MANAGEMENT OF VASODILATORY SHOCK AFTER CARDIAC SURGERY: IDENTIFICATION OF PREDISPOSING FACTORS AND USE OF A NOVEL PRESSOR AGENT

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Background: Cardiopulmonary bypass can be associated with vasodilatory hypotension requiring pressor support. We have previously found arginine vasopressin to be a remarkably effective pressor in a variety of vasodilatory shock states. We investigated the incidence and clinical predictors of vasodilatory shock in a general population of cardiac surgical patients and the effects of low-dose arginine vasopressin as treatment of this syndrome in patients with heart failure. **Methods:** Patients undergoing cardiopulmonary bypass ($n = 145$) were studied prospectively. Preoperative ejection fraction, medications, and perioperative hemodynamics were recorded, and postbypass serum arginine vasopressin levels were measured. Vasodilatory shock was defined as a mean arterial pressure lower than 70 mm Hg, a cardiac index greater than 2.5 L/min/m^2 , and norepinephrine dependence. Predictors of vasodilatory shock were investigated by logistic regression analysis. The hemodynamic responses of patients who received arginine vasopressin infusions for vasodilatory shock after cardiopulmonary bypass for left ventricular assist device placement or heart transplantation were analyzed retrospectively. **Results:** Eleven of 145 general cardiac surgery patients (8%) met criteria for postbypass vasodilatory shock. By multivariate analysis, an ejection fraction lower than 0.35 and angiotensin-converting enzyme inhibitor use were independent predictors of postbypass vasodilatory shock (relative risks of 9.1 and 11.9, respectively). Vasodilatory shock was associated with inappropriately low serum arginine vasopressin concentrations ($12.0 \pm 6.6 \text{ pg/mL}$). Retrospective analysis found 40 patients with postbypass vasodilatory shock who received low-dose arginine vasopressin infusions, resulting in increased mean arterial pressure and decreased norepinephrine requirements. **Conclusions:** Low ejection fraction and angiotensin-converting enzyme inhibitor use are risk factors for postbypass vasodilatory shock, and this syndrome is associated with vasopressin deficiency. In patients exhibiting this syndrome after high-risk cardiac operations, replacement of arginine vasopressin increases blood pressure and reduces catecholamine pressor requirements. (J Thorac Cardiovasc Surg 1998;116:973-80)

Cardiopulmonary bypass (CPB) can be complicated by a systemic inflammatory response characterized by profound vasodilation.¹ This vasodilatory shock syndrome, which is especially noted after extended CPB,² is attributed to endothelial injury³ and the re-

lease of cytokines and other inflammatory mediators.⁴ Pressor catecholamines are commonly administered to support systemic arterial pressure in these cases,⁵ but their effectiveness is limited by frequent catecholamine resistance⁶ and by significant toxic effects at high

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Table I. Demographics of 145 patients undergoing CPB

Characteristic	Total		With VS	
	No.	%	No.	%
Sex				
Male	102	70	9	82
Female	43	30	2	18
Operation				
Coronary artery bypass	98	59	7	64
Mitral valve replacement	14	8		
Aortic valve replacement	17	10	1	9
LVAD	4	3	2	18
OHT	5	3	1	9
Lung transplantation	1	1		
Ross procedure	1	1		
Atrial septal defect repair	3	2		
Aortic aneurysm repair	1	1		
Right ventricular resection	1	1		
CPB time* (min)	158 ± 59		168 ± 66	
Preoperative medications				
Diuretics	45	31	7	64
Digoxin	24	17	3	27
ACE inhibitors	31	21	8	73
β-Blockers	49	34	2	18
Calcium-channel blockers	29	20	3	27
Low ejection fraction (<35%)	26	18	7	64

VS, Vasodilatory shock.

*Mean ± SD.

doses.⁷ Alternative pressor agents could therefore be useful.

Arginine vasopressin (AVP) has little vasoconstrictive effect in hemodynamically normal subjects⁸ but is an effective pressor in states associated with arterial hypotension.^{9,10} We previously observed a hypersensitivity to the pressor effects of AVP in vasodilatory septic shock,¹¹ and we recently reported a similar sensitivity in patients with vasodilatory shock after placement of left ventricular assist devices (LVADs).¹² In most cases AVP levels on weaning from CPB were inappropriately low for the degree of arterial hypotension, and this finding contrasted with the elevated levels usually found after CPB.¹³ On the basis of this experience, we have used AVP extensively to treat patients with vasodilatory shock after CPB for LVAD placement and for heart transplantation (OHT). The general incidence of vasodilatory hypotension and the concordance with AVP deficiency remains to be defined, as does the therapeutic role of AVP in the management of this syndrome.

