Central venous pressure and cardiac function during spaceflight

RONALD J. WHITE1 AND C. GUNNAR BLOMQVIST2

1Baylor College of Medicine, Houston, Texas 77030; and 2University of Texas Southwestern Medical Center, Dallas, Texas 75235

White, Ronald J., and C. Gunnar Blomqvist. Central venous pressure and cardiac function during spaceflight. J. Appl. Physiol. 85(2): 738–746, 1998.—Early in spaceflight, an apparently paradoxical condition occurs in which, despite an externally visible headward fluid shift, measured central venous pressure is lower but stroke volume and cardiac output are higher, and heart rate is unchanged from reference measurements made before flight. This paper presents a set of studies in which a simple three-compartment, steady-state model of cardiovascular function is used, providing insight into the contributions made by the major mechanisms that could be responsible for these events. On the basis of these studies, we conclude that, during weightless spaceflight, the heart relaxes with a concomitant shape change that increases the volume of the closed chest cavity. This leads to a decrease in intrapleural pressure, ultimately causing a shift of blood into the vessels of the chest, increasing the transmural filling pressure of the heart, and decreasing the central venous pressure. The increase in the transmural filling pressure of the heart is responsible, through a Starling-type mechanism, for the observed increases in heart size, left ventricular end-diastolic volume, stroke volume, and cardiac output.

extracardiac pressure; modeling; microgravity

CONTINUOUS MEASUREMENTS of central venous pressure (CVP) made in humans during the initial phase of spaceflight consistently show a decrease, within seconds of entering the microgravity environment of space, to values below those obtained from the same crew members in the seated or supine position before launch (1, 2, 6). In fact, the average measured CVP in three subjects decreased from 11 mmHg (measured relative to standard atmospheric pressure and sea-level gas composition) 1 h before launch in the supine leg-up position to 1.8 mmHg 10 min after entry into orbit, and the recorded CVP values remained low for as long as they had been measured in space, 9–44 h. During this period of low CVP, heart size, left ventricular end-diastolic volume, stroke volume, and cardiac output, as estimated from echocardiographic data, are all elevated above the levels recorded from crew members in the supine position before launch, whereas mean arterial blood pressure and heart rate change little (2). At the same time, after the removal of the gravitational force that induces the normal fluid distribution found in the dominant upright body position on Earth, both intravascular and extravascular fluid shifts from the lower toward the upper body (14). This total constellation of physiological changes, including the expected headward fluid shifts, increased heart size and cardiac output, nearly normal arterial blood pressure and heart rate, and the decreased CVP, was not predicted by ground-based experimental models such as head-down bedrest. Developing a coherent explanation of these events challenges our understanding of cardiovascular function [but see an early analysis of some related events (4)].

This study utilizes a simple model to gain insight into the mechanisms responsible for these cardiovascular events occurring at the beginning of spaceflight. Through modeling it is possible to examine the parallel and competing physiological mechanisms likely to be operative during the first few minutes of near-weightlessness, clarify their role and likely importance, and reconcile the experimental data with established physiological principles. Although definitive conclusions concerning the events occurring within the body during this period are not warranted without further experimental data, this study strongly supports the following hypothesis. The removal of the effective force of gravity removes the weight of all of the cells, tissues, and organs of the body, including the weight of the skeleton. This reduction in weight of the body components changes the forces acting along the body’s supporting structures and relaxes the usual deformations caused by the weight of the body. Thus removal of the weight of the chest wall and of the need to support that wall causes a relaxation of the chest with a concomitant shape change that increases the volume of the closed chest cavity, leading, in turn, to a decrease in intrapleural pressure. This decrease in the effective pressure on the heart and great vessels of the chest leads to a shift of blood into the vessels of the chest, an increase in the transmural filling pressure of the heart, and, despite the fluid shift, a decrease in the CVP. The increase in the transmural filling pressure of the heart is then responsible, through a Starling-type mechanism, for the observed increases in heart size, left ventricular end-diastolic volume, stroke volume, and cardiac output.

BASIC MODEL DESCRIPTION

This study utilizes a simple cardiovascular model to represent blood flow within the body by a nonpulsatile,
three-compartment closed system with a nonlinear pump but with linear relations between other compartmental pressure differences and flows and with linear relations between pressure and volume in each compartment. The steady-state version of this highly idealized model is surprisingly useful (e.g., see Refs. 12, 24, and chapt. 15 in Ref. 9) in the analysis of the principal characteristics of the cardiovascular responses to a wide variety of physiological challenges, and it is in this spirit that we develop this model here.

