STUDIES OF ANAESTHESIA IN RELATION TO HYPERTENSION

VII: Adrenergic Responses to Laryngoscopy

J. M. LOW, J. T. HARVEY, C. PRYS-ROBERTS AND J. DAGNINO

Reflex cardiovascular effects of laryngoscopy and tracheal intubation in anaesthetized patients have been described previously and include a pressor response, and tachycardia despite the increase in systemic arterial pressure (King et al., 1951). Increased cervical sympathetic activity in the anaesthetized cat following mechanical stimulation of the nasopharynx and epipharyngeal region was recorded by Tomori and Widdicombe (1969); hypertension and tachycardia are common responses in normotensive patients (Dingle, 1966; Forbes and Dally, 1970; Prys-Roberts et al., 1971; Takki et al., 1972; Fox et al., 1977; Lehtinen, Hororka and Widholm, 1984). Although the direct recording of sympathetic nervous activity is difficult in man, measurements of the plasma concentrations of catecholamines have consistently demonstrated increases in noradrenaline following laryngoscopy (Russell et al., 1981; Derbyshire et al., 1983; Marty, Couture and De Champlain, 1983; Cummings et al., 1984) and so confirmed sympathetic mediation in this response. Complications of the pressor response following laryngoscopy include myocardial ischaemia (Prys-Roberts et al., 1971; Roy, Edelist and Gilbert, 1979), cardiac failure and intracranial haemorrhage (Fox et al., 1977), and increases in intracranial pressure (Burney and Winn, 1975). These complications are serious enough in normotensive patients, but

an exaggerated response to laryngoscopy has been reported in hypertensive patients (Prys-Roberts et al., 1971) and, in particular, surgical patients with ischaemic heart disease or hypertension, or both, have been shown to carry an increased risk of perioperative complications (Goldman and Caldera, 1979). Previous interpretation of the mechanism of this exaggerated response has concentrated on an altered geometry of the arterial wall (Folkow, 1971). However, there is evidence of increased sympathetic activity in a proportion of patients with essential hypertension (De Quattro and Chan, 1972; Philipp, Distler and Cordes, 1978) and this is consistent with the observations
that the tachycardia and pressor response may be partially obtunded by the use of beta-adrenergic antagonists. The present study was planned to assess the possible role of the sympathetic nervous system in the exaggerated cardiovascular response of hypertensive patients to sympathetic stimulation.

**PATIENTS AND METHODS**

Twenty-six patients undergoing elective vascular surgery were studied; clinical details are presented in Table I. Ten patients were hypertensive (pre-treatment diastolic arterial pressure > 110 mm Hg) and were receiving therapy in the form of a beta-adrenoceptor antagonist alone, or in addition to a diuretic. Informed consent was obtained for the blood sampling which was required for the assays of catecholamine concentrations. Before the induction of anaesthesia, monitoring equipment—as described below—was connected to the patient, who was then allowed to rest on a comfortable bed, while blood was sampled and cardiovascular recordings obtained.

**Monitoring**

The electrocardiograph was recorded from bipolar leads in the CM5 configuration and displayed on an HP 78304A monitoring system. Continuous recordings of arterial pressure were obtained via an 18-gauge Teflon cannula (Abbo-cath) inserted under local anaesthesia to a brachial artery. A Gould–Statham P231D transducer was used and the arterial pressure displayed on the HP monitor. Under local anaesthesia, a central venous cannula (Drum cartridge, Abbott Laboratories) was inserted to an antecubital vein on the contralateral arm and the position of its tip verified by the venous pressure waveform. A 14-gauge cannula was inserted to an antecubital vein on the contralateral arm and the position of its tip verified by the venous pressure waveform. A 14-gauge cannula was inserted to a peripheral vein for the administration of i.v. fluids. The patient was allowed to rest comfortably for about 30 min after these procedures had been undertaken. During this resting stage, blood samples were drawn to assess catecholamine concentrations before anaesthesia. Anaesthesia was induced by an i.v. injection of thiopentone 3–4 mg kg⁻¹ and the spontaneous ventilation of 0.5% halothane in 67% nitrous oxide and oxygen. After 5 min of stable light anaesthesia, suxamethonium 1.0–1.5 mg kg⁻¹ was given to allow laryngoscopy. Manual ventilation using a coaxial Mapleson D system was undertaken until spontaneous ventilation returned. End-tidal carbon dioxide concentration was maintained at 5%.

**Sampling for measurements of catecholamine concentrations**

The plasma samples were timed to allow detection of peak concentrations following laryngoscopy. Thus, central venous blood was drawn at the following times: Baseline = patient awake but resting; anaesthesia = following induction but before suxamethonium; L = at laryngoscopy; L + 1 to L + 20 = at 1, 2, 5, 10, 15 and 20 min following laryngoscopy.

