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Acute hemodynamic impact of vasopressin on the Fontan circulation

Greg Adamson, MD
Clinical Assistant Professor
Department of Pediatrics (Cardiology)
Stanford University School of Medicine

No disclosures

Background

Population:

- 70,000 Fontan patients worldwide
- Expected to double in 15-20 years

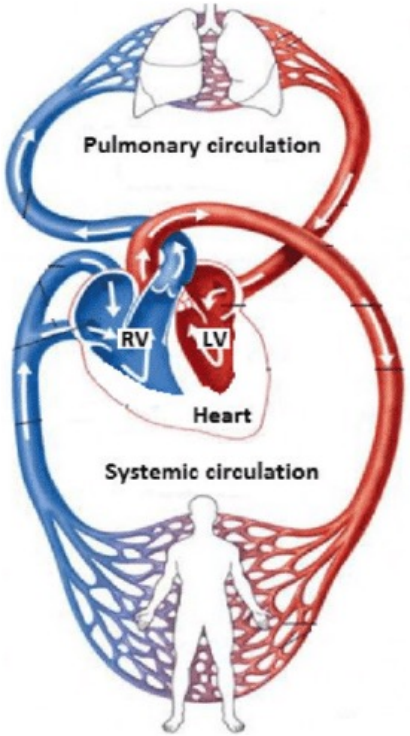
Issues:

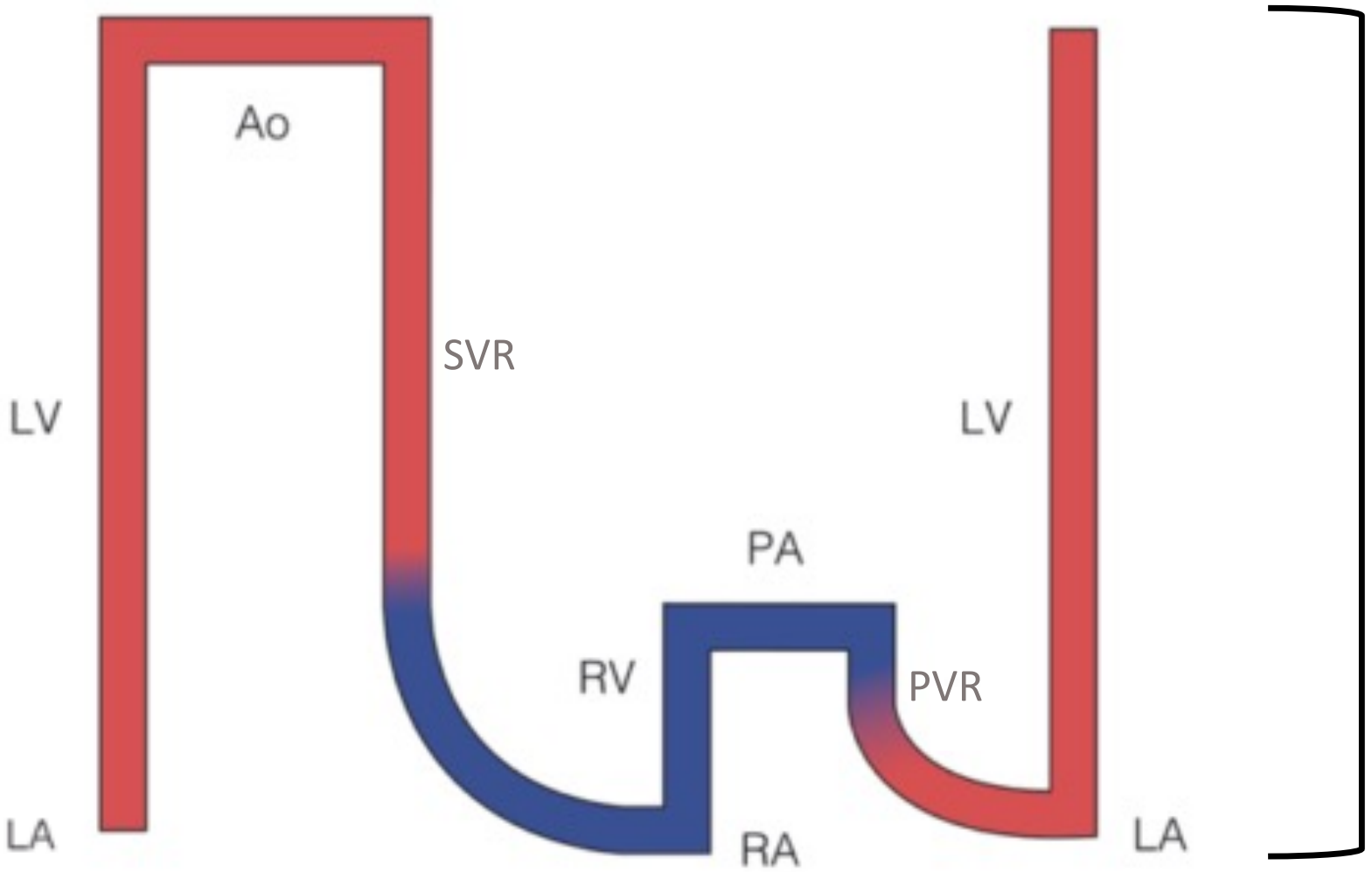
- Commonly referred for procedures requiring sedation or anesthesia
  - Hypotension elicited by medications and/or positive pressure ventilation

