THE ADRENERGIC RESPONSE TO SURGERY INVOLVING CARDIOPULMONARY BYPASS, AS MEASURED BY PLASMA AND URINARY CATECHOLAMINE CONCENTRATIONS


SUMMARY
Plasma and urinary catecholamine concentrations have been measured in 13 patients undergoing cardiac surgery involving cardiopulmonary bypass. The large and progressive increase in plasma catecholamines during bypass reported in previous studies has not been confirmed, and this may be a result of improvements in surgical, anaesthetic and perfusion techniques. The interpretation of urinary findings was complicated by the finding of a positive correlation between catecholamine excretion and urine flow-rate. The findings suggest the need to modify current concepts of the adrenergic response to cardiac surgery and bypass, and question the validity of measuring the urinary catecholamine concentration as an index of stress in these circumstances.

It is generally believed that catecholamine secretion is increased during cardiopulmonary bypass (Blackburn et al., 1954; Clement, 1971), and that a progressive increase in catecholamine secretion during bypass may produce an irreversible shock-like state and the low cardiac output syndrome seen occasionally after bypass (Lillehei et al., 1964). Factors contributing to this spiral of increasing peripheral vasoconstriction and decreased tissue perfusion, leading to tissue hypoxia, acidosis and further release of catecholamines, have been variously postulated as (a) relative inefficiency of tissue perfusion during bypass (Mueller et al., 1970; Gilston, 1971), (b) the effects of acute haemodilution in causing lightening of the plane of anaesthesia (Blackburn et al., 1954; Long et al., 1966), (c) the change from pulsatile to continuous blood flow during bypass (Blackburn et al., 1954), and (d) the stress of surgical trauma (Lillehei et al., 1964; Howat, 1971).

Studies of the adrenergic response to surgery by measurement of circulating catecholamines have been few (Hammond, Aranow and Moore, 1956; Nikki et al., 1972; Kehlet et al., 1974) and have shown no overall increase in the catecholamine concentration during the operation. Replogle and colleagues (1962), however, describe a significant, progressive increase in plasma catecholamine concentration in patients undergoing cardiopulmonary bypass. In the light of continuing improvement in methods of plasma catecholamine assay, together with changes in surgical, anaesthetic and perfusion techniques, a reappraisal of the adrenergic response to cardiac surgery and bypass was undertaken.

PATIENTS AND METHODS
During a 4-week period, 13 patients (mean age 50 yr; range 11–68 yr) undergoing cardiac surgery involving cardiopulmonary bypass were studied. Apart from the insertion of arterial and central venous cannulae before the induction of anaesthesia, no attempt was made to alter or influence the surgical or anaesthetic procedures for the purpose of the study. Details of the patients are shown in table I. The patients were premedicated, 60–90 min before induction of anaesthesia, with either papaveretum or pethidine, combined with either hyoscine or promethazine, given i.m. All patients except one (case 3) were judged to be satisfactorily premedicated on arrival at the theatre. After pre-oxygenation, anaesthesia was induced with thiopentone 2.5% solution (dose range 50–125 mg i.v.) and maintained with 66% nitrous oxide in oxygen, supplemented with i.v. phenoperidine or fentanyl, or by the addition of halothane ≤ 0.5% to the inspired gas. Neuromuscular block was achieved with either pancuronium or tubocurarine and intermittent positive pressure ventilation.
TABLE I. **Details of the 13 patients studied**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Wt. (kg)</th>
<th>Operation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>34</td>
<td>70</td>
<td>Mitral valve replacement</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>51</td>
<td>68</td>
<td>Mitral valve replacement</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>50</td>
<td>85</td>
<td>Vein graft to coronary artery*</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>58</td>
<td>52.5</td>
<td>Aortic valve replacement</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>11</td>
<td>31.5</td>
<td>Aortic valvotony</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>50</td>
<td>52.4</td>
<td>Mitral valve replacement</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>53</td>
<td>70</td>
<td>Aortic valve replacement†</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>50</td>
<td>58</td>
<td>Mitral and aortic valve replacement</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>64</td>
<td>52.5</td>
<td>Mitral valve replacement</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>60</td>
<td>56</td>
<td>Mitral valve replacement</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>68</td>
<td>55</td>
<td>Left ventricular aneurysm repair†</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>50</td>
<td>50</td>
<td>Mitral valve replacement</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>48</td>
<td>75</td>
<td>Aortic valve replacement</td>
</tr>
</tbody>
</table>