The three compartments are identified as follows: 1) the heart and lungs taken together, 2) the (systemic) arteries, and 3) the (systemic) veins. In this paper, numbers 1–3 will be used as subscripts to identify these three compartments. In addition to the general assumptions, some realistic and others merely convenient, implicit in idealized models of this general type and discussed in several papers (9, 11, 12, 15–18, 20, 22, 26), only a few explicit assumptions are made in this analysis. First, it is assumed that the entire heart/lung compartment is subjected to a constant external (intrapleural) pressure of amount Pe. (All model pressures are defined relative to atmospheric pressure and are given in mmHg.) The normal value of this intrapleural, compartmental pressure of amount Pe. (All model pressures are defined relative to atmospheric pressure and are given in mmHg.) The normal value of this intrapleural, and thus extracardiac, pressure is taken to be –4 mmHg (5). Second, the systemic veins just outside the chest are assumed to collapse when the pressure in the heart/lung falls below the value Pm, taken for convenience to be –2 mmHg (see the discussion of venous collapse on p. 179–180 of Ref. 9). Third, the flow out of the heart/lung compartment (cardiac output) is assumed to be related to the pressure within the compartment through Starling-type cardiac function curves, as defined, explained, and used extensively by Guyton and co-workers (7, 9, 10). Fourth, CVP is assumed to be identical to pressure in the heart/lung compartment.

The dynamic (time-dependent) equations representing this closed (nonleaking) three-compartment system are particularly simple but generally nonlinear. System dynamics are not discussed in this paper; our interest is in the steady-state equations the solution of which has no time dependency. Analysis of the steady state in models of this type may take a variety of forms. The approach used in this study has already been explained in detail (26); only the results are provided here. Table 1 lists all of the model terms and provides the normal values and units used in this study. Because this simple model is used mainly to draw qualitative conclusions about the operation of the model itself, the basic independent parameters were selected to represent a "typical" case by requiring them to be compatible with other, slightly more complicated, models of this general type (3, 8, 9, 26). Later, parameter variation studies will examine the question of how model behavior is linked to parameter choices (15).

Because blood is the circulating fluid in our model, the closed nature assumed for the model requires that no blood is gained or lost by the circulation or that mass is conserved in all states of the model. This conservation law, which is valid even in dynamic, nonsteady

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition and Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>α</td>
<td>Nonlinear (sigmoidal) pressure-flow characteristics of the heart as a pump (= 7.809 . . .) (see definition of F2 below)</td>
</tr>
<tr>
<td>β</td>
<td>Nonlinear (sigmoidal) pressure-flow characteristics of the heart as a pump (= 0.381 . . . (mmHg)·l⁻¹) (see the definition of F2 below)</td>
</tr>
<tr>
<td>C1</td>
<td>Compliance of the heart/lung compartment (= 0.012 l/mmHg)</td>
</tr>
<tr>
<td>C2</td>
<td>Compliance of the arterial compartment (= 0.00355 l/mmHg)</td>
</tr>
<tr>
<td>C3</td>
<td>Compliance of the venous compartment (= 0.075 l/mmHg)</td>
</tr>
<tr>
<td>Cr</td>
<td>Total compliance (= C1 + C2 + C3 (= 0.09055 l/mmHg)</td>
</tr>
<tr>
<td>CVP</td>
<td>Central venous pressure, assumed equal to P1</td>
</tr>
<tr>
<td>F2</td>
<td>Sigmoidal cardiac function relation depicting relationship between the transmural pressure in the heart and the flow out of the heart</td>
</tr>
</tbody>
</table>

where \( S \cdot K = 1 + \alpha \cdot \exp \left[ -\beta \left( P1 - P_m \right) \right] \)

\( K \) Maximum value of F2 when \( S = 1 = (13.5 \text{l/min}) \)

\( P1 \) Pressure within the heart/lung compartment; at steady state, \( P1 = P1 = \) 0 mmHg

\( P2 \) Pressure within the arterial compartment; at steady state, \( P2 = P2 = \) 100 mmHg

\( P3 \) Pressure within the venous compartment; at steady state, \( P3 = P3 = \) 4 mmHg