We therefore undertook this analysis with 2 objectives. First, we sought to prospectively establish in a general cardiac surgical population the incidence of vasodilatory shock and the characteristics of this syn-

drome, including presence of AVP deficiency and other predisposing factors. Second, we retrospectively evaluated our clinical experience with the use of AVP in the management of vasodilatory hypotension after CPB.

Methods

Study patients and protocols. The prospective study group consisted of 102 men and 43 women with a mean age of 61 years. After they provided informed consent, subjects undergoing elective cardiac surgery were enrolled and were selected for shock during the first 30 minutes after CPB weaning on the basis of hypotension (mean arterial pressure <70 mm Hg) requiring norepinephrine administration for at least 3 hours. Serum samples were collected for AVP assay from these patients 5 minutes after weaning from CPB, and perioperative hemodynamic parameters and exogenous pressor requirements were prospectively recorded. Subjects were further classified as having cardiogenic shock (cardiac index <2.5 L/min/m²) or vasodilatory shock (cardiac index >2.5 L/min/m²).

Next a retrospective analysis of LVAD and OHT clinical databases was performed to find the cases of patients who had received AVP for the treatment of vasodilatory hypotension during a 30-month period. Inclusion criteria for this analysis included post-CPB vasodilatory hypotension (requirement for exogenous norepinephrine to maintain mean arterial pressure >70 mm Hg and cardiac index >2.5 L/min/m²) and the administration of AVP. Fourteen LVAD recipients and 26 OHT recipients met these criteria and received AVP infusions at a rate of 0.1 U/min. The study group consisted of 32 men and 8 women, with a mean age of 49.5 years.

Demographic and hemodynamic data for these 40 patients were obtained for the perioperative period and during the postoperative intensive care unit stay. The generally applied protocol for AVP administration was as follows: on identification of vasodilatory hypotension and an increasing exogenous pressor requirement, patients received AVP (Pitressin; Parke-Davis, Morris Plains, NJ) intravenously at a rate of 0.1 U/min. Subsequently catecholamine and then AVP infusions were tapered to maintain mean arterial pressure above 70 mm Hg. When hemodynamic improvement allowed discontinuation of catecholamine agents, the AVP infusion rate was progressively decreased to 0.02 U/min and then discontinued.

Vasopressin assay. Plasma AVP levels were measured by radioimmunoassay according to published protocols.¹³

Analysis of data. Hemodynamic and clinical data are reported as mean ± SD. Continuous variables were analyzed with the paired and unpaired Student *t* test and analysis of variance. The χ^2 and Fisher exact tests were applied to discrete variables. Univariable and multivariable logistic regression analyses were used to determine the relative contribution of a variety of demographic and clinical factors to the development of vasodilatory hypotension. For the multivariable regression analysis, variables from the univariate analysis were allowed to enter at the *P* < .25 level.

Fig 1. Distribution of AVP levels in cardiogenic and vasodilatory shock.

Table II. Hemodynamic characteristics and plasma AVP levels of patients with hypotension after CPB

	Vasodilatory hypotension	Cardiogenic hypotension
n	11	9
Post-CPB MAP (mm Hg)	64.6 ± 6.6	68.0 ± 1.2
Cardiac index (L/min/m ²)	2.7 ± 0.3	1.9 ± 0.6*
Post-CPB serum AVP (pg/mL)	12.0 ± 6.6	29.3 ± 15.0†

MAP, Mean arterial pressure.

* $P = .001$.

† $P = .004$.