* Clinical premedication inadequate; † Negro, HbF 30%; ‡ L.V.F. before operation, patient died.

ventilation was given using the Cape Waine anaesthetic ventilator. The respiratory rate and tidal volume were determined by the anaesthetist.

Cardiopulmonary bypass and extracorporeal circulation, in all the cases studied, employed the apparatus in standard use in the hospital at the time: the Bentley Temptrol Adult type Q100 bubble oxygenator with the Sarn modular type de Bakey roller pump. The circuit was primed with 1.5 litre of Hartmann’s solution (Compound sodium lactate solution) to which 0.25 litre mannitol 20% solution was added. Extracorporeal circulation during bypass was maintained at a (minimum) flow of 2.2 litre min⁻¹ m⁻² body surface area, subject to the anaesthetist’s assessment of the efficiency of perfusion, based on the monitoring of peripheral arterial “perfusion pressure”, the clinical observation of capillary perfusion, and repeated assessment of the acid–base state. Urinary output was measured at hourly intervals during the operation; and adequate gas exchange during bypass was confirmed by frequent blood-gas analysis.

Samples of arterial and venous blood for the purposes of this study were taken at the following times during the procedure:

(1) Before the induction of anaesthesia.
(2) After induction.
(3) Before the surgical incision.
(4) After exposure of the heart.
(5) Immediately before bypass.
(6–12) Every 30 min on bypass.

(13) Immediately after bypass.
(14) At the end of the operation.

The arterial samples were withdrawn from the peripheral arterial cannula or from the reservoir chamber of the oxygenator during bypass; venous samples were taken from the central venous line. Exact synchronization of sampling was not possible, but arterial and venous samples were taken within 1 min of each other.

In 12 of the 13 patients, the i.v. infusion of synthetic catecholamines was considered necessary at some point during the operation in order to stimulate, reinforce or maintain satisfactory cardiac performance. When this occurred the time, duration and nature of the infusion were noted. It was not possible to record the total quantities of catecholamines infused, as the rate of infusion and the strength of the catecholamine solution were changed frequently as a result of the clinical appraisal of the patient.

The catecholamine concentrations were measured by the method of Wood and Mainwaring-Burton (1975), in which total catecholamines and noradrenaline are estimated, adrenaline being deduced by difference. Cross-reaction of adrenaline in the noradrenaline assay is less than 2%, and the sensitivity on the recorder trace lies between 2 and 3 cm ng⁻¹ for both assays. In view of the findings of Carruthers and colleagues (1970), that an anti-oxidant was necessary to prevent decomposition of catecholamines in the specimen, blood was taken into a lithium-heparin tube containing sodium dithionite 5 mg as anti-oxidant, spun immediately and the plasma removed into a syringe. The plasma volume was recorded and the plasma was squirted into a plain glass tube containing 6 M perchloric acid (0.2 ml/ml plasma), shaken, centrifuged, and the supernatant separated into a capped plastic tube and stored on dry ice (−76 °C) until assayed. Samples were analysed within 8 h of collection in all cases.

Hourly urine collections were made, the total volume noted, and an aliquot was acidified for estimation of catecholamines (Wood and Mainwaring-Burton, 1975) and HMMA and metanephrines (Varley, 1967).

**RESULTS**

Twelve of the 13 patients survived operation and cardiopulmonary bypass: one patient (case 11) died following excision of a large left ventricular aneurysm, there being no recordable cardiac output despite a technically successful repair.
TABLE II. Mean noradrenaline concentrations (with 66% confidence limits) during period of study, for patients not receiving catecholamine infusions. Confidence limits have been given only when the number of patients in a particular period was 10 or more.

