



# Longer term hemodialysis-dependent chronic renal failure increases the risk of post-cardiac surgery vasoplegic syndrome

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## Abstract

**Purpose** We evaluated whether longer term hemodialysis (HD) is associated with a higher incidence of vasoplegic syndrome (VS) after cardiac surgery.

**Methods** This retrospective, single-center cohort study included 562 consecutive patients who underwent cardiac surgery in a tertiary hospital from January 2015 to December 2016. We assessed VS occurrence and its relationship with HD duration and other risk factors. To assess the effect of the HD duration on VS occurrence, we constructed ordinal variables: HD = 0 (non-HD),  $0 < \text{HD} \leq 5$  ( $\text{HD} \leq 5$  years),  $5 < \text{HD} \leq 10$ , and  $10 < \text{HD}$ .

**Results** The overall mean ( $\pm$  standard deviation) age of patients was ( $73 \pm 11$ ) years, and there were 60.9% men. Forty-one patients (7.3%) were HD dependent. Cardiac surgeries included all coronary artery bypass graft procedures, all valvular procedures, and aortic surgery involving cardiopulmonary bypass (CPB). Sixty-six patients (10%) developed VS. Most pre-operative patient characteristics were comparable between the VS and no-VS groups; a chronic HD status and a total CPB time of  $> 180$  min were significantly more common in the VS group ( $P < 0.0001$  and  $P = 0.02$ , respectively). Longer term HD significantly correlated with VS incidence ( $P < 0.0001$ ). Ordinal variables for the HD duration and age and known risk factors for VS (preoperative use of angiotensin-converting enzyme inhibitors and beta-blockers, low left-ventricular ejection fraction, and CPB time  $> 180$  min) were subjected to multivariate regression analysis. Long-term HD was identified as an independent predictor of VS (odds ratio, 2.29, 95% confidence interval, 1.66–3.18).

**Conclusions** Longer term HD may be associated with a higher VS incidence after cardiac surgery. VS should be given attention after cardiac surgery in chronic HD-dependent patients.

**Keywords** Hemodialysis · Longer term · Vasoplegic syndrome

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## Introduction

Vasoplegic syndrome (VS) frequently occurs in the early postoperative period of cardiac surgery. Its incidence rate is about 10–20% in the post-cardiac surgery setting [1]. VS occurring after cardiac surgery is the second most common cause of vasoplegia, next to sepsis [2]. It is characterized by significant hypotension, with decreased systemic vascular resistance, decreased arteriolar reactivity, increased requirements for vasopressors, and high or normal cardiac output [3, 4].

Some risk factors such as preoperative use of angiotensin-converting enzyme (ACE) inhibitors and beta-blockers, a low left-ventricular ejection fraction (EF), and cardiopulmonary bypass (CPB) surgery, among others have been reported [4–9]. Although there is an overall agreement regarding the effect of specific risk factors for VS, other factors are more controversial. In recent literature, chronic hemodialysis (HD)-dependent renal failure has been suggested to be a risk factor for VS because of its chronic inflammatory status [10, 11]. Repeated dialysis treatments in patients with chronic renal failure (CRF) are considered to promote an inflammatory response [12], although the duration of HD has not yet been examined in detail. We hypothesized that a longer period of dialysis results in an increased frequency of VS. Thus, our study aimed to evaluate whether longer term hemodialysis (HD) is associated with a higher incidence of VS after cardiac surgery.

## Methods

This single-center, retrospective cohort study was conducted after approval from the institutional review board at the Kobe City Medical Center General Hospital (Approval number: 3, March 3, 2017), which waived the requirement for informed consent because of the anonymous nature of the data. Consecutive patients who underwent cardiac surgery in a tertiary hospital in Japan from January 2015 to January 2016 were included. Patients older than 18 years who presented for elective cardiac surgery were considered eligible.

Cardiac surgery included all coronary artery bypass graft (CABG) procedures (on-pump, off-pump), all valvular procedures, and aortic surgery requiring circulatory arrest. Patients requiring mechanical support via an intra-aortic balloon pump or ventilator-assisted extracorporeal membrane oxygenation on admission to the intensive care unit (ICU) were excluded.

