Using a General Mathematical Model to Quantify the Fontan Paradox of Elevated Central Venous Pressure and Diminished Cardiac Output

Eunhye Jeon, Cayla M. Jenkins, Rebecca S. Philip, Gracelyn I. King, Spencer A. Keith, Christopher M. Quick

Physiology & Pharmacology Department, Michael E. DeBakey Institute, Texas A&M University

Introduction

Fontan procedure and its paradox

- Palliates patients with single ventricle (SV) physiology
  - Only one functioning ventricle for heart
- Connects the venous return and pulmonary circulation **(Figure 1)**
  - Low Cardiac output (CO) = Low tissue perfusion
  - High Central venous pressure (CVP) = High organ congestion
- However, common interventions either raise or lower CO and CVP simultaneously
  - This is called the "Fontan Paradox" [1]
  - Clinical interventions not effective in preventing this paradox. [2]

Limitations for current Fontan procedural models

- Computational models [3]
  - Requires assumption of specified numerical values
  - Highly individualized; Cannot be applied to general population
- Animal models
  - Difficult to manipulate the mechanical properties affecting CVP and CO
- Human population is too fragile to experiment on

Benefits of Algebraic Formulas

- Numerical parameter values are not required
- Elegance to characterize different variations of Fontan physiology
- Ease of understanding

Purpose: to derive algebraic formulas for CVP and CO to enhance the understanding of Fontan Paradox

