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Original Article

# Evaluating the Impact of a Standardized Protocol for Managing Refractory Vasoplegia After Cardiopulmonary Bypass

Andrew Teletnick, PharmD[*], Kangho Suh, PharmD, PhD[†], Michael Boisen, MD[‡], James A. Brown, MD, MS[§], Bernardine Cabral, MD[‡], Holt Murray, MD[‖], Caroline Paley, PharmD[†], Danine Sullinger, PharmD[*], Ibrahim Sultan, MD[§], Floyd Thoma, BS[¶], Joseph Williams, MD[‡], Kathirvel Subramaniam, MD[‡], Ryan M. Rivosecchi, PharmD[†,*]

[*]*Department of Pharmacy, UPMC Presbyterian Hospital, Pittsburgh, PA*
[†]*School of Pharmacy, University of Pittsburgh, Pittsburgh, PA*
[‡]*Department of Anesthesiology, University of Pittsburgh, Pittsburgh, PA*
[§]*Department of Cardiothoracic Surgery, University of Pittsburgh, Pittsburgh, PA*
[‖]*Department of Critical Care Medicine, University of Pittsburgh, Pittsburgh, PA*
[¶]*UPMC Heart and Vascular Institute, Pittsburgh, PA*

*Objectives:* This study aimed to evaluate the hemodynamic impact and cost-effectiveness of a standardized protocol for refractory vasoplegia occurring after cardiopulmonary bypass (CPB).

*Design:* Observational, pre-post study.

*Setting:* A single-center, academic teaching hospital.

*Participants:* Cardiothoracic surgery patients requiring CPB who received at least a single rescue agent (angiotensin II, hydroxocobalamin [a form of vitamin B12], or methylene blue [MB]) perioperatively for refractory vasoplegia.

*Interventions:* Refractory vasoplegia was defined as at least 0.25 μg/kg/min norepinephrine equivalents (NEeq), and a stepwise treatment protocol was developed, escalating from MB to angiotensin II and hydroxocobalamin. Patients undergoing CPB after protocol implementation were compared with patients undergoing CPB before protocol implementation, who received rescue agents at the discretion of the managing provider.

*Measurements and Main Results:* The study included 215 patients, with 119 and 96 patients in the pre- and post-protocol groups, respectively. There was no difference in mean NEeq requirement preceding rescue agent administration (0.32 μg/kg/min *v* 0.31 μg/kg/min). Post-protocol patients experienced a steeper rate of decline in percentage change in NEeq in the initial 3 hours (−2.01% NEeq per 15-minute interval, $p < 0.01$) and an average cost reduction in vasoactive agents of 30% ($p < 0.01$) and 26% ($p < 0.01$) at 24 and 48 hours, respectively. No differences in short-term clinical outcomes were observed between groups.

A. Teletnick and K. Suh contributed equally as co-first authors.

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[1]*Address correspondence to* Ryan M. Rivosecchi, PharmD, Department of Pharmacy, UPMC Presbyterian Hospital, 200 Lothrop St, Pittsburgh, PA 15213.

*E-mail addresses:* teletnicka@upmc.edu (A. Teletnick), KAS551@pitt.edu (K. Suh), boisenml@upmc.edu (M. Boisen), brownja7@upmc.edu (J.A. Brown), cabralb@upmc.edu (B. Cabral), murrhn@upmc.edu (H. Murray), cap348@pitt.edu (C. Paley), sullingerd@upmc.edu (D. Sullinger), sultani@upmc.edu (I. Sultan), thomafw3@upmc.edu (F. Thoma), williamsjr4@upmc.edu (J. Williams), subramaniamk@upmc.edu (K. Subramaniam), rivosecchirm@upmc.edu (R.M. Rivosecchi).

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*Conclusions:* Implementation of a stepwise protocol using MB, angiotensin II, and hydroxocobalamin for refractory vasoplegia resulted in significant cost savings, hastened NEeq reduction, and similar short-term clinical outcomes.

*Key Words:* refractory vasoplegia; cardiopulmonary bypass; methylene blue; angiotensin II; hydroxocobalamin

## Introduction

Vasoplegia, a form of distributive shock, occurs in patients undergoing cardiopulmonary bypass (CPB) procedures.[1] While its prevalence and mechanisms are well recognized, certain factors increase the risk and severity of its occurrence, including preoperative use of renin-angiotensin-aldosterone system inhibitors, reduced left ventricular ejection fraction (LVEF), symptomatic heart failure, prolonged duration of CPB, and surgery type or complexity.[1,2] In some cases, patients exhibit poor responses to catecholamine vasopressors, requiring high doses to achieve stability.[1] However, excessive catecholamine use carries an increased risk of ventricular arrhythmias necessitating the use of alternative non-catecholamine rescue agents.[1,3]