For each patient, we recorded the mean arterial pressure (MAP), cardiac index (CI), and central venous pressure

(CVP). A pulmonary artery flotation catheter (PAC) was inserted during surgery, and its placement was checked by chest radiography on admission to ICU. CI was measured by a continuous thermodilution catheter. MAP was measured using a femoral or radial arterial catheter inserted during surgery. CVP was measured using the proximal port of PAC. These values were documented at 0, 2, 4, 8, and 16 h after transfer to ICU. We also recorded the following preoperative variables: sex; age; type of surgical procedure; EF; use of ACE inhibitors; use of beta-blockers; and the presence of diabetes mellitus, hypercholesterolemia, systemic hypertension, stroke, obesity (body mass index [BMI] > 25 kg/m<sup>2</sup>), myocardial infarction, angina pectoris, and chronic obstructive pulmonary disease (COPD). We noted the following intraoperative variables: CPB use, pump time, and cross-clamp time.

## Definitions

There were no clear diagnostic criteria for VS; therefore, we based our definition of VS on previous reports [7], adapted to a clinical context. VS was defined as present when three of the following four conditions were met: (1) MAP < 65 mmHg, (2) a decreased systemic vascular resistance index (SVRI) < 1.600 dyn•s/cm<sup>5</sup>/m<sup>2</sup>, (3) a high CI (CI > 2.5 L/min/m<sup>2</sup>), and (4) requirement of pharmacological support from norepinephrine (> 0.03 µg/kg/min) or vasopressin. Patients who met these criteria at two consecutive time points within 0, 2, 4, 8, and 16 h after transfer to ICU were diagnosed with VS. More specifically we categorized VS as mild if MAP was between 50 and 60 mmHg and one vasopressor was being administered; moderate if MAP was between 50 and 60 mmHg and two or more vasopressors were being administered, or MAP was < 50 mmHg and one vasopressor was being administered; severe if MAP was < 50 mmHg and two or more vasopressors were being administered, based on the previous literature [10]. The vasopressors utilized included norepinephrine, vasopressin, and epinephrine.

## Statistical analysis

Nominal variables are reported as counts and percentages, while continuous variables are reported as means and standard deviations (SDs). Chi-square and Fisher's exact tests for nominal variables and *t* test for continuous variables were used to compare patients who developed VS with those who did not. A multivariate logistic regression model was used to assess the risk factors for VS. Age and known risk factors for VS reported in a previous study (preoperative use of ACE inhibitors and beta-blockers, a low left-ventricular EF, and CPB time > 180 min) were subjected to multivariate

analysis. To assess the effect of the HD duration on the occurrence of VS, we constructed ordinal variables, namely non-HD (HD = 0),  $0 < \text{HD} \leq 5$  ( $\leq 5$  years),  $5 < \text{HD} \leq 10$ , and  $10 < \text{HD}$ , and included them in the multivariate logistic model. A two-tailed  $P$  value of  $< 0.05$  was considered statistically significant. All statistical analyses were performed using JMP 13 software (SAS Institute Inc., Cary, NC).

## Results

During the study period, a total of 598 patients who had undergone elective cardiac surgery were identified. In total, 32 patients were excluded because they required mechanical support via an intra-aortic balloon pump or ventilator-assisted extracorporeal membrane oxygenation on admission to ICU. Four patients were excluded because of missing data. Finally, 562 patients were included. The demographic data of all patients are shown in Table 1. Except for hypertension, preoperative patient characteristics were not significantly different between the two groups. The overall mean ( $\pm$ SD) age of patients was ( $73 \pm 11$ ) years. The prevalences of hypercholesterolemia, systemic hypertension, stroke,

obesity ( $\text{BMI} > 25 \text{ kg/m}^2$ ), myocardial infarction, angina pectoris, and COPD were not significantly different between the two groups.

## Number of operations

Cardiac surgeries included all CABG procedures (on-pump [ $N = 101$ ] and off-pump [ $N = 37$ ]), all valvular procedures ( $N = 259$ ), and large vascular surgery involving CPB ( $N = 149$ ; Table 2). Aortic surgery involved ascending aorta replacement, aortic root replacement, aortic arch replacements, and descending aorta replacement.

## Perioperative parameters

In total, 66 patients (10%) developed VS; 27 (40.9%), 15 (22.7%), 15 (22.7%), and 9 (13.6%) were diagnosed at 0–2, 2–4, 4–8, and 8–16 h after transfer to the ICU, respectively. Of these 66 patients, 48 (72.7%) had mild, 15 (22.7%) had moderate, and 3 (4.5%) had severe VS. Overall, 41 (7.3%) patients were chronically HD dependent, while the

