Attenuation of the Stress Response to Cardiopulmonary Bypass by the Addition of Pulsatile Flow

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SUMMARY The effect of pulsatile flow during cardiopulmonary bypass on the hormonal stress response was studied in 26 patients. Thirteen had routine bypass and 13 had pulsatile bypass with an average pulse pressure of 50 mm Hg. Plasma vasopressin levels were significantly elevated during bypass in both groups, but were lower with pulsation (66 ± 11 vs. 36.3 pg/ml, p < 0.05). Epinephrine levels increased in both groups during bypass, but were higher after bypass (1179 ± 448 vs. 713 ± 140 pg/ml, p < 0.05) and in the recovery room (1428 ± 428 vs. 699 ± 155 pg/ml, p < 0.05) in the nonpulsatile group. The same response was noted in the norepinephrine levels (924 ± 225 vs. 465 ± 90 pg/ml, p < 0.05; 1915 ± 491 vs. 717 ± 112 pg/ml, p < 0.05). There were no significant changes in renin activity in either group, but the increase after cardiopulmonary bypass was greater in the nonpulsatile group (2.0 ± 0.7 vs. 1.36 ± 0.4 ng/ml/hr, NS). These data suggest that pulsatile flow significantly attenuates the vasopressin and catecholamine stress response to cardiopulmonary bypass. This may explain the increased flow requirements and better tissue perfusion and organ function and the decreased incidence of postoperative hypertension after bypass using pulsatile flow.

THE USE of pulsatile flow during cardiopulmonary bypass is controversial. The reported advantages of pulsatile over nonpulsatile bypass include improved myocardial preservation and a lower incidence of perioperative infarction \(^1\) and improved organ blood flow and function. \(^2\) Others have reported no improvement in either whole organ blood flow or myocardial blood flow or contractility. \(^3\) \(^4\) The stress response to nonpulsatile bypass in man has been shown to produce a marked elevation in plasma arginine vasopressin, the antidiuretic hormone in man, \(^5\) which appears to be significantly attenuated by the addition of pulsatile flow. \(^6\) We examined the effect of pulsatile flow on the stress response to cardiopulmonary bypass as reflected by the changes in plasma vasopressin, epinephrine and norepinephrine levels and plasma renin activity.

Materials and Methods

Twenty-six male patients scheduled for elective aortocoronary bypass graft surgery were selected for study and arbitrarily divided into two groups. The groups were comparable for age, type of operation, duration of procedure and duration of bypass. Group 1 patients had routine perfusion and in group 2 the AVCO pulsatile bypass pump was used. Informed consent was obtained from all patients and the protocol was approved by the Human Studies Committee of the hospital.

Before induction of anesthesia, each patient had monitoring electrocardiographic (ECG) leads placed. Percutaneous radial artery, central venous and pulmonary artery thermodilution catheters were introduced under local anesthesia. All patients were anesthetized with halothane and a mixture of 50% oxygen-50% nitrous oxide. An indwelling urinary catheter was placed after induction of anesthesia and connected to a collecting bag.

The study was divided into eight periods: (1) control — after placement of monitoring devices and before induction of anesthesia; (2) anesthesia — 15 minutes after induction; (3) operation — 15 minutes after surgical incision; (4) bypass I — at 15 minutes of bypass; (5) bypass II — during rewarming; (6) postbypass I — at 15 minutes; (7) postbypass II — 1 hour; and (8) in the postoperative recovery room. Along with routine hemodynamic measurements, plasma epinephrine, norepinephrine and vasopressin levels, and plasma renin activity were measured during each period.

Plasma vasopressin levels were determined by radioimmunoassay using rabbit antibodies, \(^1^1\) plasma catecholamines by a radioenzymatic assay \(^1^2\) and plasma renin activity by a radioimmunoassay. \(^1^3\)

After control measurements were obtained in all patients, anesthesia was induced as previously described. Patients were then intubated, catheterized, and prepared for surgery. The heart was approached through a median sternotomy and cannulation for bypass utilized the ascending aorta and both venae cavae via the right atrium. A Bentley disposable bubble oxygenator was used during bypass with 3 liters of lactated Ringer's prime. During bypass, all patients were cooled systemically to 28°C. In group 2 patients, the pulsatile bypass pump was inserted into the arterial circuit just proximal to the aortic perfusion cannula and triggered from the ECG until fibrillation.
occurred. Patients were then pulsed at 70 beats/min during bypass with an average pulse pressure of 30 mm Hg. Pulsatile flow was created by the use of air pressure in an inflatable membrane separated from the blood circuit by a second membrane lined with Avcothane.