There are several non-catecholamine medications available for the treatment of hypotension and vasoplegia, such as vasopressin.[3] Vasopressin is widely used in patients with various shock subtypes, including those undergoing cardiothoracic surgery. Other agents, such as methylene blue and hydroxocobalamin, are mechanistically unique, working through nitric oxide–based mechanisms to induce vasoconstriction.[2] Studies examining these agents have found improvements in mean arterial pressure (MAP) and systolic vascular resistance, although the impact on clinical outcomes is still unclear.[3-7] Angiotensin II is another non-catecholamine vasopressor that mimics endogenous angiotensin II, stimulating the renin-angiotensin-aldosterone system and resulting in vasoconstriction.[2] Current evidence for the use of angiotensin II in the cardiothoracic surgery population is limited, but randomized controlled trials in intensive care unit (ICU) populations have shown improvements in MAP and reductions in catecholamine vasopressor requirements.[8-10]

Despite evidence supporting non-catecholamine medications as rescue therapies, there is currently no guidance on optimal integration in the cardiothoracic surgery population. Furthermore, institutional cost is a factor that may influence the accessibility of these therapies. This study aimed to investigate the comparative efficacy and fiscal impact of a standardized institutional protocol for the management of refractory vasoplegia in patients undergoing CPB versus the previous standard of care.

## Methods

### *Study Population*

This observational, pre-post cohort study was conducted at a single academic medical center performing a high volume of index and non-index cardiothoracic surgical procedures including complex aortic, durable left ventricular assist device (VAD), and thoracic transplantation cases. Eligible patients were adults (age $\geq$ 18 years) undergoing cardiothoracic surgery requiring CPB between January 1, 2023, and December 1, 2024, who received at least one intraoperative rescue agent for refractory vasoplegia. Rescue therapy administration was identified through medication charge data, whereas patient data were obtained through reconciliation with the local cardiothoracic surgery database. Patients were excluded if the first rescue agent was administered postoperatively, they had incomplete medication administration records, or they died within 48 hours after surgery given the inability to complete a full cost analysis. Patients treated before the implementation of the standardized vasoplegia management protocol (January 1, 2024) formed the pre-protocol cohort, whereas those treated after implementation constituted the post-protocol cohort.

### *Study Design*

The institutional protocol, implemented on January 1, 2024, established a standardized, sequential approach to managing refractory vasoplegia intraoperatively. Angiotensin II was concurrently added to the study site formulary in January 2024, restricted only to use within the refractory vasoplegia protocol. This protocol replaced prior provider-directed management, which relied on discretionary use of methylene blue or hydroxocobalamin throughout the operation. The study was reviewed and approved by the institution's quality review committee and determined not to require full institutional review board review.

### *Diagnosis, Definition, and Standard Management of Vasoplegia*

The diagnosis of vasoplegia was made in real time by the multidisciplinary surgical and cardiac anesthesia team, defined as MAP less than 65 mmHg associated with a cardiac index greater than 2.2 L/min/m$^2$. Intraoperative monitoring consisted of transesophageal echocardiography in conjunction with thermodilution cardiac output (via the Edwards continuous cardiac output pulmonary artery catheter; BD, Franklin Lakes, NJ) or pulse contour analysis (via Edwards Acumen hypotension prediction index; BD).

Norepinephrine equivalents (NEeq, in micrograms per kilogram per minute) were used to standardize vasopressor requirements and were calculated based on the equivalence ratios used in the ATHOS-3 (Angiotensin II for the Treatment of High-Output Shock) trial, in which 0.1 μg/kg/min of norepinephrine was approximately equivalent to 0.1 μg/kg/min

of epinephrine, 15 μg/kg/min of dopamine, 1 μg/kg/min of phenylephrine, and 0.04 U/min of vasopressin.[8] Ino-dilating agents such as dobutamine or milrinone were not part of the NEeq normalization.[8] In the post-protocol group, vasoplegia was defined as NEeq requirement of at least 0.25 μg/kg/min.

For vasoplegia occurring during CPB, the local protocol includes increasing the CPB flow rate to 2.5 L/min/$m^2$ prior to rescue agent administration. In addition, adjunctive therapies, such as blood products, crystalloids, corticosteroids, and midodrine, are administered at the discretion of the treatment team. Anesthetic depth was titrated to maintain a bispectral index in the range of 40 to 60, remaining unchanged for patients with or without vasoplegia. All postoperative hemodynamic management was left to the multidisciplinary critical care medicine team in collaboration with the cardiothoracic surgery team. Excluding the study protocol, there were no protocolized changes in patient management during the study period, with norepinephrine, epinephrine, vasopressin, dopamine, hydroxocobalamin, and methylene blue available for use.