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Arterial</th>
<th>Venous</th>
<th></th>
<th></th>
<th></th>
<th>On bypass (min)</th>
<th>Off bypass</th>
<th>End of operation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before induction</td>
<td>After induction</td>
<td>Incision</td>
<td>After thoracotomy</td>
<td>Before bypass</td>
<td>30</td>
<td>60</td>
<td>90</td>
</tr>
<tr>
<td>Arterial</td>
<td>0.46 (0.21–1.02)</td>
<td>0.40 (0.15–1.08)</td>
<td>0.28 (0.15–1.03)</td>
<td>0.32 (0.12–0.84)</td>
<td>0.27 (0.10–0.84)</td>
<td>0.78 (0.33–1.79)</td>
<td>0.63 (0.24–1.69)</td>
<td>0.67 (0.26–1.69)</td>
</tr>
<tr>
<td>Venous</td>
<td>0.42 (0.21–0.83)</td>
<td>0.36 (0.14–0.73)</td>
<td>0.24 (0.12–0.61)</td>
<td>0.51 (0.24–1.10)</td>
<td>0.49 (0.20–1.21)</td>
<td>0.70 (0.17–2.78)</td>
<td>0.61 (0.23–1.63)</td>
<td>0.56 (0.20–1.63)</td>
</tr>
</tbody>
</table>

TABLE III. Mean adrenaline concentrations (with 66% confidence limits) during period of study, for patients not receiving catecholamine infusions. The use of confidence limits is as in table II.

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Arterial</th>
<th>Venous</th>
<th></th>
<th></th>
<th></th>
<th>On bypass (min)</th>
<th>Off bypass</th>
<th>End of operation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before induction</td>
<td>After induction</td>
<td>Incision</td>
<td>After thoracotomy</td>
<td>Before bypass</td>
<td>30</td>
<td>60</td>
<td>90</td>
</tr>
<tr>
<td>Arterial</td>
<td>0.39 (0.16–0.97)</td>
<td>0.47 (0.14–1.51)</td>
<td>0.42 (0.23–0.93)</td>
<td>0.61 (0.20–1.35)</td>
<td>0.53 (0.28–1.00)</td>
<td>0.57 (0.28–1.16)</td>
<td>0.65 (0.31–1.40)</td>
<td>0.94 (0.46–1.90)</td>
</tr>
<tr>
<td>Venous</td>
<td>0.26 (0.08–0.85)</td>
<td>0.26 (0.26–1.13)</td>
<td>0.33 (0.21–0.97)</td>
<td>0.45 (0.21–0.97)</td>
<td>0.29 (0.09–0.94)</td>
<td>0.37 (0.15–0.87)</td>
<td>0.46 (0.12–1.73)</td>
<td>0.23 (0.07–0.61)</td>
</tr>
</tbody>
</table>
The mean times elapsing between the taking of blood samples for catecholamine assay were as follows:

Post-induction–pre-incision (2–3): 34 min (range 20–60 min).
Exposure of heart–pre-bypass (4–5): 25 min (range 5–50 min).

The mean duration of cardiopulmonary bypass was 105 min (range 45–225 min) and the average interval between the end of bypass and the end of the operation was 100 min (range 70–165 min).

Twelve of the patients received infusions of exogenous catecholamines to reinforce cardiac function after the surgical repair. One (case 4) received adrenaline alone; four (cases 1, 5, 9 and 13) received isoprenaline alone; and the remainder (cases 2, 3, 6, 8, 10, 11 and 12) received both adrenaline and isoprenaline infusions (in case 11, noradrenaline infusion was used also). In the method of assay which was used, isoprenaline is detected as "adrenaline".

As the rate, concentration and even the type of infusion were subject to alteration by the anaesthetist, it was impossible to assess the relative contribution of exogenous catecholamines accurately. Therefore, for the purposes of this study, the results of catecholamine assays during periods when patients were receiving an infusion of synthetic catecholamines have been excluded from the calculations.

