

Risk assessment and outcomes of vasoplegia after cardiac surgery

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Abstract

Objective The aim of this study was to analyze risk factors and outcomes of vasoplegia after cardiac surgery based on our experience with almost 2000 cardiac operations performed at our institution.

Methods We retrospectively analyzed patients who underwent cardiac surgery with cardiopulmonary bypass (CPB) between 2011 and 2013. Data were available for a total of 1992 patients. We defined vasoplegia as hypotension with persistently low systemic vascular resistance (<800 dyn/s/cm) and preserved Cardiac Index (>2.5).

Results The rate of vasoplegia in our cohort was 20.3% ($n = 405$). The incidences of mild, moderate, and severe vasoplegia were 13.2, 5.7, and 1.5%, respectively. Factors that increased risk of vasoplegia included valve operations, heart transplants, dialysis-dependent renal failure, age >65, diuretic therapy, and recent myocardial infarction. B blocker therapy was protective against vasoplegia.

Conclusion Vasoplegic syndrome is still a frequently occurring adverse event following cardiac surgery. In high risk patients for vasoplegia, it may be sensible to proceed with preoperative volume loading (instead of diuresis), initiation of low dose vasopressin therapy if needed, and attempting to up titrate beta-blocker therapy.

Keywords Vasoplegia · Cardiac surgery · Risk stratification · Outcomes

Introduction

Profound hypotension caused by systemic inflammatory response is a well established phenomenon after cardiopulmonary bypass [1–4]. This vasodilatory state known as “vasoplegic syndrome” is caused by release of cytokines, such as interleukin-6, interleukin-8, bradykinin and by endothelial injury [5–7]. Incidences vary from 10 to 30% of cardiac surgical procedures, depending on how vasoplegia is defined [1–3, 8]. It is associated with significant morbidity, prolonged ICU stay, greater transfusion requirements and increased mortality [2, 3, 9–11]. Several risk factors have been identified such as low ejection fraction (EF <35%), longer duration of CPB, the preoperative use of angiotensin converting enzymes (ACE) inhibitors, male sex, valve procedures, heart transplants, LVADs and blood transfusions [9–11]. Moreover, it is known to increase the length of hospital stay and early readmissions [2, 8, 9]. Thus, it is prudent to better define predisposing factors and determine better treatment strategies for vasoplegia, to improve patient outcomes and also alleviate the economic burden on healthcare systems, especially in the current era of extensive healthcare reforms. A wide array of definitions has been published in the literature with aims at understanding prevention, early identification, and efficient treatment [1–4, 8–11]. Despite this, there is yet to be a consensus on risk factors, diagnostic criteria, and the approach to treatment. The aim of this study was to analyze risk factors and outcomes of vasoplegia after cardiac surgery based on our experience with approximately 2000 cardiac operations performed at our institution.

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Methods

With Institutional Research board approval, we retrospectively obtained information on patients from a large single academic center who underwent cardiac surgery with cardiopulmonary bypass (CPB) between 2011 and 2013. Data were available for a total of 1992 patients. Hemodynamic data included blood pressure (BP), Cardiac Index (CI), systemic vascular resistance (SVR), heart rate (HR), central venous pressure (CVP), and pulmonary artery pressure (PA) and were obtained at the time of induction of anesthesia, prior to commencing CPB, after CPB every 15 min, on admission to the cardiothoracic intensive care unit (CT ICU) and then every 4 h for up to 24 h. During these time frames, inotropic and pressor support was also documented.