Results

Incidence and clinical predictors of postbypass vasodilatory shock and relationship with plasma arginine vasopressin levels. Of 145 patients studied prospectively, 20 (14%) met criteria for post-CPB hypotension, with 11 cases (8%) meeting criteria for vasodilatory shock. This low incidence contrasts with the 42% observed in our earlier study of LVAD recipients.¹² Univariate regression analysis of this data set examined the variables listed in Table I and found low ejection fraction ($<35\%$, $P < .0001$) and the preoperative use of angiotensin-converting enzyme (ACE) inhibitors ($P < .0001$) and diuretics ($P = .02$) to be predictors of post-CPB vasodilatory shock. A multivariable logistic regression analysis analyzed a number of factors (ejection fraction, preoperative diuretics, digoxin, ACE inhibitors, β -blockers, and calcium-channel blockers), and found low ejection fraction ($P = .003$) and the use of ACE inhibitors ($P = .001$) to be independent predictors of increased risk of post-CPB vasodilatory

Table III. Demographics of 40 patients receiving AVP for vasodilatory shock

Characteristic	No.	%
Age* (y)	49.5 ± 15.8	
Sex		
Male	32	80
Female	8	20
Operation		
LVAD	14	35
OHT	26	65
Preoperative medications		
Diuretics	18	45
Digoxin	24	60
Ejection fraction $<35\%$	40	100
Timing of AVP infusion		
After CPB	33	83
During CPB	7	17

*Mean ± SD.

shock. The relative risks of post-CPB vasodilatory shock, as described by odds ratios, were 9.1 (confidence interval 2.1-38.8) for low ejection fraction and 11.9 (confidence interval 2.7-53.1) for use of ACE inhibitors. Demographics for this group and for the 11 patients with vasodilatory shock are summarized in Table I.

The identification of low ejection fraction as a predictor of vasodilatory shock in our cohort is consistent with the high incidence of this syndrome previously reported for our LVAD population (all with low ejection fraction). In our population of general cardiac surgical patients, 26 of 145 patients (18%) had a low preoperative ejection fraction; among these patients there were 7 cases of vasodilatory shock, corresponding to

Fig 2. Relationship between degree of baseline hypotension and increase in mean arterial pressure (MAP) after AVP infusion in 40 LVAD and OHT recipients.

Table IV. Hemodynamics before and after administration of AVP, stratified according to degree of initial hypotension

	All patients (n = 40)			Moderate hypotension (n = 12)			Severe hypotension (n = 13)			Profound hypotension (n = 15)		
	Before AVP	After AVP*	Δ	Before AVP	After AVP*	Δ	Before AVP	After AVP*	Δ	Before AVP	After AVP*	Δ
MAP (mm Hg)	57.6 ± 11.0	81.7 ± 13.8	24.2 ± 15.0	68.6 ± 4.2	86.1 ± 3.6	17.5 ± 11.3	56.8 ± 1.9	78.6 ± 15.3	21.7 ± 15.5	44.6 ± 7.3	79.7 ± 11.9	35.1 ± 13.1†
P		<.0001			<.0001			.0003			<.0001	
NE (μg/min)	14.4 ± 13.7	8.0 ± 10.8	-6.4 ± 11.6	10.3 ± 5.1	4.1 ± 5.5	-6.2 ± 6.7	14.0 ± 11.8	7.9 ± 8.8	-6.1 ± 13.2	19.8 ± 20.7	12.9 ± 15.7	-7.7 ± 15.2
P		.001			.003			.15			.37	
SVR (dyne-cm ⁵)	771 ± 304	1192 ± 337	400 ± 349	1018 ± 242	1169 ± 306	152 ± 340	749 ± 223	1253 ± 406	413 ± 307	581 ± 269	1164 ± 331	583 ± 269‡
P		<.0001			.24			.005			<.0001	
CI (L/min/m ²)	2.9 ± 0.1	2.9 ± 0.1	0	3.0 ± 0.6	2.9 ± 0.3	-0.1 ± 0.6	2.9 ± 0.5	2.9 ± 0.6	0	2.7 ± 0.4	2.8 ± 0.6	0.2 ± 0.6
P		1.0			.64			1.0			.67	

MAP, Mean arterial pressure; NE, norepinephrine; SVR, systemic vascular resistance; CI, cardiac index. All values expressed as mean ± SD.

*Values after AVP determined at time of peak blood pressure measurement within 2 hours of AVP administration.

†P < .05 versus severe hypotension and P < .01 versus moderate hypotension (analysis of variance).