### *Refractory Vasoplegia Stepwise Study Protocol (Post-Implementation Group)*

The study protocol was initiated intraoperatively when NEeq reached the threshold of 0.25 μg/kg/min with failure to maintain the target MAP of 65 mmHg. A protocolized and sequential administration of rescue agents then was performed: first, methylene blue, followed by angiotensin II and, subsequently, hydroxocobalamin. Doses of methylene blue were bracketed based on patient weight, aiming to administer a dose of approximately 1 to 2 mg/kg of actual body weight given via intravenous bolus (<60 kg, 100 mg; 60-80 kg, 150 mg; >80 kg, 200 mg). If failure to maintain the MAP target after methylene blue administration occurred, an infusion of angiotensin II was initiated at 10 ng/kg/min and titrated by 5 ng/kg/min every 5 minutes. Failure to maintain the MAP target with angiotensin II at a maximum infusion rate of 80 ng/kg/min resulted in progression to the third step, an intravenous bolus dose of 5 g of hydroxocobalamin administered over a period of 15 minutes. The timing of progression through the algorithm was at the discretion of the treatment team in the operating room. Because of formulary constraints, angiotensin II utilization was limited to a maximum of 2 infusions (0.5 mg/100 mL) or 24 hours postoperatively, whichever was reached first. Education was provided to prioritize angiotensin II de-escalation postoperatively but was not protocolized. Additionally, education was provided to all anesthesia providers regarding potential contraindications to methylene blue therapy, such as concern for serotonin syndrome, severe pulmonary hypertension, or known glucose-6-phosphate dehydrogenase deficiency—allowing the initial dose of methylene blue to be omitted.

### *Baseline Characteristic Covariates and Outcomes*

Patient demographic data and baseline clinical characteristics, such as age, sex, operative type (index, non-index, or transplant/VAD surgery), urgency status (elective, urgent, emergent, or salvage), preoperative inotrope or vasopressor use, active endocarditis, LVEF, and initial vasopressor dose (in NEeq), were collected from medical records. Index cases included isolated coronary artery bypass grafting, aortic valve replacement, or mitral valve repair or replacement and the combination of coronary artery bypass grafting and single left-sided valve intervention as defined by the Society of Thoracic Surgeons (STS).[11] Primary transplantation or durable VAD implantation surgical procedures were examined separately from other non-index procedures performed at the site.

Two co-primary outcomes were selected a priori for this study: effectiveness and cost outcomes. The effectiveness outcome was defined as the percentage change in vasopressor requirements expressed in NEeq (%ΔNEeq) measured at sequential 15-minute intervals within the first 3 hours after first rescue agent initiation. The percentage change in MAP also was assessed throughout the same 3-hour period to evaluate patient hemodynamic response. The cost outcome was defined as total vasopressor drug costs incurred from initial rescue agent administration to the initial 48 hours postoperatively. Total vasoactive agent costs were tabulated by reconciliation of the total amount of drug administered for the observed period and rounded up to the next unit package size, multiplied by cost. Drug costs were obtained using the Federal Supply Schedule as it is recommended for health economics research.[12,13] The assigned costs (in US dollars) were as follows: methylene blue, $112.67/50 mg; angiotensin II, $440.95/0.5 mg; hydroxocobalamin, $977.65/5 g; norepinephrine, $28.59/16 mg; epinephrine, $165.83/16 mg; vasopressin, $39.30/40 U; and dopamine, $11.13/800 mg.

Additionally, secondary outcomes were assessed with exploratory intent. These included serum lactate levels on postoperative days 0 to 2, time to vasopressor discontinuation, ICU length of stay, and 30-day mortality. The following were evaluated for any occurrence within 7 days of the initial operation: acute kidney injury, new-onset tachyarrhythmia, need for new mechanical circulatory support, and initiation of renal replacement therapy.

### *Statistical Analysis*

The primary efficacy outcome (%ΔNEeq) was analyzed using generalized estimating equations with an autoregressive correlation structure (first-order autoregression), chosen to account for repeated measures within individuals at regular intervals. This model included terms for group (pre- *v* post-protocol), time (15-minute intervals after baseline), and group-by-time interaction, and covariates included age, sex, surgery group (non-index, index, or transplant/VAD surgery), surgery type by urgency (elective, urgent, emergent, or salvage), preoperative inotropic or vasopressor use within 48 hours of surgery, active endocarditis at the time of surgery, and baseline LVEF. Additionally, a sensitivity analysis was conducted adjusting for the first rescue agent to determine whether the observed effects were attributable to protocol structure independent of agent choice.

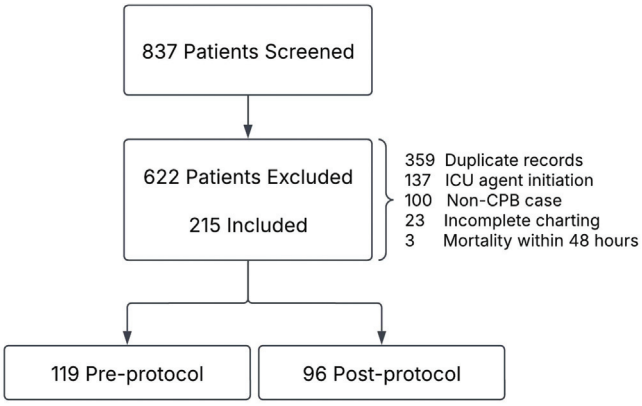


Fig 1. Inclusion and exclusion flowchart. ICU, intensive care unit; CPB, cardiopulmonary bypass.

