

# Endocrine changes during anesthesia and cardiopulmonary bypass

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Patients who are subjected to anesthesia and surgical stress generally undergo several endocrine changes in response to stress. The endocrine changes may vary according to the physical status of the patient, severity of the surgical procedure, type of anesthetic used, level of anesthesia, and other factors. In patients undergoing cardiac operations, the typical endocrine response may be further modified by the use of cardiopulmonary bypass and the simultaneous effect of hemodilution produced by the bypass. Also during extracorporeal circulation, patients are perfused with a low mean arterial pressure and in most cases this perfusion is of a nonpulsatile nature. Because of the multiplicity and interaction of these endocrine systems, investigations into the endocrine changes associated with anesthesia and surgery have been difficult. Most investigators have attempted to study endocrine responses by measuring circulating hormonal levels at different times during operative procedures. These studies have focused primarily on the responsiveness of the pituitary, adrenocortical, and adrenal medullary endocrine systems during anesthesia and surgery. Some of these studies have attempted to correlate changes in blood pressure with hormonal changes, particularly during and after cardiopulmonary bypass. As a result of these investi-

gations, we are beginning to understand the precipitating causes of hypertension that frequently occur after cardiopulmonary bypass.

### Antidiuretic hormone

The antidiuretic hormone (ADH) has been studied probably more than any other endocrine hormone during anesthesia and cardiopulmonary bypass. A major portion of this research has been done by Philbin et al.<sup>1</sup> In their early studies, ADH secretion was found to be influenced by surgical stimulation, but not by light halothane or morphine anesthesia. By increasing the depth of morphine anesthesia they were able to prevent the ADH increase due to surgical stimulation.<sup>2</sup> These findings were confirmed in studies by Wu and Zbuzkova<sup>3</sup> and Simpson and Forsling.<sup>4</sup> Stanley et al<sup>5</sup> expanded these findings, showing that high-dose fentanyl anesthesia also blocks the increase in ADH levels to surgical stimulation.

Numerous studies have shown that ADH levels increase dramatically during cardiopulmonary bypass with most of the increase occurring in the first 45 minutes of bypass<sup>1, 3, 5-7</sup> These ADH changes during bypass occur with a variety of anesthetics including morphine, fentanyl, halothane, and enflurane and are not attenuated by deep anesthesia or a large fluid load with the decline in urine osmolality. Lactated Ringer's solution or blood used as the bypass pump prime fluid also has no effect on the posterior pituitary response to cardiopulmonary bypass. Philbin et al<sup>1, 2, 6</sup> have suggested that the introduction of the unphysiologic state of cardiopulmonary bypass produces a marked stress response with a subsequent outpouring of ADH. The degree of hemodilution does not appear to be related to the ADH response, although it has been suggested that the loss of pulsatile flow

and the rapid decline in left arterial pressure may be important factors in the ADH release. Hypersecretion of ADH during bypass far exceeds the physiologic need for control of water excretion, and Philbin et al<sup>1, 2, 6</sup> postulated that the ADH response may rather be related to the vasopressor action of ADH. During bypass the increase in ADH release may be involved with increased catecholamine release to correct the hypotension that occurs upon initiation of cardiopulmonary bypass. An alternate explanation for the rise in ADH is that the increased ADH levels reflect diminished ADH degradation due to hypothermia during bypass; however, this explanation is not widely accepted, since ADH levels remain elevated even after body temperature returns to normal.

### Anterior pituitary function

In 1978 reports from Taylor et al<sup>8-10</sup> and Bremner et al<sup>11</sup> indicated that the anterior pituitary response to thyrotrophin-releasing hormone was abnormal in patients undergoing cardiopulmonary bypass by standard nonpulsatile normothermic bypass perfusion. In both studies, the patients were anesthetized with nitrous oxide, oxygen, and morphine. Preoperatively and postoperatively the patients had normal responses to thyrotrophin-releasing hormone, but during cardiopulmonary bypass there was marked suppression of responsiveness of the anterior pituitary to administered thyrotrophin-releasing hormone. It was suggested that hypofunction of the anterior pituitary may exist during periods of cardiopulmonary bypass with the use of nonpulsatile perfusion and that recovery of pituitary function is evident within the first hour postbypass. In a follow-up study, Taylor et al<sup>9</sup> compared anterior pituitary function in two groups of patients subjected to pulsatile