Patient data

Patient demographics, preoperative characteristics and comorbidities included age, sex, race, body surface area, body mass index (BMI), preoperative myocardial infarction (within 5 days of surgery), previous percutaneous coronary intervention (PCI), heart failure (ejection fraction <35%), arrhythmia, pacing device, preoperative albumin, liver function tests, hypertension (HTN), diabetes mellitus, (DM), chronic renal insufficiency (CRI), dialysis, chronic obstructive pulmonary disease (COPD), thyroid disease, peripheral vascular disease (PVD) and previous sternotomy. Chronic renal insufficiency was defined as GFR <60 ml/min/m² in patients that do not require dialysis. Dialysis-dependent renal failure was defined for patient who were on chronic hemodialysis or peritoneal dialysis, or if they received one or more dialysis sessions postoperatively. Operative characteristics included type of surgery, cardiopulmonary bypass (CPB) times, and cross clamp (XCI) times. Outcome variables were 30-day survival, 30-day readmission, length of ICU stay, length of hospital stay and complications. Complications included acute renal failure (ARF), stroke, gastrointestinal bleeding (GIB), pneumonia, reoperation for bleeding, heart failure, utilization of mechanical/extracorporeal assist device (ECMO, IABP, VAD), respiratory failure, tracheostomy. Data were also collected on preoperative medications such as antiplatelet agents, angiotensin-converting enzymes (ACE) inhibitors, beta blockers, statins, diuretics, a-blockers, nitrates, antiarrhythmics, steroids, thyroxine, and anticoagulants.

Definition of vasoplegia

We defined vasoplegia as hypotension with low systemic vascular resistance (<800 dyn/s/cm) and preserved Cardiac

Index (>2.5). More specifically we categorized vasoplegia as: mild: (1) mean arterial pressure (MAP) 50–60 mmHg, (2) administration of one vasopressor, moderate: (1) MAP 50–60 mmHg, (2) administration of two or more vasopressors, or MAP <50 mmHg and administration of one vasopressor and severe: (1) MAP <50 mmHg, (2) administration of two or more vasopressors. Vasopressors utilized vasopressin, phenylephrine, epinephrine or norepinephrine depending on each surgeon's preference.

We collected data at several time points for each patient and as a result many patients experienced vasoplegia of varying severity at different times. For the purpose of our analysis, the worst severity of vasoplegia experienced by each patient was taken into consideration. Intraoperative cardioplegia corresponded to blood pressures, cardiac function and the need for vasopressors after coming off bypass. Pressures during the CPB run were not considered.

Statistical analysis

Data were compared between patients that developed vasoplegia and those who did not using Chi-squared tests for nominal data and Wilcoxon two-sample tests for continuous variables. Nominal data were reported as count and percent whereas, continuous variables were reported as mean, standard deviation, minimum and maximum. Alternatively, Fisher exact tests were used if expected counts were not sufficiently large. Logistic regression models were used to assess the various covariates effect on vasoplegia. A backward stepwise routine was used to generate the most parsimonious model where all variables included were significant. Tests were considered significant at $p < 0.05$. Analyses were performed using SAS 9.2.

Results

Survival, length of ICU and hospital stay and 30-day readmissions

We identified a total of 1992 patients, of which 405 patients (20.3%) had vasoplegia of any severity. Patient demographics, comorbidities and operative characteristics for the vasoplegia and non-vasoplegia groups are demonstrated in Table 1. Within the cohort that developed vasoplegia, 263 (64.9%) had mild, 113 (27.9%) had moderate and 29 (7.2%) had severe vasoplegia. The overall incidences of mild, moderate, and severe vasoplegia were 13.2, 5.7, and 1.5%, respectively. The average SVR in our cohort was 1137 dyn/s/cm⁵ with a range of 241–3146. Vasoconstrictors used for patients with mild vasoplegia were vasopressin (123/263, 47%), epinephrine (72/263, 27%), phenylephrine (45/263, 19%) and norepinephrine

Table 1 Patient demographics, comorbidities and operative characteristics for vasoplegia and non-vasoplegia groups

