Early On–Cardiopulmonary Bypass Hypotension and Other Factors Associated With Vasoplegic Syndrome

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Background—Vasoplegic syndrome is a form of vasodilatory shock that can occur after cardiopulmonary bypass (CPB). We hypothesized that the severity and duration of the decline in mean arterial pressure immediately after CPB is begun can be used as a predictor of patients will develop vasoplegia in the immediate post-CPB period and of poor clinical outcome. We quantified the decline in mean arterial pressure by calculating an area above the mean arterial blood pressure curve.

Methods and Results—We retrospectively analyzed 2823 adult cardiac surgery cases performed between July 2002 and December 2006. Of these 2823, 577 (20.4%) were vasoplegic after separation from CPB. We found that 1645 patients (58.3%) had a clinically significant decline in mean arterial pressure after starting CPB (area above the mean arterial blood pressure curve >0) and were significantly more likely to become vasoplegic (23.0% versus 16.9%; odds ratio, 1.26; 95% confidence interval, 1.12 to 1.43; $P<0.001$). These patients were also far more likely either to die in hospital or to have a length of stay >10 days (odds ratio, 3.30; 95% confidence interval, 1.44 to 7.57; $P=0.005$). Additional risk factors for developing vasoplegia that were identified included the additive euroSCORE, procedure type, prebypass mean arterial pressure, length of bypass, administration of pre-CPB vasopressors, core temperature on CPB, pre- and post-CPB hematocrit, the preoperative use of β-blockers or angiotensin-converting enzyme inhibitors, and the intraoperative use of aprotinin.

Conclusions—The results of this investigation suggest that it is possible to predict vasoplegia intraoperatively before separation from CPB and that the presence of a clinically significant area above the mean arterial blood pressure curve serves as a predictor of poor clinical outcome. **(*Circulation*. 2009;120:1664-1671.)**

Key Words: blood pressure ■ cardiopulmonary bypass ■ hemodynamics

Vasoplegic syndrome (vasoplegia) is a well-described form of vasodilatory shock that potentially can occur after separation from cardiopulmonary bypass (CPB). It is a state of low systemic arterial pressure despite high cardiac output and adequate fluid resuscitation characterized by markedly low systemic vascular resistance.[1] The reported incidence ranges from 9% to 44%,[2–5] yet the origin has not been completely elucidated. Vasoplegia has been associated with long-term use of certain drugs (eg, angiotensin-converting enzyme inhibitors, calcium channel antagonists, amiodarone, and heparin),[2–7] as well as patient-specific risk factors such as left ventricular ejection fraction $<35\%$, symptoms of congestive heart failure, and diabetes mellitus.[7,8]

Clinical Perspective on p 1671

Vasoplegia is associated with a poor prognosis. In particular, norepinephrine-refractory vasoplegia has been associated with increased morbidity and mortality.[7,9] Furthermore, the duration of catecholamine-refractory vasoplegia significantly influences outcome. Mortality rates as high as 25% were reported when postoperative vasoplegia persisted for >36 to 48 hours.[10,11] High-dose vasoconstrictor therapy also may lead to the development of ischemia of the distal portions of the upper and lower extremities and mesenteric ischemia.[12,13]

For these reasons, perioperative identification of patients at high risk of developing vasoplegia is an appealing concept that could be of clinical benefit. We hypothesized that the severity and duration of the decline in mean arterial pressure (MAP) immediately after CPB is started, as quantified by the area above the MAP curve (AAC), can be used to identify patients likely to experience post-CPB vasoplegia. As a secondary end point, we looked to determine whether there was a difference in clinical outcome between patients who experienced a significant episode of early on-CPB hypotension and those who did not.

Received August 13, 2008; accepted August 26, 2009.

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Circulation **is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.108.814533**

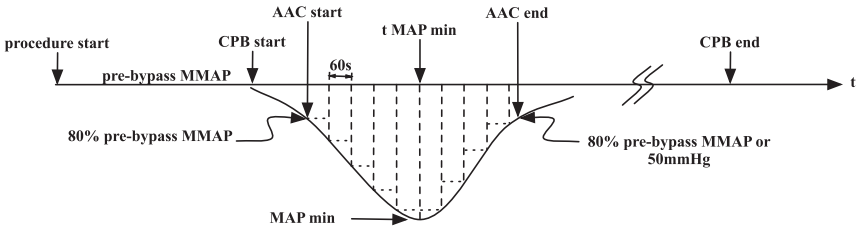

Figure 1. Illustration of AAC calculation.

