be adequate: the patients in the present study were all well oxygenated and cardiac output is known to be normal or slightly increased during induced hypotension with nitroprusside (Wildsmith et al., 1973). Changes in $P_{CO_2}$, particularly hypocapnia, affect lactate concentration (Cohen and Woods, 1976) and for that reason we maintained normocapnia. Infusion of glucose can increase blood lactate (Cohen and Woods, 1976); we gave the drugs in saline. Blood was withdrawn from an arterial cannula to avoid stasis. All glassware was iced and the specimen for lactate decanted into perchloric acid as soon as possible so that the effect of red cell glycolysis after withdrawal was minimal.

Lactate and pyruvate data are often expressed as the ratio of the two, but we do not believe this to be valuable. In the one patient with clear changes, this ratio decreased when it would have been expected to increase. This was because there was a greater proportional increase in pyruvate than in lactate. Excess lactate has also been used to indicate changes in lactate concentration independent of alterations in pyruvate (Huckabee, 1958). Mathematically, however, this figure is not independent of pyruvate (Cohen and Woods, 1976) and in one patient the change was the reverse of that which would be expected.

The results show that hypotensive anaesthesia with trimetaphan is not associated with any evidence of

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**TABLE III.** Lactate, pyruvate, lactate/pyruvate ratio and bicarbonate data (means ± SD) of patients studied. Groups (n = 9) in comparative study and (n = 6) the additional group who received nitroprusside. I = samples at start of procedure, II = samples at end of procedure and III = samples 1 h after the procedure. Detailed figures are available from the authors.

<table>
<thead>
<tr>
<th>Groups (n=9)</th>
<th>Nitroprusside</th>
<th>Trimetaphan</th>
<th>Nitroprusside (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactate (mmol litre$^{-1}$)</td>
<td>0.85 (0.30)</td>
<td>0.87 (0.22)</td>
<td>1.05 (0.44)</td>
</tr>
<tr>
<td>Pyruvate (mmol litre$^{-1}$)</td>
<td>0.050 (0.019)</td>
<td>0.043 (0.018)</td>
<td>0.064 (0.024)</td>
</tr>
<tr>
<td>Lactate/pyruvate ratio</td>
<td>17.5 (5.9)</td>
<td>26.4 (17.5)</td>
<td>16.8 (5.7)</td>
</tr>
<tr>
<td>Bicarbonate (mmol litre$^{-1}$)</td>
<td>23.2 (2.0)</td>
<td>22.3 (1.4)</td>
<td>21.2 (2.3)</td>
</tr>
<tr>
<td>Dose rate (mg kg$^{-1}$ min$^{-1}$)</td>
<td>12.1 (9.9)</td>
<td>—</td>
<td>12.6 (15)</td>
</tr>
<tr>
<td>Total dose (mg kg$^{-1}$)</td>
<td>0.68 (0.5)</td>
<td>—</td>
<td>0.38 (0.3)</td>
</tr>
</tbody>
</table>
cellular hypoxia. Mean lactate concentration decreased slightly with this agent, presumably because peripheral perfusion was improved by vasodilatation. Increased oxygen tension during anaesthesia or simple physical inactivity could also have been responsible, but normotensive halothane anaesthesia produces a slight increase in lactate concentration (Chamberlain and Lis, 1968; Yamazaki et al., 1975). Sodium nitroprusside in low doses also decreased lactate concentrations and it has been used (Taradosh and Jacobsen, 1973) to treat idiopathic lactic acidosis associated with poor peripheral perfusion.

With larger doses, the lactate concentration may increase, presumably as the toxic effect begins to counter the effect on perfusion. The patient who showed resistance to the hypotensive effect of sodium nitroprusside required 1.6 mg kg⁻¹ and had the greatest increase in lactate concentration (fig. 1). Although the increase was small and recovery uneventful, this case shows the need to limit total dosage in acute administration, and these results would support the suggested maximum dose of 1.5 mg kg⁻¹ based on cyanide studies (Vesey, Cole and Simpson, 1976). Suggestions have also been made regarding the maximum safe dose rate (Editorial, 1978)—a dose of 10 μg kg⁻¹ min⁻¹ being quoted. While this may apply to administration over a period of days, our results indicate little relationship to dose rate during hypotensive anaesthesia.

The increase in blood lactate concentration in the resistant patient could have been caused by a reduction in hepatic clearance because of a reduction in liver blood flow, rather than by increased production of lactate. Little is known about liver blood flow during administration of nitroprusside, but clearance of indocyanine green has been used as an indicator of this and is not influenced by infusion of nitroprusside during halothane anaesthesia (Abdel Salam et al., 1976).

This study investigated the effects of clinical use of sodium nitroprusside on metabolism. Instead of measuring cyanide concentrations, and attempting to deduce toxicity indirectly, we looked for alteration in the metabolic state. When it is used within its known toxic concentrations, there is no significant metabolic upset. This means that for practical purposes the drug can be administered in normal doses without fear of producing metabolic acidosis, except in patients with known contraindications (Cole, 1978).