The primary cost outcome (total vasopressor costs at 48 hours) was assessed using generalized linear models (GLMs) with a gamma distribution and log-link function, adjusting for the same covariates as the primary efficacy model and baseline NEeq dose. Afterward, marginal (ie, adjusted predicted) mean costs attributable to inclusion in the post-protocol group compared with inclusion in the pre-protocol group were estimated using the margin command in Stata (StataCorp, College Station, TX).[14]

Secondary binary outcomes (30-day mortality, tachyarrhythmia, acute kidney injury, renal replacement therapy, and new mechanical support) were evaluated using logistic regression models. Skewed continuous outcomes (ICU length of stay and lactate concentrations) were analyzed using GLMs with a gamma distribution and log-link function. Time to vasopressor discontinuation was modeled using a Cox proportional hazards model. All analyses used 2-sided hypothesis testing with the level of statistical significance set at $p < 0.05$. Statistical analyses were performed using Stata, Standard Edition (version 18.0; StataCorp).

### *Subgroup Analysis*

Pre-specified subgroup analyses examined outcomes separately in two clinically relevant surgical groups. The first comprised STS index surgeries, and the second comprised heart and/or lung transplantations or durable VAD implantations. Within each subgroup, analyses of effectiveness and cost outcomes were repeated.

## Results

The study included 215 patients, with 119 in the pre-protocol group and 96 in the post-protocol group (Fig 1). The mean age was similar between the groups (63.15 ± 13.90 years in pre-protocol group *v* 62.82 ± 14.62 years in post-protocol group, p = 0.87), with a majority of male patients in both groups (78.15% *v* 82.29%, p = 0.45) (Table 1). Surgical case

Table 1
Baseline Characteristics

| | Pre-Protocol Group (n = 119) | Post-Protocol Group (n = 96) | p Value |
|---|---|---|---|
| Age, mean (SD), y | 63.15 (13.90) | 62.82 (14.62) | 0.87 |
| Male sex | 93 (78.15) | 79 (82.29) | 0.45 |
| Surgery group | | | 0.03 |
| Non-index | 45 (37.82) | 41 (42.71) | |
| Index | 47 (39.50) | 46 (47.92) | |
| Transplant/VAD | 27 (22.69) | 9 (9.38) | |
| Surgery type by urgency | | | 0.39 |
| Elective | 52 (43.70) | 47 (48.96) | |
| Urgent | 57 (47.90) | 46 (47.92) | |
| Emergent | 9 (7.56) | 3 (3.12) | |
| Salvage | 1 (0.84) | 0 (0.00) | |
| Patients receiving inotropes/vasopressors within 48 h of surgery | 27 (22.69) | 11 (11.46) | 0.03 |
| Active endocarditis at time of surgery | 20 (16.81) | 14 (14.58) | 0.66 |
| Left ventricular ejection fraction, mean (SD), % | 48.44 (17.30) | 51.65 (14.34) | 0.15 |
| Vasopressor requirement as norepinephrine equivalents, mean (SD) | 0.32 (0.27) | 0.31 (0.26) | 0.82 |
| Vasopressors at time of first rescue agent | | | |
| Norepinephrine users | 106 (89.08) | 89 (92.71) | 0.36 |
| Norepinephrine dose among users, mean (SD) | 0.08 (0.04) | 0.09 (0.05) | 0.21 |
| Epinephrine users | 73 (61.34) | 70 (72.92) | 0.07 |
| Epinephrine dose among users, mean (SD) | 0.06 (0.03) | 0.07 (0.05) | 0.17 |
| Vasopressin users | 100 (84.03) | 82 (85.42) | 0.78 |
| Vasopressin dose among users, mean (SD) | 0.06 (0.05) | 0.07 (0.11) | 0.69 |
| Dopamine users | 17 (14.29) | 9 (9.38) | 0.27 |
| Dopamine dose among users, mean (SD) | 4.76 (1.11) | 5.06 (1.13) | 0.59 |
| Ino-dilators at time of first rescue agent | | | |
| Milrinone users | 2 (1.68) | 1 (1.04) | 0.69 |
| Dobutamine users | 0 (0.00) | 0 (0.00) | NA |

NOTE. Data are presented as number (percentage) unless otherwise indicated.
Abbreviations: NA, not applicable; SD, standard deviation; VAD, ventricular assist device.

Table 2
Medication Characteristics and Unadjusted Costs

| | Pre-Protocol Group (n = 119) | Post-Protocol Group (n = 96) |
|---|---|---|
| Methylene blue | 23 (19) | 90 (94) |
| Dose, mg | 214 ± 646 | 173 ± 55 |
| Hydroxocobalamin | 121 (94) | 9 (9) |
| Dose, g | 5.6 ± 1.6 | 5 ± 0.0 |
| Angiotensin II | NA | 30 (31) |
| Vials | NA | 1.0 ± 0.0 |
| Time from methylene blue to initiation, h | NA | 0.7 ± 1.0 |
| Duration, h | NA | 3.8 ± 4.1 |
| Medication costs,* US $ | | |
| Intraoperative rescue agents | 1,053 ± 387 | 628 ± 435 |
| 24 h postoperative | 1,344 ± 465 | 952 ± 532 |
| 48 h postoperative | 1,409 ± 519 | 1,037 ± 668 |

NOTE. Data are presented as number (percentage) or mean ± standard deviation as appropriate.
Abbreviation: NA, not applicable.
* Unadjusted medication costs.

