SUMMARY  Cardiopulmonary bypass (CPB) alters systemic hemodynamics and affects several biochemical systems involved in cardiovascular regulation. We investigated the changes in levels of circulating epinephrine (E) and norepinephrine (NE) and related them to events during CPB. Twenty-eight patients undergoing various surgical procedures were studied. Plasma E and NE were determined by radioenzymatic assay at eight stages of the operation. A ninefold increase in arterial E (from 75 ± 13 to 708 ± 117.3 pg/ml) occurred from prebypass (stage 1) measurements to the end of aortic cross-clamping (stage 4). The values at stage 4 were significantly higher (p < 0.05) than at all other stages. E decreased rapidly, to 360 ± 84.3 pg/ml, after myocardial and pulmonary reperfusion (stage 5). Arterial NE increased twofold from stage 1 to stage 4 (from 426 ± 66.9 to 825 ± 84.2, p < 0.05). The increase in NE from initial CPB values (stage 2) to 30 minutes of aortic cross-clamping (stage 3) was associated with an increase in mean blood pressure (r = 0.51, p = 0.02). The peak increases in catecholamines occurred when the heart and lungs were excluded from the circulation, which suggests that either or both contributed to the increase. Because the increase in E was markedly greater than that in NE, the predominant humoral response to CPB appears to be adrenomedullary release of E. This significant increase in catecholamines could jeopardize myocardial protective measures during CPB.

MARKED INCREASES in norepinephrine (NE) and epinephrine (E) concentrations in arterial blood during cardiopulmonary bypass (CPB) have been demonstrated.1-10 However, no report describes the temporal increase in NE and E in relation to the abnormal hemodynamic and biochemical events during CPB.

Methods

Patients

Twenty-eight adult patients, 10 female and 18 male, scheduled for elective cardiac surgery were studied using a protocol approved by the institutional review board of the University of Alabama. The operations performed are shown in table 1. All patients continued to take their usual medications, including propranolol, until the time of surgery. Patients taking a methyldopa were excluded from the study. Table 2 contains demographic variables describing the patient population. Comparison of catecholamines and hemodynamic data from patients with ischemic heart disease (20 patients) and those with combined ischemic and valvular or congenital heart disease revealed no significant alterations in the response to CPB. Likewise, whether or not patients were taking particular medications (e.g., propranolol or antihypertensive drugs) did not alter the catecholamine or hemodynamic response. Therefore, data from all patients are considered together.

Anesthesia

All patients were anesthetized by the same physician to ensure a consistent anesthetic approach. Anesthetic management has been reported in detail elsewhere6-11 and consisted of a combination of diazepam, fentanyl, pancuronium, nitrous oxide and oxygen, and halothane. Diazepam, 10-15 mg, and pancuronium, 0.1 mg/kg, were administered at the onset of CPB. No other anesthetic drugs were administered during CPB.

Surgery

All surgery was performed by the same physician to ensure a standardized approach. A pulmonary artery thermistor and right atrial catheter were placed before CPB for determination of cardiac output. A left atrial catheter was placed for continuous monitoring of mean left atrial pressure (LAP), and radial arterial catheters were placed before surgery for continuous measurement of systemic systolic and diastolic arterial pressures. The mean pressure (MBP) was electronically determined. The temperature of the patient was monitored from the nasopharynx and the arterial perfusate cannula during CPB. The CPB pump (Sarns Model 2000) oxygenator (SpiraFlo BOS-10) was primed with Normosol R (1000 ml) and a solution (1000 ml) of 5% dextrose and 0.45% saline. CPB was established at a flow rate of 2.2 l/min/m² and maintained at that flow or lower. No interventions other than keeping flow at 2.2 l/min/m² were made to control low perfusion pressure. If the mean perfusion pressure increased to 80 mm Hg, the pump flow was first reduced to no less than 1.3 l/min/m², and if the elevation in pressure persisted, sodium nitroprusside or droperidol was administered to keep the perfusion pressure at 80 mm Hg or lower.

