

# The acute influence of vasopressin on hemodynamic status and tissue oxygenation following the Norwood procedure



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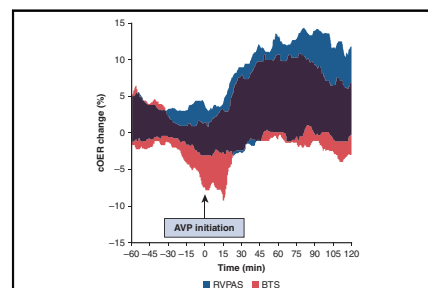
## ABSTRACT

**Objectives:** Arginine vasopressin (AVP) is used to treat hypotension. Because AVP increases blood pressure by increasing systemic vascular resistance, it may have an adverse effect on tissue oxygenation following the Norwood procedure.

**Methods:** Retrospective analysis of continuously captured hemodynamic data of neonates receiving AVP following the Norwood procedure.

**Results:** We studied 64 neonates exposed to AVP within 7 days after the Norwood procedure. For the entire group, AVP significantly increased mean blood pressure ( $2.5 \pm 6.3$ ) and cerebral and renal oxygen extraction ratios ( $4.1\% \pm 9.6\%$  and  $2.0\% \pm 4.7\%$ , respectively;  $P < .001$  for all values). In the right ventricle to pulmonary artery shunt cohort, AVP significantly increased blood pressure, arterial oxygen saturation ( $1.4\% \pm 3.8\%$ ;  $P = .011$ ), pulmonary to systemic perfusion ratio ( $0.2 \pm 0.4$ ;  $P = .017$ ), and cerebral and renal oxygen extraction ratios ( $4.6\% \pm 8.7\%$ ;  $P = .010\%$  and  $4.7\% \pm 9.4\%$ ;  $P = .014$ , respectively). The Blalock-Taussig shunt cohort experienced a less significant vasopressor response and no change in arterial oxygen saturation, pulmonary to systemic perfusion ratio, or cerebral and renal oxygen extraction ratios.

**Conclusions:** The right ventricle to pulmonary artery shunt cohort experienced a significant vasopressor response to AVP that was associated with a significant increase in pulmonary perfusion and decrease in cerebral and renal perfusion, whereas the Blalock-Taussig shunt cohort experienced a less significant vasopressor response and no change in pulmonary or systemic perfusion. The influence of AVP on tissue oxygenation following the Norwood procedure may have clinical implications that require further study. (JTCVS Open 2022;9:217-24)



Cerebral oxygen extraction was higher in RVPAS compared with BTS patients receiving AVP after NP.

## CENTRAL MESSAGE

Following the NP, we found AVP induced a significant vasopressor response in those patients who received a RVPAS, which was associated with a significant increase in pulmonary perfusion and decrease in systemic perfusion.

## PERSPECTIVE

The optimal vasoactive strategy following the NP is not known. No study thus far has evaluated the influence of AVP on pulmonary and systemic perfusion. In those patients who underwent RVPAS insertion, AVP induced a significant vasopressor response, which was associated with a significant increase in pulmonary perfusion and decrease in systemic perfusion.

See Commentary on page 225.

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Received for publication Aug 3, 2021; accepted for publication Jan 12, 2022; available ahead of print Feb 2, 2022.

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**Abbreviations and Acronyms**

ANOVA	= analysis of variance
AVP	= arginine vasopressin
BP	= blood pressure
BTS	= Blalock-Taussig shunt
CAP	= common atrial pressure
CO	= cardiac output
CPP	= coronary perfusion pressure
HR	= heart rate
NIRS	= near infrared spectroscopy
NP	= Norwood procedure
O <sub>2</sub> ER	= oxygen extraction ratio
PVR	= pulmonary vascular resistance
Qp	= pulmonary perfusion
Qs	= systemic perfusion
RVPAS	= right ventricular to pulmonary artery shunt
Sao <sub>2</sub>	= arterial oxygen saturation
SS	= steady state
SVR	= systemic vascular resistance
TSS	= time to steady state
VIS	= vasoactive infusion score

Neonates with single-ventricle variants and obstruction to systemic blood flow may undergo the Norwood procedure (NP), which includes reconstruction of the diminutive aorta, placement of either a modified Blalock-Taussig shunt (BTS), or right ventricle to pulmonary artery shunt (RVPAS) and an atrial septectomy. Over the past several years, arginine vasopressin (AVP) has been increasingly used following the NP to treat hypotension while limiting expansion of intravascular volume and increases in heart rate (HR).<sup>1,2</sup> However, because AVP increases arterial blood pressure (BP) by increasing systemic vascular resistance (SVR), it may have an adverse effect on stroke volume and cardiac output (CO).<sup>3,4</sup> Further, because the systemic and pulmonary circulations are in parallel, increasing SVR and systemic arterial BP may have an adverse effect on the distribution of total CO, increasing pulmonary perfusion (Qp) at the expense of systemic perfusion (Qs).<sup>5-9</sup>

Based on these theoretical concerns, we conducted a retrospective analysis of continuously captured physiologic data to provide a high-fidelity assessment of the acute influence of AVP on hemodynamic status and tissue oxygenation following the NP.