- Failing Fontan ICU admissions increasingly common

Rychik et. al, Circ, 2019
Kutty et. al, JAHA, 2019
Neethling et al, CJC, 2022

Normal Circulation

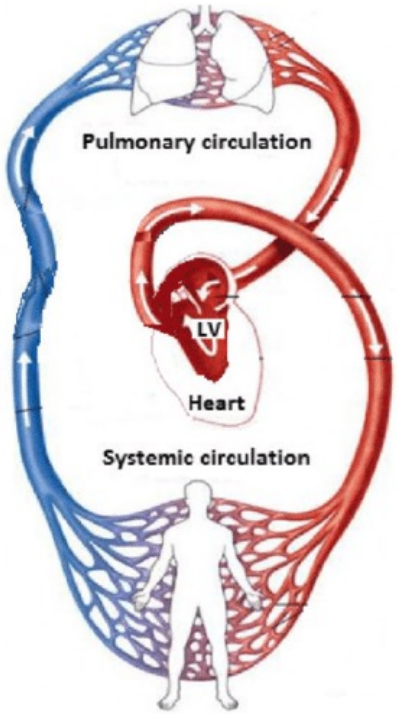


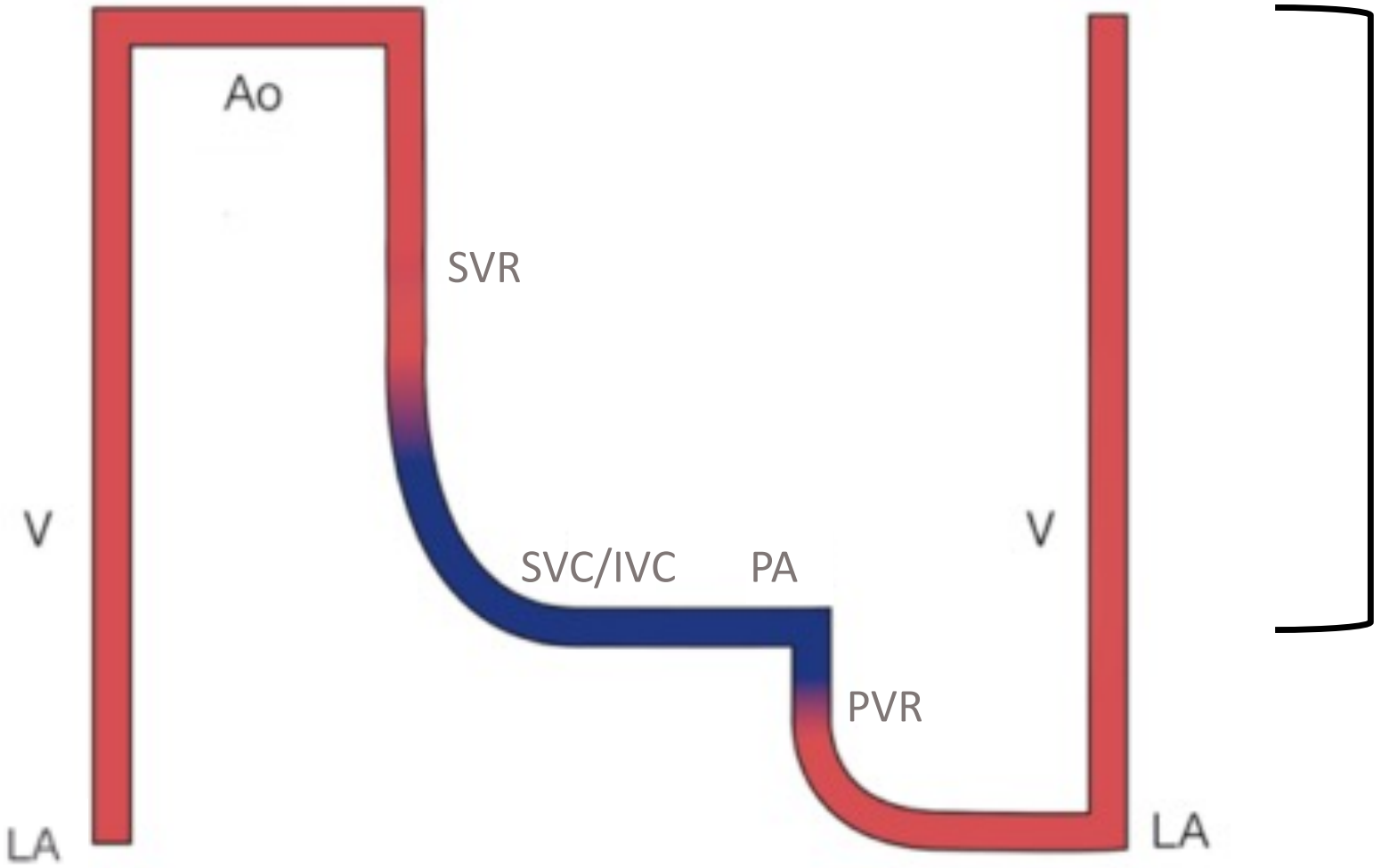


Organ Perfusion Pressure

https://canadianfontan.com/fontan-mechanics/

Fontan Circulation



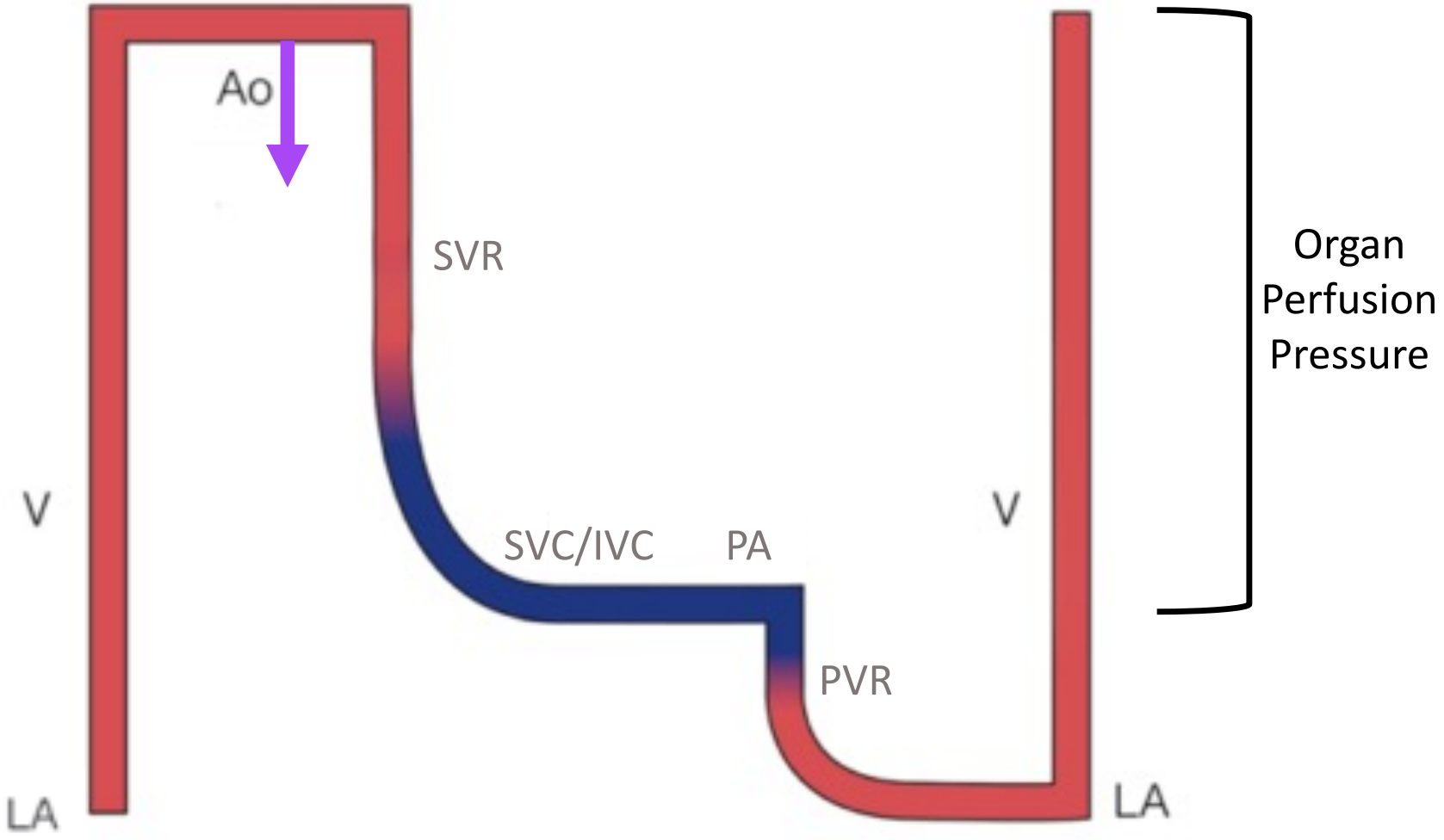


https://canadianfontan.com/fontan-mechanics/

Background

Treating **hypotension**

1) Increase preload
   - Give volume
   - Decrease PVR
2) Consider vasoconstrictors to augment SVR and perfusion pressure



Jolley et. al, Anesthesia&Analgesia, 2015
Gewillig et. al, Interact Cardiovasc Thorac Surg, 2010