Measurements

Hemodynamic variables consisted of mean systemic, LAP and right atrial pressure (RAP) and cardiac output (determined in duplicate by thermodilution before and after CPB, and during CPB by noting the pump oxygenator flow from a previously calibrated system). Cardiac index (CI) and mean systemic vascu-
lar resistance (SVR) were calculated. Arterial blood samples were obtained to measure blood gas tensions, pH, hematocrit and catecholamines. Venous blood samples (from the right atrium before and after CPB and from the CPB venous reservoir during CPB) were obtained for determination of catecholamine levels. Plasma E and NE levels were determined by a modification of the radioenzymatic method of Passon and Peuler.12

The above measurements were made at eight stages during the operation: (1) during anesthesia just before CPB at normothermia with normal pulsatile cardiac output and the lungs in the circulation; (2) during CPB before aortic cross-clamping at moderate hypothermia (32°C) with pulsatile flow and the lungs in the circulation; (3) 30 minutes after exclusion of heart and lungs from circulation, with hypothermia (28°C) and nonpulsatile flow; (4) 2 minutes after myocardial reperfusion at moderate hypothermia with nonpulsatile flow and lungs excluded from circulation; (5) during pulsatile perfusion with 38°C blood 10 minutes after myocardial and pulmonary reperfusion; (6) 2 minutes after CPB, with conditions similar to those in stage 1; (7) after administration of protamine, with conditions similar to those in stages 1 and 6; and (8) after sternal closure, with conditions similar to those in stages 1, 6 and 7.

Statistical Analysis
To determine the relationship between changes in catecholamines and changes in hemodynamic and other physiologic variables, mean values of each were determined at all eight stages of surgery and analyzed with the following tests. An overall test of differences between stages was made using Duncan’s new multiple-range test.13 Adjustment was made for differences in baseline values for each patient. Missing data were randomly encountered for a variety of technical and methodologic reasons; there was no systematic reason for data omission. Changes in variables between stages were correlated using both Pearson (product-moment) and Spearman (rank) correlation coefficients. Changes in variables from beginning to end of CPB (stages 2–4) were studied similarly. Variable changes between stages were performed on individual patients with data at both points. No adjustment of significance level was made to account for multiple correlations or for varying sample sizes. The power of detecting a significant (p < 0.05) correlation decreased with the decreased number of patients at various sampling intervals; for 28 patients the power of detecting a significant (p < 0.05) correlation coefficient of 0.4 is 56%, which decreases to 44% for 21 patients and to 18% for nine patients.

Results

Catecholamines and Temperature
Mean values for plasma catecholamine concentrations are presented in figures 1 and 2. Arterial epinephrine (E) during anesthesia and surgery before CPB was 75 ± 13.0 pg/ml; it increased with the initiation of CPB (133 ± 18.0 pg/ml) and peaked at values ninefold higher than baseline (708 ± 117.3 pg/ml) just after the release of the aortic cross clamp (stage 4). The values at stage 3 were significantly (p < 0.05) higher than those at intervals 1, 2, 6, 7 and 8 (fig. 1). The peak value at stage 4 was significantly (p < 0.05) greater than all other values. The initial increase was followed by a rapid decline over 10 minutes, to 360 ± 84.3 pg/ml (n = 12) and a gradual return over the remainder of surgery and anesthesia to values not statistically different from those before CPB. The venous epinephrine (E) levels paralleled the arterial concentrations (fig. 1). E concentrations at stages 3 and 4 were significantly greater than all others (p < 0.05). Mean arterial norepinephrine (NE) levels during anesthesia and surgery before CPB was 426 ± 66.9 pg/ml (fig. 2). The initiation of CPB did not significantly alter NE values (412 ± 56.6 pg/ml), but with excl-

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<td>Mitral valve replacement (MVR)</td>
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<td>Coronary artery bypass graft (CABG)</td>
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*Not designated in five patients.
Abbreviation: NYHA = New York Heart Association.
CATECHOLAMINES DURING BYPASS/Reves et al.

FIGURE 1. Mean plasma levels of epinephrine (Epi) during cardiac anesthesia and surgery. Bars indicate SEM.

Prior to CPB, there was a 32% increase in NEa, to 545 ± 84.6 pg/ml. NEa peaked at 825 ± 84.2 pg/ml during stage 4, which was significantly (p < 0.05) greater than all other values. With reperfusion of the lungs and heart (stage 5), there was a rapid (over 10 minutes) decline in NEa to 493 ± 79.1 pg/ml, then a gradual decrease to the range present before CPB. Venous norepinephrine (NEv) values paralleled those of NEa (fig. 2). Peak NEv occurred at stage 4 (766 ± 93.3 pg/ml). This value was significantly greater (p < 0.05) than all other NEv measurements. Values at stages 2, 3, 5 and 6 were significantly higher than those at stages 1, 7 and 8.