**Catecholamine assays**

Ten millilitre of blood was drawn from the central venous catheter and collected into previously chilled lithium heparin tubes (Seward, U.K. Ltd, No. 1502 LH/10). The blood samples were stored on ice and centrifuged within 30 min of collection at 4°C. The plasma was divided into two aliquots for assay in duplicate. Noradrenaline and adrenaline concentrations were determined by high pressure liquid chromatography with electrochemical detection by a method modified from Causon, Carruthers and Rodnight (1981). The lower limit of detection was noradrenaline 21 pg ml⁻¹ (124 fmol ml⁻¹) and adrenaline 41.6 pg ml⁻¹ (227 fmol ml⁻¹) (at a signal:noise ratio of 5:1) and we have established that detection is linear to 10 ng on column. Coefficients of variation of our method are 7.6% and 6.5% for noradrenaline and adrenaline, respectively, at 200 pg ml⁻¹ (1.2 nmol litre⁻¹). Because of skewed distributions the data were log-transformed in order to allow valid t testing.

**RESULTS**

The two groups of patients were similar with respect to weight and age (Table I). Following the induction of anaesthesia, mean values of systolic and diastolic pressure in both groups decreased (from 156/74 to 120/61 mm Hg in the normotensive patients; 179/83 to 135/66 mm Hg in hypertensive patients). The decrease in systolic pressure was of a proportion in normotensive patients (23.3%) similar to that observed in hypertensive patients (24.7%), as was the reduction in diastolic pressures (16.5% in normotensive and 19.9% in hypertensive individuals). Following laryngoscopy there was an increase in systolic pressure in both normotensive
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Table I. Clinical details of normotensive and hypertensive groups (mean values ± SEM)

<table>
<thead>
<tr>
<th></th>
<th>Normotensive (n = 16)</th>
<th>Hypertensive (n = 10)</th>
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<tbody>
<tr>
<td>Weight (kg)</td>
<td>69.1 ± 2.1</td>
<td>70.7 ± 3.5</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>62.7 ± 3.3</td>
<td>61.2 ± 3.4</td>
</tr>
<tr>
<td>Systolic art. pressure</td>
<td>148.0 ± 5.8</td>
<td>176.0 ± 7.2</td>
</tr>
<tr>
<td>before op. (mm Hg)</td>
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</tr>
<tr>
<td>Diastolic art. pressure</td>
<td>82.2 ± 2.0</td>
<td>102.0 ± 3.9</td>
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<tr>
<td>before op. (mm Hg)</td>
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(14.7%) and hypertensive patients (11.9%). The diastolic pressures were also higher following laryngoscopy (77.2 and 77.1 mm Hg, respectively). The maximum pressures were recorded 1 min following laryngoscopy, and had returned to their control values between 5 and 10 min after laryngoscopy (fig. 1).

Plasma catecholamine concentrations

In both groups of patients, the decrease in plasma noradrenaline concentration following the induction of anaesthesia (table II, fig. 2), was of similar magnitude (44.6% and 48.3% in normotensive and hypertensive groups, respectively).

Mean plasma concentrations of noradrenaline during anaesthesia before laryngoscopy were similar (1.79 and 1.98 nmol litre⁻¹). Decreases in plasma adrenaline concentrations were also observed following the induction of anaesthesia (29.3% and 27.5%, respectively) for normotensive and hypertensive patients (table III, fig. 3).

Laryngoscopy was associated with a moderate increase (59.2%) in noradrenaline concentration in normotensive patients. In contrast, however, there was an almost three-fold increase in plasma noradrenaline concentration in the hypertensive group, reaching a peak 2 min following laryngoscopy. In both groups, the plasma noradrenaline concentration returned to baseline within 10 min following laryngoscopy.

There was no significant change in plasma adrenaline concentration in normotensive patients. In the hypertensive group, however, plasma adrenaline concentration had increased significantly 1 min following laryngoscopy.

DISCUSSION

Although many studies have attempted to demonstrate the role of the catecholamines in the pathogenesis of essential hypertension, only a
TABLE II. Mean concentrations (nmol litre$^{-1}$) and 95% range of plasma noradrenaline in beta-blocked normotensive patients (β-blocked), normotensive and hypertensive patients following induction of anaesthesia and tracheal intubation. Significant differences: † P < 0.01 between groups; * P < 0.05 within the group; ** P < 0.01 within the group.