Methods

Patient Population and Data Collection

After obtaining Institutional Research Board approval, we retrospectively analyzed data from all adult cardiac surgery cases performed at our institution between July 2002 and December 2006 in which CPB was used. These data were extracted from the Anesthesia Information Management System at our institution (Compurecord, Philips Medical Systems, Andover, Mass). The extracted data included patient demographics, procedure type, preoperative medications, intraoperative drug administration and laboratory values, timing of intraoperative events (eg, procedure start time, CPB start time), and intraoperative hemodynamic measurements.

Preoperative Risk Factors

Preoperative risk was assessed with the euroSCORE.[14,15] Additionally, the following preoperative variables were examined: age, gender, preoperative hematocrit, and use of classes of medications, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, heparin, β-blockers, calcium channel blockers, amiodarone, combination antihypertensives (eg, Hyzaar), sulfonylureas, platelet aggregation inhibitors (eg, aspirin, clopidogrel), and statins. Classification of preoperative medications was done as previously described.[16] Any preoperative medications not in the above categories were ignored. Intraoperatively, we considered the hematocrit at both the start and end of CPB, prebypass median MAP (MMAP), procedure type, length of bypass in hours, use of antifibrinolytics or any vasopressors before CPB, and lowest temperature measured during CPB.

Identification of Vasoplegic Patients

The amount of vasopressor support required to separate from CPB was quantified and used as a surrogate marker of vasoplegia. This was done by determining the maximum infusion rate of the 4 most commonly used catecholamine/vasopressor medications at our institution (epinephrine, norepinephrine, dopamine, and vasopressin). We examined catecholamine/vasopressor dosages beginning 20 minutes before the recorded end-CPB time and continuing until the end of the procedure. Units were normalized to nanograms per kilogram per minute for epinephrine and norepinephrine, milligrams per kilogram per minute for dopamine, and units per hour for vasopressin, and the following cutoffs were set to define post-CPB vasoplegia: epinephrine/norepinephrine, ≥ 150 ng $\cdot$ kg^{-1} $\cdot$ min^{-1}; dopamine, ≥ 10 μg $\cdot$ kg^{-1} $\cdot$ min^{-1}; or vasopressin, ≥ 4 U/h. Any patient requiring less than these amounts or no vasopressors at all was categorized as not having experienced post-CPB vasoplegia.

Measurement of Intraoperative Hemodynamic Data

For all cases, data were recorded by the Anesthesia Information Management System from the hemodynamic monitoring system once every 15 seconds. Data were flagged as invalid either automatically (eg, MAP >200 mm Hg) or manually by the anesthesiologist. Cases with incomplete systemic pressure data (continuous gaps exceeding 1 minute) between the start and end of CPB were excluded, as were cases with duplicate events.

Calculation of AAC

First, a baseline MAP was established by calculating the MMAP from the start of the procedure until the onset of CPB. A priori, we defined a clinically significant AAC (AAC >0) as a decline in MAP from this baseline of $>20\%$ within the first 5 minutes of CPB that lasted >2 minutes. These cutoffs were chosen on the basis of general consensus among clinicians that a 20% intraoperative variation in MAP is not clinically significant for most patients[17] and that any decrease $>20\%$ beyond the first 5 minutes likely represented manipulation by the perfusionist. If the MAP never declined $>20\%$ within the first 5 minutes of CPB, the AAC was by definition set to be 0.

Once a case with a clinically significant AAC was identified, the on-CPB period was divided into 1-minute epochs, and an MMAP was calculated for each epoch. A 1-minute median was used to filter out any monitoring artifacts or episodes of transient hypotension related to intentional decreases in perfusion pressure to facilitate surgical maneuvers (eg, aortic cross-clamp application).[18] The end point for the AAC calculation was the time at which the MMAP returned to 80% of the baseline MMAP, or 50 mm Hg, for 2 consecutive epochs. If this criterion was not met, then the off-CPB time was used as the end point. Multiple potential end points were required to ensure that all cases were processed correctly and not assigned a potentially "infinite" AAC.

The AAC was then calculated by multiplying the magnitude of each epoch (ie, epoch MMAP minus baseline MMAP) by the duration of each epoch (1 minute$=0.017$ hours) and summing the results for all epochs in the interval between AAC start and AAC end. The result was an approximation of the AAC measured in millimeters of mercury per hour (Figure 1).