**Table 1** Demographic characteristics and patients' comorbidities

Characteristic	Vasoplegic ( $n = 66$ )	No vasoplegic ( $n = 496$ )	$P$
Demographics			
Age (mean years $\pm$ SD)	71 ( $\pm 10$ )	73 ( $\pm 11$ )	0.19
Men	42 (63.6%)	300 (60.5%)	0.62
Comorbidities			
Obesity	12 (18.2%)	104 (21%)	0.59
Hypertension	26 (39.4%)	260 (52.4%)	0.04
Stroke	3 (4.5%)	35 (7.6%)	0.44
Diabetes	16 (24.2%)	98 (19.8%)	0.39
COPD	2 (3.0%)	7 (1.4%)	0.32
Previous myocardial infarction	6 (9.1%)	21 (4.2%)	0.08
Dyslipidemia	5 (7.6%)	76 (15.3%)	0.09

Values presented as  $n$  (%), unless otherwise indicated

COPD chronic obstructive pulmonary disease, SD standard deviation

**Table 2** Number of operations

	Vasoplegic ( $n = 66$ )	No vasoplegic ( $n = 496$ )	Total ( $n = 562$ )	$P$
On-pump CABG	8 (12.1%)	29 (5.8%)	37	0.0081
Off-pump CABG	10 (15.2%)	91 (18.3%)	101	
Valvular procedures	40 (60.6%)	219 (44.1%)	259	
Aortic surgery	5 (7.6%)	5 (1.0%)	149	
Others	1 (1.5%)	15 (3.0%)	16	

Values presented as  $n$  (%)

“Others” included pericardiectomy, surgical myxoma resection, etc.

CABG coronary artery bypass graft

**Table 3** Perioperative parameters according to the development of postoperative vasoplegic syndrome

	Vasoplegic ( <i>n</i> = 66)	No vasoplegic ( <i>n</i> = 496)	<i>P</i>
Chronic HD dependent (%)	16 (24.2%)	25 (5.0%)	< 0.0001
LVEF < 40% (%)	2 (2.8%)	14 (3.0%)	0.92
Use of CPB (%)	54 (81.8%)	396 (79.8%)	0.70
CPB time > 180 min (%)	32 (48.5%)	170 (34.3%)	0.02
CPB time (mean minutes ± SD)	174 (± 105)	155 (± 87)	0.02
Preoperative medications			
Beta-blockers (%)	23 (34.9%)	145 (29.2%)	0.35
ACE inhibitors (%)	8 (12.1%)	43 (8.7%)	0.36
ARB (%)	9 (13.6%)	77 (15.5%)	0.68

Values presented as *n* (%)

ACE angiotensin-converting enzyme, ARB angiotensin II receptor blocker, CPB cardiopulmonary bypass, HD hemodialysis, LVEF left ventricular ejection fraction

remaining 521 (92.7%) were not. Table 3 shows the perioperative parameters for the patients. Chronic HD dependence and a total CPB time exceeding 180 min were significantly more common in the VS group than in the control group ( $P < 0.0001$  and  $P = 0.02$ , respectively). Preoperative use of ACE inhibitors and beta-blockers was not statistically significantly different between the two groups.

## Postoperative parameters and clinical course

The postoperative variables are shown in Table 4, which reveals the cardiovascular data and requirement for vasopressor and inotropic agents for the two groups. For the

purpose of our analysis, minimal MAP, minimal SVRI, maximal CI, and the actual maximum dosage of norepinephrine required by each group are listed in Table 4. Minimal SVRI and minimal MAP were significantly lower in the VS group than in the control group ( $P < 0.001$ , respectively). Maximal CI was significantly higher in the VS group than in the control group (3.6 (± 0.66) vs 2.9 (± 0.64) L/min/m<sup>2</sup>,  $P < 0.001$ , respectively). The dosage of norepinephrine required was significantly higher in the VS group than in the control group (0.076 (± 0.07) vs 0.004 (± 0.052) µg/kg/min,  $P < 0.001$ , respectively). The overall mean duration of norepinephrine infusion for the VS patients was 12.05 (± 5.98) h, while the duration for the patients with mild, moderate, and severe VS was 10.11 (± 6.03) h, 14.45 (± 5.78) h, and 8.23 (± 3.77) h.

**Table 4** Postoperative parameters and clinical course of patients with or without vasoplegic syndrome after cardiac surgery