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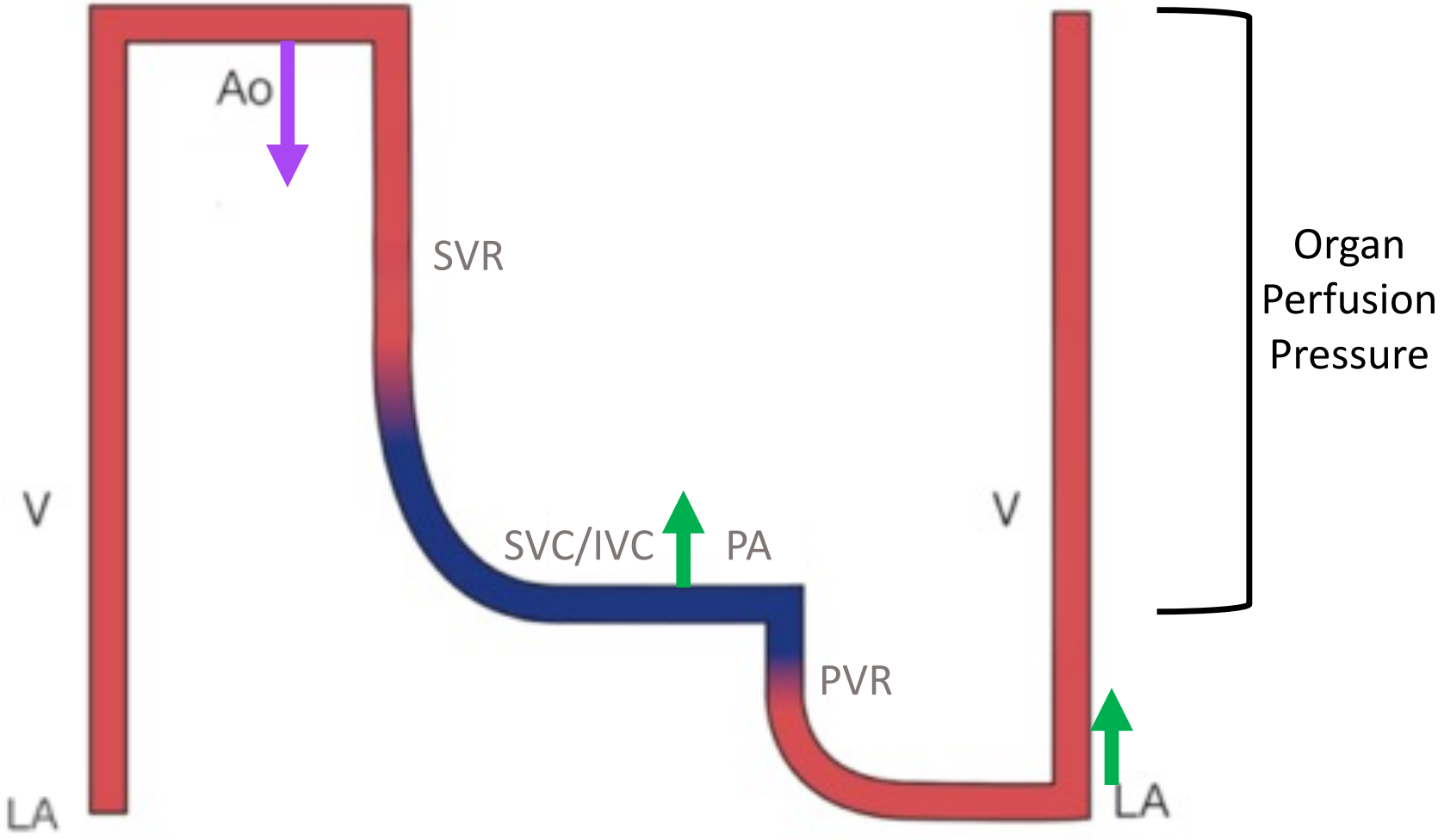

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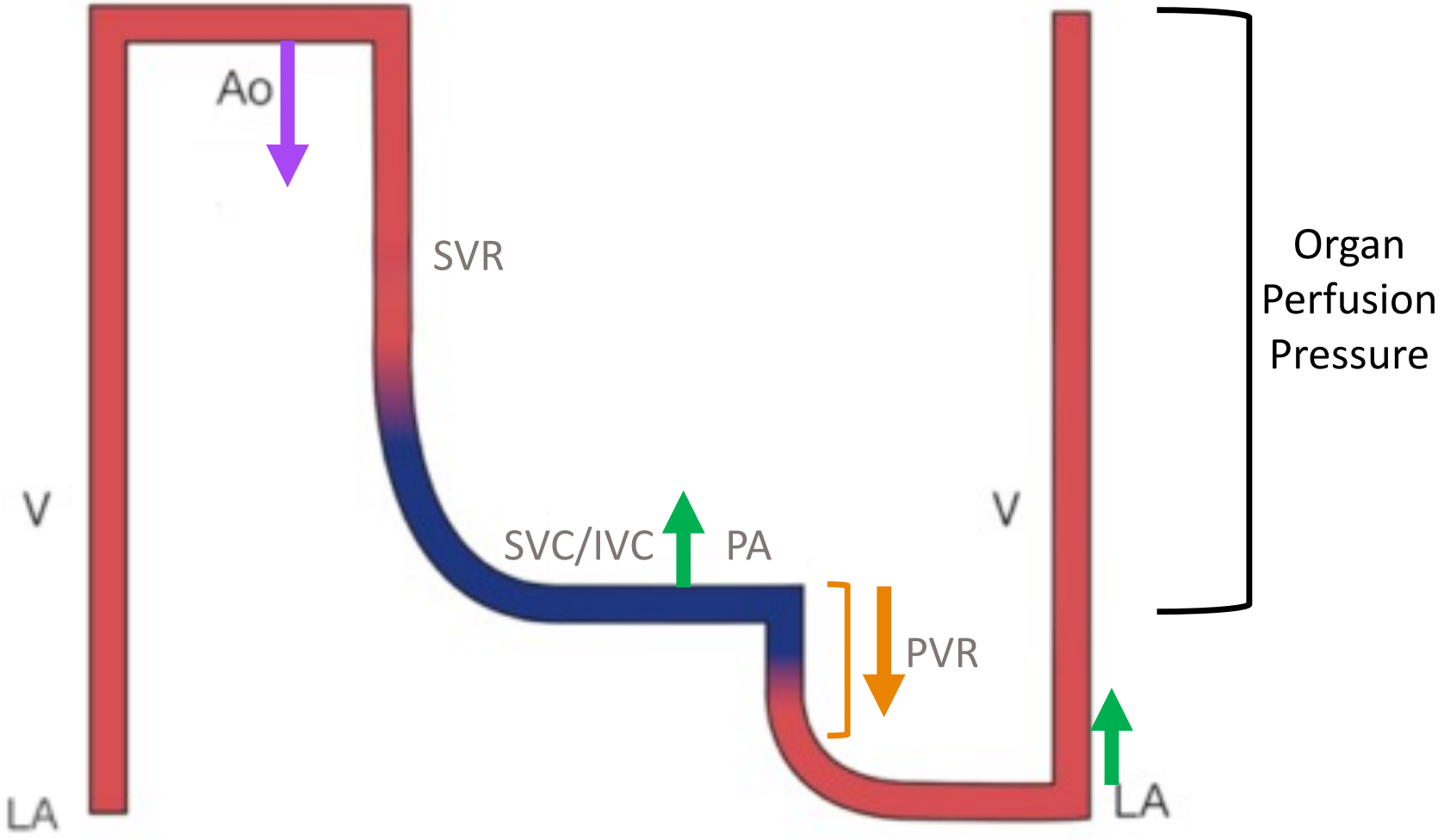