Methods

Minimal Closed-loop Heart Model

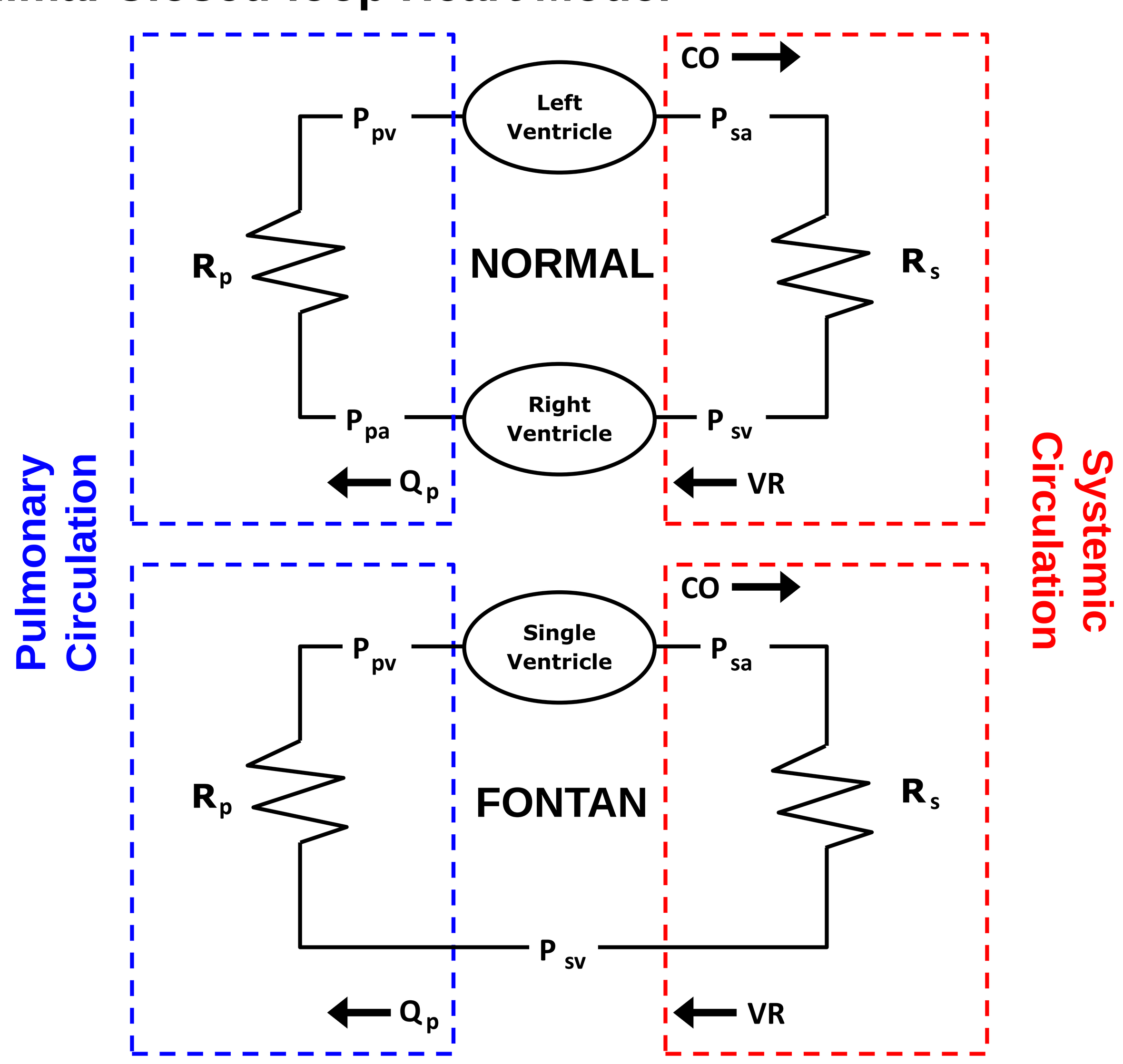

Figure 1: Minimal Closed-loop model of normal heart (top) and single ventricle heart after Fontan procedure (bottom). Arrows represent the blood flow. **Systemic circulation** is highlighted by the red rectangle, and the **pulmonary circulation** is highlighted by the blue rectangle. VR and pulmonary circulation are connected serially. Qp: pulmonary flow; VR: venous return; other symbols are defined in **Table 2**.

