Cardiac Surgery

Vasoplegia Syndrome is Not Associated with Higher Mortality Rate after Heart Transplant

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Background: Vasoplegia syndrome (VS) is characterized by severe refractory hypotension, metabolic acidosis, and decreased systemic vascular resistance (SVR), with a high associated risk and mortality rate. The objective of this retrospective study was to determine the incidence and prognosis of VS after a orthotopic heart transplant (HT), identify the possible risk factors, and review the current management strategy for VS.

Methods: Between November 2002 and July 2010, 47 consecutive patients underwent orthotopic HT in the Tri-Service General Hospital, Taipei City, Taiwan. The mean age was 48 ± 12 years, 74.5% (35/47) were male, and donor ischemic duration was 153 ± 72 min. Twelve of 47 (24.5%) developed VS which was defined as SVR < 800 dyne sec per cm^5 with serum bicarbonate (HCO_3^-) < 20 mEq/l. We used Mann-Whitney, Fisher's exact, and chi-squared tests to compare variables and to determine significance.

Results: VS had an incidence of 24.5% without early mortality post HT in our study. Only elevated pre-operative recipient serum creatinine level and body height showed statistical significance to predict VS. Furthermore, patients who developed VS did not demonstrate higher hospital mortality rates in our study.

Conclusion: The risk factors include higher pre-operative recipient serum creatinine level, and body height. However, the condition has a reduced mortality rate with the progressive improvement of intensive care treatment in recent years. Nonetheless, additional prospective and large scale studies are still needed to clarify the precise mechanisms, predisposing factors and more effective treatments for post-HT VS.

Key Words: Acidosis • Heart transplant • Hypotension • Vasoplegia syndrome

INTRODUCTION

In Taiwan, the average survival rate after heart transplantation (HT) is about 80% at one year, and 72% at three years.[1] HT is well-accepted as a suitable treatment for patients with refractory heart failure. In recent decades, vasoplegia syndrome (VS), characterized by severe hypotension, metabolic acidosis, decreased systemic vascular resistance (SVR), and normal or increased cardiac output, has been observed more frequently after HT, and is considered to be associated with a high morbidity and mortality rate.[2] The utilization of cardiopulmonary bypass (CPB) may activate the release of pro-inflammatory cytokines. It should be one of the reasons for the systemic inflammatory response that causes generalized vasodilatation and hypotension.[3,4]

There is limited literature on the incidence and risk factors of VS after HT. We conducted this study in 47 consecutive patients who underwent HT at Tri-Service General Hospital from 2002 to 2010, with the aim to identify independent predictors for the development of

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VS, and therefore better understand this serious post-HT complication and its management.

MATERIALS AND METHODS

Population

The study population consisted of 47 consecutive patients undergoing orthotopic HT between 2002 and 2010. The mean age of recipients was 48 ± 12 years, with males predominant (74.5%). The underlying etiology for HT was dilated cardiomyopathy in 35 patients (74%), ischemic cardiomyopathy in 9 patients (19%), and other cardiac disease in 3 patients (6%). According to criteria of the United Network for Organ Sharing, the recipient status was classified as status I in 20 of 47 recipients (43%), and as status II in the remaining 27 recipients (57%). Before HT, 19 patients (40%) received β-blockers, 7 patients (15%) received angiotensin-converting enzyme inhibitors (ACEI), 7 patients (15%) received amiodarone, 19 patients (40%) received antiplatelet agents, 15 patients (32%) received nitrates, 19 patients (40%) received digoxin, 1 patient (2%) received calcium channel blockers, 6 patients (13%) received intravenous heparin, 9 patients (19%) received warfarin and 9 patients (19%) received inotropic support (defined as any type of inotropic support of any dosage). A left ventricular assist device (LVAD) (Thoratec PVAD, Thoratec Corp, Berkeley, CA, USA) was present at the time of HT in only one (2%) of the 47 patients. The mean waiting time for HT was 305 days.