The results of the plasma noradrenaline and adrenaline analyses are shown in tables II and III respectively and measurement of total catecholamines are shown in figure 1. The individual operation patterns of the patients, with hourly intervals superimposed, are shown in figure 2.

**ANALYSIS OF RESULTS**

Catecholamine concentrations have been found to be distributed in a log-normal fashion, and log-trans-
ADRENERGIC RESPONSE TO CARDIOPULMONARY BYPASS

• Surgery without bypass or synthetic catecholamines
• On bypass
• On bypass + synthetic catecholamines i.v.
• On synthetic catecholamines i.v. post-bypass

Fig. 2. The individual operation patterns of the 13 patients, with hourly intervals superimposed.

formations have therefore been performed before applying paired t tests to the results.

(a) Arterio-venous differences
When all samples from periods 1–7 were considered together, a significantly higher adrenaline concentration was found in arterial blood (P<0.005) but no such difference was seen in the noradrenaline or total catecholamine concentrations.

(b) Sequential changes
(i) Comparison with pre-anaesthetic values. When compared with the concentrations before induction (sample 1), the concentrations of both total catecholamines and adrenaline showed no statistically significant changes at any sample point up to 60 min on bypass (sample 7), after which too few patients remained on bypass without catecholamine infusions to permit a valid comparison. However, noradrenaline concentrations showed significant changes; a decrease between samples 1 and 3 (P<0.025) and increases between samples 1 and 4 in venous blood, and between samples 1 and 6 in arterial blood.

(ii) Comparison of consecutive samples. The induction of anaesthesia produced no significant change in catecholamine concentrations as evidenced by comparison of samples 1 and 2.

The period of preparation for operation between samples 2 and 3 was accompanied by a significant decrease in venous total catecholamine and noradrenaline concentrations (P<0.05); whereas the surgical manoeuvres of thoracotomy and exposure of the heart, performed between samples 3 and 4, were associated with a significant increase (P<0.005) in these measurements. No significant changes were shown by comparing samples 4 and 5, which covered the period of preparation of the heart for bypass.

Twelve patients were not receiving catecholamine infusions after 30 min on bypass (sample 6); and in comparison with pre-bypass (sample 5) concentrations, small but significant increases in total catecholamine concentrations (P<0.025 in arterial and venous blood) and in noradrenaline (P<0.025 in arterial blood) were observed. However, in the 10 patients who did not receive catecholamine infusion after 60 min of bypass (sample 7), there was no significant change in any catecholamine concentration when compared with the preceding values in sample 6.

(iii) Comparison with pre-bypass samples. The comparison between samples 5 and 6 has been considered already; if the concentrations after 60 min of bypass (sample 7) were compared with pre-bypass concentrations, significant increases in the concentrations of total catecholamines (P<0.0025 arterial, P<0.025 venous) and of noradrenaline (P<0.05 arterial) were found. Adrenaline concentrations were found also to be significantly increased (P<0.025 arterial and venous) at this point. The number of patients on bypass at 90 min and 120 min without exogenous catecholamine support was too small to permit statistical analysis, but it was apparent from the results that their catecholamine concentrations remained within the range observed previously. Similarly, the concentrations of the two patients weaned from cardiopulmonary bypass without the help of infused catecholamines did not show marked deviation from the previous values.

(c) Case reports
(i) Case 7. A 53-year-old Negro male, weighing 70 kg and with 30% haemoglobin F, underwent aortic valve replacement. His condition during the course of his operation was such that infused
catecholamines were unnecessary. The noradrenaline concentrations remained below the mean, showed very little change as a result of thoracotomy or bypass, and reached their highest values in the post-bypass phase. The adrenaline concentrations, which were near to the mean for the series throughout the operation, showed a moderate increase in response to thoracotomy and to bypass and again reached their highest concentration in the post-bypass phase. Figure 3, trace B, shows this patient's catecholamine concentrations, while trace A, for comparison, shows the concentrations in another patient (case 12) who was on bypass for a similar period of time, and who received a catecholamine infusion.

