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SYMPATHOADRENAL RESPONSES TO ANAESTHESIA AND SURGERY

D. R. DERBYSHIRE AND G. SMITH

Nociceptive surgical stimulation is accompanied by increased hypothalamo–pituitary activity which is generally referred to as the stress response to injury. This is manifest by a release of trophic hormones from the hypothalamus which in turn stimulate release of ACTH, TSH, GH, FSH, luteinizing hormone and prolactin in addition to ADH from the pituitary. Consequently, there is increased secretion of cortisol and thyroxine with suppression of insulin and increase in blood sugar concentrations. These responses may be partly attenuated by large doses of opioid analgesic drugs and some local anaesthetic techniques used during general anaesthesia. These endocrine changes have recently been reviewed elsewhere (Kaufman 1982, 1984; Weatherill and Spence, 1984).

In addition, increased hypothalamic activity induced by nociceptive stimulation is accompanied by increased traffic in sympathetic efferent tracts. This is manifest by the well known signs which are conventionally used to diagnose unduly light levels of anaesthesia — notably dilatation of the pupils, sweating, tachycardia and hypertension. Thus measurements of heart rate, arterial pressure and skin resistance have been used as indirect indices of the level of sympathetic activity to assess both the efficacy of premedication and depth of anaesthesia.

Increased sympathetic tone involves augmented release of noradrenaline by presynaptic sympathetic fibres and also increased secretion of catecholamines from the adrenal medulla. Thus attempts have been made for a number of years to assess sympathetic activity "directly" by measurement of plasma catecholamine concentrations.

Until recently, assays were not available with sufficient sensitivity to measure resting concentrations of plasma catecholamines. However, with the advent of radioenzymatic assay (REA) and, over the past 5–6 years, high pressure liquid chromatography (HPLC) techniques for measurement of catecholamines in plasma, there has been a large number of studies of changes in plasma catecholamines during anaesthesia.

It is the purpose of this article to review briefly the recent literature on plasma catecholamine responses to anaesthesia and surgery. To place these data in perspective, however, it is important to appreciate that a single measurement of plasma adrenaline and noradrenaline represents only a brief glimpse of the overall extent of sympathoadrenal activity.

Since the majority of noradrenaline released at the sympathetic nerve ending is taken back up into the presynaptic nerve terminal, it would be unduly optimistic to expect that changes in plasma noradrenaline activity would follow faithfully the extent of sympathetic efferent traffic. However, during conditions of stress, it may be possible to demonstrate a good correlation between plasma noradrenaline concentrations and systolic arterial pressure (see below). In addition, direct microelectrode recordings from sympathetic nerves demonstrate increased activity during change in posture from the supine to the erect position (Burke, Sundole and Wallin, 1977) and this manoeuvre is known also to be associated with increased concentrations of plasma noradrenaline (see below). Thus there is indirect evidence that increased plasma noradrenaline changes reflect increased sympathetic activity during stress; although in the resting state, there is little correlation (Bravo and Tarazi, 1982).

During surgery, changes in plasma catecholamines exhibit the same trends as other hormonal changes involved in the neuroendocrine response to stress. In addition, recent studies demonstrate a correlation between changes in simple cardiovascular variables (heart rate, arterial pressure) and plasma catecholamines; thus one concludes that measurement of these hormones, whilst not providing a complete reflection of sympathoadrenal activity, serves to augment haemodynamic measurements as indirect indices.

This review is intended to provide an indication of the problems involved in the interpretation of plasma catecholamine measurements and it describes those studies of relevance to anaesthesia. Data related to pathological conditions, notably

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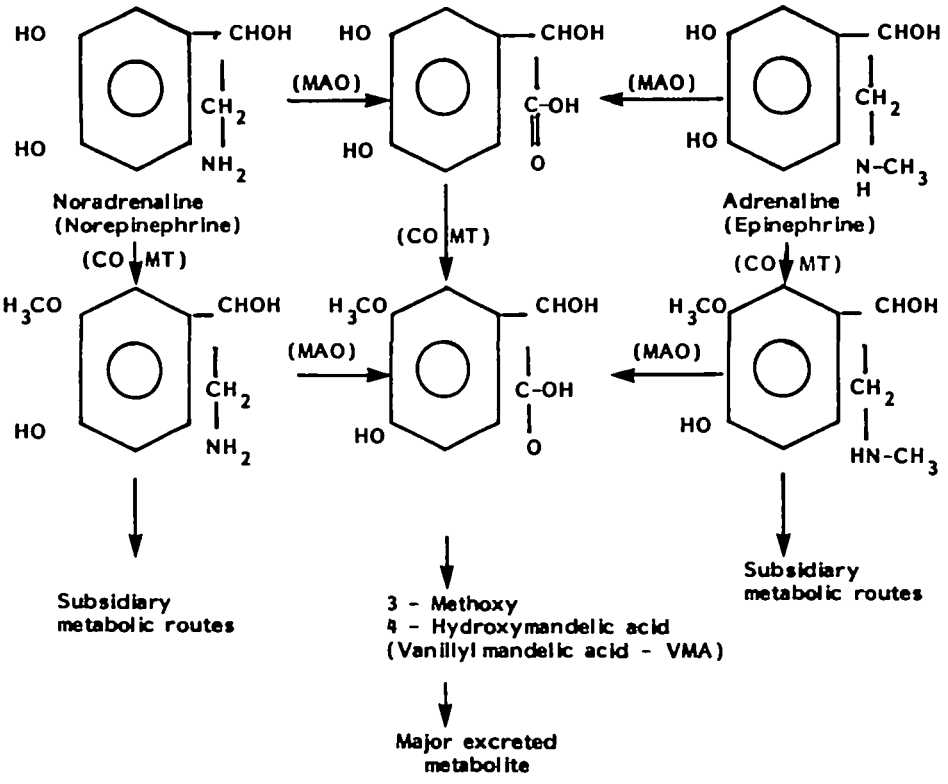

FIG. 1. Pathways of catabolism of the catecholamines.

phaeochromocytoma, are described elsewhere in this issue (Desmonts and Marty, 1984).