All allografts were examined by echocardiography and cardiac catheterization and were explanted in hemodynamically stable donors. Donors had a mean age of 42 ± 12 years, and 81% (38/47) were males. Inotropic support was administered in 72% (34/47) of the donors before heart procurement. Mean donor ischemic time was 154 ± 72 min. The principal cause of death was spontaneous intracerebral hemorrhage (55%), followed by head trauma (30%), hypoxia (9%), and others (6%).

Peri- and post-operative management

All patients were operated on employing the same general anesthesia regime, using intravenous midazolam hydrochloride, fentanyl citrate, propofol, and pancuronium bromide. Cardiopulmonary bypass (CPB) was conducted under moderate systemic hypothermia (28 to 30 °C), with nonpulsatile, filtered arterial flow and gravity venous drainage. The cardiac anastomoses had been performed with the bi-caval technique by the same surgeon (C-S Tsai).

During the perioperative period, all patients received various degrees of inotropic support, generally starting at the dosage that the organ donor received at procurement. Besides, all patients received isoproterenol for chronotropic support. Standard immunosuppression consisted of 500 mg methylprednisolone before starting reperfusion, 250 mg immediately at the conclusion of the operation, and two other doses of 125 mg at 8 hours and 16 hours postoperatively. Oral mycophenolate (1 gm/day, adjusted to keep WBC 5,000~7,000/μL) was started 12-24 hours after HT, prednisolone was started with 0.4 mg/kg after the final dose of methylprednisolone, and cyclosporine (5-10 mg/kg/day) was started beginning on the third postoperative day. Intravenous rabbit anti-thymocyte-globulin (ATG) (3-5 mg/kg/day) was administered for the first three days.

Postoperative monitoring consisted of a central venous catheter, a pulmonary artery catheter, a peripheral arterial line, transcutaneous oxygen saturation, and electrocardiogram. Patients with a high probability of VS were given fluid support, pressors cathecholamines with dopamine (doses varying from 2 to 20 μg/kg/min), norepinephrine (doses varying from 0.015 to 0.05 μg/kg/min) and sodium bicarbonates to increase SVR and maintain a mean blood pressure > 65 mmHg, and bicarbonate > 20 mEq/L.

Data collection

The study was retrospective, and we obtained data from exhaustive review of the patients' medical records. Specifically, we collected 51 items of preoperative donor and recipient variables, five perioperative variables, and 27 postoperative variables (Tables 1 to 3). We defined VS as a single reading of both a SVR of < 800 dyne sec/per cm^5 and a serum bicarbonate of < 20 mEq/liter post-HT. Based on these criteria, we divided the 47 consecutive HT patients into 2 groups: 12 (26%) who developed VS, and 35 (74%) who did not develop VS.