Variable	Non-vasoplegia (<i>N</i> = 1587)	Vasoplegia (<i>N</i> = 405)	<i>p</i> value
Age	53.9 ± 12.1	51.9 ± 12.5	0.525
Female	667 (42%)	190 (47%)	0.4
Male	920 (58%)	215 (53%)	
Caucasian	1126 (71%)	320 (79%)	0.836
African American	222 (14%)	69 (17%)	
BSA	2.0 ± 0.3	2.0 ± 0.3	0.943
BMI	28.4 ± 5.6	28.2 ± 6.0	0.867
DM	539 (34%)	211 (52%)	0.05
HTN	1333 (84%)	247 (61%)	0.07
CRF	270 (17%)	93 (23%)	0.06
Dialysis-dependent	16 (1%)	32 (8%)	0.01
COPD	286 (18%)	89 (22%)	0.63
PVD	159 (10%)	69 (17%)	0.49
AST	43.0 ± 78.4	45 ± 120.1	0.845
ALT	40.1 ± 71.3	41.6 ± 57.2	0.98
Creatinine	1.3 ± 0.5	1.7 ± 0.6	0.12
CPB time	139.9 ± 41.0	179.7 ± 58.0	0.03
XCl time	82.1 ± 33.9	121.3 ± 31.7	0.01
Resternotomy	143 (9%)	49 (12%)	0.723
Number of transfused PRBC	1.0 ± 3.4	1.5 ± 4.6	0.09
Cardiac Index	2.4 ± 0.54	2.5 ± 0.51	0.828
SVR	1263.0 ± 352	720 ± 151	0.027

p values <0.05 in bold are statistically significant

(23/263, 8%); for patients with moderate vasoplegia, vasopressin (81/113, 71%), epinephrine (72/113, 63%), phenylephrine (51/113, 44%) and norepinephrine (22/113, 19%) and for severe vasoplegia, vasopressin (96%, 28/29), epinephrine (93%, 27/29) and phenylephrine (3/29, 10%).

The overall postoperative mortality rate in our patient cohort was 2.2% (45/1992). Among non-survivors, 68.9% (31/45) experienced vasoplegia of any severity. Of the 1947 patients that survived, vasoplegia was observed in 19.2% (*n* = 374) (*p* < 0.01).

The mean length of ICU stay for non-vasoplegic patients was 3.4 days compared to 6.8 days in those who experienced vasoplegia (*p* < 0.01). Mean time from surgery to discharge in the non-vasoplegic group was 7 days compared to 12 days in vasoplegic patients (*p* < 0.01). The total hospital length of stay averaged 9.5 days among patients who did not experience vasoplegia, while those having experienced vasoplegia averaged 16.1 days (*p* < 0.01).

Being cognizant that other factors impact length of stay, we ran an analysis of covariance to isolate the effect of vasoplegia. The presence of vasoplegia of any severity was associated with an increase in hospital length of stay [mean of +2.87 days, 95% CI (0.83–4.91 days)], intensive care unit length of stay [mean of +1.17 days, 95% CI (0.51–1.83 days)], and days from surgery to discharge [mean of +2.37 days, 95% CI (0.49–4.25 days)]. The occurrence of

vasoplegia of any severity was associated with an increase in 30-day readmission (OR 1.45, 95% CI 1.03–2.05). Finally, vasoplegia was also associated with increased risk of 30-day mortality (OR 3.44, 95% CI 1.58–7.50).

Among the entire patient population (*n* = 1992), there were 233 (11.7%) readmissions within 30 days of discharge. Of those readmitted, 27.5% (64/233) were patients who experienced vasoplegia, whereas 19.4% (341/1759) of patients that were not readmitted, experienced vasoplegia (*p* = 0.01).

We further explored vasoplegia categorized by severities in terms to outcomes of readmission and mortality. Among the 263 patients with mild vasoplegia, 19% (*n* = 50) were readmitted within 30 days and 3.8% (*n* = 10) had postoperative mortality. Among the 113 patients with moderate vasoplegia, the readmission rate was 9.7% (*n* = 11), and mortality was 13.3% (*n* = 15). Among the 29 patients who experienced severe vasoplegia, 10.3% (*n* = 3) were readmitted within 30 days and 20.7% (*n* = 6) had postoperative mortality (Fig. 1).

