# Deriving Algebraic Solutions to Characterize the Stages of Physiological Responses to Hypovolemia


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## Principles of Hypovolemia

**Classification systems for Hemorrhagic Shock**

- The physiological response to hypovolemia is conventionally characterized in terms of clinical symptoms rather than fundamental homeostatic mechanisms
- These current classification systems use the physical observation of clinical symptoms to predict the quantity of intravascular fluid loss that has occurred but fail to consider the complex changes in the mechanical properties of the cardiovascular system

**Numerical solutions are complex and difficult to interpret**

- Complex mathematical models have been developed to predict how changes in mechanical properties affect hemodynamic variables. However, these models are vastly complex due to the nonlinear relationships between variables, as well as the requirement to assume various parameter values characterizing the subject
- Given these limitations, numerical solutions do not yield generalized information regarding ventricular and vasculature interactions

**Algebraic solutions are easier to interpret and more generalized**

- As an alternative, the minimal closed-loop model may be solved algebraically, providing general algebraic formulas applicable to any mammal in both health and disease

## Specific Aim

The purpose of the present work is to use the minimal closed-loop model to develop algebraic formulas to characterize the response to progressive hypovolemia in terms of the mechanical properties of the cardiovascular system.

## Methods

The minimal closed loop model depicted in **Figure 1** was used to characterize homeostatic intervention to maintain cardiac output (CO) and systemic arterial pressure ($P_{SA}$) levels.

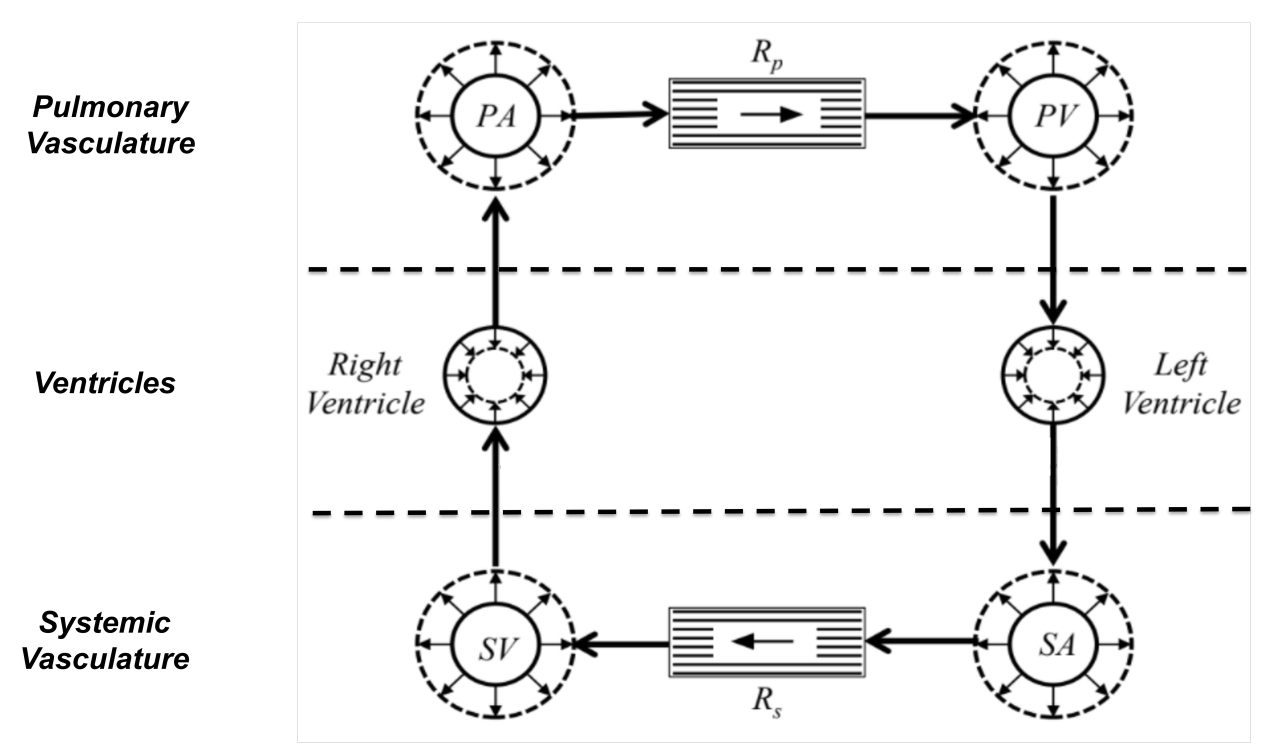


**Figure 1.** The minimal closed-loop model reduces the complexity of the cardiovascular system into eight components: four vascular compartments, two ventricles, and two peripheral resistances [1].