<table>
<thead>
<tr>
<th></th>
<th>β-Blocked</th>
<th>Normotensive</th>
<th>Hypertensive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean 95% Range</td>
<td>Mean 95% Range</td>
<td>Mean 95% Range</td>
</tr>
<tr>
<td>Control</td>
<td>1.6 1.3-2.0</td>
<td>3.4 0.7-15.9</td>
<td>3.8 1.0-14.3</td>
</tr>
<tr>
<td>Anaesthesia</td>
<td>1.0** 0.8-1.1</td>
<td>1.9** 0.5-6.6</td>
<td>2.0** 0.6-6.1</td>
</tr>
<tr>
<td>Laryngoscopy</td>
<td>1.7 1.3-2.2</td>
<td>2.2 0.6-8.2</td>
<td>†4.9* 0.7-30.5</td>
</tr>
<tr>
<td>L+1</td>
<td>2.2 0.6-3.8</td>
<td>2.2 0.4-11.1</td>
<td>†5.4** 0.8-35.5</td>
</tr>
<tr>
<td>L+2</td>
<td>3.4* 1.1-5.0</td>
<td>2.5 0.4-14.9</td>
<td>†5.5** 2.1-14.4</td>
</tr>
<tr>
<td>L+5</td>
<td>4.2** 4.0-4.4</td>
<td>2.9** 0.7-13.1</td>
<td>3.7 1.0-14.1</td>
</tr>
<tr>
<td>L+10</td>
<td>2.5* 1.1-3.8</td>
<td>2.5 0.5-11.8</td>
<td>2.8 1.1-7.5</td>
</tr>
<tr>
<td>L+15</td>
<td>1.9 1.2-2.6</td>
<td>2.1 0.8-6.0</td>
<td>2.4 0.8-6.8</td>
</tr>
<tr>
<td>L+20</td>
<td>0.9 0.6-1.1</td>
<td>1.9 0.5-6.5</td>
<td>2.2 1.1-4.4</td>
</tr>
</tbody>
</table>

Fig. 2. Changes in mean plasma noradrenaline concentrations in normotensive (●—●) and hypertensive (○—○) patients following induction of anaesthesia and tracheal intubation. *Significant difference (P < 0.01) between groups.

A subgroup of hypertensive patients seem to show a consistent increase in plasma noradrenaline concentration (De Quattro and Chan, 1972; Goldstein, 1981). Other attempts at recording responses to a variety of stress tests have also failed to demonstrate differences between hypertensive and normal patients. In one study (Eliasson, Hjemdahl and Kahan, 1983), a two-fold increase in plasma noradrenaline concentration was demonstrated following both orthostatic testing and the cold pressor test, but no differences were observed between normal and hypertensive patients. Further, although there were significant circulatory changes following Stroop's colour-word conflict test (a quantifiable form of mental stress), little difference could be found between normotensive and hypertensive patients. In contrast, we have been able to demonstrate an exaggerated sympathoneuronal response in our hypertensive group to the stimulus of laryngoscopy.
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**Table III.** Mean concentrations (nmol litre\(^{-1}\)) and 95% range of plasma adrenaline concentration in normotensive and hypertensive patients following induction of anaesthesia and tracheal intubation. Significant differences: †P < 0.05 between groups; *P < 0.05 within the group.

<table>
<thead>
<tr>
<th>Time following laryngoscopy (min)</th>
<th>Normotensive</th>
<th>Hypertensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>1.3</td>
<td>1.9</td>
</tr>
<tr>
<td>Anaesthesia</td>
<td>0.9*</td>
<td>1.3</td>
</tr>
<tr>
<td>Laryngoscopy</td>
<td>1.1</td>
<td>1.7</td>
</tr>
<tr>
<td>L + 1</td>
<td>1.0</td>
<td>†2.8</td>
</tr>
<tr>
<td>L + 2</td>
<td>1.1</td>
<td>2.2</td>
</tr>
<tr>
<td>L + 5</td>
<td>1.2</td>
<td>2.1</td>
</tr>
<tr>
<td>L + 10</td>
<td>1.1</td>
<td>1.4</td>
</tr>
<tr>
<td>L + 15</td>
<td>0.7</td>
<td>1.3</td>
</tr>
<tr>
<td>L + 20</td>
<td>0.9</td>
<td>2.0</td>
</tr>
</tbody>
</table>

**Fig. 3.** Changes in mean plasma adrenaline concentrations in normotensive (●—●) and hypertensive (○—○) patients following induction of anaesthesia and tracheal intubation. *Significant difference (P < 0.05) between groups.

We noted a significant decrease in both adrenaline and noradrenaline concentrations following the induction of anaesthesia, consistent with previous observations in normotensive patients (Russell et al., 1981; Derbyshire et al., 1983; Marty, Couture and De Champlain, 1983). Although our measurements of plasma noradrenaline concentration at the awake stage were higher than those reported by Derbyshire and colleagues (1983), following induction of anaesthesia noradrenaline concentrations were similar to theirs. The differences in pre-induction catecholamine concentrations may be explained by the fact that our patients were given no premedication, although the group of treated hypertensives received their normal anti-hypertensive treatment on the morning of surgery.