**MATERIALS AND METHODS**

This study was conducted under an institutional review board protocol (No. H-40094), which was approved by the Baylor College of Medicine on November 30, 2016. The need for written consent was waived. Retrospective electronic medical records were obtained for each patient who received AVP in the cardiac intensive care unit within 7 days following the NP from

September 1, 2014, through May 1, 2021. The indication for AVP was persistent hypotension despite volume administration and existing vasoactive support.

**AVP Infusion and Study Epochs**

Data were evaluated according to the following epochs: 1 hour before initiation of the AVP infusion, which established baseline hemodynamic parameters; the hour following the initiation of drug which, based on the 10- to 15-minute half-life of AVP, represented the time to steady state (TSS); and the second hour (ie, 60-120 minutes) following the initiation of AVP, which represented the steady state (SS). The subsequent re-initiation of AVP infusions were also studied, which required an additional initial hour following discontinuation of the infusion, allowing for complete clearance of AVP before analyzing the aforementioned epochs.

**Hemodynamic Parameters Data Extraction**

The Sickbay platform (Medical Informatics Corporation) was used to continuously capture hemodynamic data at a frequency of 0.5 Hz from bedside patient monitors (GE B850 monitors) and included HR, systolic BP, diastolic BP, mean BP, and common atrial pressure (CAP). The coronary perfusion pressure (CPP = diastolic BP - CAP) was also calculated. The physiological signals are time synchronized, stored onsite, and made available for analysis. Data analysis was completed using MATLAB (MathWorks).

**Oximetric Data Extraction**

Arterial pulse oximetry oxygen saturations (Sao<sub>2</sub>) were continuously captured at a frequency of 0.5 Hz and stored on the Sickbay platform. All patients following cardiac surgery are monitored with the Medtronic INVOS 7100 near infrared spectroscopy (NIRS) oximeter (Medtronic); however, intermittent connectivity between the INVOS monitor and the Sickbay platform for a minority of patients led to incomplete data capture. NIRS oxygen saturations were captured at a frequency of 0.2 Hz and stored on the Sickbay system. Qp to Qs ratio (Qp:Qs) was calculated using an assumed pulmonary venous oxygen saturation of 99% and the cerebral NIRS oxygen saturation was used for the central venous oxygen saturation.

**Hemodynamic Parameter and Oximetric Data Analysis**

The baseline, TSS and SS time periods were divided into 15-minute blocks to calculate a moving average for each hemodynamic and oximetric parameter. The TSS and SS averages were then compared with the baseline averages for each patient and each physiological parameter using paired *t* tests. This statistical design ensures that each patient serves as his or her own control. The association between 2 different physiological parameters was established using Kendall's correlation analysis.

**Modified Vasoactive-Inotropic Score**

A modified vasoactive-inotropic score (VIS) was used to assess changes in concurrent vasoactive infusions. The VIS was modified to exclude AVP: 100 × epinephrine infusion rate plus 10 × milrinone infusion rate plus 100 × norepinephrine infusion rate (μg/kg/min).<sup>10</sup> Dopamine was excluded from the modified VIS based on institutional practice. An average modified VIS was determined for baseline, TSS and SS time periods. The change in VIS was analyzed using a repeated measures analysis of variance (ANOVA).

**Confounders**

The potential influence of confounding therapies administered during the TSS or SS periods on BP was analyzed. We chose the following potential confounders a priori: alterations in vasoactive support (utilizing the modified VIS), boluses of 5% albumin or normal saline, and boluses of

calcium. These confounding therapies were categorized as binary variables, depending on whether or not they were administered during the AVP infusion. The relationship between confounders and BP response was assessed using ANOVA analysis. The relationships between AVP dosing (low vs high dose, defined as  $<$  or  $\geq 0.0003$  U/kg/min) and BP response, and between initial and reinitiated AVP doses and BP response were assessed using ANOVA analysis.

AVP infusions were excluded in the case that a blood transfusion was initiated during the TSS or SS. Eleven AVP infusions were excluded due to concomitant blood cell transfusions. An AVP infusion that was associated with a delayed sternal closure occurring during any of the time periods was excluded. All patients were on a continuous infusion of calcium to maintain an ionized calcium of  $>1.3$  mmol/L. All patients were on fentanyl and dexmedetomidine infusions, which were titrated according to unit protocol to achieve a negative state behavioral scale score of  $-1$  to  $-2$ .

## RESULTS

### Patient Demographic Characteristics and AVP Exposures

A total of 135 patients underwent the NP during the study period, of which 64 were treated with AVP during the first 7 postoperative days. The median weight and age at the time of surgery was 3.3 kg (interquartile range [IQR], 3.00-3.60 kg) and 8.3 days (IQR, 4.7-10.8 days), respectively. Anatomic subtypes for the 64 patients included 59 patients with hypoplastic left heart syndrome, 3 patients with double outlet right ventricle with systemic outflow obstruction, 1 patient with right dominant atrioventricular canal with systemic outflow obstruction, and 1 patient with a systemic left ventricle (double inlet left ventricle with systemic outflow obstruction). Amongst NP patients exposed to AVP, 33 underwent RVPAS insertion (52%) and 31 underwent BTS insertion (48%). For patients undergoing RVPAS insertion, 82% ( $n = 27$ ) received a 6-mm diameter shunt, whereas 15% ( $n = 5$ ) received a 5-mm shunt and 3% ( $n = 1$ ) a 4-mm shunt. For those patients undergoing a BTS, 81% ( $n = 25$ ) patients received a 3.5-mm diameter shunt, whereas 13% ( $n = 4$ ) received a 4.0-mm shunt, and 6% ( $n = 2$ ) a 3.0-mm shunt.