Table 3
Generalized Estimation Equation Model Predicting Percentage Change in Norepinephrine Equivalents

| | Coefficient | 95% CI |
|---|---|---|
| Post-protocol (*v* pre-protocol)* | 19.01† | 3.42 to 34.59 |
| Time (15-min intervals) | −1.31† | −2.31 to −0.30 |
| Post-protocol × time | −2.01‡ | −3.36 to −0.66 |
| Age (per additional 1 y) | 0.05 | −0.47 to 0.57 |
| Male sex | −8.06 | −25.60 to 9.47 |
| Surgery group | | |
| Non-index | Reference | |
| Index | −9.92 | −25.01 to 5.18 |
| Transplant/VAD | −0.60 | −19.85 to 18.64 |
| Surgery type by urgency | | |
| Elective | Reference | |
| Urgent | −5.72 | −20.84 to 9.40 |
| Emergent | −17.82 | −39.64 to 3.99 |
| Salvage | 13.56 | −3.01 to 30.14 |
| Use of inotropes/vasopressors within 48 h of surgery | 1.57 | −14.73 to 17.86 |
| Active endocarditis at time of surgery | 3.58 | −14.73 to 21.90 |
| Left ventricular ejection fraction (per additional 1%) | −0.25 | −0.69 to 0.19 |

NOTE. Model estimates reflect the change in percentage norepinephrine equivalents over time. Positive coefficients reflect a higher percentage change in norepinephrine equivalents administered.
Abbreviations: CI, confidence interval; VAD, ventricular assist device.
* Representative of baseline norepinephrine equivalents.
† $p < 0.05$.
‡ $p < 0.01$.

mix and use of inotropes or vasopressors within 48 hours of surgery differed significantly ($p < 0.05$). Surgery urgency, prevalence of endocarditis, ejection fraction, and NEeq dose at baseline did not differ significantly between the two groups. The pre-protocol group primarily received hydroxocobalamin (94%) at a dose of 5 g, with only 19% receiving a dose of methylene blue. Alternatively, methylene blue (94%) and angiotensin II (30%) were the most administered rescue agents in the post-protocol group (Table 2). Approximately 70% of patients in the post-protocol group maintained the target MAP of 65 mmHg following administration of methylene blue without requiring an additional agent. Twenty-seven patients (30%) required escalation to angiotensin II, with an additional 5 patients (17%) subsequently progressing to hydroxocobalamin. Five patients (17%) received an additional dose of methylene blue after angiotensin II administration was completed.

### *Primary Effectiveness Outcome*

Implementation of the vasoplegia management protocol resulted in a significant decrease in NEeq requirement from baseline over the initial 3 hours after initiation. Specifically, patients treated under the protocol had an additional 2.0 percentage-point %ΔNEeq reduction per 15-minute interval compared with pre-protocol patients (interaction coefficient, −2.01%; 95% confidence interval [CI], −3.36% to −0.66%) (Table 3). At the first measured interval (15 minutes after initiation), the model-adjusted difference in %ΔNEeq reduction from baseline between the post-protocol and pre-protocol groups was 17.00% (95% CI, 2.06% to 31.93%), with the pre-protocol group exhibiting a greater initial reduction. However, the post-protocol group demonstrated a more rapid decline in %ΔNEeq reduction from baseline over time (Fig 2). For clinical interpretability, if the average patient had a starting NEeq dose of 22.4 μg/min, the current model estimates that the pre-protocol group experienced an average reduction in NEeq of 1.31% every 15 minutes (main effect of time). In contrast, patients in the post-protocol group experienced an additional 2.01% reduction per 15-minute interval (interaction effect), resulting in a total decline of 3.32% per 15-minute interval. Over the first 2 hours (8 intervals), this corresponds to a reduction from 22.4 to 20.2 μg/min (9.8% decrease) in the pre-protocol group and from 22.4 to 17.1 μg/min (23.7% decrease) in the post-protocol group. In the sensitivity analysis that additionally adjusted for first rescue agent, the protocol-by-time interaction remained −2.01 percentage points per 15-minute interval (95% CI, −3.37 to −0.66), essentially

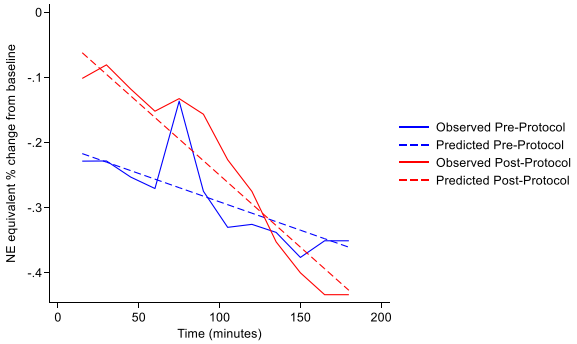


Fig 2. Observed and predicted percentage change in norepinephrine (NE) equivalent dose over time: pre− versus post−protocol.