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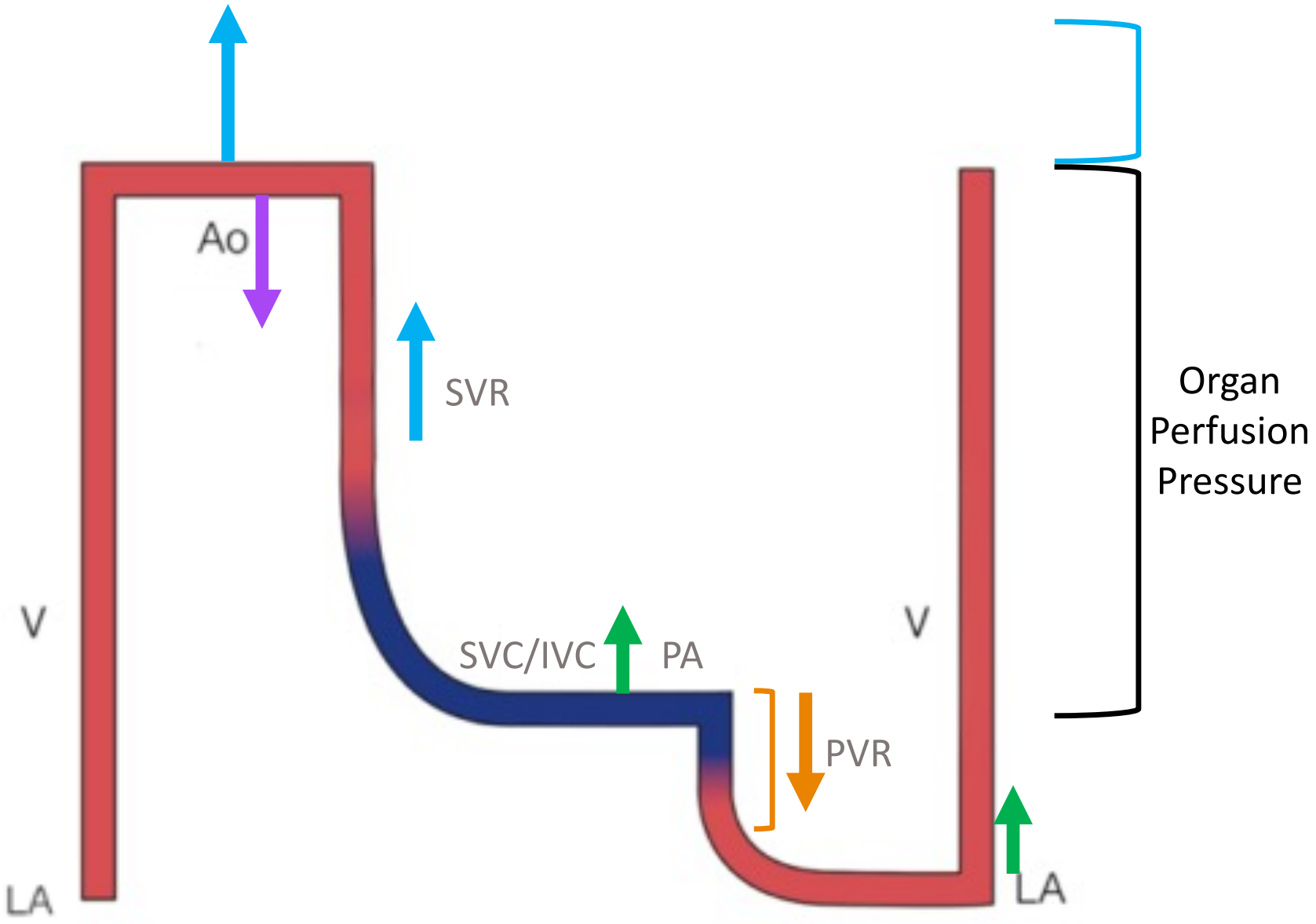
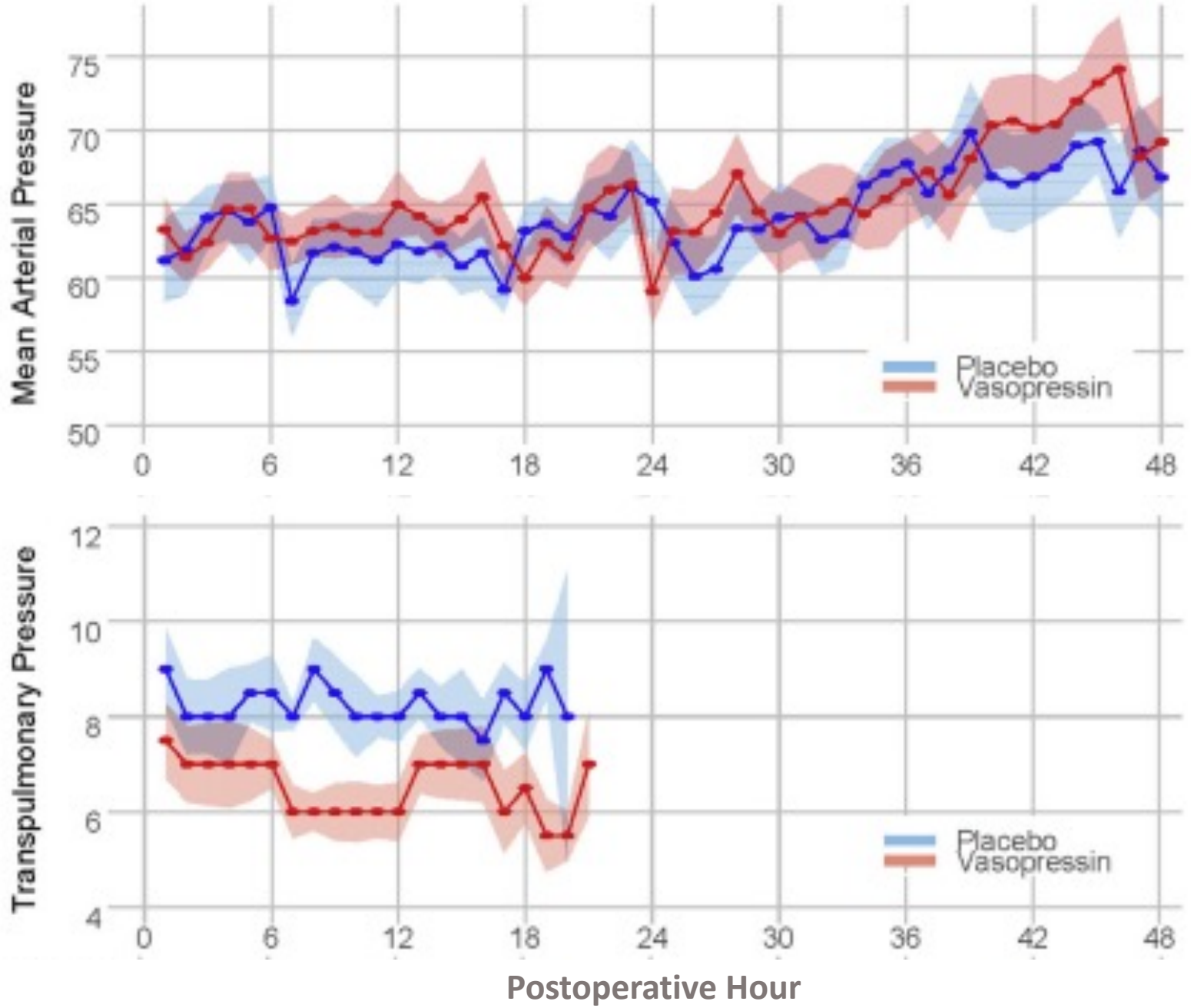


Background: Vasopressin

Increases	No Impact
• Systemic vascular resistance • Endothelial nitric oxide	• Myocardium • Arrhythmogenicity

Siehr et. al, PCCM, 2016
Dunser et. al, Circulation, 2003
Rehberg et. al, Am J Physiol Heart Circ Physiol, 2012
Russ et. al, Am J Physiol, 1992
Evora et. al, Chest, 1993

Background



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Bigelow et. al, Annals of Thoracic Surgery, 2019.