The 64 patients were exposed to 142 AVP infusions, of which 64 were initial infusions and 78 reinitiated infusions in the same patient. Of the 142 infusions, 76 infusions had cerebral NIRS oximetry monitoring and 72 infusions had renal NIRS oximetry monitoring. The initial infusion was initiated at a median time following surgery of 1.0 day (IQR, 0.2-3.4 days), with a majority of AVP infusions occurring during the first 2 postoperative days. The average AVP infusion dose over the 2-hour study period was 0.0002 U/kg/min for 90 infusions (63%), 0.0003 U/kg/min for 36 infusions (25%) and 0.0004 U/kg/min or greater for the remaining infusions ( $n = 16$  [12%]).

### Baseline Hemodynamic Parameter Data

The baseline hemodynamic parameters for the entire cohort and according to shunt type are listed in Table 1.

**TABLE 1. Baseline hemodynamic and oximetric parameters for entire cohort and shunt types**

Parameter	Entire cohort	RVPAS	BTS	Comparison <i>P</i> value*
mBP (mm Hg)	48.4 ± 7.3	50.5 ± 7.5	46.3 ± 6.8	<.001
sBP (mm Hg)	68.3 ± 11.6	67.3 ± 10.6	68.9 ± 13.6	.599
dBp (mm Hg)	36.8 ± 7.0	41.2 ± 6.6	32.6 ± 4.9	<.001
CAP (mm Hg)	8.7 ± 2.4	9.0 ± 2.4	8.4 ± 2.4	.189
CPP (mm Hg)	27.8 ± 6.4	31.7 ± 5.9	24.2 ± 5.1	<.001
Sao <sub>2</sub> (%)	82.7 ± 4.9	81.9 ± 5.3	83.5 ± 5.0	.048
Qp:Qs	1.2 ± 0.6	1.1 ± 0.7	1.2 ± 0.7	.286
cO <sub>2</sub> ER (%)	41.2 ± 14.4	40.9 ± 15.8	41.3 ± 13.6	.802
rO <sub>2</sub> ER (%)	32.4 ± 15.6	33.3 ± 17.6	31.3 ± 14.9	.754

Values are presented as mean ± SD. RVPAS, Right ventricular to pulmonary artery shunt; BTS, Blalock-Taussig shunt; HR, heart rate (bpm); mBP, mean blood pressure; sBP, systolic blood pressure; dBp, diastolic blood pressure; CAP, common atrial pressure; CPP, coronary perfusion pressure; Sao<sub>2</sub>, arterial oxygen saturation; Qp:Qs, pulmonary blood flow to systemic blood flow ratio; cO<sub>2</sub>ER, cerebral oxygen extraction ratio; rO<sub>2</sub>ER, renal oxygen extraction ratio. \**P* values are computed using the 2-sample *t* test to compare the RVPAS and BTS groups.

The BTS cohort had a significantly lower diastolic BP, and as result mean BP and CPP than the RVPAS cohort.

### BP Response

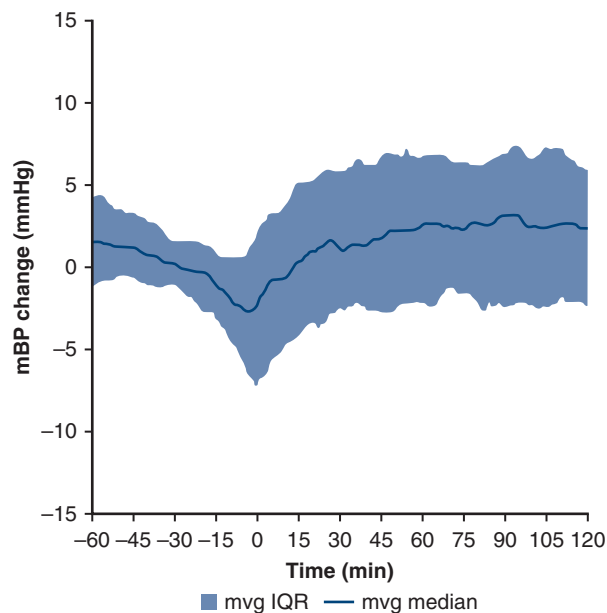
Figure 1 demonstrates the change in mean BP from baseline through SS. Of note, the mean BP rises over the initial 45 minutes or so of the TSS and then plateaus consistent with the pharmacokinetics of AVP. The AVP dose did not have a statistically significant effect on the change in mean BP ( $P = .28$ ). When comparing the initial AVP exposure to subsequent infusions, the change in mean BP was greater for the initial AVP infusion than for the subsequent infusions ( $P = .003$ ).