The shape of the curve (ie, duration and minimum MAP) was characterized by examination of several variables (Table 1). These variables were chosen on the basis of the hypothesis that a short steep decline and recovery might have different physiological implications compared with a more gradual decline and/or recovery.

Statistical Methods

For 2-group comparisons, we used χ^2 tests for categorical variables and either Student t tests or nonparametric Wilcoxon tests for continuous variables as appropriate. To compare whether any of the AAC descriptive variables listed in Table 1 served as better predictors of vasoplegia than the AAC, logistic regression analysis was performed for each variable, stratified by whether the MAP decreased within the first minute (early decline) or between minutes 1 and 5 inclusive (late decline). The analysis was repeated without stratification to test whether an early MAP decline was itself an effect modifier. For continuous variables, an additional quadratic term was assessed for its significance. The P value and the area under the receiver-operating characteristic curve (ie, c statistic) were used to evaluate predictive strength.

Multivariable Modeling

Stepwise logistic regression analyses were performed to identify significant predictors of vasoplegia. The covariates considered in the initial model included clinically significant AAC (yes/no); all AAC-related variables listed in Table 1; early MAP decline (yes/no); age; gender; euroSCORE; preoperative, prebypass, and postbypass hematocrit; pre-CPB to post-CPB change in hematocrit; prebypass MMAP; temperature on CPB; procedure type; length of CPB in hours; use of any of the preoperative medications listed in Table 2;

Table 1. AAC Parameters

Parameter	Mean	SD	Median	IQR	Range
Baseline MMAP, mm Hg	78.34	9.16	78.31	72.69–83.92	29.69–131.09
AAC, mm Hg · h	…	…	1.5	0.9–2.6	0.2–31.7
AAC length, s	…	…	180	120–240	0–3900
Delay before MMAP decline, s	…	…	0	0–60	0–240
Minimum MMAP, mm Hg	38	7	38	33–44	20–50
Time to reach minimum, s	…	…	60	30–120	30–1800
MAP at end of AAC, mm Hg	61	11	59	53–67	40–106
Maximum MAP decline, mm Hg	40	10	40	33–47	12–81
Relative MAP decline, %	50.6	10.3	50.9	43.5–57.9	20.6–78.6
Initial slope, mm Hg/s	−0.74	0.42	−0.68	−1.00–−0.41	−2.05–−0.02
Recovery slope, mm Hg/s	…	…	0.24	0.12–0.43	0–2.54

IQR indicates interquartile range. n=1645.

and the intraoperative use of antifibrinolytics or any vasopressors before CPB. For the euroSCORE, the correlation between the additive score and the log-transformed logistic score was 0.99; therefore, only the additive score was used. The stepwise procedure for model selection allowed AAC-related variables to enter the model in place of or in addition to the AAC binary variable. Results were reported as odds ratios (ORs) and 95% confidence intervals (CIs) for the identified risk factors. Figure 2 was generated through the use of the smoothing technique, which involves local least-squares fitting of the data with a quadratic polynomial function.[19] The biased-corrected Akaike's information criterion was used as a guide for choosing the smoothing parameter, which was chosen to be 1 because it had the smallest Akaike's information criterion value.

Model Validation

We used the bootstrap method to validate the model selection procedure.[20] We generated 1000 internal bootstrap samples with replacement. For each sample, the same stepwise model selection procedure was used, leading to potentially different selection of significant vasoplegia predictors. The robustness of this procedure was evaluated by the consistency of the selected covariates. The bootstrap estimate of the coefficient for a clinically significant AAC was then compared with that from the model using the whole data. The predictive strength of the model selected by this procedure was assessed by calculating the area under the receiver-operating characteristic curve with the nonparametric 0.632 estimate. This estimate uses a weighting of $0.368\times apparent + 0.632\times$average (*test*) to correct for overoptimism in the sample estimate, where *apparent* is the estimate from the entire data set and *test* is the estimate from patients not selected in the bootstrap sample.[21,22]

All statistical analyses were carried out with SAS version 9.1.3 (SAS Institute, In., Cary NC). The level of statistical significance for hypothesis testing and entry and stay criteria for stepwise regression was set at 0.05.