Background

- At our institution, vasopressin is being used more frequently to treat hypotension in Fontan patients
- Hemodynamic effects of vasopressin on the Fontan circulation have not been systematically evaluated

Aims

In Fontan patients referred to cath lab, determine impact of vasopressin on:

1) PVR/SVR ratio
2) Systemic blood pressure, cardiac output, and atrial pressure

Hypothesis

SVR will increase and PVR will not increase, such that the PVR/SVR ratio will decrease

Methods

- Prospective, open-label, nonrandomized trial
  - Registered at clinicaltrials.gov (NCT04463394)
  - Ethical approval Stanford IRB (Protocol ID 56875)
  - Written parental consent and participant assent obtained

- Enrollment criteria
  - Inclusion: Fontan patients aged 3 to 50 undergoing catheterization
  - Exclusion: Patient unable to tolerate prolonged catheterization
  - Timeframe: September 2020 through goal enrollment of 28 patients (February 2022)

Anesthesia management

- Standard ASA monitoring
- Premedication with midazolam when required for anxiolysis
- Propofol (25-200 mcg/kg/min) + ketamine (0.5-2 mg/kg/hr) infusions
- Spontaneous ventilation with facemask, cannula, or LMA (airway pressure < 10 mmHg)
- FiO2 21%

Catheterization

- First completed clinical catheterization, including all indicated interventions

Study sequence

1) Confirm pH of 7.35 to 7.45 and end-tidal CO2 of 35-50 mmHg
2) Perform repeat comprehensive baseline hemodynamics
3) Administer vasopressin:
    - Bolus: 0.03 U/kg IV (max dose 1 unit) over 5 minutes
    - Maintenance infusion: 0.3 mU/kg/min (max dose 0.03 U/min)
4) Repeat hemodynamics

Data collection

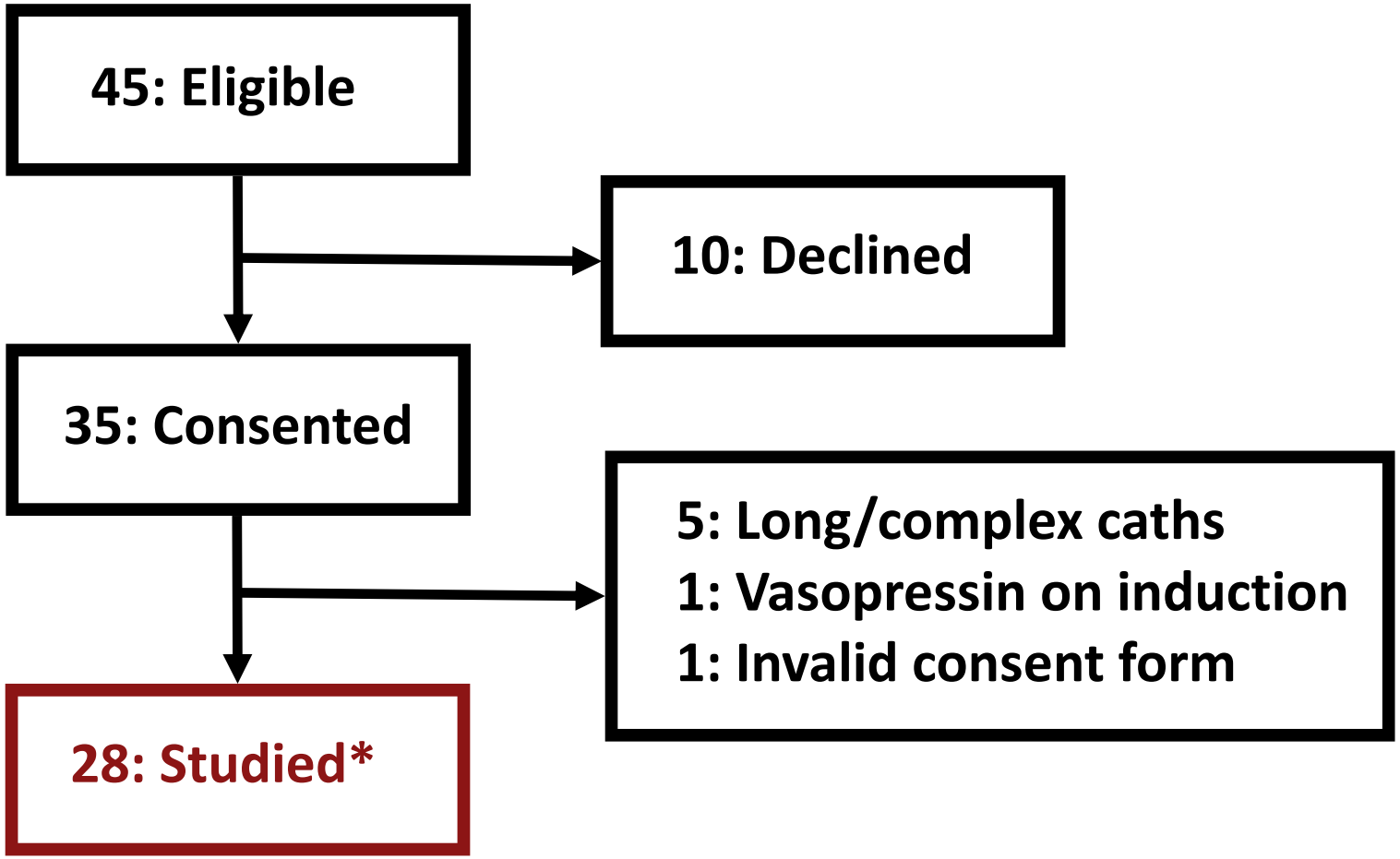
- Data recorded prospectively in secure REDCap database

- Fontan dysfunction defined as 1 or more of the following:
  - Moderate or severe ventricular dysfunction (blinded echo review)
  - Moderate or severe atrioventricular valve regurgitation (blinded echo review)
  - Lymphatic dysfunction (clinical PLE or PB requiring medical management)
  - Atrial or ventricular end-diastolic pressure > 12 mmHg (baseline cath)
  - PVRi > 3 Wood Units (baseline cath)

Data analysis

- Normal vs. non-normal distribution:
  - Data: Mean +/- or median (Q1, Q3)
  - Paired comparisons: Paired t-test or Wilcoxon signed rank test
  - Non-paired comparisons: Simple t-test or Mann Whitney U test
- Pre- and post-vasopressin data paired for each patient
- Statistical significance set at a p-value < 0.05
- SPSS version 28 (IBM, Armonk, New York)

Results



* 1 minor protocol violation: endotracheal intubation due to inadequate seating of the LMA

No adverse events

Baseline Characteristics	n = 28
Age, years	13.5 (9.8, 17)
Female sex	6 (21%)
Weight, kg	50.3 ± 23.8
Single right ventricle	16 (57%)
Fontan dysfunction	12 (43%)*
Lymphatic dysfunction (PLE or PB)	5 (28%)
Moderate to severe systolic dysfunction	3 (11%)
Moderate to severe AVVR	3 (11%)
LA > 12 mmHg	4 (13%)
PVRi > 3 WU	1 (4%)
Large venovenous collateral burden	4 (14%)
Large aortopulmonary collateral burden	4 (14%)
Hemoglobin, g/dL	14.4 ± 1.5
pH	7.33 ± 0.45

*1 patient with both moderate-severe systolic dysfunction and moderate-severe AVVR; 1 patient with both lymphatic dysfunction and LVEDP > 12 mmHg; 1 patient with lymphatic dysfunction, moderate-severe systolic dysfunction, and LVEDP > 12 mmHg.