### Confounders and BP Responsiveness

The association between concurrent interventions and BP response was assessed. The modified VIS medians for the 3 epochs were 6.6 (baseline), 6.5 (TSS), and 6.5 (SS). There were no significant changes in the modified VIS over the 3 epochs ( $P = .13$ ), and there was no association between change in VIS and BP response ( $P = .53$ ). Twenty of the 142 infusions (14%) received 1 or more normal saline or albumin boluses. There was no association between normal saline or albumin boluses and BP response ( $P = .53$  and  $P = .77$ , respectively). Five of 142 infusions received a calcium bolus. We did not find an association between calcium boluses and blood pressure response using ANOVA analysis ( $P = .76$ ).

### Analysis of All Shunt Types

For all patients, there was a significant increase in BP and CPP (Table 2). By the end of the SS, the systolic BP,



**FIGURE 1.** Moving median and moving interquartile range (IQR) for the change in mean blood pressure (mBP) with respect to its baseline values. Arginine vasopressin infusions start at time 0. mvg, Moving.

diastolic BP, mean BP, and CPP had increased by  $4.1 \pm 9.6$  mm Hg,  $1.8 \pm 4.6$  mm Hg,  $2.5 \pm 6.3$  mm Hg, and  $2.0 \pm 4.7$  mm Hg, respectively ( $P < .001$  for all). There was no change in mean BP in 32% of infusions; the mean BP increased by 0 to 5 mm Hg in 34% of infusions, by 5

**TABLE 2.** Changes in hemodynamic parameters for the entire cohort\*

Time (min)	mBP		CAP		
	Mean $\pm$ SD	P value†	Mean $\pm$ SD	P value†	
60-75	2.5 $\pm$ 6.2	<.001	-0.1 $\pm$ 1.9	.478	
75-90	2.5 $\pm$ 6.3	<.001	-0.1 $\pm$ 2.0	.461	
90-105	2.4 $\pm$ 6.2	<.001	0.0 $\pm$ 2.1	.483	
105-120	2.5 $\pm$ 6.3	<.001	0.0 $\pm$ 2.1	.504	
		sBP		CPP	
60-75	4.2 $\pm$ 9.8	<.001	2.2 $\pm$ 4.4	<.001	
75-90	4.1 $\pm$ 9.8	<.001	2.1 $\pm$ 4.5	<.001	
90-105	4.1 $\pm$ 9.6	<.001	2.0 $\pm$ 4.6	<.001	
105-120	4.1 $\pm$ 9.6	<.001	2.0 $\pm$ 4.7	<.001	
		dBp		HR	
60-75	1.8 $\pm$ 4.5	<.001	1.2 $\pm$ 8.7	.105	
75-90	1.8 $\pm$ 4.5	<.001	1.2 $\pm$ 9.0	.116	
90-105	1.8 $\pm$ 4.5	<.001	1.1 $\pm$ 9.4	.166	
105-120	1.8 $\pm$ 4.6	<.001	1.0 $\pm$ 9.5	.192	

mBP, Mean blood pressure; CAP, common arterial pressure; sBP, systolic blood pressure; CPP, coronary perfusion pressure; dBp, diastolic blood pressure; HR, heart rate. \*Values are changes in parameters with respect to their baseline values. †P values are computed using 1-sample t tests with mean equal to 0 as the null hypothesis.

to 10 mm Hg in 25% of infusions and by  $> 10$  mm Hg in 10% of infusions. There was a significant increase in  $SaO_2$  and cerebral and renal oxygen extraction ratio ( $O_2ER$ ) ( $2.5\% \pm 6.3\%$ ,  $4.1\% \pm 9.6\%$ , and  $2.0\% \pm 4.7\%$ ;  $P < .001$  for each) (Table 3). There was no appreciable change in the Qp:Qs. Figure 2 demonstrates the change in cerebral and renal  $O_2ER$  through SS. Of note, there is a progressive increase in the cerebral and renal  $O_2ER$  over the initial 45 minutes of the TSS period, mirroring the change in mean BP.

Kendall’s correlation demonstrated a positive association between changes in BP and changes in  $SaO_2$  ( $P < .001$ ), Qp:Qs ( $P = .011$ ), cerebral  $O_2ER$  ( $P = .041$ ), and renal  $O_2ER$  ( $P < .001$ ).

**Analysis According to Shunt Subtype**

Of the 64 patients exposed to AVP, there were 31 in the BTS group (48%) and 33 in the RVPAS group (52%). Seventy-two and 70 of the infusions occurred in BTS and RVPAS patients, respectively. The RVPAS cohort experienced a significant increase in systolic BP ( $4.6 \pm 9.5$  mm Hg;  $P = .008$ ), diastolic BP ( $2.5 \pm 5.4$  mm Hg;  $P < .001$ ), mean BP ( $3.2 \pm 6.5$  mm Hg;  $P < .001$ ), and CPP ( $2.7 \pm 5.2$  mm Hg;  $P = .001$ ) (Table 4). There was no significant change in CAP or HR. The RVPAS cohort also experienced a significant increase in  $SaO_2$  ( $1.4\% \pm 3.8\%$ ;  $P = .011$ ), Qp:Qs ( $0.2 \pm 0.4$ ;  $P = .017$ ), and cerebral and renal  $O_2ER$  ( $4.6\% \pm 8.7\%$ ;  $P = .010$ , and  $4.7\% \pm 9.4\%$ ;  $P = .014$ ) (Table 5). The BTS cohort experienced a significant increase in diastolic BP and mean BP ( $1.1 \pm 3.8$  mm Hg;  $P = .031$  and  $1.8 \pm 6.2$  mm Hg;  $P = .008$ ) but no significant change in systolic BP or CAP. As a result, the CPP increased significantly during the SS epoch. However, the change in CPP lost significance by the end of the SS period because the increase in diastolic BP became less significant (Table 4). There was a significant increase in HR ( $3.2 \pm 10.0$ ;  $P = .015$ ). There was no significant change in  $SaO_2$ , Qp:Qs, or cerebral or renal  $O_2ER$  (Table 5). Figure 3 provides an overview of the results of this analysis.