- The three individual graphs depicted in **Figure 2** represent the three functional elements of the cardiovascular system: the ventricular pumps, the resistive conduits, and the vasculature [1].
- Using analytical methods developed by Sunagawa et al. [2], and refined by Stiles et al. [3], the relationships between the elements of the closed-loop model were linearized into a set of fundamental algebraic equations (**Table 1**)

| Parameter | Symbol | Value |
|---|---|---|
| Cardiac Output | $CO$ | 79 (mL/min) |
| Heart Rate | $HR$ | 1.25 (beats/second) |
| Blood Volume | $VB$ | 4800 (mL) |
| Systemic Arterial Pressure | $P_{SA}$ | 88 (mmHg) |
| Maximum Cardiac Contractility | $E_{max}$ | 3.60 (mmHg/mL) |
| Minimum Diastolic Stiffness | $E_{min}$ | 0.21 (mmHg/mL) |
| Systemic Arterial Compliance | $C_{SA}$ | 2.00 (mL/mmHg) |

**Table 2.** Symbols denoting hemodynamic and mechanical parameters and their respective values.

## Functional Elements

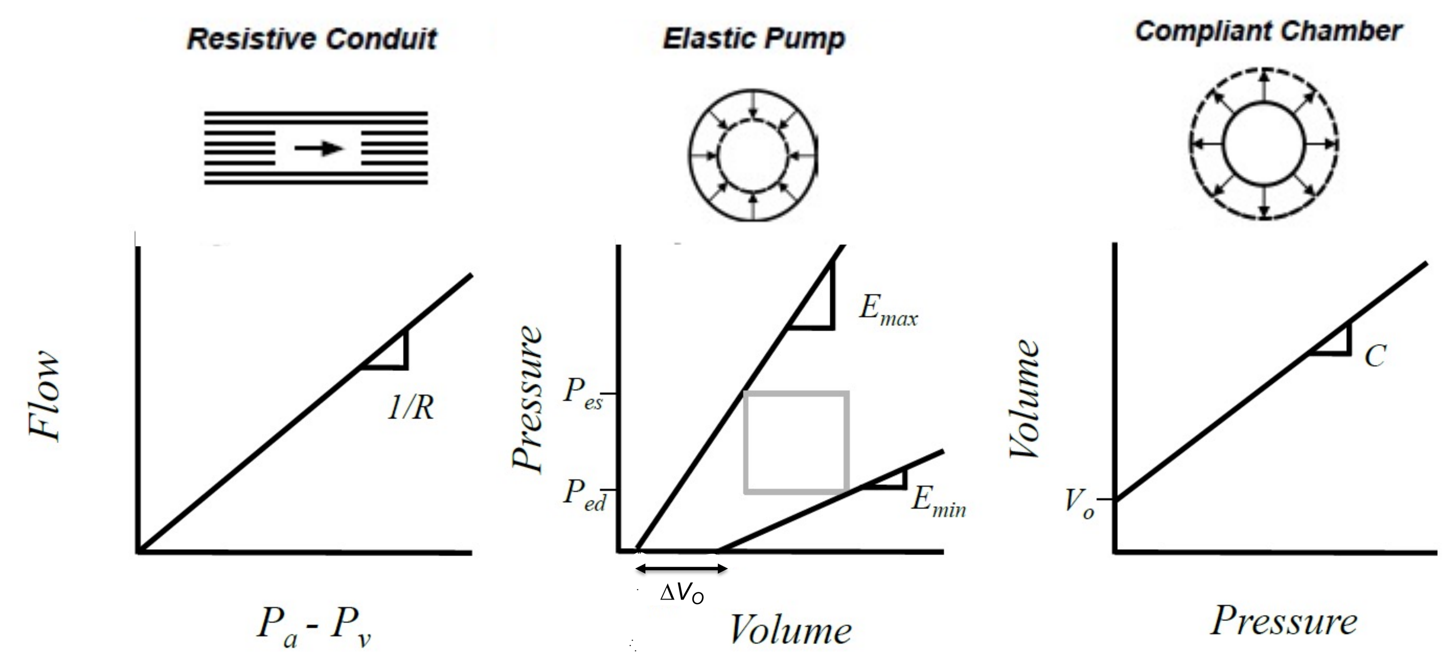


**Figure 2.** Displays the three functional elements of the cardiovascular system, and their relative components [3].

- ***Resistive Conduit*** – Characterizes CO as a linear function of Resistance, dependent on the differences between arterial and venous pressures.
- ***Elastic Pump*** – The end-systolic pressure-volume relationship (*ESPVR*) and the end-diastolic pressure-volume relationship (*EDPVR*) are assumed to be linear, characterized by their slopes ($E_{max}$ and $E_{min}$), and differences in intercepts ($\Delta V_O$)