Mild vasoplegia had an impact on 30-day readmissions (OR 1.79, 95% CI 1.24–2.60), but did not reach statistical significance for postoperative mortality (OR 2.29, 95% CI 0.858–6.09). Moderate vasoplegia had a statistically significant impact on 30-day readmissions (OR 1.81, 95% CI 1.410–1.92), and on 30-day mortality [OR 4.86, 95% CI

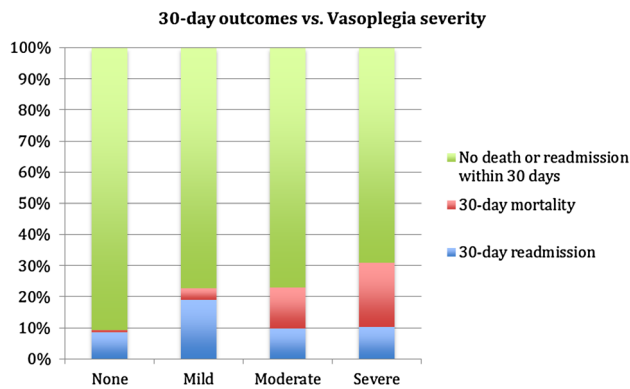


Fig. 1 Outcomes for mild, moderate, and severe vasoplegia

(1.94–12.19)]. Finally, severe vasoplegia had a statistically significant impact on 30-day readmissions [OR 1.68, 95% CI (1.187–2.50)], and on postoperative mortality [OR 4.58, 95% CI (1.14–18.50)].

Vasoplegia risk factor analysis

Univariate analysis revealed several variables that were both risk and protective factors for the development of vasoplegia (Table 2). After these variables were adjusted with multivariate analysis, the majority of factors did not maintain statistical significance (Table 3). Notably, patients who were on chronic beta blocker therapy preoperatively were protected from vasoplegia (OR 0.656, 95% CI 0.5–0.861, $p = 0.01$). There was no correlation between beta blocker dosage and the occurrence of vasoplegia. At our institution the beta blocker we routinely utilize is metoprolol. The average dose of metoprolol in the vasoplegia group was 39.5 vs 37.6 mg in the non-vasoplegia group ($p = 0.525$). Factors that increased risk of vasoplegia included MVR, MVr, other valve operations (tricuspid or pulmonary) OHT, LVAD implantation, DDRF, age >65, diuretic therapy and preoperative (within 5 days) MI (Table 3).

Vasoplegia risk factor analysis by timing

There were three unique profiles of timing such that each vasoplegic patient fell singularly into one category: intraoperative vasoplegia only, postoperative vasoplegia only, and both intraoperative and postoperative vasoplegia. The majority of vasoplegia was experienced intraoperatively. Of the 405 vasoplegic patients, 233 (58%) experience vasoplegia intraoperatively only, 95 (23%) experience vasoplegia postoperatively only, and 77 (19%) experience vasoplegia both intraoperatively and postoperatively. Risk factors for intraoperative vasoplegia include AVR, MVR, MVr, ventricular assist device (VAD), OHT, increasing

age, CPB time, DM, MI, DDRF, and diuretics (Table 4). Protective factors included aspirin and beta blocker therapy. Risk factors for postoperative vasoplegia include operation on pulmonary or tricuspid valves, increasing age, heart failure, CPB time, VDRF, and alpha-antagonist therapy. Beta blocker therapy was protective (Table 5).

Discussion

Although vasoplegia is a well described complication following cardiopulmonary bypass, the substantial impact that this phenomenon has on cardiac surgery outcomes is not entirely appreciated. In our patient cohort, the incidence of vasoplegia was 20.2% and had a significant effect on survival, length of hospital stay and early 30-day readmissions. Univariate analysis revealed several variables that were both risk and protective factors for the development of vasoplegia (Table 2), but after these variables were adjusted, the majority of factors did not maintain statistical significance (Table 3). One would not expect diuretic therapy to maintain significance after multivariate analysis, as these drugs are more commonly utilized in heart failure or patients undergoing valve operations, which are independently significant for causing vasoplegia. Nevertheless, diuretics remained significant after adjustment. Preoperative were protective against vasoplegia. Our other significant risk factors that increased the risk of vasoplegia in our analysis, such as age, valve procedures, heart transplants, VAD implantations, have also been described in previously published data [1–3, 9–11]. There are several new findings to be taken from this large study. Preoperative MI, dialysis-dependent renal failure, and diuretics significantly increased the risk of postoperative vasoplegia, whereas ACE inhibitors, which are traditionally considered as potent vasoplegic agents, were not associated with the occurrence of vasoplegia. Most vasoplegic patients only had mild vasoplegia, which predominantly occurred intraoperatively. Our definitions for mild, moderate, and severe vasoplegia, correlated with increasingly worse outcomes which reinforces the appropriateness and usefulness of these definitions.