Clinical Outcome

For outcomes, we examined hospital length of stay and in-hospital mortality. A bad outcome was defined as the composite of length of stay >10 days or death in the hospital. Odds ratios were calculated to determine the likelihood of a bad outcome among patients with/without a clinically significant AAC and with/without post-CPB vasoplegia. We also calculated the MMAP from 20 minutes before separation from CPB to 30 minutes after separation from CPB to gain insight into how well the post-CPB vasoplegic state was pharmacologically managed.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Table 2. Patient Characteristics

Variable	Mean or Median (SD or IQR)/N(%)
Mean age, y	62.91 (14.38) [18–99]
EuroSCORE	
Additive	7.09 (3.75) [0–24]
Logistic	7.03 (3.19–15.96) [0.88–95.82]
Male gender, n (%)	1753 (62.1)
Preoperative medications, n (%)	
ACE inhibitor	557 (19.7)
ARB	257 (9.1)
Heparin	187 (6.6)
β-Blocker	992 (35.1)
Calcium channel blocker	333 (11.8)
Class 3 antiarrhythmic	49 (1.7)
Combination antihypertensive	33 (1.2)
Sulfonyl hypoglycemic	153 (5.4)
Platelet aggregation inhibitor	857 (30.4)
HMG-CoA reductase inhibitor (statins)	901 (31.9)
Intraoperative medications, n (%)	
Aprotinin	841 (29.8)
Aminocaproic acid	1356 (48.0)
Pre-CPB pressor	168 (6.0)
Procedure type, n (%)	
Coronary artery bypass grafting*	1195 (42.3)
Valve repair/replacement	838 (29.7)
Aortic graft/repair†	389 (13.8)
Heart failure treatment‡	35 (1.2)
Reoperation CABG or valve	72 (2.6)
Other§	294 (10.4)
Mean length of CPB, min	164.40 (70.78) [12–631]
On-pump temperature, °C	28.7 (6.6) [10.0–37.0]
AAC >0	1645 (58.3)
Vasoplegic as per criteria	577 (20.4)

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; and CABG, coronary artery bypass graft surgery. Values are mean or median (SD) [interquartile range] as appropriate.

*Includes single-vessel and multivessel grafts and any graft type.

†Includes ascending, transverse, and thoracic grafts.

‡Includes heart transplants, ventricular assist device implantation, and ventriculostomies.

§Includes all cases with undocumented procedure codes (6%) or infrequently performed procedures (<1%).

Results

Between July 2002 and December 2007, 3322 adult cardiac surgeries were performed at our institution. Of these, 499 cases (15%) were excluded because of data entry errors, missing data, or incomplete data. The final data set included 2823 cases. Outcomes data were available for 2636 patients

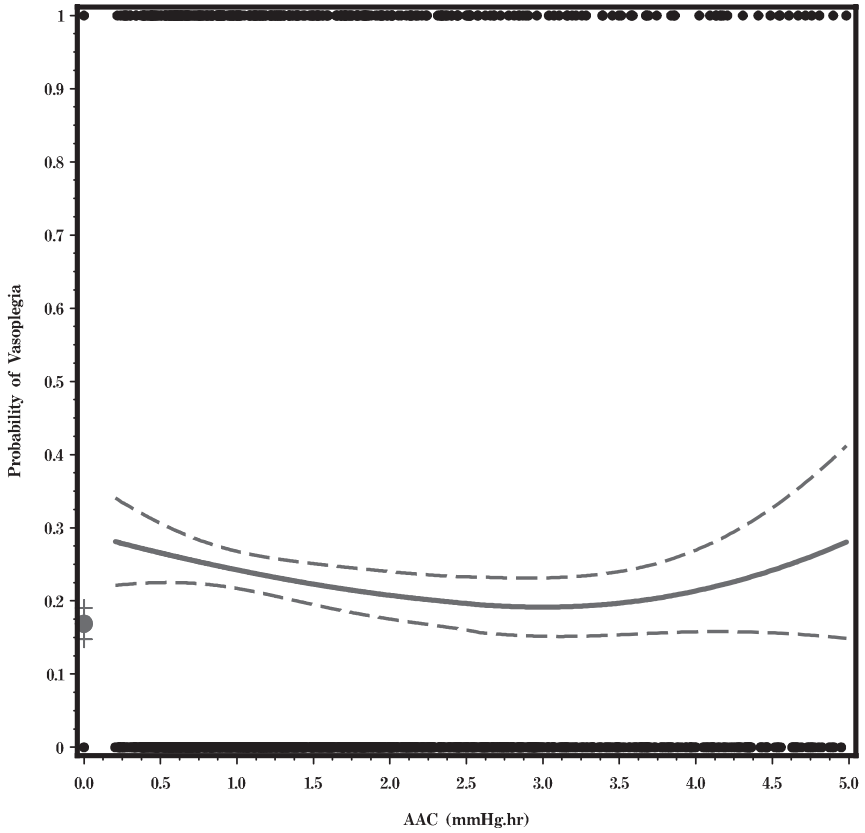

Figure 2. Probability of vasoplegia as a function of AAC.