History

The pressor effect of extracts from the adrenal gland was described independently by Oliver and Schäfer (1895) from University College London, and by Szymonowicz (1895) and Cybulski (1895) in Poland. The latter authors attributed the action to a central effector mechanism. Oliver and Schäfer observed that, following incremental i.v. injections of suprarenal extract to an 11-kg dog ". . . when the blood pressure had attained its full height, the ventricle passed into a condition of fibrillar contraction. . . ." Several years later, the vasoactive constituent of the suprarenal extract was isolated and termed "epinephrine" by Abel of Johns Hopkins University. Takamine (1901) postulated that Abel's "epinephrine" was an impure extract and he applied the term "adrenalin" to a crystalline extract obtained from the adrenal gland — the difference in trans-Atlantic nomenclature dates from this time.

Adrenaline was synthesized independently by Stolz in 1904 and Dakin in 1905, and in the same era Elliott (1904) observed that the similarities between the actions of "adrenalin" and sympathetic nerve stimulation resulted from release of this transmitter substance at sympathetic nerve endings.

In 1910, Barger and Dale, at the Wellcome Research Institute, coined the term "sympathomimetic" to describe the action of a large number of aliphatic and aromatic amines on the arterial pressure of the decerebrate cat. At this time, very little was known on the effects of either hormones in general or catecholamines in particular, in the human. Until recently, there were only two methods of assessing the extent of sympathoadrenal activity occurring either in pathological conditions or in response to the stress of anaesthesia and surgery: by inference from physiological changes in the cardio-

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vascular system and by measurement of the quantities of metabolic products of the catecholamines. Measurements of the urinary excretion of catecholamine breakdown products (fig. 1) allow an integrated assessment of circulating catecholamine concentrations over periods as short as 1 h. The quantities of homovanillic acid (or hydroxymandellic acid) excreted in urine provide a useful index of gross variations in sympathoadrenal activity, for example in confirming the diagnosis of a suspected phaeochromocytoma.

Because the quantity of unchanged catecholamine excreted in urine over a 24 h period is relatively large (in comparison with the amount in plasma), it is possible to measure urine concentrations using the relatively insensitive fluorimetric technique. This method was applied to plasma samples by Lund in 1950 and it permits measurement of both total catecholamines (excluding dopamine) and adrenaline. (Noradrenaline concentrations are calculated by subtraction.) However, the fluorimetric technique is used at the limit of its sensitivity (Price, 1966) for measurement of catecholamine concentrations in plasma. Nonetheless, despite the inaccuracies inherent in this method, it is possible to detect *gross* changes in plasma catecholamine concentrations and Price and colleagues (1959) were able to demonstrate an increase in noradrenaline and adrenaline concentrations during anaesthesia with diethyl ether.

In 1968, the description of a radioenzymatic method of plasma assay, of greater sensitivity and accuracy than the fluorimetric technique, led to an upsurge of interest in this field (Engelman, Portnoy and Lovenberg, 1968). The double radioisotope method involves the enzymatic conversion of the catecholamines in the presence of catechol ortho methyl transferase (COMT) and radiolabelled ^{14}C-S-adenosylmethionine to their respective 3,0-methyl derivatives (^{14}C-normetadrenaline and metadrenaline). Possible inaccuracies arise from a degree of cross-reactivity with common drugs—notably methyldopa and isoprenaline. The original method permitted measurement of total catecholamines (excluding dopamine) and was modified subsequently by the use of thin layer chromatography to separate the labelled derivatives and obviate chemical transformation of the labelled met-compounds to vanillin. The second isotope in the technique, ^{3}H-catecholamine, was used to estimate the extent of recovery from plasma. This method, although much more sensitive than fluorimetry, is complex, time consuming and requires pre-extraction and concentration of catecholamines from relatively large volumes of plasma.

Modifications of the double isotope assay resulted in single isotope methods (Passon and Peuler, 1973; Cryer, Santiago and Shah, 1974) which are reported to possess assay coefficients of variation of less than 5% for noradrenaline and less than 10% for adrenaline within physiological concentrations of the hormones. Radioenzymatic techniques which are used currently are usually modifications of more recent methods described by either Da Prada and Zurcher (1976) or Peuler and Johnson (1977).

Although these radioenzymatic methods have been used extensively for studies of sympathoadrenal responses during anaesthesia, the associated high initial capital cost, large recurrent expenses and tedious technical procedures have restricted these techniques to relatively few departments of anaesthesia.

In 1978, Hallman and others reported the application to *plasma* catecholamine assay of HPLC, which had been developed originally for tissue catecholamine measurements (Keller et al., 1976). The radioenzymatic and HPLC assays were compared by Hjelmdahl, Daleskog and Kahan (1979), who concluded that the radioenzymatic assay had the advantage of slightly greater sensitivity, but was more expensive and tedious. In addition, HPLC also allows samples to be analysed more rapidly, and over the past few years there has been considerable growth in the use of the technique by academic departments of anaesthesia in the United Kingdom.

In comparing data from different studies reported in the anaesthetic literature, it is important that the reader is aware of the difference between the assay techniques used because of the differences in accuracy and sensitivity. In simple terms, the fluorimetric technique is valueless, whilst HPLC techniques are used at the limit of sensitivity for measurements of resting, plasma concentrations of catecholamines in healthy premedicated patients.

Stability of catecholamines

Carruthers and colleagues (1970) suggested that catecholamines degraded considerably during storage. However, using HPLC assay, Falconer, Lake and MacDonald (1982) have demonstrated that catecholamines in blood do not degrade if stored at room temperature for up to 1 h before separation of plasma. Furthermore, plasma samples were stable during storage for up to 6 months at -20 °C.

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Catecholamines require extraction from plasma before assay. The amount extracted as a percentage of the total is designated the recovery. It is obvious that a higher recovery ensures a more accurate assay, since calculation and measurement errors are reduced.

Frequently, the container into which blood samples are drawn contains an antioxidant such as sodium metabisulphite, glutathione, or EDTA. The role and value of these substances is disputed. It has been suggested that the percentage recovery is enhanced by the use of such antioxidants (Eriksson and Persson, 1982). However, Falconer, Lake and MacDonald (1982) have shown that there is little difference between measurement in samples collected with or without glutathione/EDTA, either immediately or after storage.

Catecholamines and sampling

It is well known that many subjects anticipate venepuncture with apprehension or anxiety and it is therefore important to assess the effects of sampling techniques upon plasma concentrations of catecholamines.

This question was examined in 1970 by Carruthers and colleagues using a fluorimetric assay. They obtained samples simultaneously from an indwelling central venous catheter and peripheral venepuncture and concluded that blood from the former has a plasma catecholamine concentration similar to that obtained from a separate venepuncture. Subsequently, samples were obtained from an indwelling central venous catheter (unknown to the subject) to assess "resting" plasma catecholamine concentrations. They were able to demonstrate a significant, although small, increase in plasma adrenaline concentrations occurring with venepuncture. However, the use of the fluorimetric technique and a 22% variation in reported results (between means in different aspects of the study) cast doubt on the accuracy of these data.