Low EF patients are of particular interest. Vasoplegia is common in heart failure patients, who obviously do not tolerate preoperative volume loading. It could be that low EF patients develop postoperative vasoplegia because of preoperative diuresis. This also potentially explains why heart transplant and LVAD patients are prone to postoperative vasoplegia (reviewer 2, comment 1). Low EF patients, that have normal CI and low SVR, are potentially hypotensive because of the occurrence of vasoplegia, and not necessarily from low EF. Beta-blocker therapy and low

Table 2 Univariate association of variables with the development of vasoplegia of any severity

	Odds ratio	95% confidence interval		<i>p</i> value
Coronary arterial bypass graft	1.37	0.94	2.00	0.1
Aortic valve replacement	1.22	0.89	1.66	0.21
Mitral valve replacement	2.28	1.43	3.66	0.01
Mitral valve repair	1.50	1.02	2.20	0.04
Other valve procedure	2.52	1.42	4.46	0.01
Ventricular assist device	12.31	2.63	57.56	0.01
Heart transplant	3.53	1.46	8.55	0.02
Increasing age, per 1 year increase	1.02	1.01	1.03	0.01
Sex	0.90	0.69	1.18	0.45
Caucasian	0.65	0.35	1.21	0.18
African American	1.10	0.57	2.10	0.78
CPB time (10 min increase)	1.08	1.07	1.10	0.01
Diabetes	1.34	1.00	1.79	0.05
Hypothyroidism	0.98	0.52	1.83	0.95
Chronic obstructive pulmonary disease	1.07	0.70	1.63	0.76
Smoking	0.75	0.58	0.98	0.03
Hypertension	0.77	0.58	1.02	0.07
Hyperlipidemia	0.89	0.67	1.17	0.39
Congestive heart failure	1.20	0.85	1.69	0.3
Atrial fibrillation	1.10	0.78	1.54	0.58
Myocardial infarction	1.80	1.29	2.52	0.01
Dialysis-dependent renal failure	3.86	1.72	8.66	0.01
Chronic renal failure	1.10	0.70	1.72	0.68
Stroke	0.72	0.41	1.27	0.26
ACE inhibitors	1.04	0.79	1.38	0.77
Angiotensin receptor blockers	0.86	0.59	1.27	0.45
Aspirin	0.82	0.62	1.07	0.14
Beta blockers	0.66	0.50	0.86	0.01
Steroids	1.74	1.04	2.89	0.03
Nonsteroidal anti-inflammatory drugs	0.59	0.24	1.42	0.24
Preoperative intravenous heparin	1.68	1.07	2.63	0.02
Digoxin	0.97	0.55	1.72	0.91
Alpha-antagonists	1.29	0.62	2.71	0.49
Non-dihydropyridine calcium channel blockers	0.58	0.34	1.00	0.05
Dihydropyridine calcium channel blockers	0.98	0.68	1.43	0.93
Hydralazine	1.43	0.62	3.26	0.4
Nitrates	1.28	0.83	1.98	0.27
Statins	1.09	0.82	1.45	0.57
Levothyroxine	1.10	0.61	1.99	0.75
Diuretics	1.53	1.16	2.02	0.01
Re-exploration for bleeding	1.15	1.06	1.21	0.22
PRBC transfusion (for every 1 unit)	1.25	1.11	1.35	0.09

p values <0.05 in bold are statistically significant

dose vasopressin, would be more appropriate for preventing vasoplegia in this group of patients.