\( Pe \) Extracardiac (intrapleural) pressure (= 4 mmHg)

\( Pm \) Pressure of venous collapse (= –2 mmHg)

\( Pmc \) Mean circulatory or systemic pressure (= 7.23 . . . mmHg)

\( Q \) Flow between the three compartments; at steady state, \( Q = Q = 5.000 \text{l/min} \)

\( R_a \) Arterial resistance (19.2 mmHg l⁻¹·min⁻¹)

\( R_v \) Venous resistance (0.8 mmHg l⁻¹·min⁻¹)

\( R_vr \) Resistance to venous return (1.446 . . . mmHg l⁻¹·min⁻¹)

\( S \) Heart’s pumping effectiveness (1)

\( TPR \) Total peripheral resistance \( = R_a + R_v \) (20 mmHg l⁻¹·min⁻¹)

\( V_1 \) Volume of blood in heart/lung compartment \( = V_1 = V_1 = 2.920 \text{l} \)

\( V_2 \) Volume of blood in arterial compartment \( = V_2 = V_2 = 5.000 \text{l} \)

\( V_3 \) Volume of blood in venous compartment \( = V_3 = V_3 = 4.345 \text{l} \)

\( V_{1,0} \) Unstressed volume of heart/lung compartment \( = V_{1,0} = V_{1,0} = 0.780 \text{l} \)

\( V_{2,0} \) Unstressed volume of arterial compartment \( = V_{2,0} = V_{2,0} = 1.446 \text{l} \)

\( V_{3,0} \) Unstressed volume of venous compartment \( = V_{3,0} = V_{3,0} = 4.496 \text{l} \)

\( V_{1,0} \) Component of \( V_{1,0} \) independent of \( Pe \) \( (= 0.852 \text{l}) \)

\( V_{blood} \) Blood volume \( (= 5.000 \text{l}) \)

\( V_{blood,0} \) Unstressed blood volume contained in noncapacitive regions \( (= 0.400 \text{l}) \)

\( V_{1,0} \) Total unstressed volume \( = V_{blood} + V_{1,0} + V_{2,0} + V_{3,0} \)

\( V_0 \) Total blood volume \( (= 4.345 \text{l}) \)

states of the model, implies the constancy of the total compartmental volume. For our simple model

\[ V_{blood} = V_{blood,0} + V_1 + V_2 + V_3 \] (1)

where \( V_{blood} \) is the (constant) total blood volume, \( V_{blood,0} \) is the unstressed blood volume contained in the nonca-
pactive regions, and \( V_i \) is the volume in compartment \( i \). Linear pressure-volume relations are assumed for each compartment, with

\[
P_i = \frac{V_i - V_{i,0}}{C_i}
\]

(2)

where \( V_{i,0} \) is termed “the unstressed volume,” \( C_i \) is the compliance, and \( P_i \) is the pressure of compartment \( i \). By using Eq. 2, the conservation law, Eq. 1 may be rewritten so as to involve pressures instead of volumes. When this is done, it is convenient to define and use a new constant pressure term

\[
C_T \cdot P_{mc} = C_1 \cdot P_1 + C_2 \cdot P_2 + C_3 \cdot P_3
\]

(3)

Here \( P_{mc} \) is the (constant) mean circulatory pressure (equal in this simple model to the mean systemic pressure), \( C_T = C_1 + C_2 + C_3 \) is the total compliance, and \( V_{T0} = V_{blood,0} + V_{1,0} + V_{2,0} + V_{3,0} \) is the total unstressed volume. Note that \( V_{1,0} \) is explicitly dependent on \( P_e \) in a model of this type (see Table 1), so that \( P_{mc} \) exhibits a (slight) direct dependency on average intrapleural pressure.

In the steady state, where the three flows between the three compartments are all equal (to the value of flow between the compartments \( Q \), assumed to be nonnegative), this mass-conservation relation becomes

\[
Q = F_1(P_1) = \begin{cases} 
P_{mc} - \frac{C_1}{C_T} P_1 & P_m > P_1 \\
\frac{P_{mc} - P_1}{R_v} & P_{mc} \geq P_1 \geq P_m \\
0 & P_1 > P_{mc}
\end{cases}
\]

(4)

where the resistance to venous return \( (R_v) \) is defined as

\[
R_v = C_T (R_a + R_v) + C_3 \cdot R_v
\]

and

\[
P_{mc} = P_{mc} - \frac{C_2 + C_3}{C_T} P_m
\]

Thus all pairs of values of \( P_1 \) and \( Q \) satisfying Eq. 4 must also satisfy the mass-conservation relation. Equation 4 is the form that will be used to represent the first of the fundamental steady-state model equations: the mass conservation relation, \( Q = F_1(P_1) \). This relation has been termed the “venous return curve” (8) or the “vascular function curve” (12) in the literature, but those names do not convey the fundamental nature of the conservation law involved and will not be used here.