‡P < .05 versus moderate hypotension (analysis of variance).

an incidence of 26.9%, whereas only 4 cases of vasodilatory shock occurred among 119 patients with normal ejection fraction (3.3%). Similarly, 30 of 145 patients were receiving preoperative ACE inhibitor therapy, and vasodilatory shock developed in 8 of these (26.7%), compared with only 3 of 115 patients (2.6%) not receiving these agents. The identification of ACE inhibitor therapy as an independent contributor to the

development of this syndrome underscores the risk in patients with preoperative heart failure.

The mean post-CPB AVP level in patients with cardiogenic shock was 29.3 ± 15.0 pg/mL, compared with 12.0 ± 6.6 pg/mL in patients with vasodilatory shock ($P = .004$), suggesting that AVP deficiency contributes to the development of vasodilatory shock. The hemodynamics and AVP levels in these 2 populations are

Fig 3. Relationship between degree of baseline hypotension and increase in systemic vascular resistance (SVR) after AVP infusion in 40 LVAD and OHT recipients. MAP, Mean arterial pressure.

listed in Table II, and the distribution of serum AVP values is depicted in Fig 1.

Retrospective analysis of therapeutic use of arginine vasopressin in the management of vasodilatory shock. Twenty-six patients undergoing OHT and 14 receiving LVADs met criteria for post-CPB vasodilatory hypotension during a 30-month evaluation period, and demographic characteristics of this group are summarized in Table III. AVP infusions were instituted from 5 minutes to several hours after weaning from CPB (33 patients) or while the patient was still on CPB to facilitate weaning (7 patients). Hemodynamic responses are summarized in Table IV. AVP administration resulted in dramatic increases in mean arterial pressure and systemic vascular resistance. The increases in blood pressure and vascular tone were accompanied by a significant reduction in mean norepinephrine doses and no appreciable change in cardiac index.

Catecholamine pressors frequently lose their effectiveness in severe vasodilatory shock. In contrast, the hemodynamic response to AVP infusion was proportional to the severity of vasodilatory hypotension. This relationship is apparent when patients are divided into 3 groups on the basis of the degree of hypotension (Figs 2-4, Table IV). After hemodynamic stabilization (mean arterial pressure >70 mm Hg without exogenous catecholamine pressor support), AVP was tapered slowly to 0.01 U/min and then discontinued. In many cases, initial attempts to discontinue AVP resulted in significant hypotension, underscoring the importance

Fig 4. Relationship between degree of baseline hypotension and decrease in norepinephrine (NE) requirements after AVP infusion in 40 LVAD and OHT recipients. MAP, Mean arterial pressure.

of the hormone in the maintenance of vascular tone in these patients. Duration of AVP infusion ranged between 1 hour and 6 days. Although a few patients were rapidly weaned from AVP because hypotension gave way to significant hypertension, there were no episodes of malignant hypertension, mesenteric

ischemia, or peripheral ischemia during the postoperative period. There were 3 perioperative deaths, 1 each from sepsis, hemorrhagic shock, and multisystem organ failure.

Discussion

CPB with membrane oxygenation is known to induce a variety of metabolic, hematologic, and neurohumoral effects, most of which are reversible unless CPB is excessively prolonged. A common effect is post-CPB vasoconstriction, which occasionally necessitates vasodilator administration and is due to temporary elevations in several vasoactive substances, including catecholamines, serotonin, and AVP.¹⁴ Patients undergoing aortocoronary bypass operations have been shown to exhibit increases of more than 6 times in circulating AVP levels during and as long as 12 hours after CPB,¹⁵ to levels often exceeding 100 pg/mL.¹³ However, a few authors have documented cases of post-CPB AVP deficiency manifesting as diabetes insipidus,^{16,17} whereas others have described a clinical vasodilatory syndrome responsive to such agents as octreotide¹⁸ and angiotensin II.¹⁹

In our study of 145 cardiac surgical patients, the incidence of vasodilatory shock in the early post-CPB period was 8%, although this syndrome was significantly more common (27%) among patients with low ejection fraction. In a previous communication we reported that this syndrome developed in 42% of patients undergoing LVAD insertion for end-stage heart failure during a 1-year period. Perhaps not surprisingly, multivariate analyses of our study population found low ejection fraction and use of ACE inhibitors to be independent predictors of vasodilatory shock. Among the 11 patients with post-CPB vasodilatory shock, most had AVP levels that, although within the normal osmoregulatory range for healthy normotensive subjects (5-15 pg/mL),²⁰ were inappropriately low for the degree of arterial hypotension that was present (≤ 15 pg/mL).