(93.4%). Baseline characteristics of the patients are shown in Table 2. Five hundred seventy-seven patients (20.4%) received infusions of at least 1 high-dose catecholamine or vasopressor agent and were classified as having experienced post-CPB vasoplegia (Table 3). The majority of vasoplegic patients (>70%) required >1 agent. The mean baseline MMAP among all patients was 78.34 mm Hg (SD, 9.16 mm Hg). The AAC was clinically significant in 1645 patients (58.3%). In all cases with a clinically significant AAC, the MAP returned to 80% of baseline, and the alternate end-point definitions were not used. The median length of early on-CPB hypotension among patients with a clinically significant AAC was 180 seconds (range, 0 to 3900 seconds), with a mean MMAP of 38 mm Hg. These results are summarized in Table 1.

Univariable Analysis: AAC Parameters

Of the parameters listed in Table 1, only the initial decline in MAP (both relative and absolute) was identified as being associated with an increased risk of vasoplegia (β coefficient, -0.038, $P<0.001$ for absolute decline; -0.022, $P=0.0002$ for relative decline). However, the direction of the association was nonintuitive; a smaller decline was associated with a greater chance of vasoplegia. The only other descriptive variable that showed some degree of association with vasoplegia was the slope of the initial decline in MAP. This association was nonlinear (quadratic) and apparent only among patients with a late decline in MAP (β coefficient, -2.863, $P=0.04$ for the linear component; -3.732, $P=0.007$ for the quadratic component). Threshold analysis plus visual inspection of the smoothed curve of slope versus the probability of vasoplegia revealed a cutoff point around -0.55 mm Hg/s (data not shown). For all of these descriptive measures, the c statistic was weak (between 0.50 and 0.62; data not shown), suggesting that even when significant the association with post-CPB vasoplegia was poor.

Table 3. Mean Infusion Rates in Vasoplegic Patients

Infusion Drug	n (% vasoplegic patients)	Mean (SD) Infusion Rate
Vasopressin, U/h	249 (43.2)	5.8 (12.6)
Epinephrine, $ng \cdot kg^{-1} \cdot min^{-1}$	440 (76.3)	177.4 (83.6)
Norepinephrine, $ng \cdot kg^{-1} \cdot min^{-1}$	352 (61.0)	166.3 (95.7)
Dopamine, $\mu g \cdot kg^{-1} \cdot min^{-1}$	14 (2.3)	5.5 (2.3)

Association of AAC With Post-CPB Vasoplegia

In contrast, the average probability of vasoplegia for all patients with a clinically significant AAC was 23.0% compared with 16.9% for patients with no measurable AAC (OR, 1.26; 95% CI, 1.12 to 1.43; $P<0.001$). Figure 2 graphically illustrates the relationship between the AAC and post-CPB vasoplegia. The curve demonstrates a nonlinear, nonmonotonic increase in the risk of vasoplegia as the AAC increases. To further characterize this relationship, we quantized the AAC into 1-mm Hg · h increments (Table 4), which showed that patients with either a small AAC (<2 mm Hg · h) or a very large AAC (>4 mm Hg · h) were at increased risk, whereas those with a moderate AAC were not.

Table 4. OR of Vasoplegia per Interval Increase in AAC

AAC, mm Hg · h	OR for Vasoplegia (95% CI)			
	Univariable Analysis	*P*	Multivariable Analysis	*P*
0	…		…	
>0–1	1.79 (1.40–2.31)	<0.001	1.82 (1.34–2.48)	0.001
>1–2	1.38 (1.08–1.78)	<0.011	1.74 (1.29–2.35)	0.003
>2–3	1.14 (0.81–1.60)	0.442	1.42 (0.95–2.11)	0.086
>3–4	1.22 (0.76–1.95)	0.415	1.43 (0.80–2.55)	0.233
>4	1.58 (1.10–2.28)	0.014	1.87 (1.17–2.95)	0.007

For the univariable analysis: AAC >0 to 1 versus >2 to 3, $P=0.014$; versus AAC >3 to 4, $P=0.07$; versus AAC >4, $P=0.53$. For the multivariable analysis: all pairwise comparisons among the 5 groups of AAC >0 had $P>0.2$.