Hemodynamics

The results of hemodynamic measurements are shown in figure 3 and table 3. The cardiac index ranged from 1.6 ± 0.08 l/min/m² during aortic cross-clamping to 2.9 ± 0.20 l/min/m² approximately 30 minutes after CPB (stage 7). Mean arterial pressure ranged from 59 ± 3.1 mm Hg at the initiation of CPB to 84 ± 2.5 mm Hg after protamine administration. During CPB there was a steady increase in MBP. SVR ranged from 1240 ± 69.9 to 1819 ± 121.6 dyn-sec-cm⁻². During CPB, the SVR changes were remarkable in that there was an initial decrease (from 1564 ± 143.3 to 1240 ± 69.9 dyn-sec-cm⁻²), followed by a significant (p < 0.05) increase during myocardial and lung exclusion to a peak of 1819 ± 121.6 dyn-sec-
cm⁻³. The peak increase in SVR accompanied the peak increase in catecholamines during aortic cross-clamping (stages 3–4). With myocardial reperfusion, the SVR decreased to 1288 ± 56.8 dyn-sec-cm⁻³ accompanied by decreases in circulatory NE and E, but within 10 minutes increased to 1694 ± 129.2 dyn-sec-cm⁻³ despite a continued decrease in circulating catecholamines.

Correlations

Pearson and Spearman analyses of the data were similar. Table 4 shows Pearson correlation coefficients for absolute changes in venous catecholamines with a variety of physiologic variables for consecutive stages 1–4. There was a positive correlation (r = 0.51, p = 0.02) between the increases in NE and MBP that followed aortic cross-clamping (interval 2 vs 3) (fig. 4). There was no association between changes (decreases) in CI and SVR with changes (slight increases) in E and NE after the initiation of CPB (interval 1 vs 2). Also of note is the weak association of changes in temperature with changes in catecholamines. Overall, there were few good correlations of catecholamine changes with changes in CI, MBP, SVR and temperature during CPB.

Discussion

The striking finding in this study is the substantial increase in circulating catecholamines when the lungs and heart were excluded from the circulation (stages 3–4) and when nonpulsatile blood flow and moderate hypothermia were being maintained. The increase in circulatory E (ninefold) was greater than the simultaneous increase in NE (twofold), which suggests that the major response to the stress of cardiopulmonary bypass may be adrenomedullary release of E rather than sympathetic neuronal discharge. The increments in circulatory catecholamines during CPB were compared to those recorded by other investigators in response to stressful stimuli. The E response to CPB was of the same order of magnitude as that reported by Robertson et al. in two patients with syncope and by Nadeau and de Champlain in 26 patients with acute myocardial infarction. The increases in NE approached the level reported with the stresses of strenuous exercise, orthostasis and caffeine. The rapid decline from peak levels in the 10 minutes after release of aortic cross-clamping probably reflects rapid clearance (reuptake and metabolism) of catecholamines during the period of cardiac, pulmonary and whole body perfusion.

Except for an association between increased NE and MBP during aortic cross-clamping, there was no correlation between plasma catecholamines and hemodynamic variables during CPB. The peak NE values (825 pg/ml) are half those reported to cause significant effects in normal man, and during CPB there were only weak associations between changes in mean perfusate.

Table 3. Hemodynamic and Temperature Data

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<tr>
<td>LAP (mm Hg)</td>
<td>9.5 ± 1.49</td>
<td>0.5 ± 0.18</td>
<td>0.7 ± 0.67</td>
<td>3.1 ± 0.87</td>
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<td>RAP (mm Hg)</td>
<td>6.2 ± 0.65</td>
<td>0.1 ± 0.09</td>
<td>0.2 ± 0.6</td>
<td>0.6 ± 0.43</td>
<td>0.9 ± 0.47</td>
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<td>26</td>
<td>14</td>
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<tr>
<td>Hematocrit (%)</td>
<td>35 ± 1.0</td>
<td>25 ± 0.7</td>
<td>25 ± 0.8</td>
<td>26 ± 0.8</td>
<td>27 ± 1.1</td>
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<td>27 ± 0.8</td>
<td>27 ± 0.7</td>
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<td>14</td>
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<td>22</td>
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<tr>
<td>Temp NP (°C)</td>
<td>34.4 ± 0.14</td>
<td>31.7 ± 0.22</td>
<td>27.7 ± 0.33</td>
<td>32.6 ± 0.43</td>
<td>35.0 ± 0.43</td>
<td>36.4 ± 0.14</td>
<td>35.5 ± 0.17</td>
<td>34.7 ± 0.14</td>
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<tr>
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<tr>
<td>Temp P (°C)</td>
<td>26.9 ± 1.12</td>
<td>27.9 ± 0.98</td>
<td>35.7 ± 0.68</td>
<td>38.4 ± 0.23</td>
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<tr>
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Abbreviations: LAP = left atrial pressure; RAP = right atrial pressure; Temp NP = nasopharyngeal temperature; Temp P = temperature of perfusate.
fusión pressure and changes in NE. The striking mean increase in SVR for all patients during aortic cross-clamping paralleled the mean increases in E and NE, but statistical analysis failed to show a significant correlation for individual patients. Therefore, the increases in SVR and MBP during aortic cross-clamping appear to be related to either the cumulative effect of simultaneous increments in NE and E or to other mechanisms, such as increased antidiuretic hormone or activation of the renin-angiotensin system.19 Continuation of various medications, including propranolol and antihypertensive drugs, until surgery might have interfered with the cardiovascular response to circulating catecholamines. However, when patients taking propranolol and antihypertensive drugs were compared with those who were not, there were no significant differences in hemodynamic responses or patterns of catecholamine release.