This problem has been re-examined by Fell and his colleagues in our laboratory using the more sensitive HPLC assay (Fell, Derbyshire, Larsson and Smith, in preparation). In this study a sampling cannula was inserted, without local analgesia, to a peripheral vein. Samples were taken immediately after insertion and at intervals for a period of 2 h thereafter. Although minor changes in plasma catecholamine concentrations occurred between 0 and 15 min, these were not statistically significant and overall there was little change throughout the period of sampling. Based upon the assumption that any anxiety related to venepuncture would settle over the subsequent 2-h period in which the cannula remained *in situ*, it was concluded that cannulation *per se* did not result in significant changes in plasma catecholamine concentrations. Since the data are similar to values for plasma catecholamines obtained in unstressed healthy anaesthetized patients before surgical stimulation, it is concluded that the data of Carruthers and colleagues (1970) are unsubstantiated.

Venepuncture in healthy, stable volunteers may be regarded as a very mild stimulus to anxiety. Other situations which may be presumed to be associated with more severe degrees of anxiety are discussed below.

Posture. Baroreceptor reflexes play a significant role in cardiovascular homeostasis during alteration of posture. The efferent limb of this reflex involves alteration in the rate of firing of noradrenergic peripheral nerve terminals and, possibly, changes in the "overspill" of noradrenaline from the nerve terminal into the circulation. This hypothesis was examined by Johnson, Pueler and Baker (1977), who demonstrated that measurable changes in plasma catecholamines occurred during postural reflexes. Thirty healthy volunteers rested supine for 30 min before insertion of a venous cannula. Samples were taken immediately after insertion and 30 min later. Using a radioenzymatic assay, it was shown that, whilst there was no difference in catecholamine concentrations in the supine state, plasma noradrenaline concentrations increased from a resting supine value of 1 pmol ml^{-1} to a value of 3.79 pmol ml^{-1} 10 min after the subjects had assumed the erect position. Ambulation produced values of approximately 2 pmol ml^{-1}, which was significantly greater than the mean values for the supine position. Plasma adrenaline concentrations changed in a manner similar to those which occurred in noradrenaline. These findings were confirmed by Saar and Gordon (1979) who demonstrated that *total* catecholamine concentrations doubled in subjects who assumed the erect position after 30 min recumbency. They also found that *total* plasma catecholamine concentrations were slightly but significantly lower in subjects who had wakened from sleep, compared with values in the same subjects after 30 min recumbency in a conscious state. Furthermore, Watson, Littler and Eriksson (1980) demonstrated increases during isometric exercise in

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both hypertensive and normotensive volunteers.

Thus, it is clear that the position of the subject is important during studies in which measurement of catecholamine concentrations are required, and posture should therefore be standardized.

Site of sampling. Catecholamines have a short biological half-life and catabolism may therefore alter significantly the values in blood samples obtained from different sites.

Using *in vitro* models, Ginn and Vane (1968) demonstrated that noradrenaline underwent significant catabolism in the lungs. This was confirmed in the human by Sole and colleagues (1979). Recently, Russell, Frewin and Jonsson (1983) demonstrated in critically ill patients, that central venous blood samples possessed dopamine, adrenaline and noradrenaline concentrations which were 25% greater than those in blood samples obtained simultaneously from arterial sites.

Derbyshire and colleagues (1983) have confirmed in patients that noradrenaline is catabolized during passage through the lungs. Significantly lower concentrations of noradrenaline, but not adrenaline, were observed in arterial (in comparison with central venous) blood samples during changes occurring in response to induction of anaesthesia and tracheal intubation.

Both halothane and nitrous oxide have been shown to decrease the pulmonary metabolism of circulating catecholamines (Naito and Gillis, 1973).

Catecholamines and severe anxiety

Carruthers and Taggart have examined the effects on plasma catecholamine concentrations of numerous "anxiety" provoking situations including rock climbing, motor car racing and parachute jumping. No attempt was made to quantify the stress other than in a time-related fashion (for example, immediately before the race, on the starting grid, immediately after the race) (Taggart and Carruthers, 1971, 1972; Carruthers, 1975). An increase in plasma adrenaline concentrations (but not noradrenaline) was demonstrated in the presence of extreme anxiety. There was also an increase in circulating concentrations of plasma free fatty acids which did not correlate with plasma adrenaline concentrations. These findings have been used elsewhere to provide evidence for the theory of a causal relationship between "stress" and cardiovascular diseases, including hypertension and coronary artery disease.

CATECHOLAMINES AND ANAESTHESIA

Preoperative period

In view of the generally held tenet in anaesthetic practice, that anxiety before operation is associated with increased sympathoadrenal activity, the question arises as to whether or not the extent of stress before surgery is associated with measurable increases in circulating plasma catecholamine concentrations. Although considerable effort has been expended in quantifying anxiety by psychological testing in the preoperative phase, little information is available on the effects of preoperative anxiety upon circulating plasma catecholamine concentrations. Early work using the fluorimetric assay failed to show any change in plasma catecholamine concentrations at 3 h before surgery (compared with 1–3 days before operation) in patients about to undergo elective abdominal surgery (Butler et al., 1977).

Studies currently in progress in the authors' laboratory have revealed a small increase in plasma adrenaline concentrations in premedicated patients immediately before induction of anaesthesia. However, there is no correlation with linear analogue scores for anxiety, suggesting that measurement of plasma concentrations of adrenaline will probably prove of no value as an assessment of the extent of anxiety in an individual patient before surgery. Further studies are required to investigate the correlation between other measures of "anxiety", or "stress", and starvation and changes in plasma catecholamine concentrations. It may be that, in group studies, the efficacy with which drugs attenuate the plasma adrenaline concentrations immediately before operation may be used as one index by which the value of pharmacological premedication may be judged.

A recent study has suggested that different premedications may lead to an alteration in sympathoadrenal responses during surgery (Sigurdsson, Lindahl and Nordén, 1983) (see below).

