Development of an Algebraic Formula to Compare Mechanical Properties Responsible for Differences in Acute and Chronic Ejection Fraction

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Introduction

- Left ventricular ejection fraction (EF), the fraction of blood expelled during heart contraction, is used clinically to evaluate cardiac function.
- Interpreting the value of EF is difficult because it can depend on properties of the right ventricle and pulmonary vasculature.
- Because it is not possible to experimentally alter mechanical properties of the cardiovascular system independently, investigators have used mathematical modeling to derive a standard formula,
    - EF=1/(1+Ea/Ees)
      where Ea is the effective arterial elastance and Ees is the end-systolic elastance.
- However, this standard formula does not incorporate regulation of mean arterial pressure, a fundamental homeostatic mechanism. Therefore, the purpose of the present work is to develop alternative algebraic equations that incorporate acute and chronic pressure regulation.

Methods

First, we assumed the minimal closed-loop model consisting of two ventricles, systemic and pulmonary resistances, and arterial and venous compartments.

Minimal Closed-Loop Model

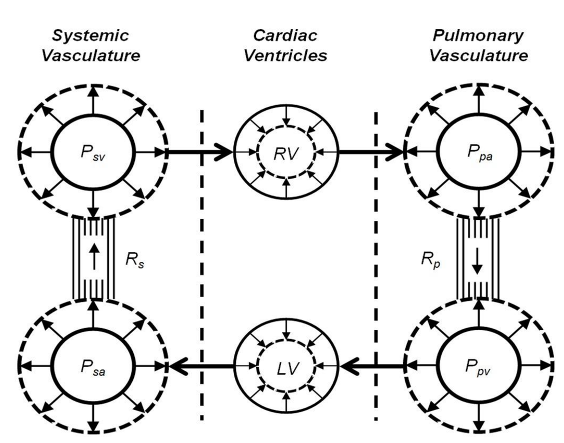


Figure 1. Minimal Closed Loop Model Schematic. Derived from Sagawa et. al

The program Mathematica was used to help solve for EF, and subsequently conduct algebraic simplification of the obtained equation. The initial model equations and parameter values were referenced from Stiles' paper (see references).

To characterize pressure regulation, systemic arterial pressure was treated as a constant parameter. Formulas for EF in acute and chronic conditions were then derived assuming that either systemic resistance or blood volume were variables, respectively. Systemic Resistance (Rs) replaced Psa as a variable due to Baroreflex regulation in acute conditions. Blood Volume (Vb) replaced Psa as a variable due to the Renal system in chronic conditions.

To assist in the interpretation of the results, common parameters affecting ejection fraction were plotted.

Model Equations

EF = (Vedlv – Veslv)/Vedlv
CO = HR (Vedlv – Veslv)
Psa = (Veslv – Voeslv) Emaxlv
Ppv = (Vedlv – Voedlv) Eminlv
CO = (HR/Eminrv) Psv – (HR/Emaxrv) Ppa + **Δ**Vorv HR
CO = (Ppa – Ppv)/Rp
CO = (Psa – Psv)/Rs
Vstressed = Csa Psa + Csv Psv + Cpa Ppa + Cpv Ppv

Figure 2. Model Equations. Derived from Stiles et. al

Defined Variables

HR	Heart Rate	C	Compliance
l, r	left, right	P	Pressure
v, a	venous, arterial	Vstressed	Stressed volume (Vb – Votot)
p, s	pulmonary, systemic		
Emax	Contractility	Vb	Blood Volume
Emin	Diastolic Stiffness	V	Volume
Votot	Unstressed Blood Volume	ed	End-diastolic
		es	End-systolic
CO	Cardiac Output		
R	Resistance	EF	Ejection Fraction

Figure 3. Defined Variables. Derived from Stiles et. al

Parameter Values

HR	1.25 (beats/sec)	Rp	.14 (mmHg s/mL)
Emaxlv	3.6 (mmHg/mL)	Csa	2.0 (mL/mmHg)
Eminlv	0.21 (mmHg/mL)	Csv	111 (mL/mmHg)
ΔVolv	59 (mL)	Cpa	6.6 (mL/mmHg)
ΔVorv	60 (mL)	Cpv	25 (mL/mmHg)
Emaxrv	0.47 (mmHg/mL)	Psa	88 (mmHg)
Eminrv	.079 (mmHg/mL)	Voeslv	0 (mL)
Rs	1.10 (mmHg s/mL)	Voedlv	59 (mL)
Vb	5000 (mL)	Vstressed	754.08 (mL) (calculated)