- ***Compliant Chamber*** – Characterizes the blood volume within each vascular compartment as a linear function of transmural pressure, dependent on vascular compliances ($C$) and vascular unstressed volumes ($V_O$) [3].

## Fundamental Equations

| Description | Equation |
|---|---|
| *Pulmonary Vasculature* | $CO = \dfrac{P_{PA} - P_{PV}}{R_P}$ |
| *Systemic Vasculature* | $CO = \dfrac{P_{SA} - P_{SV}}{R_S}$ |
| *Left Ventricle* | $CO = \dfrac{HR}{E_{minLV}} P_{PV} - \dfrac{HR}{E_{maxLV}} P_{SA} + \Delta V_{oLV} HR$ |
| *Right Ventricle* | $CO = \dfrac{HR}{E_{minRV}} P_{SV} - \dfrac{HR}{E_{maxRV}} P_{PA} + \Delta V_{oRV} HR$ |
| *Total Blood Volume* | $VB = V_{otot} + C_{SA}P_{SA} + C_{SV}P_{SV} + C_{PA}P_{PA} + C_{PV}P_{PV}$ |

**Table 1.** Parsimonious equations providing the basis for the physiological conditions in which hypovolemic shock is occurring

These algebraic equations were used to simultaneously solve for the appropriate variables within each of the three respective stages:

- ***Compensatory Stage:*** Regulation of both systemic arterial pressure and cardiac output
  - ***Variables:*** $E_{maxLV}$, $HR$, $P_{SV}$, $P_{PV}$, and $P_{PA}$
- ***Pre-Shock Stage:*** Regulation of mean arterial pressure only
  - ***Variables:*** $CO$, $Rs$, $P_{SV}$, $P_{PV}$, and $P_{PA}$
- ***Shock Stage:*** Complete loss of regulation
  - ***Variables:*** $CO$, $P_{SA}$, $P_{SV}$, $P_{PV}$, and $P_{PA}$