Intragroup data were analyzed for significance by a correlated t test and intergroup data by analysis of variance.

**Results**

There were no significant changes in either group in serum osmolality or electrolytes, although serum K+ decreased during bypass. Arterial blood gases reflected the change in inspired oxygen content, but were otherwise unremarkable. The hemodynamic variables were comparable for both groups except during bypass. The pulsatile patients (group 2) required a slightly higher flow (2.6 ± 0.1 vs 2.4 ± 0.2 l/min/m², NS) for a lower mean arterial pressure (78 ± 6 vs 81 ± 5 mm Hg, NS) during this period.

The major hormonal data for group 1 are listed in table 1. The plasma vasopressin level increased significantly with surgery and was further elevated during bypass. It decreased after bypass, but remained significantly elevated. Plasma renin activity did not change significantly. Plasma epinephrine levels increased during bypass and were even more elevated after bypass. Plasma norepinephrine levels increased during surgery, declined at first during bypass and then increased to significant levels after bypass. Table 2 contains the data for group 2 patients, who received pulsatile flow. These data were similar to those in group 1.

The vasopressin levels during bypass were significantly higher in group 1 (nonpulsatile) than in group 2 (66 ± 11 vs 36.3 ± 3 pg/ml, p < 0.05; 39.1 ± 9 vs 21.6 ± 2 pg/ml, p < 0.05) (fig. 1). The plasma epinephrine levels appeared to be equally elevated during bypass, but were significantly greater in the nonpulsatile group in the postbypass periods (1179 ± 448 vs 713 ± 140 pg/ml, p < 0.05; 1215 ± 452 vs 955 ± 157 pg/ml, p < 0.05). This was also true in the recovery room (1428 ± 428 vs 699 ± 155 pg/ml, p < 0.05). The plasma norepinephrine values were also significantly higher in the nonpulsatile group in the postbypass periods (924 ± 225 vs 465 ± 90 pg/ml, p < 0.05; 1696 ± 483 vs 628 ± 92 pg/ml, p < 0.05) and in the recovery room (1915 ± 491 vs 717 ± 112 pg/ml, p < 0.05) (fig. 2).

There were no significant differences in plasma renin activity between groups, although the post-

**Table 1. Hormonal Data in the Nonpulsatile Group**

<table>
<thead>
<tr>
<th>Period</th>
<th>Vasopressin (pg/ml)</th>
<th>Renin (ng/ml/hr)</th>
<th>Epinephrine (pg/ml)</th>
<th>Norepinephrine (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>9.2 ± 2</td>
<td>1.64 ± 0.5</td>
<td>247 ± 76</td>
<td>485 ± 133</td>
</tr>
<tr>
<td>Anesthesia</td>
<td>9.9 ± 1</td>
<td>2.4 ± 0.5*</td>
<td>128 ± 31*</td>
<td>643 ± 119</td>
</tr>
<tr>
<td>Operation</td>
<td>31 ± 6†</td>
<td>2.46 ± 0.6*</td>
<td>295 ± 69</td>
<td>833 ± 156*</td>
</tr>
<tr>
<td>Bypass I</td>
<td>66 ± 11‡</td>
<td>1.13 ± 0.3</td>
<td>261 ± 47</td>
<td>463 ± 97</td>
</tr>
<tr>
<td>Bypass II</td>
<td>39.1 ± 9†</td>
<td>1.45 ± 0.4</td>
<td>670 ± 193*</td>
<td>960 ± 186*</td>
</tr>
<tr>
<td>Postbypass I</td>
<td>39.5 ± 11‡</td>
<td>1.36 ± 0.5</td>
<td>1179 ± 448*</td>
<td>924 ± 225*</td>
</tr>
<tr>
<td>Postbypass II</td>
<td>31.7 ± 7†</td>
<td>2.00 ± 0.7*</td>
<td>1215 ± 252*</td>
<td>1696 ± 483*</td>
</tr>
<tr>
<td>Recovery room</td>
<td>19.5 ± 5*</td>
<td>1.47 ± 0.5</td>
<td>1428 ± 428*</td>
<td>1915 ± 491*</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.
* p < 0.05.
† p < 0.01.
‡ p < 0.001.