Statistical analysis

For categorical variables, two-tailed Fisher's exact

Table 1. Preoperative variables

	Vasoplegia syndrome + (n = 12)	Vasoplegia syndrome – (n = 35)	p
Recipient demographic data			
Recipient sex (male)	11 (91.7)	24 (68.6)	0.14
Median age (years)	43.8 (12, 62)	50.4 (19, 68)	0.09
Median height (cm)	169.8 (150, 184)	163.5 (150, 178)	0.01
Median weight (kg)	71.3 (50, 97)	63.9 (41, 80)	0.13
Median body mass index (kg/m^2)	24.6 (19.0, 33.6)	23.8 (16.2, 30.0)	0.79
Median body surface area	1.8 (1.4, 2.1)	1.7 (1.3, 2.0)	0.37
Ischemic cardiomyopathy	3 (25.0)	6 (17.1)	0.67
Dilated cardiomyopathy	9 (75.0)	26 (74.3)	0.85
Recipient medical history			
Hypertension	7 (58.3)	12 (34.3)	0.18
Diabetes mellitus	6 (50)	9 (25.7)	0.15
Hyperuricemia	5 (41.7)	11 (31.4)	0.72
Hyperlipidemia	4 (33.3)	6 (17.1)	0.25
Cerebral vascular disease	2 (16.7)	4 (11.4)	0.63
Atrial fibrillation	4 (33.3)	14 (40.0)	0.74
Wait list for transplant(days)	303.4 (9, 1335)	306.4 (2, 1855)	1.00
UNOS I	4 (33.3)	16 (45.7)	0.69
UNOS II	8 (66.7)	19 (54.3)	0.69
NYHA Fc IV	11 (91.7)	30 (85.7)	0.79
Median EF (%)	17.8 (13, 35)	20.0 (10, 61)	0.29
Redo-surgery	4 (33.3)	16 (45.7)	0.69
Cytomegalovirus positive	10 (83.3)	35 (100)	0.06
Epstein-Barr virus positive	12 (100)	32 (91.4)	0.56
Herpes simple virus positive	12 (100)	27 (77.1)	0.09
Intra-aortic balloon pump	1 (8.3)	5 (14.3)	1.00
Ventricular assist device	1 (8.3)	0 (0.00)	0.25
ECMO	1 (8.3)	5 (14.3)	1.00
Recipient medication			
β-blockers	6 (50.0)	13 (37.1)	0.50
ACEI	2 (16.7)	5 (14.3)	1.00
Amiodarone	1 (8.3)	6 (17.1)	0.65
Anti-platelet agents	6 (50.0)	13 (37.1)	0.50
Nitrates	4 (33.3)	11 (31.4)	1.00
Digoxin	6 (50.0)	13 (37.1)	0.50
Calcium channel blockers	1 (8.3)	0 (0.00)	0.25
Intra-venous heparin	2 (16.7)	4 (11.4)	0.63
Warfarin	3 (25.0)	6 (17.1)	0.67
Inotropic agents	2 (16.7)	7 (20.0)	1.00
Diuretics	9 (75.0)	28 (80.0)	0.70
Ubidecarenone	8 (66.7)	17 (48.6)	0.33
Mexiletine	1 (8.3)	3 (8.6)	1.00
Recipient laboratory data			
Median BUN (mg/dl)	30.6 (13, 65)	22.3 (9, 76)	0.15
Median creatinine (mg/dl)	1.69 (0.7, 3.8)	1.07 (0.5, 2.4)	0.02
Median bilirubin (mg/dl)	1.00 (0.4, 1.7)	1.12 (0.4, 2.3)	0.50
Median GOT (U/l)	23.8 (12, 39)	36.6 (17, 136)	0.30
Median GPT (U/l)	25.1 (10, 91)	38.0 (7, 362)	0.28
Median hemoglobin (g/dl)	12.9 (8.2, 16.0)	13.6 (6.9, 17.1)	0.39
Median bicarbonate (mEq/l)	24.4 (19.9, 30.2)	23.4 (9.5, 30.6)	0.97

Table 1. Contiuned

	Vasoplegia syndrome + (n = 12)	Vasoplegia syndrome – (n = 35)	p
Median weight (kg)	71.7 (52, 88)	65.5 (42, 80)	0.09
Donor inotropic agent use	9 (75.0)	25 (71.4)	1.00
Mismatch of sex	1 (8.3)	14 (40.0)	0.07
Mismatch of body weight (Recipient/Donor body weight ratio < 0.8 or > 1.2)	1 (8.3)	6 (17.1)	0.65

Parenthesis containing only one number means percentage. Parenthesis containing two numbers means range.
ACEI, angiotensin-converting enzyme inhibitors; BUN, blood urea nitrogen; ECMO, extracorporeal membrane oxygenation; EF, left ventricular ejection fraction; GOT, aspartate aminotransferase; GPT, alanine aminotransferase; NYHA, New York Heart Association functional class; UNOS, united network of organ sharing.

test was used, and the Mann-Whitney test was used for continuous variables. A p value < 0.05 was used to indicate statistical significance. Statistical analysis was performed using STATA 6.0 Windows.