(ii) Case 11. A 68-year-old male, weighing 68 kg, was in left ventricular failure on arrival at the operating theatre for repair of a large left ventricular aneurysm; his pre-induction catecholamine concentrations, however, were within the normal range. During the pre-bypass phase of the operation a progressive increase in the noradrenaline concentration occurred, which was further exaggerated during the first 60 min on bypass. Little change in adrenaline concentrations occurred during this time. On completion of the repair it proved impossible to wean the patient from bypass with an adequate spontaneous cardiac output, despite the infusion of a variety of sympathetic agonists and antagonists. The massive increases in noradrenaline and "adrenaline" concentrations beyond 60 min of bypass were associated with catecholamine infusion. Figure 4 shows the patient's plasma catecholamine concentrations.

(d) Urine analysis

When the results of assay of the urinary specimens were analysed, several statistically significant correlations were discovered. However, in view of the large variations in urinary flow (0-19 ml min⁻¹) and the positive correlation found between urinary volume and all measurements except metanephrine excretion (table IV), no attempt has been made to draw conclusions from these data; furthermore, the authors counsel caution in the use of these measurements as indices of surgical stress under these conditions.
DISCUSSION

Few studies have investigated the adrenergic response to surgery, and in those which have been published, no consistent or significant increase in circulating catecholamines has been reported (Hammond et al., 1956; Nikki et al., 1972; Britton et al., 1974). All of these studies were performed during elective abdominal surgery. Lillehei and colleagues (1964), however, quote from the results of Replogle and colleagues (1962) in describing progressive increases in plasma catecholamine concentrations to approximately 8–16 μg litre\(^{-1}\) during cardiopulmonary bypass, with a rapid return, after bypass, to the concentrations observed before operation.

The results from the present series did not reproduce these findings, however, in that the plasma catecholamine concentrations did not at any time increase much above pre-anaesthetic values, except when synthetic catecholamines were infused. Furthermore, the mean concentrations found in this series are less than those following exhaustive exercise by healthy volunteers, whose plasma adrenaline concentrations reached a mean of 1.65 μg litre\(^{-1}\). The mean resting concentrations of plasma catecholamines observed in the 23 subjects of the same study (Hawkey et al., 1975) (venous total catecholamines 0.71 μg litre\(^{-1}\) (66% confidence limits 0.37–1.36), noradrenaline 0.48 μg litre\(^{-1}\) (0.24–0.98), and adrenaline 0.10 μg litre\(^{-1}\) (0.02–0.50)) correspond well with the pre-induction concentrations from this study, using a similar method of assay.

The decrease in catecholamine concentrations after induction of anaesthesia may be a result of the removal of the psychological component of stress before surgery. Subsequent increases coinciding with surgical trauma may result from the incomplete suppression of sympathetic activity inherent in anaesthetic techniques used in cases requiring minimal cardiovascular depression, but it is of interest that this fails to increase plasma concentrations beyond the range seen in the pre-induction sample.

It is tempting to attribute the increase in noradrenaline concentrations at the onset of cardiopulmonary bypass to the diversion of the pulmonary circulation, since it has been reported that up to 30% of blood-borne noradrenaline is removed during passage through the lungs (Gillis et al., 1972). Such a mechanism presupposes that all the peripheral uptake mechanisms are saturated,—such an event is improbable. The plasma catecholamine concentrations have not been corrected to allow for haemodilution occurring on bypass, but it is unlikely that major changes in plasma values would be masked by this effect, and many other variables, including the degree of saturation of peripheral uptake mechanisms, would require consideration.

The infusion of synthetic catecholamines was detectable by the assay methods used, and a significant increase in both "adrenaline" (P<0.01 arterial, P<0.02 venous) and total catecholamine concentrations (P<0.005 arterial, P<0.01 venous) was seen after the commencement of infusion. The fact that noradrenaline concentrations did not increase significantly in association with infusions of adrenaline or isoprenaline is confirmation of the specificity of the assay method, and suggests that there is little, if any, cross-reaction in terms of a noradrenergic response to increases in concentrations of other catecholamines.