	Vasoplegic ( <i>n</i> = 66)	Non-vasoplegic ( <i>n</i> = 496)	<i>P</i>
Cardiovascular data			
Minimal MAP (mmHg)	56 (± 6.94)	64 (± 9.09)	< 0.0001
Minimal SVRI (dyn•sec/cm <sup>5</sup> /m <sup>2</sup> )	1144.8 (± 210)	1600 (± 269.0)	< 0.0001
Maximal CI (L/min/m <sup>2</sup> )	3.6 (± 0.66)	2.9 (± 0.64)	< 0.0001
Vasopressor and inotropic agents			
Maximal norepinephrine (µg/kg/min)	0.076 (± 0.07)	0.004 (± 0.052)	< 0.0001
Vasopressin	1 (1.5%)	4 (0.008%)	0.3419
Dobutamine	4 (6.06%)	7 (1.41%)	0.0321
Epinephrine	2 (3.03%)	1 (0.2%)	0.0247
Clinical course			
ICU stay (days)	6 (± 5.49)	5 (± 1.8)	< 0.001
Hospital stay (days)	21 (± 18.9)	19 (± 16.6)	0.03
ICU deaths	3 (4.6%)	4 (0.8%)	0.04
Hospital deaths	5 (7.6%)	5 (1.0%)	0.002

Values are presented as *n* (%) or mean (SD)

CI cardiac index, ICU intensive care unit, MAP mean arterial pressure, SVRI systemic vascular resistance index

The lengths of ICU stay and overall hospital stay were significantly longer in the VS group than in the control group ( $P < 0.001$  and  $P = 0.03$ , respectively), while ICU and hospital mortality rates were higher in the VS group ( $P = 0.04$  and  $P = 0.002$ , respectively).

### Association between HD duration and VS incidence

Figure 1 shows the association between the HD duration (HD = 0,  $0 < HD \leq 5$ ,  $5 < HD \leq 10$ ,  $10 < HD$ ) and the incidence of VS. The incidences of VS were 9.6% (HD = 0), 31.3% ( $0 < HD \leq 5$ ), 33.3% ( $5 < HD \leq 10$ ), and 50% ( $10 < HD$ ), respectively. We found that longer term HD was significantly correlated with an increasing VS incidence ( $P < 0.0001$ ).

### Multivariate analysis

Ordinal variables for HD duration (HD = 0,  $0 < HD \leq 5$ ,  $5 < HD \leq 10$ ,  $10 < HD$ ), age, and known risk factors for VS (preoperative use of ACE inhibitors and beta-blockers, a low left ventricular EF, and CPB time > 180 min) were subjected to multivariate regression analysis (Table 5), which identified long-term HD as an independent predictor for post-cardiac surgery VS (odds ratio [OR], 2.29; 95% confidence interval [CI], 1.66–3.18). A total CPB duration of > 180 min was another independent predictor (OR, 1.81, 95%CI, 1.05–3.10).

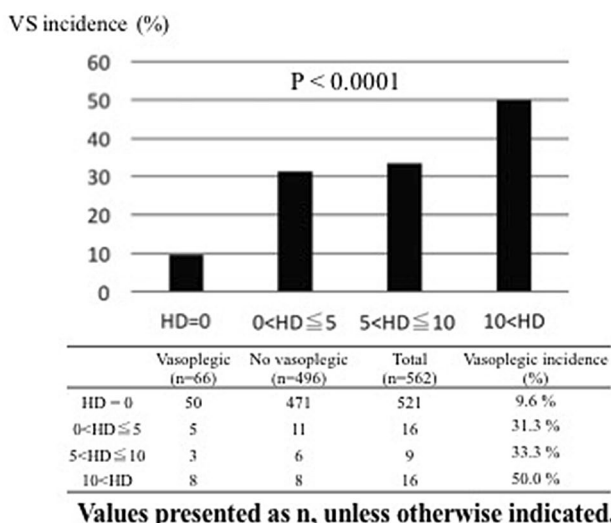


Fig. 1 Association between the hemodialysis duration and incidence of vasoplegic syndrome after cardiac surgery

Table 5 Multivariate predictors of vasoplegic syndrome

	OR	95% CI	P
HD duration	2.29	1.66–3.18	<0.0001
Age	0.99	0.46–8.68	0.30
Beta-blockers	1.46	0.80–2.64	0.21
ACE inhibitors	1.73	0.68–3.99	0.21
LVEF < 40%	0.83	0.11–3.61	0.83
CPB time > 180 min	1.81	1.05–3.10	0.03

ACE angiotensin-converting enzyme, CI confidence interval, CPB cardiopulmonary bypass, HD hemodialysis, LVEF left ventricular ejection fraction, OR odds ratio

### Discussion

In our study, longer term HD and prolonged CPB were identified as predictors of VS after cardiac surgery. Our results are supported by the recent observations of Tsiouris et al. [10], who reported that HD-dependent renal failure is a predictive factor for VS. Hossne Junior et al. [11] demonstrated that CABG procedures with CPB in patients with CRF requiring dialysis therapy were an independent risk factor for the development of postoperative VS. However, accurate assessment of chronic HD as an independent risk factor for VS was difficult because of the small number of patients with chronic HD. In the present study, we demonstrated this by directly comparing chronic HD-dependent patients with non-dependent patients and adjusting the results for confounding factors in a multivariate regression analysis. We then examined the association between HD duration and the incidence of VS and found that a longer period of dialysis resulted in more frequent occurrences of VS, with a statistically significant difference. To the best of our knowledge, this is the first report to show that longer term HD increases the risk of VS after cardiac surgery.