RESULTS

Of the 47 patients in our study, 12 (24.5%) satisfied the criteria for VS with SVR of 666 ± 89 dyne.sec.cm^{-5} (533 to 767 dyne.sec.cm^{-5}) and bicarbonate of 16.3 ± 2.7 mEq/liter (12 to 20 mEq/liter). The demographic data and pre-HT co-morbidities of the 47 recipients are summarized in Table 1. Patients who developed VS were more likely to have younger median age (43.8 vs. 50.4, p = 0.09), and higher body height (169.8 vs. 163.5, p = 0.01). The use of preoperative medication (Table 1), etiology of cardiomyopathy, previous medical history, and the use of a mechanical circulatory device did not differ between the two groups. The preoperative presentation of positive finding of IgG of cytomegalo virus (CMV) seemed to be correlated with a lower rate to develop VS (83.3 vs. 100, p = 0.06). Preoperative laboratory values (Table 1) were compared in the two groups. Serum creatinine levels statistically differed between the VS and non-VS recipients (1.69 vs. 1.07, p = 0.02). Donor data (Table 1) revealed younger age, higher body height, and heavier body weight (p = 0.08, 0.05, 0.09 for each) in those recipients who were prone to develop VS without reaching statistical significance. There was no difference in any intraoperative variables (Table 2), including blood transfusion units with packed red blood cell, fresh frozen plasma, platelet, ischemic time, or pumping time.

Postoperative recipient hemodynamic and morbidity and mortality data are shown in Table 3. In 75% of these cases the syndrome appeared within 6 hours and in all cases within 24 hours after CPB. The VS group presented significantly lower blood pressure, SVR, and metabolic acidosis even after use of inotropic agents and fluid support. In terms of postoperative variables (Table 3), there is no significant difference between the two groups in median intensive care unit stay, length of stay, ventilation days, and hospital mortality.

DISCUSSION

To our knowledge, this is the first study which con-

Table 2. Intraoperative confounding factors

	Vasoplegia syndrome + (n = 12)	Vasoplegia syndrome - (n = 35)	p
Median units PRBC	7.2 (4, 20)	6.7 (2, 18)	0.71
Median units FFP	8.7 (8, 16)	8, 12 (8.34)	0.96
Median units platelets	1.17 (0, 3)	1.14 (0, 2)	0.90
Median ischemic time (mins)	157.2 (89, 276)	152.7 (85, 331)	0.61
Median pumping time (mins)	161.3 (137, 209)	165.6 (112, 291)	0.89

Numbers in parentheses mean range.
FFP, fresh frozen plasma; PRBC, packed red blood cell.

Table 3. Postoperative results

	Vasoplegia syndrome + (n = 12)	Vasoplegia syndrome - (n = 35)	p
Hemodynamic data			
Median SBP (mmHg)	74 (60, 90)	94 (50, 111)	0.00
Median DBP (mmHg)	45 (40, 67)	56 (33, 88)	0.01
Median MAP (mmHg)	58 (48, 74)	68 (47, 97)	0.01
Median SVR (dyne.sec/cm^5)	666 (533, 767)	955 (396, 1186)	0.00
Median pH	7.25 (7.0, 7.4)	7.31 (7.0, 7.4)	0.02
Median bicarbonate (mEq/l)	16.3 (12, 20)	19.3 (10, 27)	0.01
Median base excess (mEq/l)	-9.3 (-19.0, -5.6)	-6.0 (-21.9, 2.5)	0.03
Median lactate (mg/dl)	12.0 (2.9, 15.0)	9.2 (2.6, 15.0)	0.10
Median hemoglobin(g/dl)	8.3 (7.8, 10.9)	8.4 (7.7, 10.8)	0.92
Median SVO2 (%)	60.5 (39, 76)	50.5 (19, 101)	0.03
Median SPAP (mmHg)	23 (16, 28)	24 (9, 43)	0.39
Median DPAP (mmHg)	14 (9, 22)	14 (4, 26)	0.91
Median PAP (mmHg)	18 (14, 25)	18 (7, 34)	0.96
Median PCWP (mmHg)	13 (9, 17)	12 (6, 20)	0.23
Median CO (l/min)	5.2 (2.2, 9.0)	4.4 (1.8, 11.3)	0.08
Median CI (l/min per m^2)	2.9 (1.3, 5.6)	2.6 (1.1, 5.9)	0.38
Median CVP (mmHg)	9.0 (3, 15)	10 (4, 21)	0.31
Morbidity and mortality			
Median ICU stay (days)	12 (7, 28)	10 (5, 47)	1.00
Median length of stay (days)	46 (22, 128)	31 (5, 74)	0.13
Median ventilation days	8 (1, 35)	5 (1, 47)	0.38
Hospital mortality	0 (0.00)	4 (11.4)	0.56
Hospital morbidity	6 (50.0)	8 (22.9)	0.14
Dialysis	1 (8.3)	4 (11.4)	1.00
Ventilator dependence	2 (16.7)	3 (8.6)	0.59
Pneumonia	1 (8.3)	3 (8.6)	1.00
Reoperation for bleeding	2 (16.7)	3 (8.6)	0.59
Acute rejection	2 (16.7)	3 (8.6)	0.59
Cytomegalovirus infection (blood PCR positive)	2 (16.7)	0 (0.00)	0.06