A ninefold increase in E and a twofold increase in NE occurred at stage 4, when the lungs and heart were excluded from the circulation. At this time, blood flow was nonpulsatile and hypothermia was most pronounced. Any of these abnormal conditions could increase the release or impair the metabolism of catecholamines and therefore contribute to the increase in circulating levels. The correlations of decreases in temperature with increases in NE and E at stages 2 and 3 were poor (table 4). There is no consensus on the effect of temperature on catecholamine release during CPB,20 although profound hypothermia (<18°C) may be associated with marked increments in circulating catecholamines.5,21 In our study, the lowest perfusion temperature attained was 26°C, well above profound hypothermia levels. These data suggest that hypothermia was not responsible for the changes in catecholamines in the present study.

The lungs have been shown to extract 26% of circulating NE from the venous blood of awake man22 and 30% from the venous blood of anesthetized patients with ischemic heart disease.23 Because exclusion of the lungs and heart from the circulation occurred simultaneously in our study, it is impossible to dissociate the two as possible factors in the rise of E and NE. Isolation of the heart from perfusion may have been an important stimulus of the increase in plasma E in this study. Cardiac reflexes,24,25 which have sympathetic...

**TABLE 4. Pearson Correlation Coefficients for Absolute Change in Venous Catecholamines with Absolute Changes of Various Physiologic Variables**

<table>
<thead>
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<td>ΔMBP</td>
<td>ΔE</td>
<td>ΔE</td>
<td>ΔE</td>
</tr>
<tr>
<td>n</td>
<td>0.25</td>
<td>0.18</td>
<td>0.51</td>
</tr>
<tr>
<td>p</td>
<td>12</td>
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<td>21</td>
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<tr>
<td>ΔSVR</td>
<td>0.09</td>
<td>0.28</td>
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<tr>
<td>n</td>
<td>9</td>
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<tr>
<td>p</td>
<td>(NS)</td>
<td>(NS)</td>
<td>(NS)</td>
</tr>
<tr>
<td>ΔTemp NP</td>
<td>-0.07</td>
<td>-0.12</td>
<td>0.26</td>
</tr>
<tr>
<td>n</td>
<td>12</td>
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</tr>
<tr>
<td>p</td>
<td>(NS)</td>
<td>(NS)</td>
<td>(NS)</td>
</tr>
<tr>
<td>ΔCI</td>
<td>-0.32</td>
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<td>0.23</td>
</tr>
<tr>
<td>n</td>
<td>9</td>
<td>9</td>
<td>21</td>
</tr>
<tr>
<td>p</td>
<td>(NS)</td>
<td>(NS)</td>
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Abbreviations: ΔNE = change in norepinephrine; ΔE = change in epinephrine; ΔMBP = change in mean blood pressure; ΔSVR = change in systemic vascular resistance; ΔTemp NP = change in nasopharyngeal temperature; ΔCI = change in cardiac index.

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**Figure 4.** Linear regression analysis of change in norepinephrine (NEpi) with change in mean blood pressure (MBP) before aortic cross clamp (stage 2) to cross clamp of 30 minutes (stage 3). r = Spearman correlation coefficient.
efferent limbs triggered by myocardial ischemia and acidosis, could initiate the increases in E and NE during aortic cross-clamping. Such a mechanism could account for the observation that myocardial infarction in awake man results in increases in combined circulating E and NE levels of the same magnitude as the increase during the period of myocardial hypoxia in the current study. Wollenberger and Shahab demonstrated release of NE from the anoxic isolated heart. We recently confirmed this local sympathetic response of the heart by measuring more NE in coronary sinus blood than arterial blood in the first minute of cardiac reperfusion. This observation suggests that a profound sympathetic stimulus occurs during aortic cross-clamping, presumably on the basis of myocardial hypoxia. The response is characterized by the regional sympathetic neuronal release of norepinephrine and the adrenomedullary release of epinephrine. The cardiogenic hypertensive chemoreflex initiated by serotonin may be important as well, because platelet destruction and presumed release of free serotonin parallel each other during CPB. The efferent sympathetic limb of this reflex could contribute to the increases in circulating E and NE.