**DISCUSSION**

This study provides a high-fidelity assessment of the acute effects of a vasopressor on hemodynamic parameters and tissue oxygenation following the NP according to shunt type. The short half-life of AVP and the continuous capturing of hemodynamic data enabled us to evaluate the acute influence of this agent on the circulation while minimizing the influence of clinically relevant confounders.

For the entire group of patients, AVP induced a significant increase in BP and significant decrease in cerebral and renal tissue oxygenation. A Kendall’s correlation analysis demonstrated a positive association between changes in BP and changes in  $SaO_2$ , Qp:Qs, and cerebral and renal

TABLE 3. Changes in oximetric parameters for the entire cohort\*

Time (min)	Sao <sub>2</sub>		Qp:Qs		
	Mean ± SD	P value†	Mean ± SD	P value†	
60-75	2.5 ± 6.2	<.001	-0.1 ± 1.9	.478	
75-90	2.5 ± 6.3	<.001	-0.1 ± 2.0	.461	
90-105	2.4 ± 6.2	<.001	0.0 ± 2.1	.483	
105-120	2.5 ± 6.3	<.001	0.0 ± 2.1	.504	
		cO <sub>2</sub> ER		rO <sub>2</sub> ER	
60-75	4.2 ± 9.8	<.001	2.2 ± 4.4	<.001	
75-90	4.1 ± 9.8	<.001	2.1 ± 4.5	<.001	
90-105	4.1 ± 9.6	<.001	2.0 ± 4.6	<.001	
105-120	4.1 ± 9.6	<.001	2.0 ± 4.7	<.001	

Sao<sub>2</sub>, Arterial oxygen saturation; Qp:Qs, pulmonary blood flow to systemic blood flow ratio; cO<sub>2</sub>ER, cerebral oxygen extraction ratio; rO<sub>2</sub>ER, renal oxygen extraction ratio. \*Values are changes in parameters with respect to their baseline values. †P values are computed using 1-sample *t* tests with mean equal to 0 as the null hypothesis.

O<sub>2</sub>ER. Figure 2 illustrates the temporal association between rise in BP and increase in cerebral and renal O<sub>2</sub>ER. When evaluating the response to AVP according to shunt type, the RVPAS cohort experienced a more robust vasopressor response than did the BTS group, which based on the Sao<sub>2</sub>, Qp:Qs, and cerebral and renal O<sub>2</sub>ER, increased Qp at the expense of Qs. The BTS cohort experienced a less significant vasopressor response to AVP with no change in pulmonary or systemic perfusion. The RVPAS group experienced a significant increase in diastolic BP and CPP throughout the entire SS period. During the initial

30 minutes of the SS period, the BTS group experienced a significant increase in diastolic BP and CPP yet continued increases in diastolic BP during the latter 30 minutes was less robust and was insufficient to overcome the oscillations in CAP.

These findings are in line with the effects of a vasopressor such as AVP on the circulation.<sup>3-9</sup> AVP vasoconstricts systemic arterial resistance vessels, increasing SVR, and systemic arterial BP. Without a change in contractility and ventricular end diastolic volume, the ejection fraction and stroke volume decrease as BP rises.<sup>3,4</sup> In patients with single ventricle physiology, changes in SVR and/or pulmonary VR (PVR), alter the distribution of total CO between the systemic and pulmonary circulations.<sup>5-9</sup> As the SVR to PVR ratio increases, so too does Qp:Qs,<sup>5-9</sup> which for a given total CO, increases Qp at the expense of Qs. It is logical to conclude that the decrease in tissue oxygenation in the RVPAS group resulted at least in part from an increase in SVR:PVR and rise in systolic BP, as the Sao<sub>2</sub>, Qp:Qs, and cerebral and renal O<sub>2</sub>ER increased significantly. The BTS group experienced a less robust vasopressor response to AVP and no change in Qp or Qs.