Induction of anaesthesia

Intravenous anaesthesia

Normally, arterial pressure decreases to a variable extent following induction of anaesthesia and this leads to a baroreceptor-mediated tachycardia in healthy patients. Any change in plasma catecholamines at this stage may be expected to reflect a balance between diminished central sympathetic activity resulting from loss of consciousness and increased baroreceptor-mediated activity. It

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would appear that the former effect predominates and consequently there is a small reduction in plasma catecholamines on induction of anaesthesia. In addition, it is known that thiopentone depresses baroreceptor reflex activity (Skovsted, Price and Price, 1970).

Many of the data for this period have been obtained after administration of a combination of induction agent (usually sodium thiopentone) *and* neuromuscular blocking drug (Russell et al., 1981; Cummings, Russell and Frewin 1983; Cummings, et al.,1983; Derbyshire et al.,1983). However, recent work in a group of elderly patients (in whom the effect of the induction agent was examined in isolation), demonstrated that no change in plasma noradrenaline occurred following administration of a sleep dose of sodium thiopentone 2–3 mg kg^{-1}. Moreover, a significant decrease in plasma catecholamine concentrations (particularly noradrenaline) occurred in patients in whom anaesthesia was induced with midazolam 0.2 mg kg^{-1} (Derbyshire et al., 1984) although comparison of the two induction agents did not reveal a significant difference between the two.

Joyce and colleagues (1982) have recently examined the effect of thiopentone in the absence of surgical stimulation. Three groups of patients were given thiopentone 3 mg kg^{-1} followed by one of three regimens: thiopentone 0.2–0.3 mg kg^{-1} min^{-1} with 100% oxygen; halothane 1.5% in oxygen; or 70% nitrous oxide in oxygen.

In the group given thiopentone by infusion, there was a small decrease in plasma noradrenaline concentrations, but there was no change in the other groups, suggesting that thiopentone decreases tonic sympathetic activity (Joyce, Roizen and Eger, 1983).

A less conventional method (for routine abdominal surgery) of ensuring stability of plasma catecholamine concentrations at induction of anaesthesia is the use of large doses of opioids. Either fentanyl 25 μg kg^{-1} or morphine 2–3 mg kg^{-1} induces unconsciousness and satisfactory induction of anaesthesia with little alteration in mean arterial pressure or plasma catecholamine concentrations (Stanley et al., 1980; Hoar et al., 1981).

Inhalation anaesthesia

Many years ago it was shown that induction of anaesthesia with diethyl ether "... resulted in a marked increase in plasma concentrations of a substance resembling noradrenaline. . . ." This study by Price (1957) was beset by methodological problems related to the fluorimetric assay. Repeating the work a few years later, again with a fluorimetric assay, Price and his co-workers were able to demonstrate a correlation between plasma catecholamine concentrations and depth of anaesthesia induced by diethyl ether, chloroform and cyclopropane (Price et al, 1959).

Recently it has been shown that halothane may also cause an increase in plasma catecholamine concentrations. Joyce and colleagues (1982) observed a significant increase in plasma noradrenaline concentrations in unpremedicated subjects in whom anaesthesia was induced with halothane in oxygen or oxygen – nitrous oxide. These increases continued into the third stage of anaesthesia.

It has been suggested that the hypotension which frequently accompanies the administration of halothane results largely from a reduction in myocardial contractility (Smith, 1981). Thus the increase in plasma catecholamine concentrations seen by Joyce and his co-workers may reflect an autonomic response to a decrease in mean arterial pressure. However, they were unable to demonstrate any correlation between changes in "cardiovascular variables . . . and plasma noradrenaline". In addition, halothane is known to block the baroreceptor responses which would lead to increased baroreceptor activity (Duke, Fownes and Wade, 1977).

It was suggested by Joyce and his colleagues (1982) that the increase in plasma noradrenaline resulted from:

(a) patient excitement during the second stage of anaesthesia, or
(b) greater depression of inhibitory rather than excitatory synapses, or
(c) a direct effect on the nerve ending causing release of noradrenaline.

In the same study, Joyce and colleagues noted a transient increase in noradrenaline release from an *in vitro* cat spleen model and they suggested that their observations might be explained most readily by an action of halothane at sympathetic nerve endings.

The extent of the increase in noradrenaline was of a similar magnitude when nitrous oxide was added to the halothane–oxygen mixture. This suggests either that nitrous oxide *alone* does not exert any effect upon the sympathoadrenal system, or that the

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effect of a concentration of 70% at 1 atmosphere absolute is too weak to result in detectable changes in plasma concentrations of the hormones.

Neuromuscular blockade

There are obvious difficulties in isolating the effects of neuromuscular block *per se* on the sympathoadrenal system since the majority of studies of responses to tracheal intubation have used neuromuscular blocking and anaesthetic induction drugs administered in rapid sequence. However, Nigrovic and his colleagues (1983) postulated that suxamethonium alone produced a significant increase in plasma noradrenaline concentrations. They induced anaesthesia with thiopentone and for maintenance used nitrous oxide and halothane in oxygen before the institution of neuromuscular blockade. An increase in noradrenaline was observed following administration of suxamethonium and this did not occur when dimethyl tubocurarine was substituted for suxamethonium.

This finding may be difficult to reconcile with those of other investigators. In separate studies, Cummings and colleagues (1983) and Derbyshire and colleagues (1983) have demonstrated similar resting values and small decreases in plasma concentrations of noradrenaline following induction of anaesthesia with thiopentone and neuromuscular block with tubocurarine, pancuronium bromide or suxamethonium before endotracheal intubation. It is possible that, in these studies, any potential increase in catecholamine concentrations induced by suxamethonium was masked by the effect of thiopentone. It is unlikely that insufficient time elapsed for an effect to become apparent since Cummings and colleagues (1983) waited 45 s following administration of thiopentone and suxamethonium before sampling was performed before laryngoscopy.

It is known that pancuronium bromide exhibits a sympathomimetic effect in man and it has been demonstrated in animal models (Domenech et al., 1976; Salt, Barnes and Conway, 1980) that this drug blocks the re-uptake of noradrenaline by sympathetic nerve endings. Although this might account for some of the cardiovascular effects seen with the drug in clinical practice, in several studies in patients it has been shown that pancuronium bromide does not produce a measurable increase in circulating plasma catecholamine concentrations. This does not, however, provide indisputable evidence that reduced re-uptake of noradrenaline is not a clinical entity, since measurement of catecholamines in plasma is only a poor guide to the changes which occur at the sympathetic synapse.