**Table 2. Hormonal Data — Pulsatile Group**

<table>
<thead>
<tr>
<th>Period</th>
<th>Vasopressin (pg/ml)</th>
<th>Renin (ng/ml/hr)</th>
<th>Epinephrine (pg/ml)</th>
<th>Norepinephrine (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>9.1 ± 1</td>
<td>1.73 ± 0.4</td>
<td>271 ± 75</td>
<td>461 ± 65</td>
</tr>
<tr>
<td>Anesthesia</td>
<td>8.7 ± 1</td>
<td>2.64 ± 0.7</td>
<td>149 ± 38*</td>
<td>677 ± 71*</td>
</tr>
<tr>
<td>Operation</td>
<td>32.4 ± 4†</td>
<td>2.48 ± 0.4</td>
<td>288 ± 48</td>
<td>809 ± 108†</td>
</tr>
<tr>
<td>Bypass I</td>
<td>36.3 ± 3†</td>
<td>1.03 ± 0.2*</td>
<td>235 ± 53</td>
<td>451 ± 87</td>
</tr>
<tr>
<td>Bypass II</td>
<td>21.6 ± 2†</td>
<td>1.52 ± 0.3</td>
<td>607 ± 62*</td>
<td>961 ± 220*</td>
</tr>
<tr>
<td>Postbypass I</td>
<td>29.5 ± 8†</td>
<td>1.21 ± 0.4*</td>
<td>713 ± 140*</td>
<td>465 ± 90</td>
</tr>
<tr>
<td>Postbypass II</td>
<td>26.5 ± 5†</td>
<td>1.36 ± 0.4</td>
<td>955 ± 157*</td>
<td>628 ± 92*</td>
</tr>
<tr>
<td>Recovery room</td>
<td>12.6 ± 1*</td>
<td>1.45 ± 0.3</td>
<td>699 ± 155*</td>
<td>717 ± 112*</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.
* p < 0.05.
† p < 0.01.
‡ p < 0.001.
bypass levels appeared to be higher in the nonpulsatile group (2.0 ± 0.7 vs 1.36 ± 0.4 ng/ml/hr, NS; fig. 1).

**Discussion**

The clinical use of pulsatile flow during cardiopulmonary bypass is controversial. Some investigators have suggested that pulsatile flow is more physiologic and should provide for better organ perfusion. Other studies have supported this view. However, others have reported increased urine flow and higher bypass flow requirements with the addition of pulsatile flow, but disagree as to the beneficial effects of such changes. Although some animal studies have suggested no improvements in myocardial blood flow or an actual decrease in subendocardial flow, other studies in animals and in man suggest the opposite.

Several investigators have reported a marked vasopressin stress response to cardiopulmonary bypass. As in the present study, the vasopressin levels were high enough to produce a pressor effect. Arginine vasopressin is a potent vasoconstrictor in man because of its direct arteriolar action and has significant effects on the renal, splanchnic and coronary circulation. This study confirms our previous finding that the use of pulsatile flow can attenuate the vasopressin stress response. These lower vasopressin levels in group 2 (pulsatile) support the concept of a vasopressor role for this hormone during bypass. The decreased levels with pulsation could explain, at least partially, the higher flow requirements and better tissue perfusion reported with pulsatile flow, and might account for the improved organ function, especially the kidney, reported with pulsatile flow.

Our data differ from the findings of Landymore et al. in two areas. In our study, plasma renin activity, while somewhat lower in the pulsatile patients, was not significantly different from that in the nonpulsatile group, whereas Landymore et al. reported significantly higher levels 2.5 hours after perfusion in the nonpulsatile patients and suggested a relationship with postoperative hypertension. Landymore et al. also found no significant differences in catecholamine levels. In contrast, our data suggest an attenuation of the catecholamine response to cardiopulmonary bypass. After bypass, the increases in epinephrine and norepinephrine levels were significantly greater in the nonpulsatile group. These findings suggest better tissue perfusion during bypass with a decreased stress response and may indeed be a factor in preventing the postoperative hypertension reported by others. Recent data also suggest that during periods of stress, the normal relationship between the sympathoadrenal and renin-angiotensin system can be disjointed, which would explain the catecholamine response in the presence of relatively unchanged renin activity.

There are several explanations for the differences between our data and those of Landymore et al. Our patients received their normal propranolol dosage until 12 hours before surgery, whereas their patients were weaned over 3 days, with the last dose at least 24 hours before the study. This may explain some differences in renin activity. In addition, the timing of the measurement periods after bypass was different in the two studies, with the last sample at approximately 2 hours in our study, compared with 5 hours. Finally, the pump prime and the type of pulsatile device were different. The significance of these factors is not known.