The vasopressor response to AVP in this cohort was mixed, with some patients not experiencing an increase in BP. Mastropietro and colleagues<sup>11</sup> found similar results in their analysis of patients following pediatric cardiac surgery. It is possible that the AVP dose was either inadequate or baseline neurohormonal levels influenced the response of the circulation to this exogenous vasopressor, which has been demonstrated for AVP as well as other neurohormones

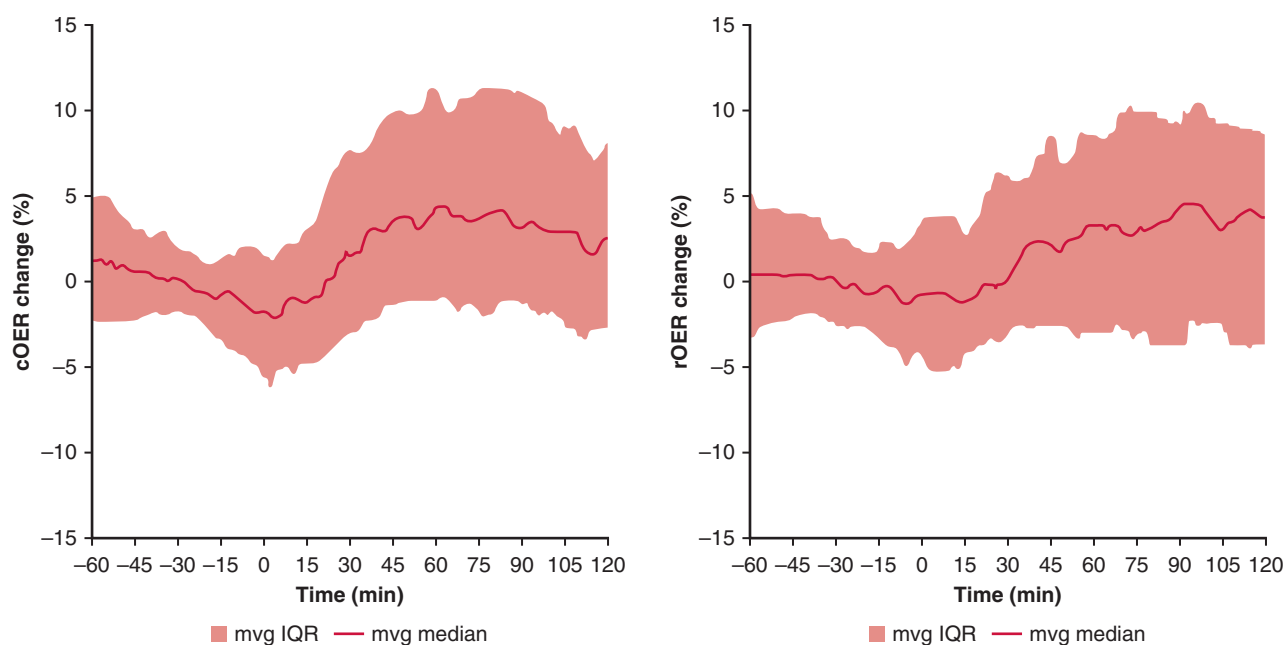


FIGURE 2. Moving median and moving interquartile (IQR) range for the change in cerebral oxygen extraction ratio (cO<sub>2</sub>ER) and renal oxygen extraction ratio (rO<sub>2</sub>ER) with respect to their baseline values. Arginine vasopressin infusions start at time 0. *mvg*, Moving.

TABLE 4. Changes in hemodynamic parameters according to shunt type\*

Time (min)	mBP				CAP			
	RVPAS	P value†	BTS	P value†	RVPAS	P value†	BTS	P value†
60-75	2.4 ± 6.6	.003	2.7 ± 6.1	.001	0.3 ± 2.1	.129	-0.4 ± 2.1	.347
75-90	2.7 ± 6.5	.002	2.4 ± 6.2	.005	0.3 ± 2.1	.135	-0.5 ± 2.1	.456
90-105	2.9 ± 6.4	<.001	2.0 ± 6.2	.006	0.3 ± 2.1	.137	-0.4 ± 2.3	.634
105-120	3.2 ± 6.5	<.001	1.8 ± 6.2	.008	0.3 ± 2.1	.141	-0.4 ± 2.4	.696
Time (min)	sBP				CPP			
	RVPAS	P value†	BTS	P value†	RVPAS	P value†	BTS	P value†
60-75	3.4 ± 10.4	.072	4.3 ± 12.0	.088	2.2 ± 5.2	.014	2.2 ± 3.8	.004
75-90	4.1 ± 10.0	.013	3.4 ± 12.6	.151	2.3 ± 5.2	.010	1.9 ± 3.9	.029
90-105	4.4 ± 9.6	.010	2.9 ± 12.9	.185	2.5 ± 5.2	.006	1.6 ± 4.1	.060
105-120	4.6 ± 9.5	.008	2.9 ± 12.8	.175	2.7 ± 5.2	.001	1.4 ± 4.1	.086
Time (min)	dBP				HR			
	RVPAS	P value†	BTS	P value†	RVPAS	P value†	BTS	P value†
60-75	2.0 ± 5.3	.003	1.7 ± 3.8	.001	-1.0 ± 9.2	.428	3.3 ± 9.0	.005
75-90	2.2 ± 5.3	.002	1.5 ± 3.9	.010	-1.1 ± 9.3	.429	3.3 ± 9.2	.007
90-105	2.4 ± 5.3	.002	1.2 ± 3.9	.022	-1.2 ± 9.5	.393	3.2 ± 9.7	.012
105-120	2.5 ± 5.4	<.001	1.1 ± 3.8	.031	-1.3 ± 9.3	.365	3.2 ± 10.0	.015

Values are presented as mean ± SD. mBP, Mean blood pressure; CAP, common arterial pressure; RVPAS, Right ventricular to pulmonary artery shunt; BTS, Blalock-Taussig shunt; HR, heart rate (bpm); sBP, systolic blood pressure; CPP, coronary perfusion pressure; dBP, diastolic blood pressure; HR, heart rate. \*Values are changes in parameters with respect to their baseline. †P values were computed using 1-sample t tests with mean 0 as the null hypothesis.

such as cortisol.<sup>12,13</sup> Mastropietro and colleagues<sup>12</sup> as well as Morrison and colleagues<sup>13</sup> did not find a relationship between perioperative AVP levels and hypotension or requirement for or response to vasopressors.