Laryngoscopy is a consistent noxious stimulus which provokes a sympathoadrenal response (Corbett, Kerr and Prys-Roberts, 1969; Tomori...
and Widdicombe, 1969; Prys-Roberts et al., 1971). It is thus a convenient method of studying the dynamic response of normal and hypertensive patients to a controlled noxious stimulus.

Our main finding was a considerable increase in plasma noradrenaline concentration following laryngoscopy and intubation of the trachea in the hypertensive group of patients. Other studies (Russell et al., 1981; Derbyshire et al., 1983; Marty, Couture and De Champlain, 1983) have shown a moderate increase in noradrenaline concentration associated with laryngoscopy. However, we recorded an exaggerated increase in noradrenaline concentration, and a moderate increase in adrenaline concentration, following laryngoscopy in hypertensive patients. The peak effect was reached at a slightly later sampling time in the normotensive group (L + 5) in contrast to the hypertensive group (L + 2). The peak concentrations detected were about three- or four-fold greater than random samples taken from a group of hypertensive patients (De Quattro and Chan, 1972). Patients who have recently suffered the pain and haemodynamic consequences of myocardial infarction exhibit noradrenaline concentrations of 5.2 ± 0.7 nmol litre⁻¹ (Videbaek, Christensen and Sterndorff, 1972). Much higher concentrations (130 nmol litre⁻¹) have been detected in patients undergoing surgery for phaeochromocytoma (Vater, Achola and Smith, 1983).

By a suitably rapid sequence of blood sampling, we have been able to demonstrate a functional difference of a transient nature in the sympathetic nervous responses of normotensive and hypertensive patients. In view of the rapid time course of secretion and clearance of noradrenaline, and the labile nature of arterial pressure, it is hardly surprising that single, isolated samples have not been able to demonstrate a positive role of noradrenaline in the pathogenesis of hypertension (Philipp, Distler and Cordes, 1978).

We have also demonstrated the very short half-life of catecholamines in vivo in the present study, and in another study in plasma adrenaline kinetics following infiltration (Low et al., 1984). These are in agreement with other studies (Taggart, Carruthers and Sommerville, 1972) in drivers before and after a motor racing meeting. Further, measurements of peripheral vein free noradrenaline and adrenaline following cold immersion, isometric and dynamic (100-W) exercise, also showed a rapid clearance of noradrenaline (Joyce et al., 1982). This rapid secretion and uptake has important implications for the method of blood sampling. Unless rapid consecutive samples are drawn, it is quite possible to miss the peak concentrations and, thus, fail to detect any increase in plasma catecholamine concentration. Although there were considerable changes in circulatory variables within minutes of stressful mental activity, the samples for plasma catecholamines were not drawn until 10 and 20 min later (Eliasson, Hjemdahl and Kahan, 1983) by which time, as we have shown, any transient sympathetic overactivity would have subsided.

As treatment with oxprenolol reduces the clearance of noradrenaline from plasma (Esler, 1982), one explanation of the generally higher concentrations of noradrenaline in the hypertensive group, is the fact that patients in this group had been treated with beta-adrenoceptor antagonists. However, with this hypothesis in mind, we compared data from normotensive patients who were treated with beta-adrenoceptor antagonists for ischaemic heart disease and were unable to demonstrate any significant difference between the noradrenaline concentrations of the groups with and without treatment by beta-adrenoceptor antagonists (table II). Our data, therefore, provide evidence for a transient sympathetic dysfunction in hypertensive patients which is not altered by treatment with beta-adrenoceptor antagonists. Our results do not exclude the possibility of a difference in vascular responsiveness to circulating catecholamines (Folkow, 1971), or alpha-adrenoceptor hyperresponsiveness (Hamilton and Reid, 1983). Indeed, our data are consistent with the hypothesis proposed by Folkow (1971) that persistent increases in sympathetic activity result in adaptive changes in the vasculature resulting in increases in peripheral vascular resistance and an alteration in the pressor response to constrictor stimuli. Thus we have provided further justification for the attenuation of an exaggerated cardiovascular response in hypertensive patients, by prior treatment with beta-adrenoceptor antagonists (Prys-Roberts et al., 1973; Fischler et al., 1985). Alternative approaches have been suggested which include deepening anaesthesia and the use of topical lignocaine (King et al., 1951; Lehtinen, Hororka and Widholm, 1984), infusions of sodium nitroprusside or phenolamine (Stoelting, 1979), and the use of fentanyl (5 µg kg⁻¹) on induction (Dahlgren and Messeter, 1981; Kauto, 1982).
ACKNOWLEDGEMENTS

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