or nonpulsatile perfusion during open heart surgery. The response of the anterior pituitary to thyrotrophin-releasing hormone was again subnormal in the nonpulsatile group, whereas in the pulsatile group a normal pituitary response to thyrotrophin-releasing hormone occurred in nine of the ten patients. Based on the results, Taylor et al<sup>9, 10</sup> suggested that the use of pulsatile bypass perfusion may prevent the hypofunction of the anterior pituitary that occurred with nonpulsatile bypass.

### **Adrenocortical response**

There is considerable controversy in cardiac surgical practice regarding steroid "adequacy" in patients and the empirical use of corticosteroids despite reported clinical benefits.

Plasma levels of cortisol, corticosterone, and nonprotein-bound cortisol were shown by numerous investigators to be significantly elevated during and after surgery without cardiopulmonary bypass. However, when cardiopulmonary bypass was used, there was an immediate fall in the plasma levels of cortisol and corticosterone with a corresponding rise in the percentage of free biologically active cortisol.<sup>12-14</sup> Further, it was shown that plasma cortisol binding capacity is reduced during bypass, which accounts for the observed increase in plasma-free cortisol. This reduction in cortisol binding maintains an adequate availability of physiologically active hormone in the presence of decreased cortisol levels during bypass.

Numerous explanations have been suggested for the reduction in plasma cortisol at the start of bypass, e.g., hemodilution of cortisol by the pump priming fluid, changes in the vascular bed of the adrenal gland, depression of anterior pituitary function, and accelerated breakdown of ACTH during bypass.<sup>10, 14</sup> Hemodilution of cortisol and

submaximal secretion of cortisol from the adrenal cortex are the explanations most frequently cited. It has been suggested that the adrenal cortex does not secrete sufficient amounts of cortisol and corticosterone to correct for the dilutional effect of the bypass prime fluid. However, the decreased cortisol secretion may not be due to adrenal hypofunction, but rather to diminished ACTH release from the pituitary. Taylor et al<sup>13</sup> have shown that stimulation of the adrenal cortex by synthetic ACTH midway through the period of cardiopulmonary bypass produces a significant rise in plasma cortisol.

In 1978, Taylor et al<sup>8-10</sup> studied the adrenocortical response during cardiopulmonary bypass using pulsatile and nonpulsatile perfusion. As previously demonstrated the plasma cortisol response during nonpulsatile flow was decreased, whereas in the pulsatile flow group of patients, plasma cortisol levels rose significantly during bypass. The authors concluded that the integrity of the adrenocortical stress response is maintained throughout cardiopulmonary bypass when pulsatile flow is used.

The reduction in plasma cortisol during nonpulsatile cardiopulmonary bypass has been stated to represent "a relative cortisol inadequacy during a highly stressful period." Further, the administration of synthetic corticosteroids during periods of cardiopulmonary bypass is claimed to improve peripheral circulation and reduce postoperative mortality.<sup>13</sup> However, until more definitive studies are carried out the value of steroid administration cannot be finally evaluated.

### **Adrenal medullary response**

The effect of anesthetic agents and cardiopulmonary bypass on the adrenal medullary response has been studied by several investigators. These studies have

consistently demonstrated that adrenal responsiveness is directly influenced by the cardiac status of the patient, the type and level of anesthesia, and whether cardiopulmonary bypass was used during the operation.

Differences in the preanesthesia resting levels of circulating catecholamines have been shown to exist between patients requiring valve replacement and patients needing coronary artery grafting. Balasaraswathi et al<sup>15</sup> reported finding elevated preanesthesia levels of circulating epinephrine and norepinephrine in patients requiring valve replacement, which is consistent with the pathophysiology of valvular disease. During surgery, with nitrous oxide, oxygen, and morphine as the anesthetic, the authors found that after initiation of cardiopulmonary bypass there was a significant increase in circulating epinephrine from the baseline level. The elevation in epinephrine persisted through the bypass and into the early postbypass period.