It is of interest that the RVPAS group experienced a more robust vasopressor response to AVP than the BTS cohort. There are important differences in physiology between shunt types that are reflected in their baseline hemodynamic data.<sup>14,15</sup> For the RVPAS, shunting is limited to ventricular systole. For the BTS, shunting occurs throughout the cardiac cycle, leading to diastolic runoff and a lower diastolic pressure compared with the RVPAS. Shunt caliber importantly influences the extent of shunting because studies

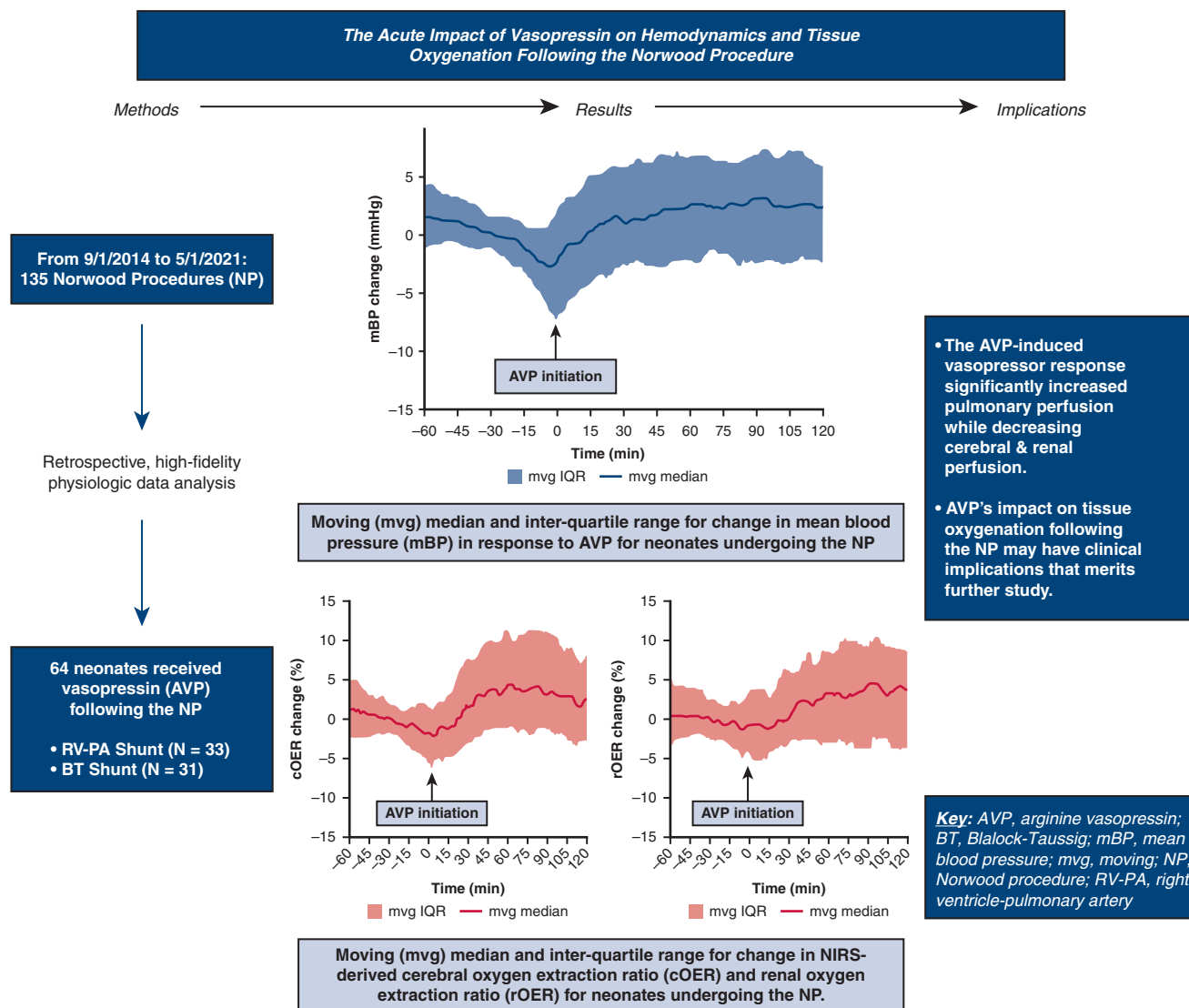
have found marked differences in Qp:Qs with changes in the caliber of shunt from 1 size to the next.<sup>14-16</sup> The difference in the response between the RVPAS and BTS to AVP following the NP warrants further investigation. The clinical implications of these findings and the optimal vasoactive strategy following the NP merits further investigation as well.