The second equation needed to completely determine the steady state (when it exists) describes the action of the cardiac pump, located in the single heart/lung compartment. For simplicity, we choose to represent the pump’s action by what is termed a “cardiac output function curve,” a second relation between the flow out of that compartment, \( Q \), and the pressure in that compartment, \( P_1 \). Furthermore, we choose to represent this cardiac function relation by the sigmoidal function shown below. Thus the form that will be used to represent the second of the fundamental steady-state model equations is the cardiac function relation

\[
Q = F_2(P_1) = \frac{S \cdot K}{1 + \alpha \cdot \exp \left[ -\beta (P_1 - P_e) \right]}
\]

(5)

where \( S \) is a redundant but convenient multiplicative factor (whose normal value is 1) introduced for later use [it can represent various states of the heart’s effectiveness as a pump (8, 26)] and where \( K, \alpha, \) and \( \beta \) are parameters that characterize the pump. The cardiac function relation and the preceding mass-conservation relation are both depicted graphically in Fig. 1.

In the steady state, both the mass-conservation relation and the cardiac function relation (Eqs. 4 and 5) must be satisfied. This is true if, and only if, the two relations have (at least one) common point. Thus

\[
F_1(P) = F_2(P)
\]

(7)

and this equation is our final, single nonlinear equation representing the steady state.

The solution of Eq. 7, the common point on the graph of the two relations, is defined as the point \( (P^*_1, Q^*) \); generally, asterisk superscript on a variable denotes the value in a steady state. Because it is assumed that \( P_1 = CVP \), solving Eq. 7 simultaneously yields the CVP and cardiac output in any steady state. It is usual to solve Eq. 7 numerically for the value of \( P^*_1 \) and determine \( Q^* \) from either Eq. 4 or 5. Figure 1 illustrates the normal case for this model; the normal steady-state mass-conservation relation and cardiac function relation are both depicted graphically in Fig. 1.
The operating point of the model has $P^* = 0$ mmHg and $Q^* = 5.000$ l/min.

**STUDIES AND RESULTS: BASIC MODEL**

The primary question we seek to answer with this simple model is the following. Given that the model begins in a “normal” state determined by the normal parameter values specified in Table 1, what are the necessary and sufficient conditions of parameter variation that will yield a new steady state where $P^*$ decreases, $Q^*$ increases, and $V^*$ (the volume in the heart/lung compartment) increases? We will answer this question using three techniques.

First, we will solve the model equations for various parameter sets and examine the results to develop insight into the way the model operates. Second, we will carry out a complete parameter-variation study; with this small model, a full sensitivity analysis is feasible and appropriate. Finally, we will utilize a graphic analysis technique to relate the graphs of the two relations depicted in Fig. 1 to the model parameter set and determine how their intersection changes as the parameters vary.

The equations that we have used to define our model have 16 embedded parameters of convenience but only 7 are independent. We choose not to carry out a minimal analysis using an independent parameter set but will instead analyze the effect of variation of any of the parameters of convenience. The model parameters may be divided into three groups: those that affect only the mass-conservation relation, those that affect only the cardiac function relation, and those that affect both. Eleven parameters affect only the mass-conservation relation: $R_a$, $R_v$, $C_1$, $C_2$, $C_3$, $V^*_{10}$, $V_{20}$, $V_{30}$, $V_{blood}$, $V_{blood0}$, and $P_m$. Four affect only the cardiac function relation: $S$, $K$, $a$, and $b$. In the basic model, only the intrapleural pressure $P_e$ affects both relations.