Characterizing the Cardiac Ventricle

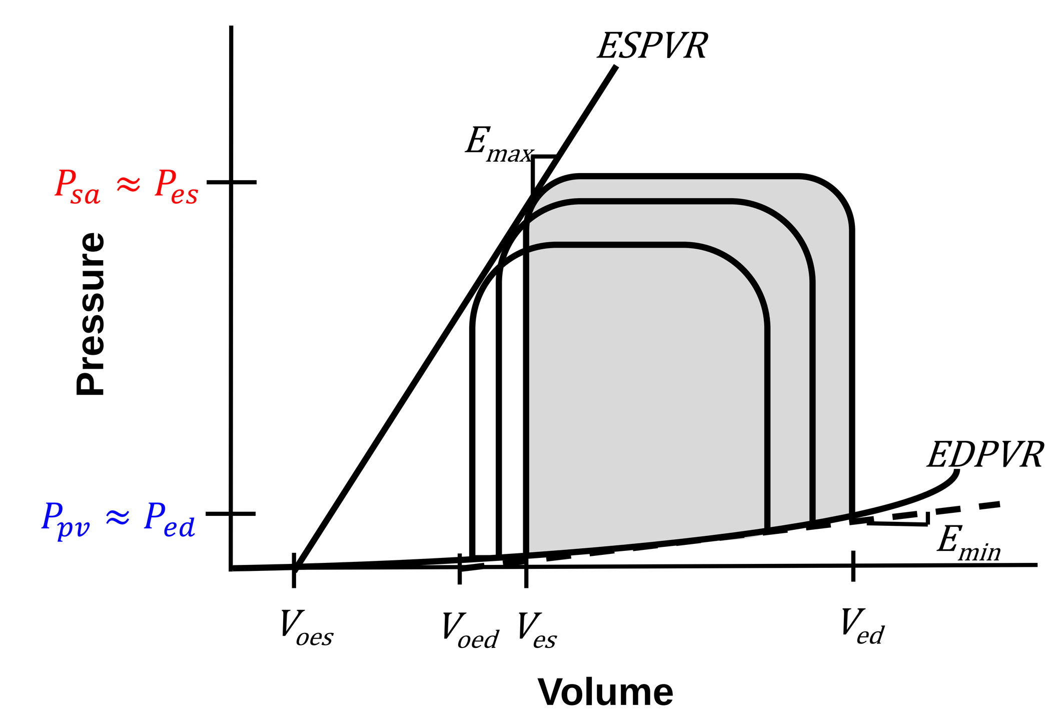

Figure 2: Standard description of ventricular pressure-volume loop. End-systolic pressure-volume relationship (ESPVR) and end-diastolic pressure-volume relationship (EDPVR) are illustrated. Although EDPVR is understood to be non-linear, it is generally linearized to maintain simplicity (**dashed line**). Although loading the ventricle with different volumes alters pressure-volume loops, but ESPVR and EDPVR remain constant.

Standard Model Equations

Table 1: Model Equations

Cardiac Ventricle	$CO = HR(V_{ed} - V_{es})$	(1)
	$P_{sa} \approx E_{max}(V_{es} - V_{oes})$	(2)
	$P_{pv} \approx E_{min}(V_{ed} - V_{oed})$	(3)
Peripheral Resistance	$CO = \frac{P_{sa} - P_{sv}}{R_s}$	(4)
	$CO = \frac{P_{sv} - P_{pv}}{R_p}$	(5)

***Mean arterial pressure is regulated by renal control of blood volume.

1. Equations 1-3 derived from **Figure 2**.
2. Equations 4-5 derived from **Figure 1**.

Table 2: Parameters

Cardiac Ventricle	CO	Cardiac output	P_{es}	Ventricular end-systolic pressure
	ΔV_o	Unstressed stroke volume; V_{oes}-V_{oed}	SV	Single ventricle
	E_{max}	Maximum end-systolic elasticity	V_{ed}	End-diastolic volume
	E_{min}	Minimum end-diastolic elasticity	V_{es}	End-systolic volume
	HR	Heart rate	V_{oed}	End-diastolic unstressed volume
	P_{ed}	Ventricular end-diastolic pressure	V_{oes}	End-systolic unstressed volume
Systemic Circulation	P_{sa}	Total systemic arterial pressure, includes Mean Arterial Pressure (MAP)		
	P_{sv}	Total systemic venous pressure, includes Central Venous Pressure (CVP)		
	R_s	Total systemic resistance		
Pulmonary Circulation	R_p	Total pulmonary resistance		
	P_{pa}	Total pulmonary arterial pressure		
	P_{pv}	Total pulmonary venous pressure		

Results & Discussion

Algebraic Formulas for CO and CVP

$$CO = \frac{\overbrace{HR\,\Delta V_o}^{(1)}\ \overbrace{\frac{E_{max}}{R_s\,HR}}^{(2)} + \left(\overbrace{\frac{E_{max}}{E_{min}}}^{(3)} - 1\right)\overbrace{\frac{P_{sa}}{R_s}}^{(4)}}{\frac{E_{max}}{R_s\,HR} + \frac{E_{max}}{E_{min}}\left(1 + \underbrace{\frac{R_p}{R_s}}_{(5)}\right)} R_s$$

$$P_{sv} = \frac{\overbrace{-HR\,\Delta V_o}^{(1)}\ \overbrace{\frac{E_{max}}{R_s\,HR}}^{(2)} + \left(1 + \left(\frac{E_{max}}{R_s\,HR} + \overbrace{\frac{E_{max}}{E_{min}}}^{(3)}\ \overset{(5)}{\frac{R_p}{R_s}}\right)\overbrace{\frac{P_{sa}}{R_s}}^{(4)}\right)}{\frac{E_{max}}{R_s\,HR} + \frac{E_{max}}{E_{min}}\left(1 + \underbrace{\frac{R_p}{R_s}}_{(5)}\right)} R_s$$