Figure 4. Parameter Values. Derived from Stiles et. al

Mathematical Results

Short-term

$$\frac{(-\text{Csa Emaxlv Emaxrv Psa} - \text{Cpa Emaxrv Eminlv Psa} - \text{Cpv Emaxrv Eminlv Psa} - \text{Csv Eminlv Eminrv Psa} + \text{Cpa Emaxlv Emaxrv Eminlv Voedlv} + \text{Cpv Emaxlv Emaxrv Eminlv Voedlv} + \text{Csv Emaxlv Eminlv Eminrv Voedlv} - \text{Cpa Emaxlv Emaxrv Eminlv Voeslv} - \text{Cpv Emaxlv Emaxrv Eminlv Voeslv} - \text{Csv Emaxlv Eminlv Eminrv Voeslv} + \text{Emaxlv Emaxrv Vstressed} + \text{Csv Emaxlv Emaxrv Eminrv } \Delta\text{Vorv})}{(-\text{Csa Emaxlv Emaxrv \textbackslash Psa} + \text{Csv Emaxrv Eminrv Psa} + \text{Cpa Emaxrv HR Psa Rp} + \text{Csv Eminrv HR Psa Rp} + \text{Cpa Emaxlv Emaxrv Eminlv Voedlv} + \text{Cpv Emaxlv Emaxrv Eminlv Voedlv} + \text{Csv Emaxlv Eminlv Eminrv Voedlv} + \text{Csv Emaxlv Emaxrv Eminrv Voeslv} + \text{Cpa Emaxlv Emaxrv HR Rp Voeslv} + \text{Csv Emaxlv Eminrv HR Rp Voeslv} + \text{Emaxlv Emaxrv Vstressed} + \text{Csv Emaxlv Emaxrv Eminrv } \Delta\text{Vorv})}$$

Short-term Simplification

$$1 - \frac{\text{Csa Psa}}{\text{Cp Eminlv Voedlv} + \text{Vstressed}}$$

Long-term

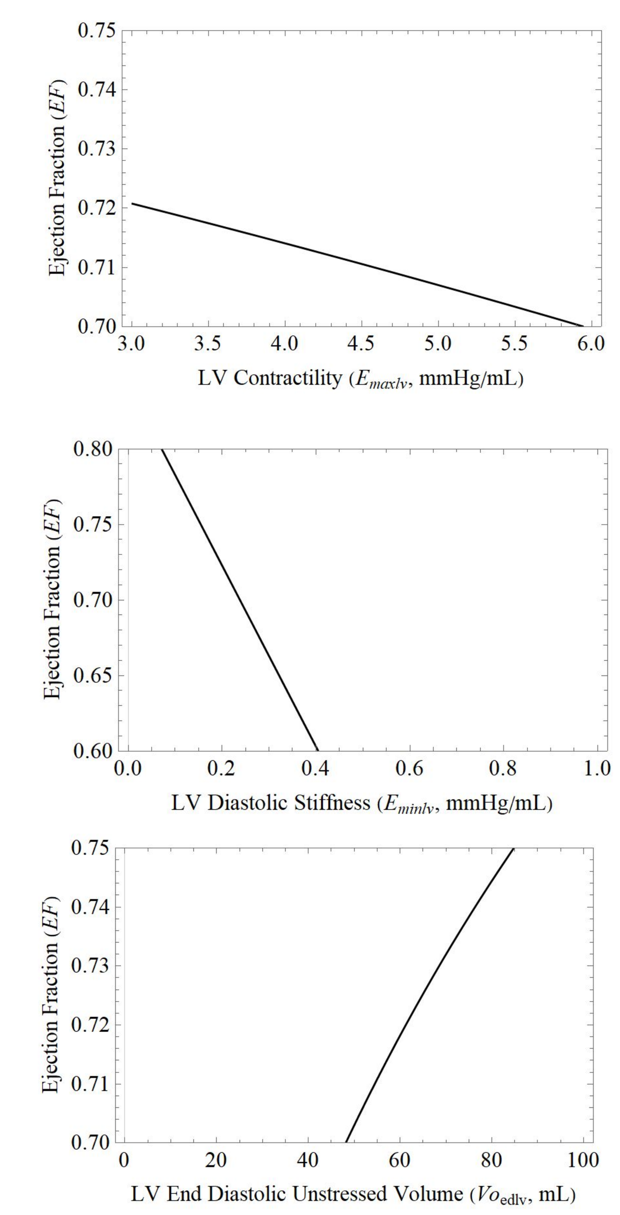
$$\frac{(\text{Emaxlv Emaxrv Psa} - \text{Eminlv Eminrv Psa} + \text{Emaxlv Eminlv Eminrv Voedlv} + \text{Emaxlv Emaxrv Eminrv } \Delta\text{Vorv})}{(\text{Emaxlv Emaxrv Psa} + \text{Emaxrv Eminrv Psa} + \text{Eminrv HR Psa Rp} + \text{Emaxrv HR Psa Rs} + \text{Emaxlv Eminlv Eminrv Voedlv} + \text{Emaxlv Emaxrv Eminrv } \Delta\text{Vorv})}$$