Figure 2 illustrates the effect of a number of one-parameter variation studies on both the mass-conservation relation and the cardiac function relation and on their common point, the new steady-state value of $(P^*, Q^*)$. Figure 2A shows how both the mass-conservation relation and the cardiac function relation shift as $P_e$, the extracardiac (intrapleural) pressure, varies. Changes in $P_e$ cause a direct translation of the cardiac function relation by the same amount and in the same direction as the change in $P_e$ (see Eq. 6) but hardly affect the mass-conservation relation at all. Thus the intersection point moves up and to the left, i.e., a decrease in $P_e$ leads to a new steady state with decreased CVP and increased cardiac output. Figure 2B shows the same type of pattern for $S$, the pumping effectiveness of the heart. Increases in pumping effectiveness, either from contractility changes or from sympathetic stimulation, lead to a new steady state that, like in the previous case, has decreased CVP and increased cardiac output. Figure 2, C and D, show what happens when $V_{30}$, the unstressed venous volume, and $C_3$, the compliance of the veins, are varied. In these cases, the patterns obtained are different from the first.

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**Fig. 2.** A: three versions of cardiac function relation and mass-conservation relation, with extracardiac (intrapleural) pressure ($P_e$) = −6, −4 (normal), and −2 mmHg. B: normal mass-conservation relation and 3 versions of cardiac function relation with heart pumping effectiveness ($S$) = 1 (normal), 1.5 (hypereffective), and 0.5 (hypoeffective). C: normal cardiac function relation and 3 versions of mass-conservation relation with unstressed venous volume ($V_{30}$) = 2.420, 2.620 (normal), and 2.820 liters. D: normal cardiac function relation and 3 versions of mass-conservation relation with the compliance of venous compartment ($C_3$) = 0.045, 0.075 (normal), and 0.105 l/mmHg.
two cases; here, the new steady state is one with increased, rather than decreased, CVP simultaneous with increased cardiac output.

These individual studies demonstrate the different types of steady states that are obtained when different parameters are varied, but it is not clear from such individual studies alone what the necessary and sufficient conditions are that lead to new steady states of interest (e.g., states with decreased CVP and increased cardiac output). However, it is clear that variation of either $P_e$ or $S$ leads to such steady states, and Figs. 3 and 4 explore the behavior of the model in more detail when these two parameters change. Figures 3A and 4A show the steady-state volume changes in each of the three model compartments, as blood shifts in response to the parameter changes. Note that, as $P_e$ decreases (Fig. 3A), blood shifts into both the heart/lung compartment and the arterial compartment from the systemic veins, but that as $S$ increases (Fig. 4A), blood shifts out of the heart/lung compartment as well as from the veins and into the arteries. This shift in blood into or out of the heart/lung compartment is shown clearly in Figs. 3B and 4B, whereas Figs. 3C and 4C show the corresponding CVP changes and Figs. 3D and 4D show the cardiac output changes. These studies demonstrate that 1) as $P_e$ decreases, blood shifts into the heart/lung compartment, pressure in that compartment (CVP) falls, and cardiac output rises; and 2) as pumping effectiveness of the heart increases, blood shifts out of the heart/lung compartment, pressure in that compartment (CVP) falls, and cardiac output rises. Case 1 has been studied previously, but as $P_e$ increases, e.g., in opening the chest (5). Case 2 represents a well-understood mechanism used to increase cardiac output (12, 21, 24).

A more general method of dealing with model behavior under parameter variation involves sensitivity analysis (23, 26). To apply this technique, we define the sensitivity function $Sen(f, z)$ as follows

$$Sen(f, z) = \left( \frac{\partial \log f}{\partial \log z_0} \right)$$

where $f$ represents any dependent model variable, $z$ represents any model parameter, and the subscript 0 denotes evaluation at the “normal” values ($f = x_0$, $z = y_0$). Table 2 presents a complete list of these sensitivity coefficients relating all of the primary dependent variables to all 16 parameters of convenience in the model. When these coefficients are used, changes in any dependent variable (x-axis of Table 2) are related to changes in a parameter set by the approximate relation

$$\frac{\Delta f}{f_0} \approx \sum Sen(f, z_i) \cdot \frac{\Delta z_i}{z_{i,0}}$$

where the term $\Delta f = f - f_0$ represents the change in the value of $f$ from normal (similarly for $\Delta z_i$), and the sum ranges over all parameters that change. Thus Eq. 9 represents a simple way of relating fractional changes in dependent variables to fractional changes in parameters, at least for small changes in the parameters.