In those patients requiring coronary artery bypass surgery, similar elevations in circulating catecholamines were observed at the start of cardiopulmonary bypass. However, this group differed from the valve replacement group in that postbypass epinephrine and norepinephrine return to their prebypass levels.

Increased adrenal catecholamine release during cardiopulmonary bypass has been demonstrated by several investigators measuring plasma and urinary catecholamine levels. Although the exact cause of the catecholamine increase is still under study, it does not appear to be due to the anesthetic agent. Morphine was the anesthetic of choice in the study of Balasaraswathi et al,<sup>15</sup> and morphine is known to stimulate adrenal catecholamine release;<sup>16</sup> however, elevations in circulating catecholamines

have also been found during bypass in patients anesthetized with enflurane. In addition, Stanley et al<sup>7</sup> reported finding similar elevations in epinephrine and norepinephrine levels during cardiopulmonary bypass in patients anesthetized with high-dose fentanyl-oxygen anesthesia. Interestingly, this anesthetic technique is reported to produce a "stress free" anesthesia in patients undergoing coronary artery grafting, at least until bypass. The authors found that high-dose fentanyl-oxygen anesthesia prevented increases in, and actually decreased, plasma concentrations of the "stress responding hormones," epinephrine, norepinephrine, dopamine, and cortisol until the start of cardiopulmonary bypass.

In a recent study, Balasaraswathi et al<sup>17</sup> reported that circulating levels of epinephrine and norepinephrine fell significantly on initiation of cardiopulmonary bypass in patients undergoing coronary artery bypass surgery anesthetized with halothane. The catecholamine levels remained lowered throughout the bypass period. This finding with halothane anesthesia differs from the catecholamine response observed during bypass with morphine, enflurane, and high-dose fentanyl anesthesia. To explain the different results, Balasaraswathi and co-workers postulate that bypass hemodilution of circulating catecholamines by the prime volume occurs with all anesthetics. With anesthetics like morphine, enflurane, and fentanyl, there is a compensatory increase in adrenal catecholamine release at the start of bypass with the observed elevation in circulating catecholamine levels. With halothane anesthesia, bypass hemodilution and the observed lowering of circulating catecholamine levels occur as a result of halothane's suppression of compensatory adrenal catecholamine

release.<sup>18</sup> In support of their postulate, the authors calculated the amount of epinephrine and norepinephrine added to the circulation during cardiopulmonary bypass with morphine and halothane anesthesia. The amount added with morphine was found to be far in excess of the amount required to maintain the prebypass level. This was in marked contrast to the patients receiving halothane, where in the amount of epinephrine and norepinephrine added to the circulation during bypass was tremendously reduced, resulting in a dilutional deficit of circulating catecholamines.

It would appear that the adrenal response during cardiopulmonary bypass is not caused by anesthetic agents themselves. Balasaraswathi et al<sup>15, 17</sup> have suggested that the increased adrenal release of catecholamines during bypass is in response to a transient drop in arterial blood pressure that routinely occurs upon initiation of bypass. The rise in catecholamine levels during bypass parallels the return of arterial pressure to the prebypass level. With halothane anesthesia the recovery of the blood pressure occurs more slowly and is probably due to activation of the renin-angiotensin system since catecholamine levels are not elevated. It is clear that a variety of adrenal medullary responses occur during anesthesia and cardiopulmonary bypass. The trigger mechanism(s) for these responses remain under investigation.

### Renin-angiotensin system

In 1975, Bailey et al<sup>19</sup> conducted a study to determine whether the renin-angiotensin-aldosterone system remains operational in the cardiac patient undergoing cardiopulmonary bypass. The study was done with patients undergoing elective cardiac surgery anesthetized

with 50% nitrous oxide, 50% oxygen and morphine, 1 to 3 mg/kg. The enzymatic activity of renin was found to increase after the operation had begun, but before cardiopulmonary bypass, which correlated closely with a rise in arterial blood pressure. During bypass, renin activity declined about 30% but was still more than double the baseline value. Aldosterone levels also increased, but only after 15 minutes on bypass with a further increase at 60 minutes. The authors concluded from their results that the renin-angiotensin-aldosterone system may play a role in blood pressure regulation during cardiopulmonary bypass and may cause decreased potassium levels due to excessive urinary excretion of potassium. The authors did not rule out the possibility that the observed renin-aldosterone changes are secondary to catecholamine increases, which have been shown to occur before and during bypass by other investigators.