Multivariable Model and Model Validation

In the multivariable analysis, stepwise logistic regression identified the variables listed in Table 5 as being associated with post-CPB vasoplegia. Of note, the binary AAC >0 variable was selected by the stepwise regression, whereas the "simpler" AAC descriptive variables (eg, minimum MAP) were not. When quantified as in the univariable analysis, most of the AAC >0 subgroups still appeared to be significantly different from the AAC=0 group; however, the contrasts among themselves became less evident (Table 4). In a similar model in which the linear and quadratic terms of continuous AAC variable were used, the β coefficient for AAC was 0.170 ($P<0.001$) for the linear component and −0.011 ($P=0.004$) for the quadratic component. Nevertheless, when the binary AAC variable was also included the model, the β coefficient for AAC was 0.035 ($P=0.585$) for the linear component and −0.004 ($P=0.284$) for the quadratic component. These results suggest that the most significant predictor of post-CPB vasoplegia is whether an AAC was present and that other descriptors of the AAC appeared to be less relevant. Other variables that appeared in the model were preoperative β-blocker or angiotensin-converting enzyme inhibitor use, procedure type, use of aprotinin or pressors before CPB, pre-CPB MMAP, length of CPB, on-CPB temperature, and pre- and post-CPB hematocrit. Validation using bootstrap showed a high degree of consistency among the covariates included in the multivariable model. The presence of a clinically significant AAC appeared in at least 99.4% of the repetitions. The 0.632 estimate of the area under the receiver-operating characteristic curve was $0.368\times0.813+0.632\times0.817=0.816$, suggesting that our model had good power.

Clinical Outcome

Outcome data were available for 2636 patients (93.4%). Of these patients, 789 (29.9%) died in hospital (n=86) or had a length of stay >10 days (n=742). Of the 1087 patients with an AAC >0, 357 (32.8%) had a bad outcome versus 432 of 1549 (27.9%) with an AAC=0 (OR, 3.30; 95% CI, 1.44 to 7.57; $P=0.005$). Among vasoplegic patients, 308 of 537 (57.4%) had a bad outcome versus 481 of 2099 (22.9%) nonvasoplegic patients (OR, 2.62; 95% CI, 2.05 to 3.36; $P<0.001$). Vasoplegic patients had a median post-CPB MAP of 70±9 mm Hg compared with 71±7 mm Hg in the group that did not require high dosages of catecholamine or vasopressor infusions ($P=0.003$).

Table 5. Risk Factors for Post-CPB Vasoplegia

Risk Factor	β Coefficient (SE)	OR (95% CI)	*P*	Appearance in 1000 Bootstrap Validations, %
Intercept	−7.810 (0.932)			100
AAC >0	0.530 (0.119)	1.70 (1.35–2.15)	<0.001	99.4
New additive euroScore, per 1 score increase	0.140 (0.017)	1.15 (1.11–1.19)	<0.001	100
Preoperative β-blocker use	0.272 (0.124)	1.31 (1.03–1.67)	0.028	62.7
Preoperative ACE inhibitor use	0.311 (0.140)	1.37 (1.04–1.80)	0.026	56.2
Procedure type	…	…	…	99.6
Valve vs CABG	0.419 (0.137)	1.52 (1.16–1.99)	0.002	…
Aortic graft/repair vs CABG	−0.743 (0.250)	0.48 (0.29–0.78)	0.003	…
Heart failure treatment vs CABG	0.714 (0.331)	2.04 (1.07–3.90)	0.031	…
Reoperation vs CABG	−0.736 (0.500)	0.48 (0.18–1.27)	0.138	…
Other vs CABG	0.316 (0.187)	1.37 (0.95–1.98)	0.026	…
Pre-CPB aprotinin use	0.403 (0.125)	1.50 (1.17–1.91)	0.001	85.3
Pre-CPB pressor use	1.240 (0.209)	3.59 (2.39–5.40)	<0.001	100
Pre-CPB hematocrit, per 5% increase	0.128 (0.048)	1.14 (1.04–1.25)	0.008	53.6
Pre-CPB MMAP, per 5-mm Hg decrease	0.188 (0.034)	1.21 (1.13–1.29)	<0.001	100
On-CPB temperature, per 1°C increase	0.102 (0.014)	1.11 (1.08–1.14)	<0.001	100
Length of bypass, per 30-min increase	0.321 (0.030)	1.38 (1.30–1.46)	<0.001	100
Post-CPB hematocrit, per 5% increase	0.299 (0.069)	1.35 (1.18–1.55)	<0.001	98.4

Abbreviations as in Table 2. The probability of vasoplegia is $P(\text{vasoplegia})=e^y/(1+e^y)$, where y is calculated from the β coefficients listed above. For binary (yes/no) variables, the indicator function I(C) is used; it is equal to 1 if the variable is present and 0 otherwise.