Fig. 3. A: changes in volume of 3 model compartments as extracardiac (intrapleural) pressure varies. B: volume of heart/lung compartment as a function of extracardiac pressure. C: model central venous pressure as a function of extracardiac pressure. D: model cardiac output as a function of extracardiac pressure.
The sensitivity coefficients in Table 2 related to the pressures are defined in terms of absolute pressure values instead of values relative to normal atmospheric pressure. Thus, in mmHg, the pressures used in the sensitivity analysis are defined as $760 + p_i$, where $p_i$ is the model blood pressure in compartment $i$.

Table 2 shows quite clearly that the changes in cardiac output and the changes in CVP are always in the same direction for ten of the parameters that affect only the mass-conservation relation; for these parameters, increases in cardiac output are accompanied by increases in CVP, just as in Fig. 2, C and D. No information is provided for $P_m$, but this parameter (the pressure of venous collapse) is of little interest here, as it simply determines the location of the (artificial) singularity in the mass-conservation relation. On the other hand, for $P_e$ and the four parameters that affect the cardiac function relation only, changes in cardiac output and changes in CVP are always in different directions: increases in cardiac output are accompanied by decreases in CVP.

In this latter group, the parameter $P_e$ stands out from the other four parameters ($S$ or $K$, $\alpha$, and $\beta$) as being the only parameter for which $V_1$, the blood volume in the

**Table 2. Sensitivity coefficients for basic model, $\text{Sen}(f,z)$**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>$Q$</th>
<th>$\text{CVP} = P_1$</th>
<th>$V_1$</th>
<th>$P_2$</th>
<th>$V_2$</th>
<th>$P_3$</th>
<th>$V_3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P_e$</td>
<td>0.30</td>
<td>-0.0036</td>
<td>0.017</td>
<td>0.032</td>
<td>0.13</td>
<td>-0.0020</td>
<td>-0.039</td>
</tr>
<tr>
<td>$S$ or $K$</td>
<td>0.36</td>
<td>-0.0035</td>
<td>-0.035</td>
<td>0.039</td>
<td>0.15</td>
<td>-0.0016</td>
<td>-0.030</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>-0.23</td>
<td>0.0022</td>
<td>0.022</td>
<td>-0.025</td>
<td>-0.097</td>
<td>0.00097</td>
<td>0.019</td>
</tr>
<tr>
<td>$\beta$</td>
<td>0.35</td>
<td>-0.0033</td>
<td>-0.034</td>
<td>0.038</td>
<td>0.15</td>
<td>-0.0015</td>
<td>-0.029</td>
</tr>
<tr>
<td>$R_a$</td>
<td>-0.33</td>
<td>-0.0018</td>
<td>-0.018</td>
<td>0.072</td>
<td>0.28</td>
<td>-0.0035</td>
<td>-0.069</td>
</tr>
<tr>
<td>$R_v$</td>
<td>-0.30</td>
<td>-0.0017</td>
<td>-0.017</td>
<td>-0.032</td>
<td>-0.13</td>
<td>0.0020</td>
<td>0.039</td>
</tr>
<tr>
<td>$C_1$</td>
<td>-0.046</td>
<td>-0.0002</td>
<td>0.051</td>
<td>-0.0056</td>
<td>-0.022</td>
<td>-0.00050</td>
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</tr>
<tr>
<td>$C_2$</td>
<td>-0.34</td>
<td>-0.0019</td>
<td>-0.019</td>
<td>-0.042</td>
<td>0.29</td>
<td>-0.0037</td>
<td>-0.019</td>
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<tr>
<td>$C_3$</td>
<td>-0.29</td>
<td>-0.0016</td>
<td>-0.016</td>
<td>-0.035</td>
<td>-0.14</td>
<td>-0.0031</td>
<td>0.042</td>
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<tr>
<td>$V_{2,0}$</td>
<td>-0.82</td>
<td>-0.0045</td>
<td>0.90</td>
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<tr>
<td>$V_{2,0}$</td>
<td>-0.41</td>
<td>-0.0023</td>
<td>-0.023</td>
<td>-0.050</td>
<td>0.35</td>
<td>-0.0044</td>
<td>-0.086</td>
</tr>
<tr>
<td>$V_{3,0}$</td>
<td>-2.54</td>
<td>-0.014</td>
<td>0.14</td>
<td>0.31</td>
<td>1.20</td>
<td>-0.027</td>
<td>0.36</td>
</tr>
<tr>
<td>$V_{\text{blood}}$</td>
<td>4.84</td>
<td>0.026</td>
<td>0.27</td>
<td>0.59</td>
<td>2.30</td>
<td>0.052</td>
<td>1.02</td>
</tr>
<tr>
<td>$V_{\text{blood}}$</td>
<td>-0.39</td>
<td>-0.0021</td>
<td>-0.022</td>
<td>-0.047</td>
<td>-0.18</td>
<td>-0.0041</td>
<td>-0.081</td>
</tr>
<tr>
<td>$P_m$</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
<td>0</td>
<td>0</td>
</tr>
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</table>