Recent evidence suggests that tubocurarine (dTC) may not cause hypotension by pharmacological blockade of sympathetic ganglia, as generally assumed (Atkinson, Rushman and Lee, 1982). It has been demonstrated recently that hypotension accompanying the administration of the drug is not accompanied by a decrease in circulating plasma catecholamines (in contrast to the decrease seen with alcuronium (Cummings, Russell and Frewin, 1983)) and it has been suggested that the mechanism of hypotension induced by dTC in the adult is related to release of histamine or other directly acting vasodilators (Cummings et al., 1983). Support for this hypothesis was provided by Moss and Roscow (1983), who obtained a significant correlation between decreases in mean arterial pressure and plasma histamine concentrations following administration of dTC. In contrast, Cummings, Russell and Frewin (1983) suggested that the mild hypotension seen after administration of alcuronium resulted from sympathetic ganglionic blockade since a significantly smaller plasma noradrenaline concentration was observed after noxious stimulation in patients given alcuronium in comparison with those given pancuronium.

Tracheal intubation

Endotracheal intubation had been practised for at least 30 years following its description by Rowbotham and Magill (1921) before the hypertensive effects of laryngoscopy and subsequent tracheal intubation were documented (King et al., 1951).

Following the demonstration in the cat, that these pressor responses were accompanied by increased activity in the cardiac sympathetic nerves, it was suggested that the effects might be attenuated by beta-blocking drugs (Prys-Roberts et al., 1971). However, beta blockade was subsequently found to be ineffective in ablating the pressor response associated with laryngoscopy. Attempts were made to confirm in patients, by measurement of plasma catecholamine concentrations, the experimental observation that this pressor response resulted from increased sympathetic efferent activity. However, until recently all attempts failed to demonstrate significant changes (Takki et al., 1972; Butler et al., 1977; Zsigmond and Kumar, 1980), almost certainly as a result of the insensitivity of the fluorimetric assays used.

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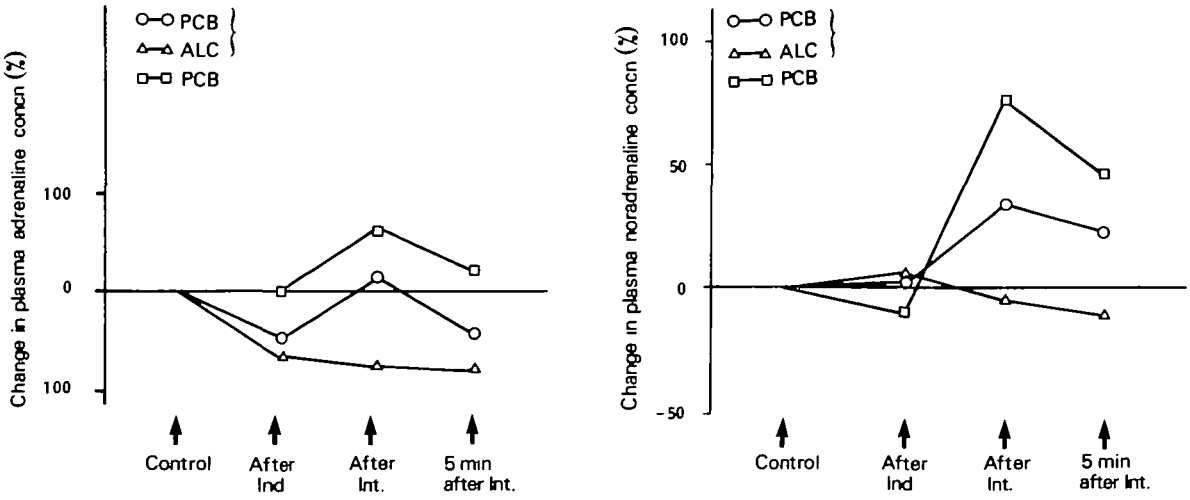

FIG. 2. Comparison of the effects of different techniques on the plasma adrenaline (left) and noradrenaline (right) responses to tracheal intubation. ○ and △ from Cummings, Russell and Frewin (1983); □ from Derbyshire and colleagues (1983). Left: Baseline control values 0.2, 0.4 and 0.5 pmol ml^{-1} respectively. Right: Control values 1.7, 1.4 and 2.0 pmol ml^{-1} respectively. After Ind. = after induction. After Int. = after intubation. PCB = Pancuronium bromide. ALC = Alcuronium chloride.

In 1981 confirmation was obtained of increased sympathoadrenal activity. Russell and co-workers (1981), using a radioenzymatic assay, observed an increase in plasma catecholamine concentrations following intubation of the trachea in patients anaesthetized with thiopentone and in whom neuromuscular block had been produced with pancuronium. They also demonstrated a significant correlation between the increase in mean arterial pressure and increases in plasma noradrenaline concentrations.

A correlation between changes in mean arterial pressure occurring at laryngoscopy and plasma catecholamine concentrations (especially noradrenaline) was confirmed in subsequent work from the group in Adelaide (Cummings, Russell and Frewin, 1983; Cummings et al., 1983) and from our own laboratory (Fell, Achola and Smith, 1982; Derbyshire et al., 1983).

It might be expected that changes in pulse pressure or heart rate would be related to plasma adrenaline concentrations. However, further examination of our own data (Derbyshire et al., 1983) has failed to reach any correlation, although a relationship exists for systolic arterial pressure and plasma noradrenaline concentrations.

Many methods have been used in an attempt to attenuate or ablate the pressor response occurring at laryngoscopy and intubation including beta blockade (Prys-Roberts et al., 1973), alpha blockade with droperidol (Curran, Crowley and O'Sullivan, 1980), lignocaine applied topically (Kautto and Heinonen, 1982) and i.v. (Stoelting, 1977, 1978), low-dose opioids (Kautto, 1982), infusion of sodium nitroprusside (Stoelting, 1979), and cervical extradural blockade (Dohi et al., 1982). None of these has gained widespread acceptance as a result of either complexity and problems inherent in the techniques or a lack of total efficacy.

There is one technique which is described as totally effective in abolishing both the pressor and the catecholamine responses at laryngoscopy and intubation. Although inappropriate for routine anaesthetic practice it has found widespread acceptance in cardiac surgery. Large doses of opioids—commonly fentanyl $> 50\ \mu g\ kg^{-1}$ or morphine $> 2\ mg\ kg^{-1}$—have been shown to produce "stress-free" induction of anaesthesia as judged by stability in plasma catecholamine concentrations and arterial pressure (Stanley et al., 1980; Hoar et al., 1981). This technique is not without its critics and a recent editorial has questioned the appropriateness of inducing unconsciousness by this method (Wong, 1983).