The variety of conflicting reports in the literature makes it difficult to assess the true contribution of pulsatile flow during cardiopulmonary bypass. This conflict may be partially explained by the variety of techniques used to create pulsation (e.g., modification of the roller pump, use of the intraaortic balloon) and by differences in species studied. Nonetheless, in human studies in which a device designed to create pulsatile flow was used, urinary flow and bypass flow requirements appear to be increased.

It is clear from our data that the use of pulsatile flow during cardiopulmonary bypass can substantially attenuate the hormonal stress response as related to both vasopressin and catecholamines. The
decreased levels recorded may be responsible, to a large extent, for the consistent reports of higher flow requirements during and better organ function after pulsatile flow. Although renin activity did not change markedly, it may have a significant role in the postoperative period; renin activity does not appear to be a factor intraoperatively. These data support the concept that vasopressin, as well as catecholamines, plays an important role in the physiologic stress response to bypass, which can be altered by the addition of pulsatile flow.

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Mitral Valve Replacement in Children with Rheumatic Heart Disease

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SUMMARY We followed 110 children, ages 6–15 years, who had undergone mitral valve replacement for rheumatic heart disease. Group 1 consisted of 74 patients with mechanical prostheses and a mean follow-up of 6.3 years. Group 2 consisted of 13 patients with porcine xenografts followed for 3.3 years. Group 3 included 23 children with dura mater bioprostheses and a mean follow-up of 1.9 years. The clinical evolution of each group was assessed according to the New York Heart Association criteria. The incidence of complications also was determined. Ninety-five percent confidence limits were calculated for all proportions from binomial distribution; lack of superposition was adopted as the criterion of significance.

In group 1, thromboembolic complications occurred in 1.7% per patient/year, infective endocarditis in 0.85% per patient/year, valvular dysfunction in 0.85% per patient/year, and death in 1.3% per patient/year. Group 2 patients had no thromboembolic complications; infective endocarditis occurred in 2.3% per patient/year, dysfunction in 16.3% per patient/year, and death in 14% per patient/year. Seven patients with Hancock porcine xenografts presented valve obstruction, and four cases that were studied anatomically showed fibrocalkific obstruction of the prosthesis. In group 3, thromboembolic episodes occurred in 2.3% per patient/year, dysfunction in 6.8% per patient/year, and death in 2.3% per patient/year. Calcific obstruction of the prosthesis was observed in one patient at necropsy. We conclude that mechanical prostheses offer the best results in children. With adequate anticoagulation, thromboembolism is of little significance, the incidence of infective endocarditis is comparable to that reported for bioprostheses, dysfunction is less frequent, and the long-term mortality rate is lower.

VALVULAR PROSTHESES have been used to treat congenital or acquired heart defects.1–8 Recently, long-term follow-up studies of bioprostheses in children have shown early dysfunction secondary to severe calcification.9–18 In this report, we present our experience with mitral valve replacement in children with rheumatic heart disease and describe the long-term follow-up of our patients with implanted mechanical or biologic prostheses.

Materials and Methods

From November 1964 to April 1980, 110 children, ages 6–15 years, were followed for at least 1.5 years after implantation of a mitral prosthesis. These patients were divided into three groups according to the type of prosthesis used: mechanical (Starr-Edwards), porcine (Hancock xenograft) and dura mater valves. The latter were preserved in glycerol.

The three groups of patients were comparable before surgery. The criteria of the New York Heart Association (NYHA) were used to evaluate all the patients between the second and the sixth postoperative months. The same criteria were used for complications in all three groups. The incidence of complications such as thromboembolism, infective endocarditis, prosthetic dysfunction and death was determined at the end of the follow-up. A transient or permanent neurologic deficit was considered a thromboembolic episode.

After bioprostheses became available, the selection of the type of valve was done randomly, completely disregarding age, sex, and clinical and hemodynamic features. In seven patients, who were in NYHA functional class III preoperatively, the use of bioprostheses was decided upon because of difficulties anticipated in following anticoagulant therapy.

Since 1964, preoperative and long-term follow-up assessments were carried out by the staff physicians at the outpatient clinic of the Department of Pediatric Cardiology. All patients with an implanted mechanical valve received anticoagulant therapy with aceno-
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Circulation. 1981;64:808-812
doi: 10.1161/01.CIR.64.4.808
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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