There are limitations to this analysis. A retrospective analysis has inherent limitations, such as the influence of interventions temporally associated with the AVP infusion that may have influenced the circulation. We did not find a significant relationship between VIS and BP response. Nor did we find a significant relationship between the

TABLE 5. Changes in oximetric parameters according to shunt type\*

Time (min)	Sao <sub>2</sub> (%)				Qp:Qs			
	RVPAS	P value†	BTS	P value†	RVPAS	P value†	BTS	P value†
60-75	1.2 ± 3.9	.029	1.1 ± 3.2	.018	0.3 ± 0.5	.009	0.2 ± 0.5	.274
75-90	1.3 ± 3.8	.021	0.9 ± 3.3	.134	0.3 ± 0.5	.009	0.1 ± 0.5	.505
90-105	1.4 ± 3.9	.014	0.6 ± 3.3	.255	0.2 ± 0.5	.016	0.1 ± 0.5	.744
105-120	1.4 ± 3.8	.011	0.4 ± 3.4	.368	0.2 ± 0.4	.017	0.0 ± 0.5	.945
Time (min)	cO <sub>2</sub> ER				rO <sub>2</sub> ER			
	RVPAS	P value†	BTS	P value†	RVPAS	P value†	BTS	P value†
60-75	5.3 ± 8.5	.003	3.9 ± 9.3	.034	2.9 ± 8.2	.084	3.4 ± 11.8	.147
75-90	5.3 ± 8.5	.002	3.5 ± 9.5	.080	3.5 ± 8.6	.061	2.9 ± 11.9	.248
90-105	4.9 ± 8.7	.007	2.6 ± 9.3	.233	4.2 ± 9.0	.022	2.1 ± 12.0	.420
105-120	4.6 ± 8.7	.010	2.1 ± 9.2	.325	4.7 ± 9.4	.014	1.6 ± 11.9	.536

Values are presented as mean ± SD. Sao<sub>2</sub>, Arterial oxygen saturation; Qp:Qs, pulmonary blood flow to systemic blood flow ratio; RVPAS, Right ventricular to pulmonary artery shunt; BTS, Blalock-Taussig shunt; cO<sub>2</sub>ER, cerebral oxygen extraction ratio; rO<sub>2</sub>ER, renal oxygen extraction ratio. \*Values are changes in parameters with respect to their baseline. †P values were computed using 1-sample t tests with mean 0 as the null hypothesis.



**FIGURE 3.** A retrospective, high-fidelity physiology data analysis of 64 neonates who were exposed to arginine vasopressin (AVP) after the Norwood procedure (NP) revealed a significant vasopressor response with increases in pulmonary to systemic perfusion ratios. IQR, Interquartile range; mBP, mean blood pressure; RV-PA, right ventricle to pulmonary artery; BT, Blalock-Taussig; mvg, moving.

administration of intravascular volume and BP response, with <15% of infusions accompanied by volume expansion. Further, one would expect volume expansion and/or vasoactive support other than AVP to either maintain or increase Qs, and the linear regression analysis and correlation analysis found a positive relationship between change in BP and SaO<sub>2</sub>, Qp:Qs, and cerebral and renal O<sub>2</sub>ER. All patients were on a continuous infusion of calcium to maintain an ionized calcium level >1.3 mmol/L. We did not find an association between calcium boluses and BP response.

All patients following cardiac surgery are monitored with the Medtronic INVOS 7100 NIRS oximeter; however, intermittent connectivity between the INVOS monitor and the Sickbay platform for a minority of patients led to

incomplete data capture. Cerebral NIRS oximetry relies on a proprietary algorithm to derive tissue oxygenation. Studies have demonstrated a good correlation between cerebral NIRS-derived oxygen saturations and superior vena cava and jugular saturations within patients.<sup>17-19</sup> Particularly relevant to this analysis, studies have also found NIRS oximetry to be highly accurate as a within-subject trend monitor.<sup>20,21</sup> In this analysis, each patient served as his or her own control, with SS NIRS oximetry data compared with baseline values for each patient. In line with other published studies, we used an assumed value of 99% for the pulmonary venous oxygen saturation when determining the relative change in Qp:Qs for each patient. We did not assess lactate levels as a surrogate for tissue

oxygenation because the levels were randomly assessed relative to our stated study periods (baseline, time to steady state, and steady state).

## CONCLUSIONS

We found that patients undergoing the NP experienced a significant vasopressor response to AVP, which varied according to shunt type. The RVPAS cohort experienced a more robust vasopressor response than the BTS group, which was associated with a significant increase in pulmonary perfusion and decrease in cerebral and renal perfusion. The BTS group experienced a less significant vasopressor response to AVP and no change in pulmonary or systemic perfusion. The influence of the vasopressor response to AVP following the NP on cerebral and renal tissue oxygenation may have implications on clinical outcomes that require further study.

## Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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**Key Words:** Norwood procedure, single ventricle, vasopressin, afterload, pulmonary to systemic perfusion ratio, oxygen delivery, near infrared spectroscopy oximetry