Parenthesis containing only one number means percentage. Parenthesis containing two numbers means range.
CI, cardiac index; CO, cardiac output; CVP, central venous pressure; DBP, diastolic blood pressure; DPAP, diastolic pulmonary arterial pressure; ICU, intensive care unit; MAP, mean arterial pressure; PAP, pulmonary arterial pressure; PCR, polymerase chain reaction; PCWP, pulmonary capillary wedge pressure; SBP, systolic blood pressure; SPAP, systolic pulmonary arterial pressure; SVO2, mixed venous oxygen saturation; SVR, systemic vascular resistence.

sists of multiple pre-, intra-, and postoperative variables to identify independent risk factors for development of VS after HT in Asia. Although the exact mechanisms of VS are not clear, depletion of vasopressive substance after CPB, extensive complement activation, and the release of vasodilatory inflammatory mediators including tumor necrosis factor, interleukin-6, and interleukin-8 are considered possible causes of VS.[3-5] It is credible that a longer pumping time in HT, compared with coronary artery bypass surgery (CABG), induces higher production of pro-inflammatory and anti-inflammatory cytokines that may contribute to the development of VS. Previous study also showed a lower incidence rate of VS in off-pump CABG compared with on-pump CABG.[6] Additionally, previous studies demonstrated higher incidence of VS after HT than other cardiac surgeries.[7-10]

Some published reports showed that preoperative obesity is associated with increased morbidity and mortality post HT.[11,12] Chemmalakuzhy et al. reported that higher recipient and donor weights increase the risk for VS, and considered them as significant risk factors for poor outcome after HT. Decreased heart function limits

physical activity in daily life, with obese patients often gaining weight day-by-day as their disease worsens. For patients with more severe heart failure, there is often a longer waiting time for HT, and they may have access to even fewer donor hearts due to issue of lowest acceptable donor weight (Table 4).[7] Other authors have claimed that patients with greater body surface are at increased risk for VS. However, except for higher recipient body height in the VS group, we find no statistical significance in body weight, body surface area, and body mass index between the VS and the non-VS group in our study.

The etiology of cardiomyopathy, preoperative comorbidities, severity of heart failure (classified with UNOS or NYHA) functional class or quantificated left ventricular ejection fraction via cardioechography, or preoperative medication of recipients had also been analyzed. Although the risk of the development of VS is increased in patients with pre-operative prescription of intravenous heparin,[8] angiotensin-conversing enzyme inhibitors[13,14] and β-blockers[7] in some reports. In our study, no statistical significance was identified (Table 4).