Discussion

The vasoplegic syndrome was first characterized as a distinct clinical entity in the mid 1990s.[10,23,24] The cause is multifactorial, with the net effect being the pathological activation of several vasodilator mechanisms and resistance to vasopressors.[1,25,26]

Although Cremer et al[23] and Kristof and Magder[27] have characterized the postoperative hemodynamics of vasoplegic patients, we believe that the present study is the first to examine the relationship between intraoperative hemodynamics and post-CPB vasoplegia. Patients who had a clinically significant decline in MAP (AAC >0) at the onset of CPB were significantly more likely to develop post-CPB vasoplegia. The relationship between AAC and vasoplegia appears to be nonlinear, with patients in the highest and lowest quartiles of the stratified AAC showing a more significant incidence of vasoplegia than those with a more moderate AAC. This led us to theorize that patients can be divided into 3 groups based on their initial response to CPB.

Group 1

This group is characterized by a small AAC with a steep initial slope. These patients appear hemodynamically stable for approximately the first minute after CPB is started but then have an immediate and profound decline in MAP. We believe that this subpopulation of patients overexpress inflammatory mediators once exposed to the CPB circuit, and the sudden decline in blood pressure at the onset of CPB may be a hypersensitivity reaction triggered by the exposure of blood to nonphysiological surfaces. Increasing the flow of the CPB machine and infusing vasoconstrictive agents provide symptomatic treatment to restore perfusion pressure but do not address the proinflammatory state, which predisposes patients to subsequent vasoplegia after separation from CPB. This is consistent with the theory that post-CPB vasoplegia can be viewed as a form of the systemic inflammatory response syndrome.[9,28]

Group 2

These patients show a long but more gradual decline in MAP that starts immediately on exposure to the CPB circuit. However, as opposed to group 1, they respond poorly and only partially to clinical interventions, as indicated by their large AAC. We believe patients in this group have endothelial dysfunction that results in derailment of the systems responsible for maintaining vascular tone. Landry and Oliver[1] proposed that the activation of ATP-sensitive potassium channels (K_{ATP} channels) in the plasma membrane of vascular smooth muscle, activation of the inducible form of nitric oxide synthase, and deficiency of the hormone vasopressin are likely responsible for the reduction in vascular tone. K_{ATP} channels are typically activated by decreased ATP concentrations and by increased intracellular concentrations of hydrogen ions and lactate.[29,30] The inflammatory state induced by CPB also leads to an overexpression of nitric oxide with subsequent vasodilatation that responds poorly to vasoconstrictors.[31] Morales et al[32] showed support for the vasopressin hypothesis by demonstrating that a significant reduction in vasopressor support was required to separate from CPB when low-dose vasopressin was administered to patients with depleted endogenous vasopressin stores. All of these factors are likely to play a role in the inability of certain patients to maintain adequate perfusion pressure at the start of CPB and their subsequent development of post-CPB vasoplegia.

Group 3

These patients showed a more rapid decline in their MAP than group 2, had a lower MAP nadir than either group 1 or 2, but responded within a reasonable time frame to clinical interventions, as evidenced by their moderate AAC. We believe that the reaction seen in this subpopulation is neither immunologically nor hormonally mediated but represents an exacerbation of the "mechanical" dysfunction of the vascular system resulting from acute hemodilution and loss of pulsatile perfusion. In other words, these patients are physiologically similar to patients with no clinically significant AAC. Consequently, as opposed to the other 2 groups, no sequelae persist after the CPB period.