## Results

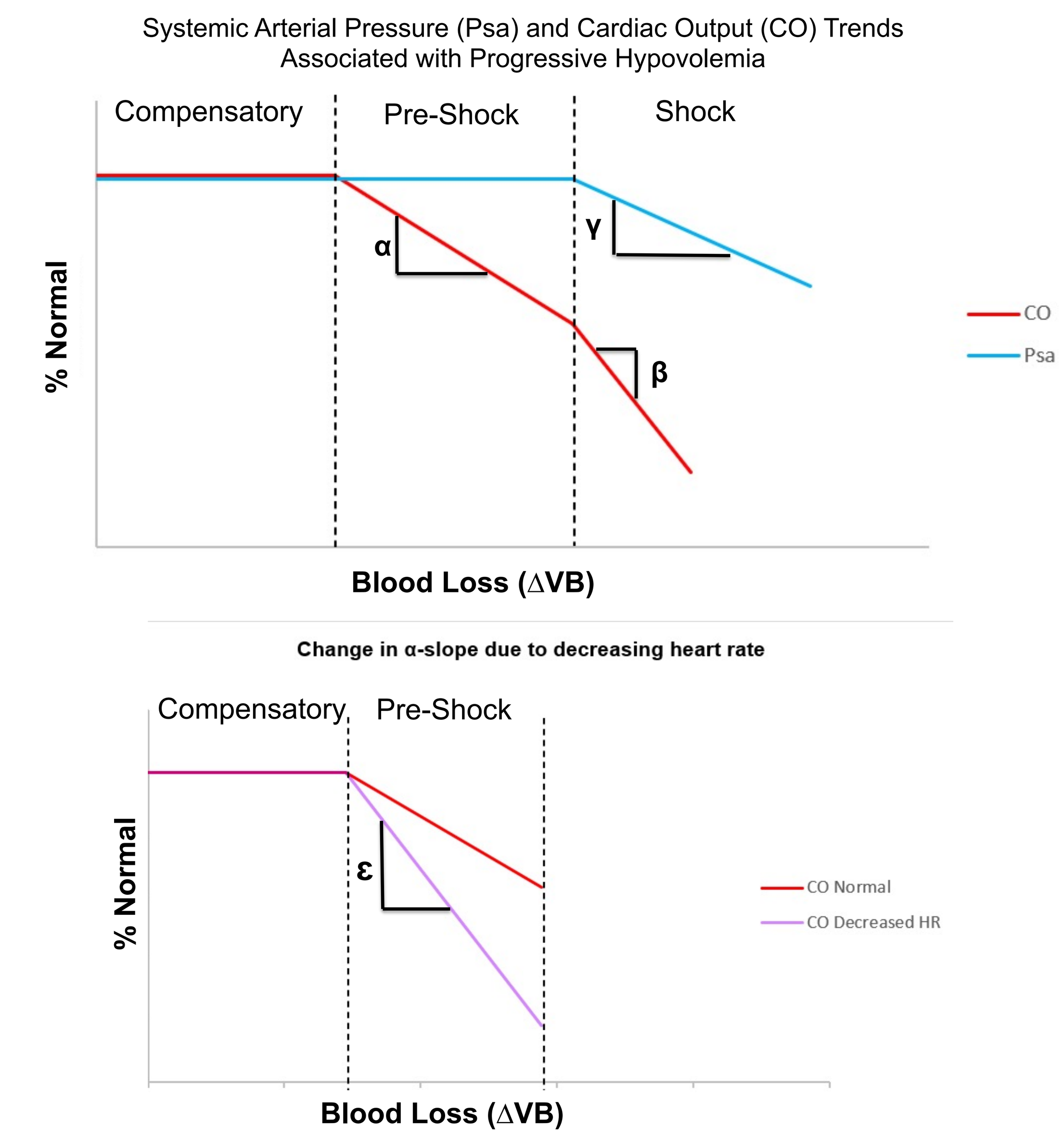


**Figure 3.** The top graph represents the three stages of progressive hypovolemia. Stage 1 (Compensatory): Regulation of both arterial pressure and cardiac output; Stage 2 (Pre-Shock): Regulation of mean arterial pressure only; Stage 3 (Shock): Complete loss of regulation. The bottom graph represents a change in slope α as a result of decreasing HR during "Pre-Shock".

- Slope **α** of **Figure 3** represents the changing CO while under mean arterial pressure regulation. After a complete loss in regulation, slopes **β** and **γ** represent the changing CO and Psa, respectively.
- By analyzing the equation below, it was determined that a decrease in the HR causes a decrease in slope **α**, which is represented by the newly formed slope **ε**.

$$\alpha = \frac{E_{maxRV}HR}{C_{PV}E_{maxRV}E_{minLV} + C_{PA}E_{maxRV}(E_{minLV} + HR\,R_P) + C_{SV}E_{minRV}(E_{maxRV} + E_{minLV} - HR\,R_P)}$$

## Discussion

- We present the first comprehensive analytical solution for understanding complex changing interactions among mechanical properties and hemodynamic variables as a function of blood loss.
- By assuming these regulated variables are constant parameters, three sets of algebraic solutions were derived. Unlike numerical solutions, these linearized algebraic results are easier to interpret and significantly less susceptible to errors arising from incorrect parameter values.
- By simplifying the equations for these three stages and solving for their respective variables, it can be determined which mechanical properties have the greatest impact on those variables.
- These general algebraic solutions provide clinical investigators with a novel tool that may be used to interpret clinical symptoms and develop interventions to maintain cardiovascular homeostasis with hypovolemia.

### References


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2. **Sunagawa K, Sagawa K, Maughan WL**. Ventricular interaction with the loading system. *Ann Biomed Eng* 12: 163-189, 1984.

3. **Stiles TW, Morfin Rodriguez AE, Mohiuddin HS, Lee H, Dalal FA, Fuertes WW, Adams TH, Stewart RH, Quick CM.** Algebraic formulas characterizing an alternative to Guyton's graphical analysis relevant for heart failure. *Am J Physiol Regul Integr Comp Physiol*, 2021.