- CVP is expressed as P_{sv}
- Composed of 5 sets of parameters:
  1. Theoretical stroke volume at zero ventricular pressure
  2. Efficiency of heart-vascular interaction
  3. Relative cardiac contractility
  4. Theoretical CO at zero CVP
  5. Relative pulmonary resistance

Solving the Paradox – pulmonary resistance

- Ideal interventions increases CO and decreases CVP
  - ***Negative correlation***
- Altering some parameters eliminate the Paradox:
  - ***ΔV_o, E_{min}, E_{max}, HR, and R_p***
- Two most common parameters lead to the paradox:
  - ***R_s and P_{sa}***

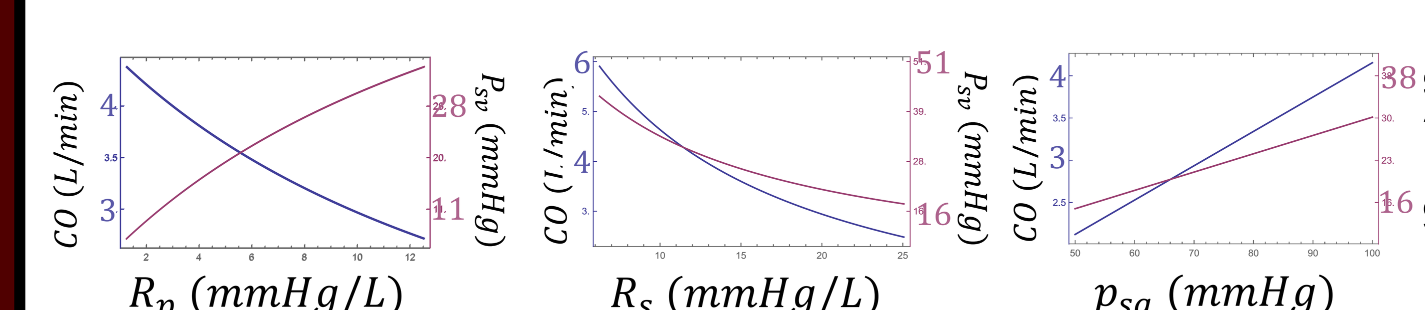

Figure 3: Change in CO (blue) and CVP (purple) by increase in R_p (left), R_s (middle), *and* P_{sa} (right). The scales and units for each y-axis are different; only the direction of relationships is notable from this figure.

- Manipulating ventricular parameters cannot be the primary solution [2]
  - Also, the ventricle is already performing near its max capacity in Fontan circulation
- Therefore, R_p is the only parameter that may reverse the paradox [1, 2, 3]

Circumventing the Paradox

- Most convenient clinical interventions:
  - altering blood volume (P_{sa}) or systemic resistance (R_s)
- Analyzed the sensitivity of CO and CVP from each parameter when R_s and P_{sa} are altered to elevate CO
  - Patients with stiff ventricle (**high E_{min}**) or high pulmonary resistance (**high R_p**) are less likely to suffer from the paradox
  - They have the most cardiac and pulmonary dysfunction

Conclusion

- Algebraic formulas explicitly relate parameters to CO and CVP to provide universal insight to Fontan physiology and Fontan paradox
- Nonlinear pressure-volume relationships were assumed to be linear, but sufficient for our purposes
- Limited to see the trend and the relationship between parameters
- Model suggests altering pulmonary resistance merits further study

References

1. De Leval, M. R. (2005). The Fontan circulation: a challenge to William Harvey?. *Nature clinical practice Cardiovascular medicine*, *2*(4), 202-208.
2. Gewillig, M., Brown, S. C., van de Bruaene, A., & Rychik, J. (2020). Providing a framework of principles for conceptualising the Fontan circulation. *Acta Paediatrica*, *109*(4), 651-658.
3. Kutty, S., Jacobs, M. L., Thompson, W. R., & Danford, D. A. (2020). Fontan Circulation of the Next Generation: Why It's Necessary, What it Might Look Like. *Journal of the American Heart Association*, *9*(1), e013691.