unchanged from the primary model. When patients who received angiotensin II (n = 30) were excluded, the protocol-by-time coefficient attenuated to −1.10 percentage points per 15-minute interval (95% CI, −2.47 to 0.27), directionally similar but no longer statistically significant. Notably, milrinone and dobutamine use remained minimal throughout the hemodynamic monitoring period, with 2 patients (1.7%) and 3 patients (3.1%) receiving milrinone within 3 hours of rescue agent administration in the pre- and post-protocol groups, respectively.

### *Primary Cost Outcome*

In unadjusted analysis, the average cost of vasopressor drugs was $1,393 (standard deviation, $45) in the pre-protocol group compared with $1,056 (standard deviation, $68) in the post-protocol group. Post-protocol implementation significantly reduced vasopressor drug costs within the first 48 hours. By use of a GLM with log-link function, the cost ratio was 0.74 (95% CI, 0.65 to 0.85), representing a 26% reduction in total 48-hour vasopressor drug expenditure after protocol implementation. The adjusted predicted mean vasopressor cost was $1,405 (95% CI, $1,311 to $1,499) for the pre-protocol group and $1,040 (95% CI, $916 to $1,165) for the post-protocol group, resulting in a significant estimated cost savings of $365 (95% CI, $210 to $519) per patient in the post-protocol group over the first 48 hours (Table 4).

### *Secondary Outcomes*

The secondary outcome of percentage change in MAP demonstrated no significant difference between the pre- and post-protocol groups at any measured interval, indicating a similar trajectory of MAP over time in both groups (Appendix Table 1). Clinical exploratory outcomes showed no statistically significant differences between the groups. Adjusted odds ratios for the post- versus pre-protocol group were 1.37 (95% CI, 0.38 to 4.99) for 30-day mortality, 1.20 (95% CI, 0.65 to 2.21) for new-onset tachyarrhythmia, 0.70 (95% CI, 0.39 to 1.28) for acute kidney injury, and 0.93 (95% CI, 0.43 to 2.00) for initiation of new renal replacement therapy. Initial ICU length of stay also was similar between groups (adjusted ratio, 0.76; 95% CI, 0.56 to 1.08), as was time to vasopressor discontinuation (adjusted hazard ratio, 0.92; 95% CI, 0.67 to 1.24). Postoperative lactate concentrations on days 0 to 2 were comparable, with adjusted ratios ranging from 0.84 to 0.91 and corresponding 95% CIs including 1.0. Finally, total vasopressor costs within the first 24 hours were significantly reduced after protocol implementation (cost ratio, 0.70; 95% CI, 0.62 to 0.80), consistent with the primary cost results (Appendix Table 2).

Table 4
Adjusted Cost Ratios for Vasopressor Costs at 48 Hours

| | Cost Ratio | 95% CI |
|---|---|---|
| Post-protocol (*v* pre-protocol) | 0.74* | 0.65-0.85 |
| Age (per additional 1 y) | 1.00 | 0.99-1.01 |
| Male sex | 1.18 | 0.99-1.41 |
| NE equivalent dose at baseline (per additional 1 μg/kg/min) | 1.11 | 0.94-1.30 |
| Surgery group | | |
| Non-index | Reference | |
| Index | 0.92 | 0.79-1.07 |
| Transplant/VAD | 1.03 | 0.79-1.34 |
| Surgery type by urgency | | |
| Elective | Reference | |
| Urgent | 1.00 | 0.85-1.16 |
| Emergent | 0.87 | 0.66-1.15 |
| Salvage | 1.72* | 1.47-2.01 |
| Use of inotropes/vasopressors within 48 h of surgery | 1.19 | 0.96-1.49 |
| Active endocarditis at time of surgery | 1.02 | 0.85-1.22 |
| Left ventricular ejection fraction (per additional 1%) | 1.00 | 0.99-1.00 |

Abbreviations: CI, confidence interval; NE, norepinephrine; VAD, ventricular assist device.
* $p < 0.01$.

### *Subgroup Analyses*

In the pre-specified subgroup analyses, the STS index surgery subgroup (n = 93) demonstrated a similar trend in %ΔNEeq, although the effect did not reach the level of statistical significance (interaction coefficient, −1.45%; 95% CI, −3.05% to 0.15%) (Appendix Table 3). However, total vasopressor costs at 48 hours remained significantly lower after protocol implementation (cost ratio, 0.67; 95% CI, 0.56 to 0.80) (Appendix Table 4). This translated to a predicted mean cost savings of $456 per patient for the post-protocol group compared with the pre-protocol group (95% CI, $270 to $642).