Besides, the proinflammatory cytokine serum decreases,[15] and the neurohormonal axis improves[16] after the support of a ventricular assist device in severe heart failure patients, and may confer protection against VS.[7] However, there was only one recipient who received pre-operative LVAD support in our study, and VS occurred in the patient after HT. We could not conclude that there is any correlation between LVAD and VS from our limited data. Other circulatory assist devices, such as IABP and ECMO, didn`t decrease risk for VS in our study, nor in other published studies.[7,8,17]

For reasons not entirely clear, higher pre-operative recipient creatinine serum level was found to be an independent risk factor for the development of postoperative VS. Chemmalakuzhy et al. showed the same correlation between higher recipient creatinine serum level and VS.[7] Reduced cardiac output in severe heart failure resulting in decreased renal perfusion might be an easy explanation for worsening renal function. Dysfunction of the kidney in heart failure patients, known as cardiorenal syndrome, didn't correlate well with the severity of heart failure to date. Besides, lower ventricular ejection fraction also did not increase the risk for development of postoperative VS. The mechanisms between higher creatinine level and VS need further study.

Interestingly, we found patients with pre-operative presentation of IgG antibody of CMV are at decreased risk for development of postoperative VS. In addition, higher post-operative CMV infection was also noted in VS group, but with a borderline statistical significance. In our study, this might be explained by the lack of antibodies to provide protection from CMV infection in the VS group. Some previous studies had demonstrated higher hospital morbidity and mortality rate in VS group.[6,8,17] However, our study didn't find any correlation between prolonged hospital stay and increased hospital morbidity in VS group, similar to observations made by Carrel et al.[18] Additionally, no patient died in the VS group in our series where patient management was utilized, including early withdrawal of vasodilators, active fluid resuscitation, use of pressors cathecholamines, and the timely correction of metabolic acidosis.

There are several alternative treatments for VS which have been developed and studied extensively in recent years, such as vasopressin,[19-21] terlipressin,[22] and

Table 4. Predisposing factors to VS

First author	Published year	Case number	Male	Mean age	Ischemia time (min)	VS prevalence rate	Predisposing factors
Chemmalakuzhy[6]	2001	70	87%	50	190	54%	Greater recipient BW Greater donor BW Longer ischemia times Longer waiting times Pre-HT use of β-blockers Pre-HT recipient creatinine level
Paniagua[17]	2003	85	-	-	-	13%	Poly transfusion
Byrne[8]	2004	147	82%	49	117	19%	Body surface area > 1.9 m^2 Pre-HT use of intravenous heparin

BW, body weight; HT, heart transplant; VS, vasoplegia syndrome.

methylene blue (MB).[19,23-26] Vasopressin and terlipressin can be infused peri-operatively and post-operatively, and can effectively reduce the necessary doses of cathecholamines. They also show they can also be instrumental in maintaining vasoconstrictive power, lowering pulmonary hypertension, decreasing supraventricular arrhythmia rate, and facilitating intensive care unit recovery. However, they should be used with caution to prevent possible side effects, which can include thrombocytopenia, reduced mesenteric and renal perfusion. As another VS treatment alternative, MB can accelerate weaning off CPB, as well as reduce renal, respiratory, arrhythmic, and septic complications and mortality, and thus facilitate recovery. It should be used with caution in view of the interference between oximeter, pulmonary hypertension, neurotoxicity, arrhythmia, and altered coronary, renal, and mesenteric perfusion. Although vasopressin, terlipressin and MB have shown that they can be therapeutically beneficial in the treatment of VS, those research studies involved patients who underwent other cardiac surgeries, and not HT.

CONCLUSION

Studies have shown that VS has an incidence of 24.5% in post HT patients, without increased early mortality post HT in our study. Elevated preoperative recipient creatinine serum level and body height are important risk factors for VS. Notwithstanding these risks, the condition is no longer highly lethal with progressive and refined intensive care. We concluded that aggressive fluid supplement, increased dosage of pressors cathecholamines and timely correction of metabolic acidosis are mostly effective in this group of patients without increasing hospital stay and morbidity rates. Further prospective and large scale studies are needed to find the precise mechanisms and predisposing factors leading to VS and effective therapies for VS after HT.

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