VS is a well-known complication after cardiac surgery [13]. Patients who develop VS after cardiac surgery exhibit increased mortality and a longer hospital stay [14]. Multiple risk factors have been identified that can help predict VS, including preoperative use of ACE inhibitors and beta-blockers, a low left-ventricular EF, and CPB use [4-9].

Chronic HD has been suggested to be a risk factor for VS, but the mechanisms remain unclear. The pathophysiological mechanisms underlying VS remain controversial; however, there is a clear association between the expression of pro-inflammatory mediators and subsequent induction of nitric oxide production and cyclic guanosine monophosphate-mediated severe vasodilation [2, 15, 16]. Moreover, chronic inflammation is prevalent in patients with CRF [17], and repeated dialysis treatments in such patients lead to leucocyte activation and consequently, cytokine production [12]. We expected that longer term HD-dependent CRF would

increase the risk of post-cardiac surgery VS. Moreover, we showed that chronic HD dependence is a risk factor for VS, and that VS develops more frequently in patients who require longer term HD. It is reasonable to surmise that the intrinsic chronic inflammatory status in patients with HD-dependent CRF promotes an inflammatory response leading to VS, and that longer term HD develops a strong tendency for this response.

Our findings can be utilized in clinical practice. When patients with chronic HD dependence, particularly long-term HD, exhibit distributive shock in postoperative care, VS should be considered as a differential diagnosis. It is very important to distinguish VS from other possible diagnoses, such as septic shock and anaphylactic shock, because this may change the treatment plans. The use of vasopressin did not produce a statistically significant improvement in the mortality rate of patients in a meta-analysis [18]. However, Hajjar et al. [14] found that vasopressin can be used as a first-line vasopressor for post-cardiac surgery VS and improves patient clinical outcomes. In the future, the threshold for vasopressin initiation for the treatment of distributive shock after cardiac surgery may change.

Our study had several limitations. First, because of the retrospective design, confounding factors may have affected our results. The influence of unknown risk factors cannot be ruled out. We included major known risk factors in the multivariate analysis to eliminate the influence of more confounding factors, but this might not have been sufficient. Second, we devised the diagnostic criteria for VS based on previous reports, because there are no clear or standardized criteria. The appropriate timing for evaluation also remains unclear. We determined the timing for evaluation as 0, 2, 4, 8, and 16 h after transfer to ICU in accordance with a previous representative report that specified these timings [5], but these different intervals may have affected VS diagnosis. The purpose of evaluation at two consecutive time points was to increase the specificity of the diagnostic criteria for VS. The early postoperative period is especially important for diagnosis because VS is characterized by occurring early after surgery; therefore, we consider our criteria to be clinically appropriate. Third, severity of VS in this study may have been relatively mild compared to previous reports. There were very few patients categorized as having severe VS, and the overall mortality rate was relatively low compared with previous reports [7, 10]. However, it cannot be said sweepingly, because there is no definitive severity classification of VS and there are very little data about VS mortality. Further studies are needed to clarify severity and prognosis of VS. Fourth, our study only assessed chronic HD dependence or non-dependence; thus, we did not assess the direct relationship between CRF and VS. It is unclear whether the main predictor of VS is HD or CRF, and whether mild CRF is a risk factor for VS. Further research is needed to assess the

relationship between CRF, renal function, disease duration, and post-cardiac surgery VS.

In conclusion, chronic HD was identified as a predictor of VS, and longer term HD was associated with a higher incidence of VS after cardiac surgery. In the postoperative care of chronic HD-dependent patients who have undergone cardiac surgery, VS should be kept in mind as a differential diagnosis.

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**Author contributions** MS: conceived and designed the study, performed the statistical analyses, and drafted the manuscript. DK: the principal supervisor of this project, organized the original study plan, and co-wrote the final manuscript. HU: conceived and designed the study and helped draft and revise the manuscript. TS: conceived and designed the study. HM: the supervisor of ethical approval. JI: revised the manuscript for important intellectual contributions. RS: revised the manuscript for important intellectual contributions. AK: revised the manuscript for important intellectual contributions. YN: conceived and designed the study. TM: helped design the study, analyze the data, and draft the manuscript.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they do not have any conflict of interest.

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