In the transplant/VAD subgroup (n = 36), the protocol also showed a trend toward improved %ΔNEeq decline after protocol implementation (interaction coefficient, −3.17%; 95% CI, −6.46% to 0.12%), as well as a similar pattern of lower vasopressor costs (cost ratio, 0.75; 95% CI, 0.52 to 1.08). However, neither effect reached the level of statistical significance.

## Discussion

In this single−center, pre−post cohort study, implementing a standardized rescue agent protocol for refractory vasoplegia management in cardiothoracic surgery was associated with faster vasopressor weaning while maintaining hemodynamic stability, as well as significant cost savings. Post−protocol patients experienced a 3.31% decrease in NEeq dose per 15-minute interval, which was more than twice the rate in the pre−protocol group. This effect persisted even after adjustment for the first rescue agent, suggesting that the improvement was not simply due to greater use of methylene blue in the post-protocol period. Excluding the 30 angiotensin II recipients made the protocol-related reduction in NEeq smaller and not significant, which may indicate that some of the protocol's effect operates through timely escalation to angiotensin II and that the smaller sample limited the study's ability to detect a

difference. Concurrently, the average per-patient vasopressor cost decreased by $365 over the first 48 hours. It is important to note that MAP trajectories remained consistent between groups at all time points, suggesting that accelerated weaning did not lead to a difference in hemodynamic efficacy.

Vasoplegia has been described across various etiologies of distributive shock; however, a universal definition of the condition has yet to be established. Several large randomized trials have defined an adequate trial of first-line vasoactive therapy as 0.2 to 0.5 μg/kg/min NEeq with consideration of therapy escalation at 0.25 μg/kg/min NEeq for septic vasodilatory shock.[8,15,16] Definitions of refractory vasoplegia further lack clarity, with previous literature combining a variety of MAP and vasopressor requirement thresholds. However, these trials similarly have required therapeutic failure of conventional vasopressors to meet refractory criteria.[2,3,17,18] Refractory vasoplegia surrounding CPB data suggests improved outcomes with earlier rather than later therapy escalation, culminating in the decision by the authors' institution to use a threshold of 0.25 μg/kg/min NEeq for rescue agent protocol initiation.[16,19] The unadjusted baseline NEeq in the study were similar between groups and fell within the realm of previously published triggers for the administration of rescue agents.

Previous literature has compared the efficacy of methylene blue and hydroxocobalamin to reverse refractory vasoplegia after CPB with mixed results.[7,20,21] Hiruy et al.[7] found that hydroxocobalamin administration resulted in lower NEeq throughout a 24-hour period compared with methylene blue; however, patients in the methylene blue group had nearly twice as high NEeq at baseline (0.59 *v* 0.34, $p < 0.001$). In contrast, a study by Kram et al.[21] demonstrated no difference in %ΔNEeq in the 2-hour period after administration of either methylene blue or hydroxocobalamin with similar NEeq (0.3 *v* 0.35, $p = 0.54$) at baseline. Additionally, when the existing literature was combined into a meta-analysis, there was no difference in vasopressor requirements between the hydroxocobalamin and methylene blue groups.[20]

When considering durability of response to these agents, both exhibit a similar duration of peak efficacy of roughly 1 hour when administered as a bolus.[20] This similar time to "wearing off" of the initial agent was seen and handled in different ways between groups at the authors' institution. In the pre-protocol group, rebound vasoplegia was largely managed with increased conventional vasopressors, corresponding to the increased NEeq requirement seen at approximately 75 minutes in Figure 2. In addition, 12 patients (10%) required re-dosing of hydroxocobalamin perioperatively and 15 patients (13%) received methylene blue in combination with hydroxocobalamin. Alternatively, the post-protocol group saw greater use of adjunctive rescue therapy as allowed with escalation to angiotensin II, which allowed for minimal rebound of NEeq requirement at the 75-minute time point and continued vasopressor weaning afterward. As a result, the post-protocol group that progressed from methylene blue to angiotensin II showed a significantly greater decline in NEeq compared with the pre-protocol group that received primarily hydroxocobalamin, after adjusting for covariates including baseline NEeq at the time of initial rescue agent administration.

While angiotensin II has traditionally been evaluated in the context of septic shock, Coulson et al.[22] have demonstrated its safety and efficacy in cardiothoracic surgery.[8,23] Angiotensin II also has been correlated with improved outcomes in patients with elevated plasma renin levels, which commonly occurs in the cardiothoracic surgery population because of underproduction of endogenous angiotensin II with saturation of angiotensin-converting enzyme in the setting of vasoplegia.[24,25] The optimal timing of escalation through rescue agents remains uncertain. Notably, a recent study by Miles et al.[23] found that initiating angiotensin II early—rather than postoperatively—was associated with improved hemodynamic response and reduced morbidity, which is further supported by findings from a post hoc analysis of the ATHOS-3 trial.[26] In the post-protocol group, angiotensin II was administered promptly on identifying methylene blue failure and proved to be an effective second-line rescue agent when initiated intraoperatively, potentially by providing an alternative mechanism of hemodynamic support outside of the inducible nitric oxide synthase pathway.