In addition to the AAC, several other intraoperative indicators of hypotension appeared in the multivariable model as being associated with post-CPB vasoplegia, notably the prebypass MAP and, more dramatically, the use of pre-CPB vasopressors (OR, 3.59). Surprisingly, aprotinin was associated with an increased, not a decreased, risk of vasoplegia (OR, 1.50; 95% CI, 1.17 to 1.91; $P=0.001$). This counterintuitive result is likely due to skew in the distribution of aprotinin use; ie, aprotinin was usually used in sicker patients undergoing more invasive procedures (mean EuroSCORE for aprotinin use, 8.69 versus 6.41 for nonuse; $P<0.0001$). Overall, no descriptive parameter of the AAC had sufficient predictive power (by receiver-operating characteristic curve analysis) to be used as a "simple" measure of the significance of on-CPB hypotension. The counterintuitive small decrease in MAP associated with a greater risk of vasoplegia was found to be the result of the fact that a small decline in MAP was highly correlated with a low prebypass MAP.

Despite the excellent management of post-CPB vasoplegia (as evidenced by the clinically irrelevant difference in post-CPB MAP between vasoplegic and nonvasoplegic patients of 1 mm Hg), the outcome among patients with a clinically significant AAC was very poor. The odds were >3 times greater to either require hospitalization for >10 days or to die while hospitalized. This strongly suggests the importance of managing the underlying factors responsible for early on-CPB hypotension.

The only cardiac surgery subset that was not at increased risk for vasoplegia versus coronary artery bypass graft surgery was the group undergoing thoracic aortic surgery. It is likely that the severe hypothermia (core temperatures, 13°C to 16°C) used for neuroprotection during periods of circulatory arrest may be related to this finding.[33,34] Extreme cooling may blunt the inflammatory response induced by CPB.[35,36] Increased plasma viscosity during hypothermic perfusion may also play an important factor. Our results corroborate the protective effect of hypothermia, with increasing on-CPB temperature associated with a 10% per 1°C increase in the probability of vasoplegia.

The patients included in this study were representative of a cardiac surgery population seen at a tertiary care hospital,[37] and the incidence of vasoplegia (20.8%) was comparable to that of other recent studies.[4,6] One limitation in our study is the lack of information on the amount and type of infusion drugs administered by the perfusionist. Thus, we were unable to quantify the degree of intervention for a given decline in MAP while on CPB. Our institutional protocol requires perfusionists to use phenylephrine as their first-line medication and norepinephrine as the secondary medication for hypotension once CPB flows exceed 2.6 $L \cdot min^{-1} \cdot m^{-2}$. We cannot, however, account for practice variability among perfusionists and anesthesiologists, who may have set different target perfusion pressures or varying transfusion algorithms.

Another possible limitation is that we did not use stricter hemodynamic criteria to identify vasoplegic patients. Although it is our practice to use pulmonary artery catheters in all patients, hemodynamic data are obtained after separation from CPB, and there are no protocols in place defining the exact timing at which these data are obtained. This made it likely that the values for systemic vascular resistance and cardiac output were obtained after treatment, which would mask the true extent of vasoplegia. Posthoc analysis of the available systemic vascular resistance and cardiac output data showed this likely to be true because there was no significant difference between the vasoplegic and nonvasoplegic groups for either parameter (data not shown).

Numerous interventions for the treatment of vasoplegic syndrome have targeted the inflammatory cascade with mixed results.[34–36] This is possibly a consequence of poor patient selection, exposing a large number of subjects unnecessarily to prophylactic interventions. A drug with promising results is methylene blue, which has been investigated as a salvage drug for patients with catecholamine-resistant vasoplegia.[11,38] To date, most investigations have used methylene blue as an intervention once catecholamine-resistant vasoplegia has already occurred. Consequently, before randomized controlled trials are undertaken, it is prudent to identify the population most at risk for post-CPB vasoplegia. The results of the present investigation provide a model that can be used for this purpose. Future developments in monitoring technology may allow the real-time calculation of an AAC or a similar measure. This information will aid in the intraoperative management of patients at risk and in the development of rational and selective inclusion criteria for trials of new therapies.

Disclosures

None.

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CLINICAL PERSPECTIVE

Vasoplegic syndrome is a well-described clinical entity that can occur after separation from cardiopulmonary bypass and is associated with a poor prognosis. The goal of this retrospective review was to explore the relationship of early arterial hypotension after cardiopulmonary bypass is begun and the subsequent development of vasoplegic syndrome after separation from cardiopulmonary bypass. Additionally, we were able to identify other factors that were associated with vasoplegic syndrome and build a model that could predict the likelihood of an individual patient becoming vasoplegic. By adequately stratifying patients according to their risk, we hope that future studies can be designed to test the effectiveness of therapeutic measures aimed at reducing the incidence of vasoplegic syndrome.