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	Baseline	Vasopressin	Difference	t-statistic* or Z-value†	p-value
Saturations					
Aorta	94.0 (90.8, 95.3)	93.0 (91.0, 95.0)	-1.0 (-1.0, 0.0)	-2.063†	0.039
SVC	71.5 ± 4.4	72.5 ± 5.5	1.04 ± 5.4	-1.015*	0.32
Left PA	69.6 ± 6.5	69.3 ± 6.8	-0.29 ± 4.5	0.334*	0.74
Right PA	70.5 ± 4.8	70.8 ± 4.7	-0.32 ± 2.7	-0.628*	0.54
Pressures					
Systolic Aorta	86.5 (83.3, 92)	104 (97.0, 114.3)	17.5 (13, 22.8)	-4.625†	< 0.001
Diastolic Aorta	54.0 (50.0, 59.0)	66.5 (63.5, 70.3)	12.5 (8.8, 16.3)	-4.603†	< 0.001
Mean Aorta	68.0 (63.8, 70.5)	81.5 (78.0, 88.3)	15.5 (11, 18.3)	-4.625†	< 0.001
PA	12.5 (11.0, 14.3)	12.5 (11.0, 14.0)	0 (-1, 1)	-0.404†	0.69
LA or PCW	7.0 (6.0, 10.3)	8.5 (7.0, 11.0)	1 (0, 2)	-3.486†	< 0.001
Hemodynamics					
Cardiac Index	3.2 ± 0.69	3.2 ± 0.77	0.09 ± 0.34	-1.390*	0.18
Qp	2.8 (2.3, 3.1)	2.8 (2.3, 3.4)	0 (-0.21, 0.27)	-0.579†	0.56
Qp:Qs	0.92 (0.82, 1.0)	0.92 (0.82, 1.0)	0 (-0.05, 0)	-1.721†	0.085
PVR	1.8 ± 0.65	1.4 ± 0.57	-0.42 ± 0.36	6.160*	< 0.001
SVR	17.1 (15.2, 20.4)	22.0 (17.8, 27.4)	3.8 (1.8, 7.5)	-4.623†	< 0.001
PVR:SVR	0.10 ± 0.034	0.064 ± 0.025	-0.039 ± 0.026	8.078*	< 0.001