Another technique described recently as associated with stability of catecholamine responses requires confirmation in further studies. Cummings, Russell and Frewin (1983) demonstrated

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little response to tracheal intubation in eight patients given neuromuscular blocking doses of alcuronium. They used a technique of non-standardized premedication, induction of anaethesia with thiopentone and intubation of the trachea following neuromuscular blockade with alcuronium (fig. 2).

Non-cardiac surgery

Earlier studies using fluorimetric techniques failed to demonstrate any changes in plasma catecholamines during abdominal or ophthalmic surgery after induction of anaesthesia or after surgical incision (Nikki et al., 1972; Butler et al., 1977). However, the introduction of more sensitive assays permitted observation of increases in catecholamine concentrations in response to surgical stimulation.

Halter, Pflug and Porte (1977) demonstrated a consistent increase in plasma catecholamine concentrations occurring immediately after surgical incision in patients anaesthetized with nitrous oxide and halothane in oxygen with neuromuscular blockade obtained with pancuronium. These observations have been confirmed subsequently by several groups of investigators (Brismar et al., 1982; Brown et al., 1982; Ponten et al., 1982; Hamberger and Jändberg, 1983).

The effect of different anaesthetic techniques on the sympathoadrenal response to surgery is not clearly defined. There seems to be agreement that supplementation of general anaesthesia with low dose fentanyl ($<10\,\mu g\,kg^{-1}$) does not confer any advantage over supplementation with either enflurane or halothane in that the increases in plasma catecholamine concentrations are of a similar magnitude (Brismar et al., 1982; Hamberger and Jändberg, 1983). Although it has been suggested that enflurane supplementation may cause greater suppression of the sympathoadrenal response to surgery than low dose fentanyl (Brown et al., 1982), this has been questioned in subsequent correspondence (McLeskey, 1982). No data are currently available comparing the effects of halothane with enflurane.

A recent study from Sweden has suggested that the premedication may alter the magnitude of the sympathoadrenal response to minor surgery in children. Children undergoing adenoidectomy under general anaesthesia received premedication with either a small dose of diazepam (without opioid) or a larger dose of diazepam in addition to morphine. The children in the second group receiving the "heavier" premedication had a significantly smaller sympathoadrenal response to surgery, as determined by plasma catecholamine concentrations and the frequency of ventricular arrhythmia (Sigurdsson, Lindahl and Nordén, 1983).

Although there may be small differences *between* anaesthetic techniques in respect of sympathoadrenal responses, the magnitude of this difference is trivial in comparison with the changes produced by surgery (Ponten et al., 1982).

Hypotensive anaesthesia

Sodium nitroprusside (SNP) has gained widespread popularity in hypotensive anaesthesia since it has a rapid onset of action and a short half-life.

It has been shown that decreasing arterial pressure by infusion of SNP results in an increase in plasma catecholamine concentrations. Whilst this occurred in patients undergoing middle ear surgery, it was not a consistent finding in patients undergoing intracranial surgery following subarachnoid haemorrhage; however, in the latter group, preoperative control values of plasma catecholamine concentrations were five times greater than those in the group scheduled for middle ear surgery and it was suggested that the subarachnoid haemorrhage group may be secreting catecholamines at a near maximal rate and therefore not capable of increasing the extent of secretion in response to surgical stimulation (Rawlinson, Loach and Benedict, 1978).

The increase in plasma catecholamine concentrations during hypotensive surgery has been re-examined recently. In a comparative study of the use of SNP and trimetaphan for the induction of hypotension during orthopaedic surgery, it was shown that infusion of SNP at a rate of $1-9\,\mu g\,kg^{-1}\,min^{-1}$ was associated with an increase in plasma catecholamine concentrations of five to eight times control values during hypotension and surgery. In contrast, patients receiving trimetaphan exhibited a slower decrease in mean arterial pressure, but increase in plasma catecholamine concentrations occurred only after cessation of infusion of trimetaphan. Plasma renin activity and angiotensin II concentrations were greater during SNP-induced hypotension in comparison with that induced by trimetaphan (Knight et al., 1983). Zubrow and colleagues (1983) confirmed this finding in respect of SNP in unstimulated ewes. They also demonstrated a marked increase in plasma vasopressin activity occurring during induced hypotension.

The lack of change in catecholamine concentrations during trimetaphan-induced hypotension

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found by Knight and colleagues (1983) is similar to that of an earlier study from the same department, in which no changes occurred during hypotensive anaesthesia induced with pentolinium and propranolol (Knight et al., 1980).

These observations may be explained readily on pharmacological grounds. SNP is a direct-acting vasodilator producing hypotension which is accompanied by reflex sympathetic activity (mediated by baroreceptors), as witnessed by tachycardia and increases in the plasma catecholamine concentrations. In contrast, the ganglion-blocking drugs and beta-blockers inhibit efferent sympathetic activity, and consequently no increase in catecholamine concentrations occurred.

Exogenous administration of catecholamines

Infiltration of tissues with solutions containing vasoconstrictors is used commonly during nasal, oral, aural, thyroid and pelvic surgery in order to reduce bleeding and improve surgical vision. A convenient form of vasoconstrictor solution comprises premixed local analgesic and adrenaline in concentrations varying from 1:80 000 (12.5 $\mu g\,ml^{-1}$) to 1:400 000 (2.5 $\mu g\,ml^{-1}$). To date there have been few studies which have examined the changes in plasma adrenaline concentrations following the use of such solutions in order to determine if values approaching arrhythmogenic thresholds are produced. Tolas, Pflug and Halter (1982) measured plasma catecholamine concentrations following injection of adrenaline 18 μg during posterior alveolar nerve block in awake patients about to undergo dental extractions. They found that plasma adrenaline concentrations had increased from 0.54 $pmol\,ml^{-1}$ to 1.26 $pmol\,ml^{-1}$ at 3 min after injection. These adrenaline concentrations were not accompanied by any gross changes in cardiovascular variables.

In a separate study, Taylor, Achola and Smith (1984) examined anaesthetized patients in whom adrenaline 20 μg (in 2 ml of 2% lignocaine) was injected before nasal surgery. They found a significant increase in circulating plasma adrenaline concentrations of nearly 400%, which was not found when felypressin was substituted for adrenaline. The dose of adrenaline used (approximately 0.4 $\mu g\,kg^{-1}$) produced plasma concentrations 100 times lower than the arrhythmogenic threshold in the dog, which is stated to be 230 $pmol\,ml^{-1}$ (produced by a dose of 4.18 $\mu g\,kg^{-1}$) (Sumikawa, Ishizaka and Suzaki, 1983).