Unfortunately, this does not mean that the problem of metabolic acidosis as a potential complication can be ignored. There is no means of predicting how much drug will be needed for any particular patient. Most require only small amounts, but occasionally doses approaching 1.5 mg kg⁻¹ are needed. It has been argued that safe use of nitroprusside requires ready access to lactate estimation (Editorial, 1978), but our results confirm animal studies which suggested that changes in lactate are mirrored by changes in bicarbonate concentration (Simpson et al., 1977). Blood-gas analysis is easier, quicker and cheaper to perform and far more readily available. We would consider that this estimation is adequate for assessing toxicity following acute administration during anaesthesia, and make it when the total dose is likely to exceed 1.5 mg kg⁻¹.

ACKNOWLEDGEMENTS

We would like to thank Dr B. A. B. Dale for allowing us to study patients in his care, the Department of Medicine, University of Edinburgh, for performing lactate and pyruvate measurements and the E.N.T. theatre staff, City Hospital, Edinburgh, for continuing support and assistance.
HYPOTENSION WITH TRIMETAPHAN AND SNP

REFERENCES


EFFETS METABOLIQUES DE L'HYPOTENSION INDUCITE PAR LE TRIMETAPAN ET LE NITROPRUSSIATE DE SODIUM

SUMARIO
En dos grupos de pacientes sometidos a hipotension inducida mediante nitroprussiato de sodio o trimetafán, no diferieron de manera significativa entre los grupos las concentraciones de lactato en la sangre y las concentraciones de piruvato y de bicarbonato normal. En los nueve pacientes a quienes fue administrado trimetafán, hubo una reducción progresiva de lactato medio, aunque no-significativa desde el punto de vista estadístico. Se halló (15 pacientes) nitroprussiato asociado con un ligero aumento de lactato medio, pero en dosis bajas, se registró una pequeña reducción. No se encontró ninguna relación con el porcentaje de las dosis de nitroprussiato en estas infusiones de corta duración. Se concluye que puede usarse en toda seguridad el nitroprussiato de sodio para hipotension inducida en dosis menores de 1,5 mg kg⁻¹ y que es adecuado un simple análisis sangre-gas para evaluar los efectos tóxicos cuando se administren dosis mayores.

STOFFWECHSELWIRKUNGEN KÜNSTLICH HERBEIGEFÜHRTER HYPOTONIE MIT TRIMETAPAN UND NITROPRUSSIDNATRIUM

ZUSAMMENFASSUNG
In zwei, sich künstlich herbeigeführter Hypotonie mit Nitroprussidnatrium oder Trimetaphan unterzogenen Gruppen von Patienten unterschieden sich die Blutkonzentrationen von Laktat, Pyruvat und Standardbicarbonat nicht wesentlich zwischen den beiden Gruppen. In den neun Patienten, die Trimetaphan erhielten, fand ein progressiver, aber statistisch unbedeutender Abfall im mittleren Laktatgehalt statt. Nitroprussid (15 Patienten) war mit einem geringen Anstieg im mittleren Laktatgehalt verbunden, aber bei niedriger Dosierung fand ein geringer Abfall statt. Bei diesen kurzfristigen Infusionen wurde keine Beziehung zur Dosierung von Nitroprussid festgestellt. Es wird der Schluss gezogen, dass Nitroprussidnatrium bei Dosen unter 1,5 mg/kg ohne Gefahr für künstlich herbeigeführte Hypotonie benutzt werden kann, und dass eine einfache Blutgasanalyse für die Beurteilung schädlicher Wirkungen bei Verwendung grösserer Dosen ausreicht.

EFFETS METABOLIQUES DE L'HYPOTENSION INDUCITE MEDIANTE TRIMETAPAN Y NITROPRUSSIATO DE SODIO

RESUME
Sur deux groupes de malades subissant une hypotension induite par le nitroprussiatae de sodium ou par le trimétophan, les concentrations de lactate dans le sang de meme que les concentrations de pyruvate et de bicarbonate standard n'ont pas grandement diffère dans les deux groupes. Sur neuf malades auxquels on avait administré du trimétophan, on a constaté une diminution progressive, mais sans grande signification statistique, de la valeur moyenne du lactate. Le nitroprussiatae (administré à 15 malades) a été associé à une légère augmentation de la valeur moyenne du lactate, mais a faibles doses, on en a constaté une légère diminution. On n'a trouvé aucune relation dose-taux de nitroprussiatae avec ces infusions à court terme. On en a conclu que le nitroprussiatae de sodium peut être utilisé en toute sécurité pour induire l'hypotension à des doses inférieures à 1,5 mg kg⁻¹ et qu'une simple analyse sang-gaz est adéquate pour évaluer les effets toxiques lorsqu'on administre des doses plus importantes.