The finding that the occurrence of vasoplegia holds a strong correlation with postoperative mortality is convincing, especially given that when regressed with other significant risk factors for death, it maintains its

significance. This finding indicates just how strongly vasoplegia is linked to mortality as opposed to simply being a clinical illness that leads to longer stays in higher risk units in the hospital.

A variety of risk factors and outcomes data have been reported in retrospective and prospective studies, but there

Table 3 Multivariate analysis of significant variables for development of vasoplegia of any severity (reviewer 1)

	Odds ratio	95% confidence interval		<i>p</i> value
Mitral valve replacement	1.91	1.55	2.86	0.01
Mitral valve repair	1.35	1.01	2.14	0.05
Other valve procedure	2.49	1.36	4.17	0.01
Ventricular assist device	12.55	2.44	57.56	0.001
Heart transplant	3.88	1.66	9.24	0.02
Increasing age, per 1 year increase	1.01	1.01	1.04	0.03
CPB time (10 min increase)	1.05	0.99	1.09	0.06
Diabetes	1.17	0.9	1.55	0.43
Smoking	0.83	0.59	1.02	0.09
Myocardial infarction	1.95	1.33	2.59	0.01
Dialysis-dependent renal failure	3.59	1.44	7.23	0.01
Beta blockers	0.65	0.5	0.86	0.01
Steroids	1.57	0.84	2.65	0.51
Preoperative intravenous heparin	1.23	0.71	2.11	0.34
Diuretics	1.36	1.07	2.38	0.04

p values <0.05 in bold are statistically significant

Table 4 Risk factors for intraoperative vasoplegia

	OR	95% confidence interval	
CABG	1.395	0.926	2.101
AVR	1.417	1.008	1.991
MVR	2.206	1.334	3.650
MV repair	1.782	1.177	2.697
Other valve procedure	2.391	1.312	4.356
VAD	10.413	2.389	45.380
Heart transplant	5.098	2.030	12.803
Increasing age	1.018	1.005	1.031
CPB 10 min increase	1.899	1.533	4.481
Diabetes	1.449	1.056	1.988
Smoking history	0.821	0.616	1.095
Hypertension	0.740	0.542	1.011
Hyperlipidemia	0.946	0.694	1.290
Heart failure	1.074	0.738	1.563
MI	2.082	1.443	3.004
Dialysis	2.570	1.084	6.095
ACE inhibitor	1.185	0.868	1.618
Aspirin	0.665	0.494	0.895
B blockers	0.685	0.507	0.926
Steroids	1.633	0.946	2.817
Preoperative intravenous heparin	1.398	0.865	2.260
Diuretics	1.539	1.135	2.086

Table 5 Risk factors for postoperative vasoplegia

	OR	95% confidence interval	
CABG	1.445	0.850	2.456
AVR	0.854	0.551	1.322
MVR	1.702	0.917	3.160
MV repair	0.836	0.470	1.487
Other valve procedures	2.293	1.110	4.736
VAD	2.040	0.350	11.881
Heart transplant	1.968	0.619	6.259
Increasing age	1.017	1.001	1.034
CPB 10 min increase	1.077	1.051	2.103
Diabetes	1.211	0.813	1.805
Smoking	0.758	0.524	1.096
Hypertension	0.748	0.503	1.111
Heart failure	1.646	1.047	2.585
MI	1.077	0.675	1.719
Dialysis	2.893	1.158	7.229
ACE inhibitor	0.883	0.590	1.322
Aspirin	0.960	0.659	1.398
B blocker	0.608	0.414	0.891
Steroids	1.545	0.781	3.054

is not universal acceptance of these results [1–3, 9–11]. The lack of consistency is hard to pinpoint, but is almost certainly multifactorial. Contributing factors include variability in definitions of vasoplegia, variability in heterogeneity of populations, and limited statistical power. In