It should be noted that, in both these studies, the dose of adrenaline used and the volumes of solution were relatively small in comparison with those used for other procedures. In addition, absorption of adrenaline may be more rapid and complete from areas of greater vascularity such as the perineum.

Cardiac surgery

It is well known that, in the cardiac surgical patient, there are two specific occasions which represent the most extreme degree of stress, namely sternotomy and cardiopulmonary bypass (CPB). A variety of anaesthetic techniques has been used to counter this stress, varying from the conventional to the "mega-opioid". In addition, much attention has focused on the necessity to attenuate the pressor response to laryngoscopy and intubation in this category of patient.

In reviewing the effects of cardiac surgery on the sympathoadrenal response, it is convenient to distinguish the massive opioid from the conventional anaesthetic technique.

Hoar and others (1980), demonstrated an increase in plasma catecholamine concentrations in patients at the time of surgical incision. Their patients, who were receiving "conventional" anaesthesia comprising nitrous oxide and halothane in oxygen, together with low-dose opioids, demonstrated a similar response to sternotomy as that exhibited by non-cardiac patients to surgical incision. However, at the end of CPB the concentrations of both adrenaline and noradrenaline were double the post-incision values and five times the awake control values, suggesting that bypass causes a considerably greater disturbance of the sympathoadrenal system than sternotomy.

Later, the same group examined the effects of induction of anaesthesia with morphine 3 $mg\,kg^{-1}$ together with diazepam 0.3 $mg\,kg^{-1}$. They were unable to demonstrate any gross increase in plasma catecholamine concentrations occurring 5 min after surgical incision (Hoar et al., 1981). A lack of response to sternotomy was found also by Stanley and colleagues (1980) and Zurick and others (1982) utilizing fentanyl in incremental dosage to 75 $\mu g\,kg^{-1}$ and 150 $\mu g\,kg^{-1}$ respectively.

Stanley and colleagues (1980) produced sympathoadrenal stability with high-dose fentanyl anaesthesia during tracheal intubation and sternotomy. However, there was a time-related increase in plasma catecholamine concentrations during CPB. Five-fold increases (compared with awake

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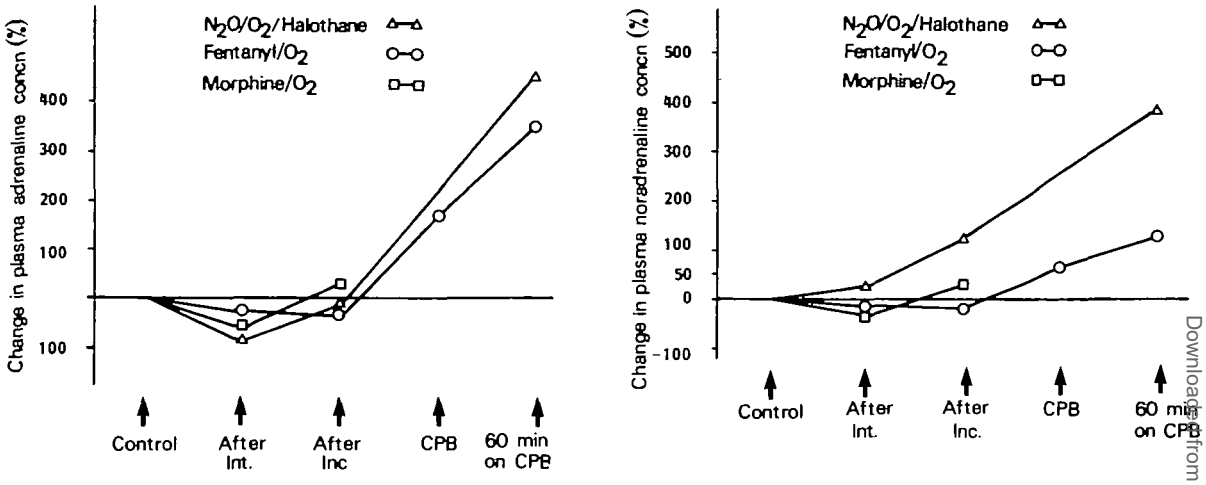

FIG. 3. Comparison of the effects of different anaesthetic techniques on plasma adrenaline (left) and plasma noradrenaline (right) changes occurring during cardiac surgery. △ from Hoar and colleagues (1980); ○ from Stanley and colleagues (1980); □ from Hoar and colleagues (1981). Left: Baseline control values 0.55, 0.26, 0.74 pmol ml^{-1}; right: Baseline control values 2.15, 1.15, 1.46 pmol ml^{-1}. After Int. = after intubation. After Inc. = after incision. CPB = Cardiopulmonary bypass.

control values) in plasma adrenaline and three-fold increases in plasma noradrenaline occurred after 60 min of CPB (fig. 3). It appears, therefore, that the sympathoadrenal response to CPB is mediated either through a different pathway from that of surgical stimulation, or that the response is of a much greater magnitude. It is interesting to note that, in an experimental rat model, Stanley and colleagues (1983) found that *analgesia* in rats is achieved by minimal occupancy of mu receptors and that *anaesthesia* is induced by 25% occupancy. Perhaps the doses of opioids used in "mega-dose" anaesthesia are still insufficient to saturate the relevant receptors and totally ablate sympathoadrenal responses to gross haemodynamic changes.

Zurick and colleagues (1982) examined a similar group of patients undergoing coronary artery bypass grafting, and failed to demonstrate any difference between fentanyl 150 $\mu g\,kg^{-1}$ and halothane–nitrous oxide–oxygen anaesthesia at induction of anaesthesia, tracheal intubation and completion of sternotomy. Their results do not accord with those described above, but it is noteworthy that very high baseline values of adrenaline were present in patients premedicated with i.m. morphine–hyoscine and transcutaneous nitroglycerin (2.8 and 0.96 pmol ml^{-1} for their respective groups) compared with a more accepted baseline of <0.55 pmol ml^{-1} (100 pg ml^{-1}) (Hoar et al., 1980) and <0.33 pmol ml^{-1} (60 pg ml^{-1}) (Stanley et al., 1980; Hicks, Mowbary and Yhap, 1981).