Oyama et al,<sup>20</sup> in a study of patients undergoing noncardiac surgery, reported that general anesthesia itself alters plasma aldosterone levels. Aldosterone levels were found to increase 2.5 times during halothane, methoxyflurane, and enflurane anesthesia with further increases occurring after surgery had begun. Plasma renin activity and ACTH also increased but to a much lesser extent. Oyama et al concluded that stimulation of aldosterone secretion from the adrenal cortex occurs during general anesthesia with most inhalation agents. Further, the direct influence of the renin-angiotensin system on plasma aldosterone during anesthesia was considered as minor, although during surgery renin and angiotensin appeared to have a major effect on aldosterone secretion.

Taylor et al,<sup>21</sup> in a 1977 study, measured intraoperative plasma angiotensin

II levels in two groups of patients, one group subjected to open heart surgery using standard normothermic, nonpulsatile bypass and one group subjected to closed mitral valvotomy (control group). Both groups received nitrous oxide, oxygen and morphine anesthesia. Preoperative angiotensin II levels were found to be normal in both groups. During the operation, angiotensin II levels in the control group rose steadily throughout the procedure increasing by 50% from baseline. Postoperatively, the levels returned to normal within 2 hours. In the bypass group, similar increases in angiotensin II levels were observed until the start of cardiopulmonary bypass, at which time there was a marked rise in angiotensin II levels that was sustained until 2 hours postbypass and then gradually returned to normal during the next 24 hours.

Taylor et al<sup>21</sup> stressed the effects of prolonged elevation in angiotensin II levels, i.e., increased peripheral vasoconstriction that may produce subendocardial ischemia with a consequent increase in afterload and reduction in left ventricular output. The reduction in cardiac output may precipitate a vicious circle, reduced renal perfusion causing progressive stimulation of the renin-angiotensin system. They suggested that this sequence of events may be of importance in the pathogenesis of the low-output syndrome.

The marked rise in angiotensin II levels reported by Taylor et al<sup>21</sup> occurred during nonpulsatile cardiopulmonary bypass. Whether or not similar endocrine changes occur with pulsatile bypass is not known. They suggested that the use of pulsatile flow bypass may reduce the rise in angiotensin II levels during and after bypass. Previously, Dunn et al<sup>22</sup> reported finding lower peripheral vascular resistance with pulsa-

tile perfusion than with nonpulsatile perfusion, which indirectly suggests that angiotensin II levels do not elevate during pulsatile bypass. Additional studies are needed before any conclusions can be drawn.

### Summary

A review of the evidence to date clearly demonstrates that anesthesia and cardiopulmonary bypass evoke a variety of responses from several different endocrine systems. Often these endocrine systems respond in unison to a given operative stress. Surgical stimulation can and does elicit endocrine responses; however, evidence thus far obtained indicates that such responses are slight, having little effect on the physical status of the patient and, for the most part, are attenuated or eliminated in deeply anesthetized patients. Individual anesthetic agents like morphine and halothane have been shown to influence endocrine responses, but again their effect is slight.

By far the greatest endocrine responses occur during cardiopulmonary bypass, particularly when nonpulsatile flow is used. During bypass major changes occur in hormonal levels of catecholamines, steroids, ADH, and pituitary hormones. These hormonal changes are most prominent with nonpulsatile bypass and they often persist well into the postbypass period. It is important to note that during bypass most of these endocrine responses cannot be completely obtunded by deep anesthesia, which suggests that cardiopulmonary bypass itself acts as a potent stress on the patient.

It is now well documented that endocrine systems and their ability to respond to stress are influenced by preexisting pathologic conditions of the patient, anesthetic agents, level of anesthe-



sia, and flow characteristics of cardiopulmonary bypass. The extent of this influence continues to be the subject of current investigation.

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