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Left PA	**69.6 ± 6.5**	**69.3 ± 6.8**	**-0.29 ± 4.5**	**0.74**
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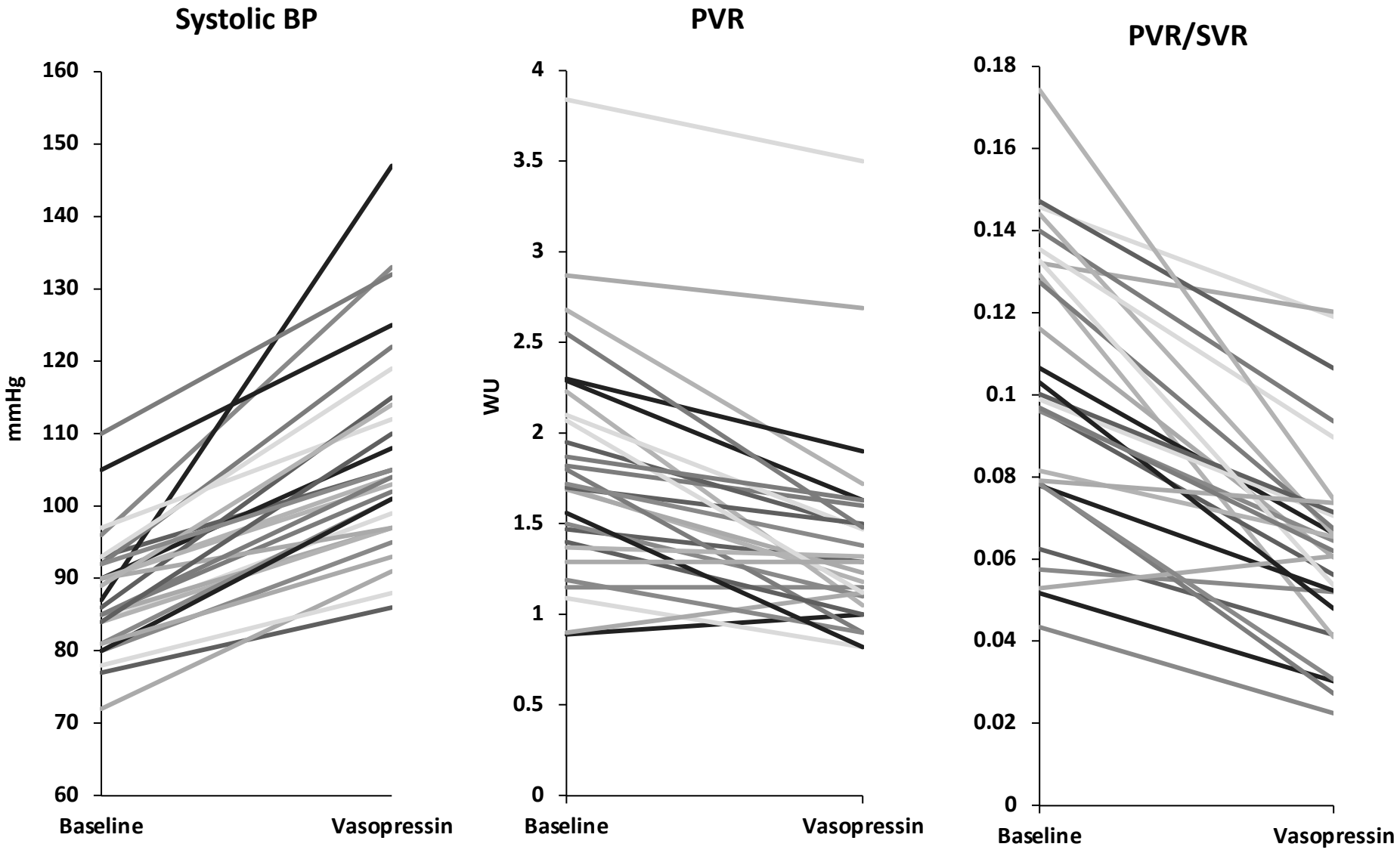
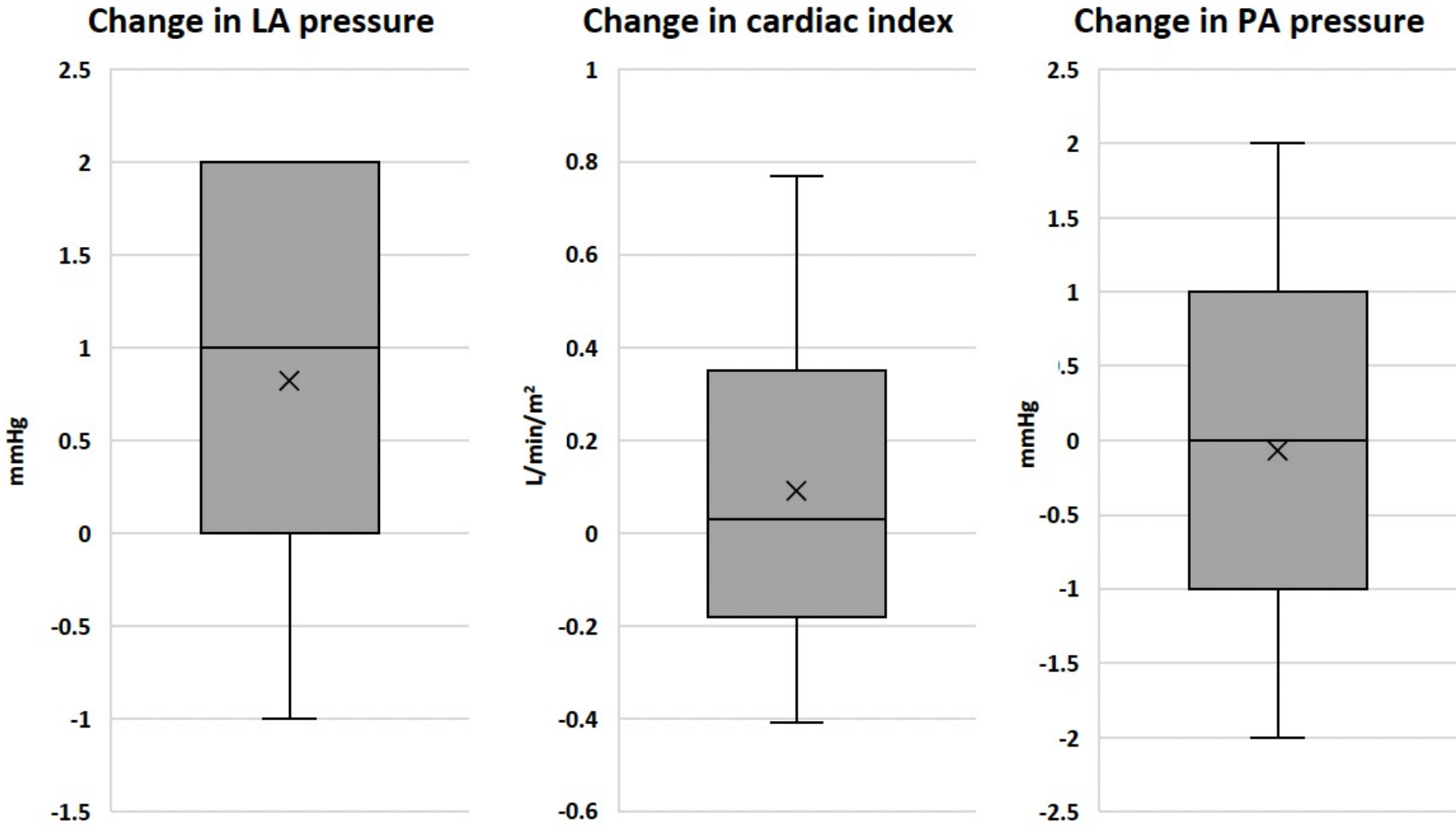
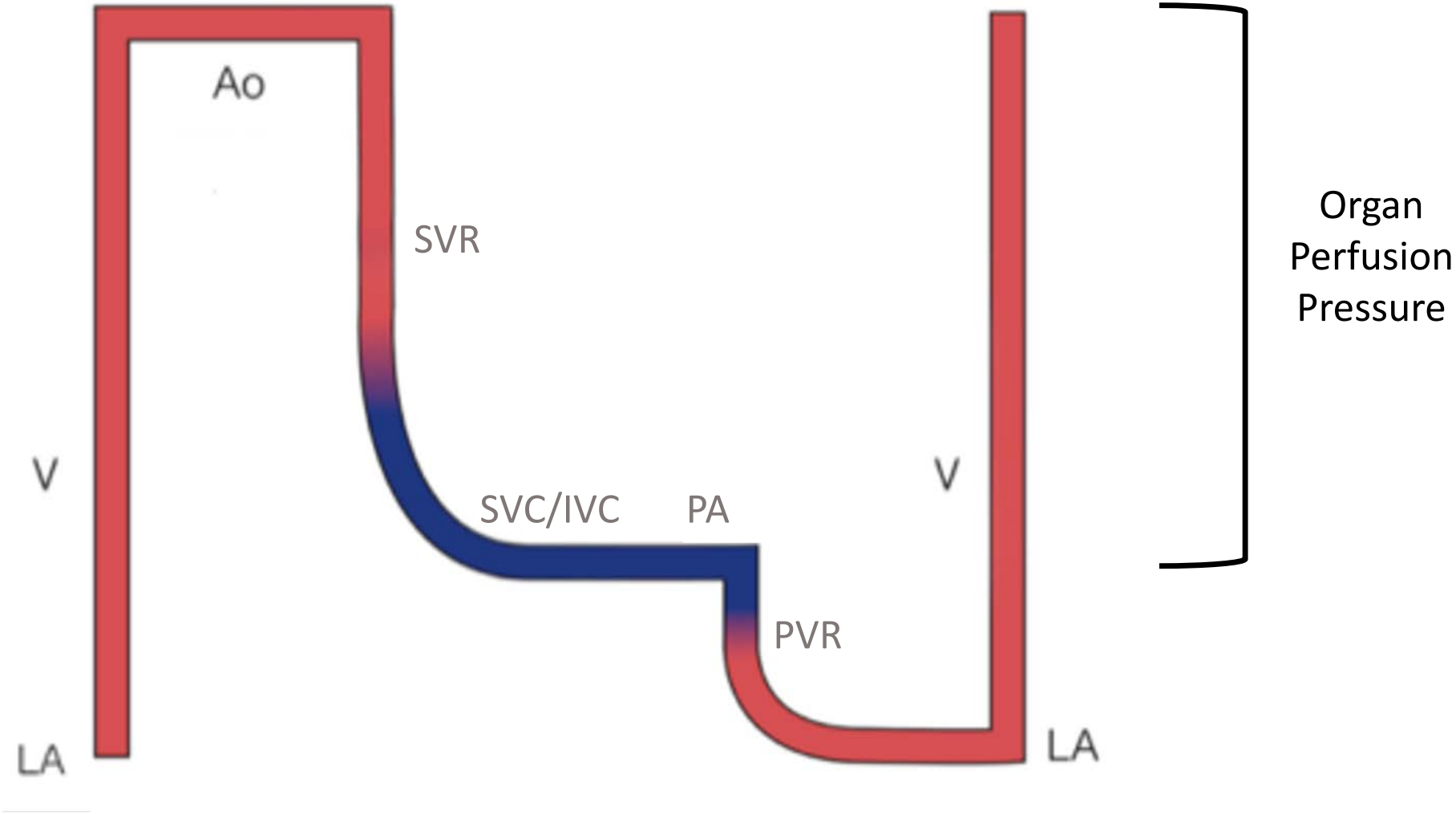

Systolic BP
160
150
140
130
120
110
100
90
80
70
60
mmHg
Baseline
Vasopressin
PVR
4
3.5
3
2.5
2
1.5
1
0.5
0
WU
Baseline
Vasopressin
PVR/SVR
0.18
0.16
0.14
0.12
0.1
0.08
0.06
0.04
0.02
0
Baseline
Vasopressin


Change in LA pressure
mmHg
2.5
2
1.5
1
0.5
0
-0.5
-1
-1.5
Change in cardiac index
L/min/m²
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
Change in PA pressure
mmHg
2.5
2
1.5
1
0
-0.5
-1
-1.5
-2
-2.5