The mechanisms contributing to AVP deficiency in this syndrome are a matter of speculation. Hyponatremia can blunt the AVP response to baroreflex-mediated stimuli,²¹ but serum sodium levels were normal (136.2 ± 1.7 mEq/L) in our patients. Similarly, activation of atrial stretch receptors is known to inhibit AVP release through vagal afferent pathways,²² but central venous pressure was not elevated (12.0 ± 1.2 mm Hg) during the period of hypotension in our patients. Nonetheless, potential neurohumoral effects of preoperative elevations in cardiac filling pressures cannot be excluded. Atrial natriuretic peptide (ANP) could be responsible for AVP deficiency because it is

also known to inhibit AVP secretion, and the serum levels of ANP are often increased after CPB.²³ Finally, autonomic dysfunction could contribute because it is associated with AVP deficiency and has been documented in patients with heart failure.²⁴

The dose of AVP administered to our patients undergoing LVAD implantation and OHT, 0.1 U/min, is between a fourth and a ninth that administered to patients with cirrhosis for the control of bleeding esophageal varices. This dose provides a steady-state plasma concentration of at least 150 pg/mL,²⁵ comparable to levels previously reported after CPB. LVAD and OHT recipients with vasodilatory shock proved to be extremely sensitive to this dose of AVP, with rapid hemodynamic responses even in the absence of a loading dose. In several cases the AVP dose was decreased to 0.01 U/min, which was sufficient to maintain blood pressure without catecholamine pressors. This dose corresponds to a plasma concentration of less than 40 pg/mL²⁵ (similar to AVP levels observed in our patients in cardiogenic shock) and could therefore constitute physiologic replacement.

The mechanisms by which AVP acts as a pressor in patients resistant to catecholamines are not clear, but a number of intriguing possibilities exist. Vasodilatory shock after CPB is likely due to pathologic activation of several vasodilator mechanisms. The interleukin 1 level is elevated in inflammatory states and ANP is increased after CPB, and both promote vasodilation through increased levels of intracellular cyclic guanosine monophosphate.^{26,27} Also, adenosine triphosphate-activated potassium channels of vascular smooth muscle are activated by tissue hypoxia and hypoperfusion (and presumably by CPB), and this activation causes vasodilation by inducing cellular hyperpolarization and inhibiting voltage-gated calcium channels.²⁸ Both catecholamines and AVP effect vasoconstriction by increasing intracellular calcium levels in vascular smooth muscle through activation of voltage-gated calcium channels, and the activation of vasodilator pathways could impair this calcium-dependent mechanism. In contrast to catecholamines, however, AVP also inhibits the production of cyclic guanosine monophosphate by interleukin 1 and by ANP^{29,30} and inhibits the adenosine triphosphate-activated potassium channels of vascular smooth muscle.²⁸ Thus the efficacy of AVP as a pressor in a variety of clinical scenarios in which catecholamines are ineffective may rest on its ability to specifically counteract pathologically activated vasodilatory mechanisms. This hypothesis may also explain the restoration of catecholamine sensitivity that we have frequently observed after AVP administration.

We found in our prospective study that vasodilatory shock after CPB is associated with AVP deficiency and that this syndrome is more common among patients with low ejection fraction and those receiving ACE inhibitors. We also retrospectively observed, in a large number of patients undergoing LVAD implantation and OHT, that AVP is an effective pressor in the setting of post-CPB vasodilation, significantly increasing mean arterial pressure while reducing the requirement for catecholamine pressor agents. All patients in vasodilatory shock responded to AVP administration, and the magnitude of the hemodynamic response was proportional to the severity of hypotension at the time of infusion initiation. Our results are preliminary, and a large-scale controlled trial of AVP for the treatment of vasodilatory shock after CPB will be required to determine the risks and benefits associated with the use of this novel agent in the management of cardiac surgical patients.

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Discussion

Dr Richard D. Weisel (*Toronto, Ontario, Canada*). The problem is important. We have all seen patients who are profoundly hypotensive after operation, but we seldom know why and our treatment is far from adequate. As you do, we give them pressor agents, and we are always afraid that the arterial grafts are going to go into spasm. Occasionally they do. This is a major concern.