See Table 1 and Eq. 8 for definitions.
heart/lung compartment, increases whenever cardiac output increases and CVP decreases. Changes in the other four parameters lead to decreases in the volume of blood in the heart/lung compartment whenever cardiac output increases.

Thus the sensitivity analysis shows clearly that, for this model, the intrapleural (extracardiac) pressure plays a unique role, being the only parameter whose variation can simultaneously lead to increased cardiac output, decreased CVP, and increased blood volume in the chest (cephalic fluid shift).

Although the sensitivity analysis is clear and definitive, it is not easy to generalize beyond the model under consideration; for that reason, we turn to a graphic analysis. Refer to Fig. 1 and note that the cardiac function relation described by Eq. 5 is an increasing function of \( P_e \), so that \( F_2(x) > F_2(y) \) whenever \( x > y \). Recall that steady-state values of CVP \( (P_1) \) and cardiac output must lie on both the cardiac function relation and the mass-conservation relation. Suppose now that a parameter only affects the mass-conservation relation and not the cardiac function relation. Then, it is always true that, in the new steady state that is obtained after the parameter is changed, the CVP and the cardiac output both change in the same direction.

To see this analytically, let two pairs of steady-state values be \((P^{*1}(1), Q^{*1}(1))\) and \((P^{*2}(2), Q^{*2}(2))\), and, for simplicity, let \( P^{*1}(2) > P^{*1}(1) \). From Eq. 5, \( Q^{*1}(1) = F_2(P^{*1}(1)) \), and because \( F_2 \) is increasing, \( Q^{*2}(2) = F_2(P^{*2}(2)) \geq F_2(P^{*2}(1)) \geq 0 \), and the result is shown. This result is of great significance because it holds for all possible combinations of parameters as well as for single parameters, so long as the individual parameters do not affect the cardiac function curve.

Now note that the mass-conservation relation is a decreasing function of \( P_1 \), up to the mean circulatory pressure (see Fig. 1 and Eq. 4). Reasoning similar to the above shows that, for parameters that affect only the cardiac function relation, changes in the steady-state values of CVP are always accompanied by steady-state cardiac output changes in the opposite direction. Thus parameter changes of this type decrease CVP and increase cardiac output in the new steady state.

In this model, the extracardiac (intrapleural) pressure \( P_e \) is the only parameter that affects both the cardiac function relation and the mass-conservation relation, but it affects the two very differently; transmural pressure \( (P_1 - P_e) \) dominates cardiac output, whereas mean circulatory pressure shows only a weak dependence on \( P_e \). Thus the dominant effect of changes in \( P_e \) is to act as if it affects only the cardiac function relation; decreases in \( P_e \) translate the cardiac function relation to the left and do little to the mass-conservation relation, leading to a new steady state with decreased CVP and increased cardiac output.

Taken together, the above studies answer the question posed at the beginning of this section in a clear and definitive way. The necessary and sufficient condition that must be satisfied in this simple model in order that parameter variation will yield a new steady state where CVP \( (P_1) \) decreases, \( Q^* \) increases, and \( V_1^* \) (the volume in the heart/lung compartment) increases is that the extracardiac or intrapleural pressure \( P_e \) must decrease. If the last component of the condition above (the increase of \( V_1^* \)) is relaxed, then any of the model parameters that affect only the cardiac function in such a way as to increase pumping effectiveness (specific changes in \( S, K, \alpha, \) or \( \beta \)) may be joined to the possible parameter choices.