In conclusion, the authors suggest that the concept of an adrenergic response to cardiac surgery involving cardiopulmonary bypass requires modification, possibly as a result of developments in surgical, anaesthetic and perfusion techniques, and improved methods of catecholamine assay. Although cardiopulmonary bypass increases the concentrations compared with those seen in the pre-bypass phase of the operation, the concentrations remain within the range observed before induction of anaesthesia. Furthermore, any immediate response to "stress", such as thoracotomy and the beginning of bypass, is mainly noradrenergic. Within the shorter duration of the bypass period typical of modern surgical practice, it has not been possible to demonstrate a significant progressive increase in plasma catecholamine concentrations.

It is well recognized that catecholamines have a half-life in the plasma of only 20–60 s in vivo because of the efficiency of the uptake mechanisms (Iversen, 1967; Vane, 1969). Therefore some doubt must be expressed as to the ability of plasma catecholamine analyses, however accurately performed, to quantitate sympatho-adrenal activity. It is of interest that Taylor and colleagues (1975) have found little change in plasma cortisol concentrations in a similar series of cardiopulmonary bypass operations, but again have expressed doubts as to the ability of cortisol concentrations to monitor stress.

ACKNOWLEDGEMENTS

The authors wish to record their thanks to the consultants in cardiothoracic surgery and anaesthesia at St Bartholomew's Hospital for their co-operation during the study and for permission to investigate patients under their care.

W. G. W. and R. W. M.-B. were supported in part by the Wellcome Trust.
REFERENCES


REACTIE ADRENERGIE A UNE INTERVENTION CHIRURGICALE METTANT EN CAUSE UN PONTAGE CARDIOPULMONAL QUE L'ON PEUT MESURER PAR LES CONCENTRATIONS DE CATECHOLAMINES DANS LE PLASMA SANGUIN ET DANS L'URINE

On a mesuré les concentrations de catécholamines dans le plasma sanguin et l'urine de 13 patients subissant une intervention chirurgicale cardiaque mettant en cause un pontage cardiaque. L'importante et progressive augmentation des catécholamines dans le plasma pendant le pontage, dont nous avons parlé dans des études précédentes, n'a pas été confirmée et cela peut être dû à une amélioration des techniques chirurgicales, anesthésiques et de perfusion. L'interprétation des observations concernant l'urine a été compliquée par l'observation d'une corrélation positive entre l'excrétion de catécholamines et le débit d'urine. Ces observations laissent penser qu'il faut modifier les concepts actuels de la réaction adrénergique à la chirurgie cardiaque et au pontage et elles mettent en doute la validité de la mesure des concentrations de catécholamines dans l'urine comme indice de la fatigue dans ces circonstances.

DIE ADRENERGISCHE REAKTION AUF CHIRURGIE FÜR DEN KARDIOPULMONALEN BYPASS, MITTELS ERMESUNG DER PLASMA- UND URIN-KATECHOLAMINKONZENTRATE

ZUSAMMENFASSUNG
LA RESPUESTA ADRENERGICA A LA CIRUGIA INCLUYENDO DERIVACION CARDIOPULMONAR SEGUN MEDICIONES DE CONCENTRACIONES DE CATECOLAMINA EN LA SANGRE Y EN LA ORINA

SUMARIO

Se han medido las concentraciones de catecolamina en la sangre y en la orina en 13 pacientes que sufrieron una cirugía cardiaca que comprendía una derivación cardiopulmonar. No se ha confirmado un aumento progresivo y considerable en catecolaminas de plasma durante una derivación de que se informó en estudios previos y esto puede ser el resultado de mejoras en las técnicas de cirugía, anestesia y perfusión. La interpretación de los datos urinarios se vio complicada por el hallazgo de una correlación positiva entre la excreción de catecolamina y la medida del caudal de orina. Los datos hallados en el estudio sugieren la necesidad de modificar los conceptos corrientes sobre la respuesta adrenérgica a la cirugía cardiaca y a la derivación, y la cuestión de la validez de medir la concentración de catecolamina urinaria como un índice de tensión en estas circunstancias.