You have previously published information about patients undergoing LVAD implantation and OHT. I think we can understand why these patients are perhaps a little bit different. Both populations have unique features that are going to make them more susceptible to this. Could you perhaps pick out for us, though, the patients who are not LVAD or OHT recipients and see whether in fact the same process is going on in these other patients—particularly those undergoing coronary bypass, who comprise the majority of the elective cardiac surgical patients?

How many patients undergoing general cardiac surgery actually had vasodilatory shock, and how many of those had low AVP levels? Did all patients with vasodilatory shock respond the same, whether or not their AVP levels were low to begin with? I wonder whether you could clarify this for me.

Otherwise I think that it is a great idea. If we can get specific information, we will probably have a more specific therapy for this disturbing complication after heart operations.

Dr Argenziano. Although we first noticed this phenomenon in LVAD recipients and then directed our attention to OHT recipients, we have also asked ourselves the question, "Is this a relevant syndrome in general cardiac surgery?" That question is really what prompted the prospective trial that we presented here today.

In this prospective trial of 145 patients there were only 4 LVAD and 5 OHT recipients. We performed a separate statistical analysis in which we pulled those patients out. Even after removing the LVAD and OHT recipients from that population of 145, we found the same statistical significance with respect to ejection fraction and ACE inhibitor therapy as predictors of this syndrome.

With respect to the number of patients in whom the syndrome developed, there were actually 11 patients in whom vasodilatory shock occurred among the 145 at whom we looked prospectively. Only 1 of those was an OHT recipient and 2 were LVAD recipients. So, after removal of the LVAD and OHT recipients there were 8 patients among 136 in whom

this complication developed. Thus vasodilatory shock is a complication that occurred in 6% or 7% of the general cardiac surgical patients whom we studied, excluding the patients undergoing LVAD implantation and OHT. AVP levels were obtained for all these patients and, as I described in my presentation, the AVP levels were inappropriately low in all but 1 of the patients who had vasodilatory shock. All the levels were below 20 pg/mL except 1 that was about 23 pg/mL.

The AVP levels that we expect in patients who are profoundly hypotensive are in the 40 to 50 pg/mL range, and they range as high as 100 pg/mL in some reports. All our patients who were in profound vasodilatory shock therefore had grossly deficient secretion of AVP.

With respect to whether all patients responded similarly to AVP, we tried to analyze this by separating patients into 3 groups according to the degree of hypotension. All patients responded, but some responded more than others. If the mean arterial pressure is 65 mm Hg and AVP is administered, the pressure rises to 80 mm Hg. If the mean arterial pressure is 45 mm Hg and AVP is administered, the pressure rises to 80 mm Hg. So you might say, "Why give AVP to patients whose mean arterial pressure is 65 mm Hg?" That is a good point. You may not want to give it to those patients. You may instead want to give those patients a little norepinephrine. You should know, however, that in our opinion this hormone seems to act as a replacement therapy for some deficiency, rather than as an exogenous pressor. We do not titrate it to increasing doses. We do not give more AVP when we want a higher blood pressure. We just give a single dose, and it seems to be effective in most cases.

Dr Karl H. Krieger (*New York, NY*). These are really compelling data. In your current practice, if you have a patient at high risk, for example a patient with poor ejection fraction who has been receiving ACE inhibitors and diuretics, might you give AVP prophylactically? Is there any contraindication to giving AVP; have you had any problems with it?

Dr Argenziano. That is a good question. Certainly, as you might imagine, AVP is now stocked in both our intensive care units and operating rooms. We use it quite frequently. We have not yet, however, given it prophylactically to patients who are not hypotensive. We have reserved it for patients with demonstrated need. It must be remembered that we are using AVP to treat vasodilatory shock. Most patients in hemodynamically unstable condition before a cardiac operation are not in vasodilatory shock but rather in cardiogenic shock, in which the vascular tone is actually quite high. We would not expect AVP to have an effect in those cases, because it is not an inotrope but rather a pure vasoconstrictor. We generally reserve AVP for patients in whom vasodilatory shock develops after CPB, but we certainly have used it in a few cases in which this syndrome developed before the operation.