**DISCUSSION AND CONCLUSION**

Although these basic model results are sharp, do they apply to the human body just after entry into weightless spaceflight? From a series of other studies that we have completed, it appears that they do. We began our analysis not with the three-compartment model presented here but with other, more complicated, models with a two-sided heart, parallel flow beds, a separate lung compartment, a leaky circulation, local autoregulation, and stress relaxation, among other things (3, 8, 26). These less-complete initial studies using more complicated models have convinced us that the simple model that we present in this paper contains the essential elements needed for this analysis and that our basic conclusion is stable to a wide variety of enhancements and perturbations.

For example, in general compartmental models with two-sided hearts, the analogous steady-state analysis to that performed here (regardless of the number and type of systemic and pulmonary compartments) requires only a modest increase in complexity over that shown in Fig. 1. The general mass-conservation relation and the two ventricular output relations define surfaces in the three-variable space consisting of flow, right atrial pressure, and left atrial pressure. In this space, the mass-conservation relation consists of a piecewise planar surface, whereas ventricular output is represented by two waves, one representing left ventricular output and the other representing right ventricular output. (These waves may involve coordinated action of the right and left sides of the heart.) The steady state is defined by the intersection point of these three surfaces; since this intersection must take place on the plane determined by mass conservation, this most general analysis may, in fact, be restricted to only the two dimensions describing the planar surface, a rather surprising fact at first glance. Thus even the most general analysis possible does not differ extraordinarily from the simple analysis presented here; special conditions (e.g., assuming a linear relation between left and right atrial pressures for a given ventricular output) can reduce the analysis entirely to that presented here. It is possible to apply the graphic analysis technique used in the last section to this more general case; results are similar to those presented here. Guyton and co-workers have reported similar successes in translating the results of his simple function curve analysis to more general settings (see the many references in Ref. 9, particularly those related to chap. 8).

Through this modeling study, we make no statement about the entire complex of physiological events that take place at the beginning of nearly weightless space-
flight. Many other changes may and certainly do occur; in modeling terms, resistances, compliances, and un-
stressed volumes probably change with time and have local variation. However, according to this study, none of these changes are necessary for the attainment of a state with reduced CVP and increased cardiac output, and none are sufficient, by themselves, for the attainment of that state.

Because it is possible to produce a state (in the model) with reduced CVP and increased cardiac output, albeit with decreased blood volume in the chest, by improving the performance of the heart as a pump, it is reasonable to ask whether there are data that might support that mechanism. The answer is clearly no. It has been pointed out previously that the heart rate data collected at the same time that CVP and cardiac output were measured do not support the possibility of increased sympathetic stimulation (1), but it should, in all fairness, be pointed out that a direct measurement of sympathetic activity has never been accomplished in space (direct recordings of peripheral sympathetic nerve activity are planned for the 1998 Neurolab mission). Similarly, the echocardiographic data on left ventricular end-systolic dimensions, ejection fraction, and the velocity of circumferential fiber shortening, combined with the heart rate data, indicate the absence of major changes in cardiac contractility, and no physiological mechanisms producing sudden increases in intrinsic diastolic myocardial compliance have been identified (2). If increased general sympathetic stimulation and increased cardiac contractility or compliance are eliminated as possibilities, then only one mechanism predicted by this modeling study remains, even if the cephalic fluid shift issue is ignored: a reduction in the extracardiac pressure that leads to an increase in the transmural pressure across the heart despite a lower CVP.

If it is true that the average extracardiac pressure is reduced at the beginning of nearly weightless spaceflight, why would that occur? To answer that question, let’s consider what happens when effective weight is reduced at the beginning of nearly weightless spaceflight. The removal of the effective force of gravity removes the weight of all of the cells, tissues, and organs of the body, including the weight of the skeleton. This reduction in weight of the body components changes the forces acting along the body’s supporting structures and relaxes the usual deformations caused by the body’s weight. Thus removal of the weight of the chest wall and of the need to support that wall causes a relaxation of the chest with a concomitant shape change that increases the volume of the closed chest cavity, leading, in turn, to a decrease in intrapleural pressure. (This hypothesis is not inconsistent with spaceflight data on pulmonary function (25).) This decrease in the effective pressure on the heart and great vessels of the chest leads to three consequences: a shift of blood into the vessels of the chest, an increase in the transmural filling pressure of the heart, and, despite the fluid shift, a decrease in the CVP. The increase in the transmural filling pressure of the heart is then responsible, through a Starling-type mechanism, for the observed increases in heart size, left ventricular end-diastolic volume, stroke volume, and cardiac output.

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REFERENCES