1998, Argenziano and colleagues [1] reported a vasoplegia rate of 8% after cardiac surgery and that preoperative EF <35% and ACE inhibitor therapy were independent predictors of vasoplegia. They also demonstrated that vasoplegic patients had low levels of serum arginine vasopressin and that low dose infusion of vasopressin significantly reduced pressor requirements. Mekontso-Dessap et al. [9], in a 2:1 case control study of patients with

preserved LV function, showed that preoperative ACE inhibitors and intravenous Heparin were independent predictors for post CPB vasoplegia. In addition they reported that vasoplegic syndrome was associated with longer length of ICU and hospital stay, but without any differences in early postoperative mortality. These results partially correspond to those reported in our analysis, especially in regards to the effect of vasoplegia on early mortality. This study though only included 36 vasoplegic patients, and was limited by statistical power. Other studies have reported a mortality rate of 10% in patients with profound vasoplegia [2, 3, 9]. Levin et al. [2], reported a vasoplegia rate of 20.4% in 2823 patients that underwent cardiac surgery and showed that vasoplegia was associated with increased mortality and length of hospital stay. In addition, they reported that both b-blocker and ACE inhibitors were risk factors for vasoplegia. Alfirevic et al. [11], in an analysis of 26,000 patients that underwent cardiac surgery with CPB, showed that red blood cells, fresh frozen plasma and platelet transfusions significantly increased the risk-adjusted odds for developing vasoplegia. Furthermore they reported that ACE inhibitors were not a risk factor for cardioplegic syndrome, whereas b-blockers were protective, which are consistent with our results.

Cost of vasoplegia

In the current era of extensive healthcare reform, there has been a heightened focus on length of hospital stay and the frequency and cause for readmissions within 30 days of discharge given that these events are not reimbursed by most providers [12]. In our study, vasoplegia was responsible for an extension of ICU stay by 1.17 days on average. Based on a cost analysis of ICU [13], the most conservative estimate of increases in cost comes to \$3738 per vasoplegic patient. More aggressive estimates from that study would pin the increase in cost associated with an extension in ICU care by 1.17 days at \$5535 per patient. A large component of this cost is the use of mechanical ventilation. The mean increase in cost of mechanical ventilation in the ICU was found to be \$1522 per patient per day in the same study. Our data demonstrated that patients who were on a ventilator for longer than 24 h were 4.59 times more likely to have been vasoplegic. According to the AHA, there are about 699,000 open-heart surgeries performed in the United States annually [14]. With an incidence of 20.3%, that leaves an estimate of 141,900 vasoplegic patients per year. Using our cost analysis from above, these vasoplegic patients translate into an increase in ICU length of stay of 166,000 days, coming to at least \$1.4 billion in cost annually. Vasoplegia appears to be a cost-enhancing syndrome that, if prevented, could potentially save in healthcare spending.

Treatment and prevention of vasoplegia

Medications are of significant interest when it comes to vasoplegia, as they are potentially modifiable factors that can prevent this phenomenon. We found that diuretics increase the risk of vasoplegia, whereas b-blockers were protective. Diuretics potentially worsen vasoplegia by reducing cardiac preload, reducing the stimulation of atrial baroreceptors and by causing electrolyte abnormalities, namely hyponatremia which can blunt the arginine vasopressin response [15]. Over the past 15 years, ACE inhibitors have been considered a predisposing agent for post CPB vasoplegia and many cardiac surgeons make every attempt to discontinue this group of medications prior to surgery. Despite this, the incidences of vasoplegia in recent years appear to not have changed. ACE inhibitors decrease angiotensin II, which is a potent endogenous vasoconstrictor and increase bradykinin, which is a vasodilator [16]. Bradykinin is catabolized in the lung, which is excluded during CPB, thus further increasing the levels of plasma bradykinin. The exact timing of discontinuing ACE inhibitors is somewhat controversial, with most recommending 12–24 h prior to surgery [17]. Nevertheless, patients on chronic therapy still have ACE inhibitors in their tissues, even days after stopping them, which can still decrease SVR in the postoperative period. Interestingly we found that ACE inhibitors were not significantly associated with vasoplegia, which has also been reported in several other studies [10, 11, 18]. We can only speculate that ACE inhibitors may be associated with mild vasoplegia, which easily managed with intravenous fluid and low dose of vasoconstrictors. B blockers have also previously been reported to protect against vasoplegia [2, 11]. The theory is that CPB impairs b adrenergic receptor function, and that b blockers attenuate this effect, thus making the myocardium more sensitive circulating catecholamines [19].