Long-term Simplification

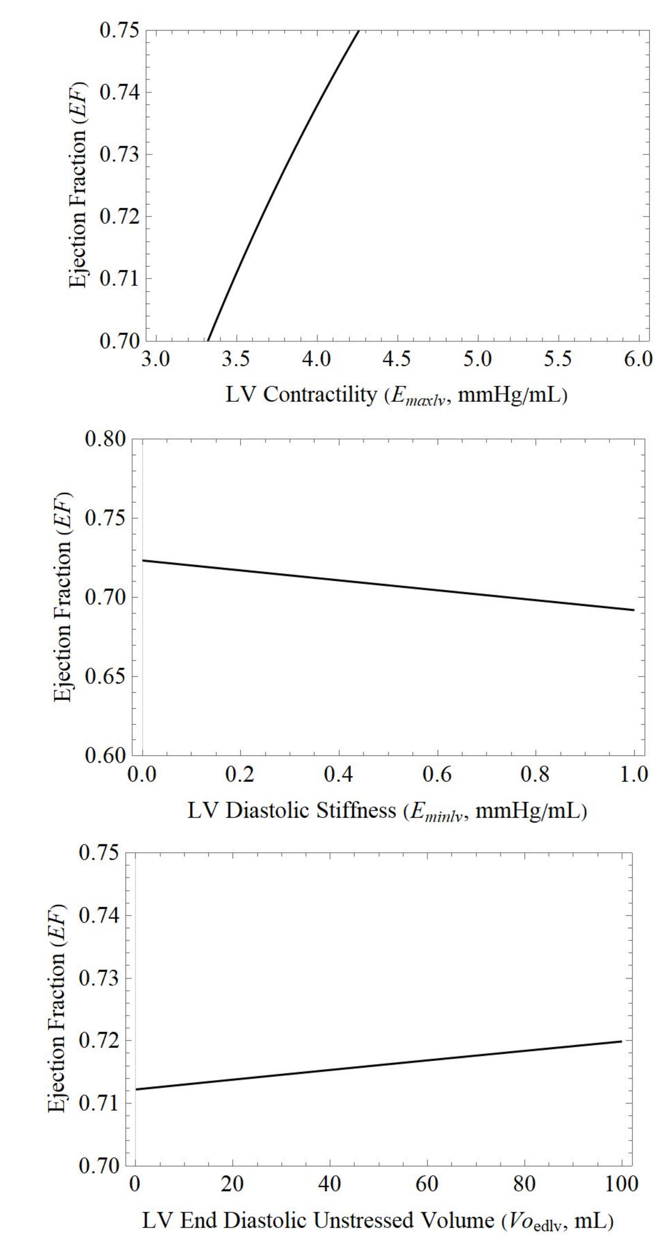
$$\frac{\text{Emaxlv}}{\text{Emaxlv} + \text{HR Rs}} \rightarrow \frac{1}{1 + \frac{\text{Ea}}{\text{Emax}}}$$

Numerical Results

Short-term



Long-term



Discussion

- The equation Ea/Emax is commonly used throughout cardiac literature in the interpretation of cardiac efficiency, where Ea/Emax = .5 represents optimal efficiency (Simone et. al)
    - The derived simplification of the long-term equation includes this expression
- The resulting equations of short and long-term ejection fraction do not match. Mathematically, short-term EF is affected primarily by Csa, Psa, Cp, Eminlv, Voedlv, and Vstressed, while long-term EF is affected by Emaxlv, HR, and Rs.
    - This suggests that Ejection Fraction is highly dependent upon the conditions in which it is measured
    - Clinicians often opt to measure EF in very different conditions, such as in a resting patient rather than following a stress-test (such as measuring EF after running on a treadmill)
        - During exercise, a decrease in systemic vascular resistance occurs, which leads to an increase in both contractility and heart rate (La Gerche et. al)
- Numerically, short and long-term EF vary in LV Contractility (Emaxlv), LV Diastolic Stiffness (Eminlv), and LV End Diastolic Unstressed Volume (Voedlv), which are all primary determinants of heart function.
    - As Emaxlv rises long-term, EF rises. This relationship is opposite in the short-term.
    - Eminlv only slightly alters EF in the long-term, while increases in Eminlv significantly decreases EF in the short-term
    - Voedlv only slightly alters EF long-term, while increases in Voedlv significantly increases EF in the short-term

- **In conclusion:** Although the figures require the assumption of a regular set of parameters, these algebraic expressions provides a generalized approach for clinical investigators. Our model effectively provides an algebraic tool of assessing parameters in a wide range of individuals while also considering short and long-term pressure regulation.

References

La Gerche, A., & Gewillig, M. (2010, September 07). What limits Cardiac performance during exercise in normal subjects and in Healthy Fontan Patients? Retrieved March 25, 2021, from https://www.hindawi.com/journals/ijpedi/2010/791291/

Sagawa, K. (1988). Cardiac contraction and the pressure-volume relationship. New York: Oxford University Press.

Simone, G. D., & Devereux, R. B. (2008). Assessing left ventricular performance. *Hypertension, 51*(2), 179-181. doi:10.1161/hypertensionaha.107.100222

Stiles, T. W., Morfin Rodriguez, A. E., Mohiuddin, H. S., Lee, H., Dalal, F. A., Fuertes, W. W., Adams, T. H., Stewart, R. H., & Quick, C. M. (2021). Algebraic formulas characterizing an alternative to Guyton's graphical analysis relevant for heart failure. *American journal of physiology. Regulatory, integrative and comparative physiology*, 10.1152/ajpregu.00260.2019. Advance online publication. https://doi.org/10.1152/ajpregu.00260.2019