While the protocol examined in this study used angiotensin II as a second-line rescue agent, a loss of a statistically significant benefit for the post-protocol group was noted when patients who received angiotensin II were removed from the analysis. Although this post hoc subgroup analysis is hypothesis generating and underpowered, it may signal that angiotensin II carried a large portion of the overall hemodynamic benefit observed. This corroborates the methods used in the study by Miles et al.,[23] in which angiotensin II served as a first-line rescue agent, and could support earlier utilization in future variations of a vasoplegia protocol.

The post-protocol group demonstrated a significant cost reduction at 24 and 48 hours after rescue agent administration. The unadjusted cost reduction was first demonstrated in the cost of the intraoperative rescue agents ($425), and a similar margin was observed throughout the study period at 24 hours ($392) and 48 hours ($372) postoperatively. Despite the high acquisition cost of rescue agents, structured protocol use enabled meaningful reductions in overall vasopressor expenditures, equating to $36,500 saved per 100 surgical procedures, underscoring the protocol's potential value in resource-constrained settings. It is important to note that the study's total vasopressor cost calculation included all vasoactive agents, not just the rescue agents. While substituting methylene blue for hydroxocobalamin reduced costs, the protocol's approach also may have resulted in more efficient use of other vasopressors. Thus, the observed cost savings likely reflect both drug substitution and broader improvements in vasoactive management.

There were several limitations in this study. The retrospective, nonrandomized pre–post design is susceptible to unmeasured confounding and secular trends. Although most patient baseline characteristics were well balanced and models were adjusted for key covariates, causality cannot be definitively established. Nuances of intraoperative patient management such as blood product administration, fluid management, and anesthetic dose titration were unable to be controlled for because of the retrospective nature of the study. Individual

practitioner practice patterns and heterogeneous surgical case mix may have varied on a case-to-case basis; however, this represents a real-world pragmatic study design with natural variation surrounding a standardized protocol.

Notably, the pre-protocol group lacked a structured approach for agent administration, which may create additional baseline variability compared with the more structured protocol population. Despite this, approximately 10% of post-protocol patients deviated from the stepwise sequence because of clinical judgment, reflecting real-world flexibility rather than protocol failure. In addition, as this was a single−center study, the results may not be generalizable to institutions with different case mixes or protocols. This includes but is not limited to the weight-based dose ranges applied to methylene blue dosing. The algorithm that was intended to ease the operational burden of calculating patient-specific doses instead opted for a range of 1 to 2 mg/kg that would encompass the vast majority of patients.

Moreover, while the overall sample (N = 215) was powered for the co−primary outcomes, subgroup analyses were underpowered and, thus, findings within these subgroups should be interpreted as exploratory. Additionally, cost analyses relied on standardized costs from the Federal Supply Schedule and did not account for downstream impacts on length of stay or other resource use, which warrant future investigation. Because the inclusion criteria of the study consisted of the administration of a rescue agent, the authors were unable to account for the effect of the protocol on avoiding the administration of a rescue agent, which may have led to underestimated cost savings. Finally, although overall vasoactive agent costs were lower in the post-protocol period, cost data in this study were not granular enough to determine how much of this reduction was driven by decreased hydroxocobalamin use versus other vasoactive agents. Therefore, the authors interpreted the cost effect as a protocol-level finding rather than attributing it to a single drug.

In the current real-world cohort, a standardized vasoplegia rescue agent protocol accelerated vasopressor weaning and generated significant vasopressor cost savings without hemodynamic compromise. These findings signal potential clinical and economic benefits, and future studies at additional centers with larger sample sizes are warranted to confirm and extend these results.

## Declaration of competing interest

The authors have nothing to declare.

## CRediT authorship contribution statement

**Andrew Teletnick:** Data curation, Investigation, Methodology, Writing − original draft, Writing − review & editing. **Kangho Suh:** Data curation, Formal analysis, Methodology, Resources, Visualization, Writing − original draft, Writing − review & editing. **Michael Boisen:** Conceptualization, Writing − review & editing. **James A. Brown:** Resources, Data curation, Writing − review & editing. **Bernardine Cabral:** Investigation, Data curation, Writing − review & editing. **Holt Murray:** Conceptualization, Writing − review & editing. **Caroline Paley:** Formal analysis, Resources, Writing − review & editing. **Danine Sullinger:** Conceptualization, Investigation, Methodology, Writing − review & editing. **Ibrahim Sultan:** Conceptualization, Supervision, Resources, Writing − review & editing. **Floyd Thoma:** Investigation, Resources, Data curation, Writing − review & editing. **Joseph Williams:** Investigation, Data curation, Writing − review & editing. **Kathirvel Subramaniam:** Conceptualization, Supervision, Writing − review & editing. **Ryan M. Rivosecchi:** Conceptualization, Data curation, Investigation, Methodology, Project administration, Supervision, Writing − review & editing.

## Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1053/j.jvca.2026.02.003.

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