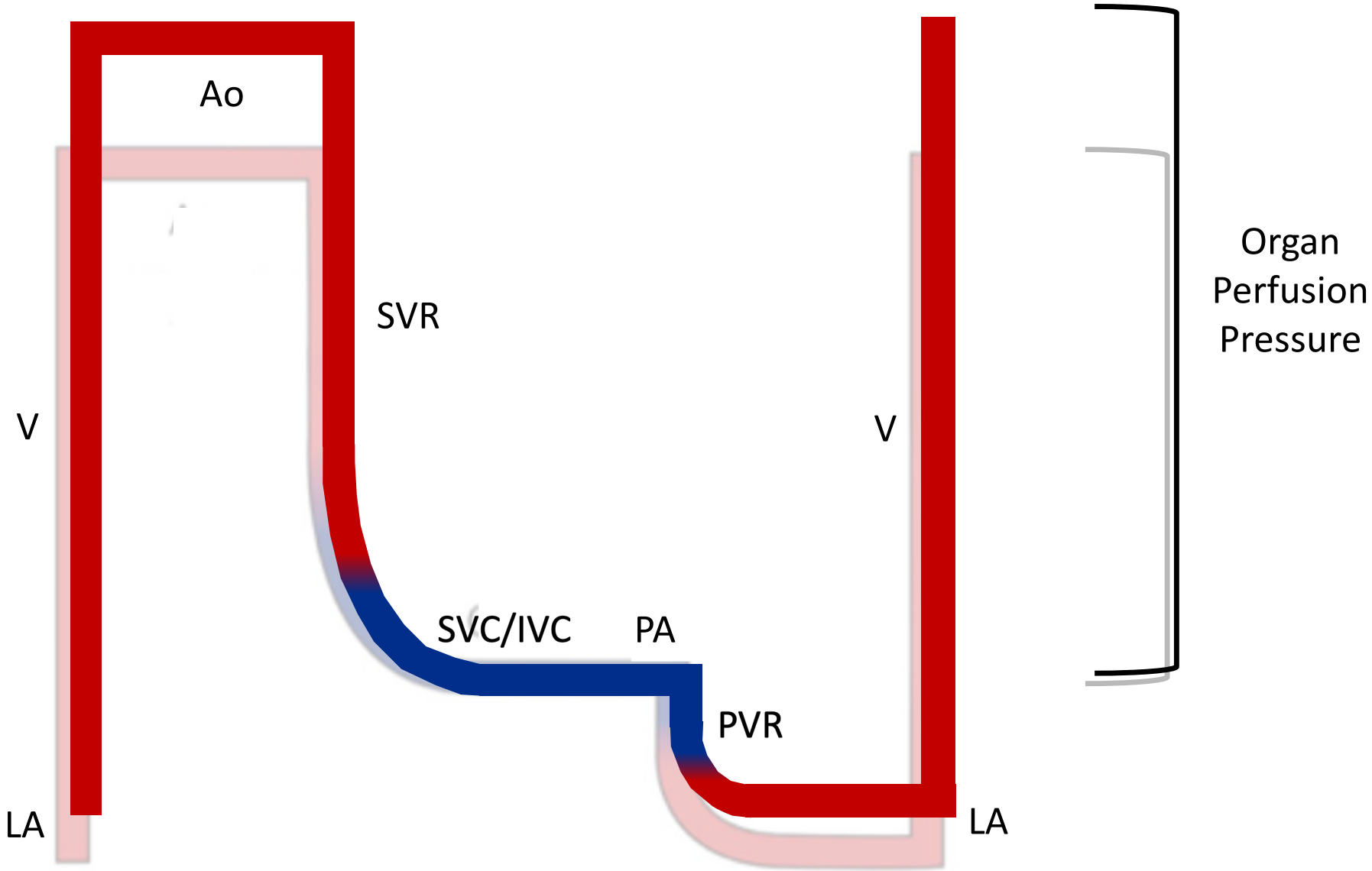
	Fontan dysfunction (n=12)	No Fontan dysfunction (n=16)	p-value
Clinical			
Age	17.9 ± 9.8	14.2 ± 8.4	0.29
Weight	**61.0 ± 24.3**	**42.3 ± 18.5**	**0.03**
Female sex	3 (25%)	3 (19%)	0.99
Single RV	8 (67%)	8 (50%)	0.46
Saturations			
Aorta	92.0 (89.3, 94.0)	94.5 (93.0, 96.8)	0.07
SVC	71 ± 3.8	71.9 ± 4.9	0.61
PA	69.6 ± 3.8	71.1 ±5.4	0.41
Pressures			
Systolic Aorta	87.0 (81.8, 92.8)	86.5 (82.0, 91.5)	0.98
PA	13.0 (11.0, 17.8)	11.0 (11.0, 13.8)	0.19
LA or PCW	9.5 (6.0, 12.8)	7.0 (6.0, 8.0)	0.11
Hemodynamics			
Cardiac Index	2.9 ± 0.59	3.3 ± 0.73	0.18
PVR	2.0 ± 0.74	1.7 ± 0.57	0.29
SVR	15.8 (14.1, 23.0)	17.2 (15.5, 20.0)	0.68
PVR:SVR	0.11 ± 0.035	0.097 ± 0.034	0.31

	Fontan Dysfunction (n=12)	No Fontan Dysfunction (n=16)	p-value
	Difference		
Pressures			
Systolic Aorta	14.0 (12.3, 19.8)	19.5 (14.3, 28.3)	0.14
Diastolic Aorta	12.0 (8.3, 16.3)	13.5 (8.3, 16.8)	0.80
Mean Aorta	14.5 (10.3, 16.8)	17.0 (11.0, 19.0)	0.42
PA	-0.5 (-1.0, 1.0)	0.0 (-0.75, 0.75)	0.43
LA or PCW	0.0 (0.0, 1.0)	1.0 (0.0, 2.0)	0.22
Hemodynamics			
Cardiac Index	0.09 ± 0.35	0.09 ± 0.35	0.99
Qp	0.1 (-0.2, 0.3)	0.0 (-0.3, 0.3)	0.66
PVR	-0.41 ± 0.24	-0.43 ± 0.43	0.92
PVR:SVR	-0.04 ± 0.02	-0.04 ± 0.03	0.63

Fontan Circulation



Fontan Circulation with Vasopressin



Discussion

SVR and blood pressure increase:
- Standard vasopressin dosing acutely increased SVR and BP in all patients
- Contradicting studies limited by confounding variables

PVR decrease:
- Similar to findings in other populations
- Subtle PVR changes have significant impact on Fontan cardiac output

Atrial pressure increase:
- Etiology: Decrement in diastolic function vs. Increase in preload
- Small increases in Fontan atrial pressure can decrease potential energy across the pulmonary vascular bed essentially increasing the afterload further

Cardiac output, no change:
- Not synonymous with blood pressure
- Competing effects of PVR, atrial pressure, and SVR

Farias et. al, Pediatric Cardiol, 2021
Loomba et. al, Pediatric Cardiol, 2021
Bigelow et. al, ATS, 2019
Jolley et. al, Anesthesia&Analgesia, 2015
Gewillig et. al, Interact CV Thorac Surg, 2010

Conclusions

In Fontan patients, vasopressin acutely…

Increases	Decreases	No Impact
• Blood pressure • SVR • Atrial pressure	• PVR (and PVR/SVR)	• Cardiac output

These data can guide management of Fontan patients who have hypotension during anesthesia or sedation.

Limitations

- Open label study subject to investigator bias
- Acute impact of vasopressin only
- Single-center experience
- May not be generalizable to awake patients
- Not powered to detect differences between patients with and without Fontan dysfunction
- No comparison to other vasoconstricting agents such as phenylephrine

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