Spinal anaesthesia

It is known that total afferent block of nociceptive surgical stimulation attenuates or ablates the endocrine response to surgery (Weatherill and Spence, 1984). Recently, it has been shown that spinal anaesthesia also totally blocks the increase in plasma adrenaline and noradrenaline concentrations which would be observed during inhalation anaesthesia. This represents a block of afferent nociceptive neuronal traffic.

In addition it has been shown that high spinal anaesthesia (T2–6) (in comparison with low spinal anaesthesia T9–12) was accompanied by a *reduction* in both plasma noradrenaline and adrenaline concentrations to less than resting baseline values. This results from blockade of sympathetic efferent activity dependent on the dermatome level of block. Furthermore, a significant relationship was demonstrated between the reduction in arterial pressure after initiation of the block and the reduction in plasma noradrenaline concentrations. The change in adrenaline is consistent with the innervation of the adrenal gland (T6–L2) (Pflug and Halter, 1981).

Postoperative period

Early

Brown and colleagues (1982) compared plasma catecholamine concentrations in patients 15 and 30 min after arrival in the recovery room following intra-abdominal surgery. There was no difference

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between patients anaesthetized with enflurane–nitrous oxide–oxygen or low-dose fentanyl–nitrous oxide–oxygen. However, they did find that there was a continuing increase in plasma catecholamine concentrations (particularly noradrenaline) in the period immediately after operation. These findings are supported by those of Ponten and colleagues (1982), who examined beta-blocked patients undergoing elective cholecystectomy with low-dose fentanyl–nitrous oxide–oxygen anaesthesia.

These results suggest, perhaps not surprisingly, that the extent of stress, reflected in neuroendocrine activity, is enhanced on restoration of the state of consciousness. It is obvious that, in the period immediately after operation there is a large number of variables which may cause changes in the concentration of plasma catecholamines, including the extent of surgery, residual effects of anaesthesia, body temperature, extent of shivering and the degree of analgesia.

The correlation between plasma noradrenaline concentrations and mean arterial pressure noted at induction of anaesthesia and tracheal intubation is not evident in the postoperative phase. The increase in plasma noradrenaline at tracheal intubation (which may be up to 100%) is accompanied by an increase of arterial pressure of perhaps 50%. This does not occur in the postoperative period, where increases in plasma noradrenaline of 200% are common, although accompanied by normal or near normal arterial pressures.

Late

It might be expected that, in the later period after operation variations in anaesthetic technique have a diminishing influence upon changes in plasma catecholamine concentrations and that other factors become more significant, for example the extent of surgery, the amount of pain and the amount or type of analgesic administered to the patient.

It is known that plasma catecholamine concentrations are increased during the late period after operation (> 24 h). Fell, Chmielewski and Smith (1982) demonstrated that plasma noradrenaline concentrations were 2.4 times control value in patients 24 h after hysterectomy and 1.8 times control in patients after cholecystectomy. Both plasma adrenaline and noradrenaline were decreasing at the end of the assessment period (48 h). The values reported in this study are similar to those of Halter, Pflug and Porte (1977), who examined patients in the early period after operation.

Fell, Chmielewski and Smith (1982) were unable to demonstrate any correlation between linear analogue pain scores and plasma catecholamine concentrations. In view of the multiplicity of factors which can alter the perception of pain and the level of sympathoadrenal activity, this is perhaps not a surprising finding.

Critical care areas

Russell, Frewin and Jonsson (1983) examined catecholamine concentrations in a group of patients in an Intensive Therapy Unit. They demonstrated a loss across the lungs of 16–49% in dopamine, adrenaline and noradrenaline concentrations in patients receiving therapeutic administration of dopamine. This loss was found also in patients who were not receiving inotropic support of the circulation.

A recent review has suggested that changes in pulmonary endothelium may be detected by alteration in the rate of catabolism of vasoactive amines including noradrenaline and serotonin. "On the basis of these observations, 5-HT and noradrenaline appear to provide sensitive metabolic indices of injury to the pulmonary endothelium. The pulmonary endothelial cell is now known to be the primary site of damage in a number of disease states and injuries of the lung including oxygen toxicity, radiation pneumonitis and adult respiratory distress syndrome" (Block and Stalcup, 1982).

It has been shown recently that, during chest physiotherapy applied to critically ill patients in the ICU, there is an abrupt increase in plasma catecholmine concentrations of a large order of magnitude (Taylor and authors' unpublished observations).

Catecholamines and endorphins

It is well known that high doses of opioids may suppress the neuroendocrine responses to laryngoscopy and, to an extent, surgery. Naloxone antagonizes this suppression in the dog model, producing an increase in plasma catecholamine concentrations (Montastruc, Montastruc and Morales-Olivas, 1981; Taborsky, Halter and Porte, 1982; Flacke et al., 1983).

From a simplistic conceptual viewpoint, the exogenous opioids may be regarded as agonists of the endogenous opioids—especially beta-endorphin. However, van Loon, Appel and Ho (1981) demonstrated in a rat model that injection of beta-endorphin into cerebrospinal fluid leads to an in-

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crease in plasma catecholamine concentrations and that this was suppressed by prior or subsequent administration of naloxone.

More recent concepts regard the exogenous opioids as agonist/antagonists of beta-endorphins in their action. Thus, naloxone may possess dual actions and either increase or decrease the "tone" of the sympathoadrenal system, depending upon the nature of the substance occupying the opioid receptors responsible for modifying neuroendocrine activity.

If exogenous opioids can reduce sympathoadrenal "tone" this may explain the beneficial effects of morphine/diamorphine in patients who have recently undergone myocardial infarction—a reduction in apprehension and improvement in cardiovascular state without necessarily a primary analgesic action.

CONCLUSION

There is considerable current interest in the effects of anaesthesia and surgery on the stress response to anaesthesia and surgery although the value of complete suppression of these responses is as yet unknown. The stress response embraces hypophyseal, adrenocortical and metabolic changes in addition to sympathoadrenal activity.

Measurement of plasma concentrations of catecholamines may be used as an adjunct to haemodynamic measurement as an index of the level of sympathoadrenal activity. However, considerable caution is necessary in the interpretation of such data since only a very small proportion of transmitter released at sympathetic nerve terminals is released into the circulation and the biological half-life of the catecholamine is less than a few minutes. In addition, as emphasized by Bravo and Tarazi in a recent editorial, "the usefulness of (plasma catecholamine) data varies in direct proportion to the care with which they have been obtained and to the precise use to which they are put."

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