Although the cause of the striking catecholamine response to CPB cannot be determined from our data, documentation of the temporal rise and fall in circulating catecholamine levels during CPB gives some clues to both the causes and effects of the increased circulating levels of catecholamines. First, the occurrence of peak levels of catecholamines during aortic cross-clamping may mean that the exclusion of heart or lung causes or contributes to catecholamine release, perhaps by chemoreceptors located in both organs. Second, peak levels of catecholamines occurred during aortic cross-clamping, when the heart was perfused only by noncoronary collateral vessels. Elevated catecholamines at this time may interfere directly with myocardial protective measures by increasing myocardial oxygen consumption and indirectly by increasing the perfusion pressure and thereby increasing the pressure-dependent noncoronary collateral blood flow. Increased collateral flow at this time would rewarm the heart more rapidly and wash out the cardioplegic agents, resulting in a warm, fibrillating heart. Third, reperfusion of the ischemic heart is critical, and reperfusion with blood containing the high concentrations of E and NE shown in this study is potentially detrimental because elevated catecholamines increase myocardial oxygen consumption. This increased demand occurs when the heart is depleted of high-energy stores. This final consideration leads us to speculate that β-adrenergic antagonists or calcium-channel blocking drugs may be useful in protecting the heart from damage related to reperfusion with catecholamine-rich fluid if the increase in catecholamines cannot be blocked. Further study is needed, as these agents have negative inotropic effects and could cause significant myocardial depression.

Acknowledgment
The authors express their appreciation to Johnny Sutherland for his technical assistance and to Rosemary Craighead and Rae Kerutis for their assistance in the preparation of the manuscript.

References
Borderline Hypertension and Obesity: Two Prehypertensive States with Elevated Cardiac Output

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GERALD R. DRESLINSKI, M.D., FRANCIS G. DUNN, M.D., ALLAN A. MACPHEE, M.D.
AND EDWARD D. FROHLICH, M.D.

SUMMARY Systemic, renal and splanchnic hemodynamics, intravascular volume, circulating catecholamine levels and plasma renin activity were compared in 39 patients with borderline hypertension and 28 normotensive subjects, who were less than 5% (n = 42, lean patients) or more than 40% overweight (n = 25, obese patients). Lean borderline hypertensive patients had greater cardiac output (p < 0.05), heart rate (p < 0.01) and renal blood flow (p < 0.05); cardiopulmonary redistribution of intravascular volume (p < 0.05); and higher circulating norepinephrine levels (p < 0.05). Obese normotensive subjects also showed an increased cardiac output (p < 0.005), stroke volume (p < 0.01), left ventricular stroke work (p < 0.05), and renal blood flow (p < 0.05) (but not respective indexes), but intravascular volume was expanded (p < 0.05) without redistribution and circulating catecholamine levels were normal. Obese borderline hypertensive patients had hemodynamic characteristics similar to those of obese normotensive subjects except for an increased peripheral resistance (p < 0.05). The data indicate that although both populations have an increased cardiac output, the lean borderline hypertensive patients have signs of enhanced adrenergic activity as evidenced by higher circulating catecholamine levels and heart rate with blood volume translocation to the cardiopulmonary circulation. In contrast, the obese subjects (whether normotensive or borderline hypertensive), who also have increased cardiac output, seem to have normal adrenergic activity and an expanded intravascular volume without cardiopulmonary redistribution.

YOUNG PATIENTS with borderline blood pressure values are at least three times more likely to develop established essential hypertension as age-matched normotensive subjects. Elevated resting cardiac output and heart rate have been identified as predictors for the development of essential hypertension into a state with more persistently elevated arterial pressure and peripheral resistance. Since the increased heart rate and cardiac output can be normalized with β-adrenergic receptor blockade, and cardiac vagal control is reduced in patients with borderline hypertension, a net increased adrenergic activity has been postulated. Obese normotensive persons are also at a greater risk of developing hypertension than comparable lean subjects. Cardiac output also has been reported to be elevated in obese patients, possibly because of increased metabolic requirements. Since both borderline hypertension and obesity are associated with a hyperdynamic circulation and tend to progress toward established hypertension, we compared systemic and renal hemodynamics, fluid volume-state, and certain humoral factors in these two groups to further characterize the underlying pressor mechanisms.
Neuronal and adrenomedullary catecholamine release in response to cardiopulmonary bypass in man.
J G Reves, R B Karp, E E Buttner, S Tosone, L R Smith, P N Samuelson, G R Kreusch and S Oparil

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