Preoperative administration of certain agents appears to reduce the severity of vasoplegia. Vasopressin, as a rescue therapy, is an alternative approach after catecholamines and fluids fail to improve hemodynamics. Several studies have investigated the utilization of vasopressin in vasodilatory shock, which has many physiologic similarities to vasoplegia. The half-life of vasopressin is 10–35 min, so it should be given as an infusion for good hemodynamic effect [20]. A control trial ($n = 48$) randomized patients to receive vasopressin and norepinephrine (NE) versus norepinephrine alone [21]. In the first 48-h post procedure, the need for NE declined significantly in the vasopressin plus NE arm ($p < 0.001$). A randomized trial by Morales et al. [22] investigated prophylactic usage of vasopressin infusion prior to commencing CPB. Vasopressin correlated with lower NE

doses, shorter duration of catecholamine use, fewer hypotensive episodes and shorter ICU stay.

A drug with promising results is methylene blue, which has been investigated for both prophylaxis and as a salvage drug for patients with catecholamine-resistant vasoplegia. Methylene blue functions by binding the heme moiety of soluble guanylyl cyclase and inhibits its action [23]. It also scavenges nitric oxide and inhibits inducible subtype of NO synthetase. Methylene blue has been loosely accepted as a rescue therapy for patients with vasodilatory shock, but there is conflicting literature about the timing and dosing of administration [24–26].

This study is not without limitations. The use of data from a single center somewhat limits the external validity. Our definition of vasoplegia, as well as the subset of severities, was based on a combination of the most commonly cited definitions, of our understanding of the pathophysiology of vasoplegia, and from basic analysis of our dataset. As a result, these definitions remain subjective and somewhat arbitrary. Conduct of CPB and myocardial protection was not standardized for the purpose of our study, as each of our six surgeons followed their own usual practices. This could potentially have an effect on the occurrence of postoperative vasoplegia. In addition, several other variables such as ACTs (activated clotting times), utilization of hemofiltration during CPB, or operations performed for infections (e.g., endocarditis) were not collected. Another potential flaw is the heterogeneity of our patient population. Our goal was to develop a risk stratification model for all patients undergoing cardiac surgery and not to define cardioplegia within the context of a specific operation. Hence, we identified specific procedures as independent risk factors. Our definitions were aimed at identifying truly vasodilated patients who otherwise had normal output. Finally, this study was retrospective in nature, and is subjected to limitations inherent to any retrospective analysis, including validation of our risk stratification model.

In summary, although several risk factors for vasoplegia have been described over the past 15 years, incidences largely remain unchanged. Vasoplegic syndrome is still a frequently occurring adverse event following cardiac surgery with significant morbidity and mortality. In our study, vasoplegia was associated with lower postoperative survival, longer length of ICU and hospital stay and frequent early readmissions. Reducing length of hospital stay and readmissions have become a primary focus in the current era of healthcare reform in the USA. We calculated that the associated consequences of vasoplegic syndrome cost approximately \$1.4 billion annually. It becomes obvious that better risk stratification for reducing vasoplegia is essential for alleviating the economic burden on the healthcare system and for improving the quality and

efficiency of care provided to patients. In high risk patients for vasoplegia, it may be sensible to proceed with preoperative volume loading (instead of diuresis), initiation of low dose vasopressin therapy if needed, and attempting to up titrate beta-blocker therapy. This obviously would not apply to heart failure patients with low EF, who require preoperative diuresis and do not tolerate volume loading. Beta-blocker therapy and low dose vasopressin, would be more appropriate for preventing vasoplegia in these patients.

Compliance with ethical standards

Conflict of interest The authors have declared that no conflict of interest exists.

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