Mathematical modeling of gravitational effects on the circulation: importance of the time course of venous pooling and blood volume changes in the lungs

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van Heusden, K., J. Gisolf, W. J. Stok, S. Dijkstra, and J. M. Karemaker. Mathematical modeling of gravitational effects on the circulation: importance of the time course of venous pooling and blood volume changes in the lungs. Am J Physiol Heart Circ Physiol 291: H2152–H2165, 2006. First published April 21, 2006; doi:10.1152/ajpheart.01268.2004.—A dip in blood pressure (BP) in response to head-up tilt (HUT) or active standing might be due to rapid pooling in the veins below the heart (preload) or muscle activation-induced drop in systemic vascular resistance (afterload). We hypothesized that, in the cardiovascular response to passive HUT, where, in contrast to active standing, little BP dip is observed, features affecting the preload play a key role. We developed a baroreflex model combined with a lumped-parameter model of the circulation, including viscoelastic stress-relaxation of the systemic veins. Cardiac contraction is modeled using the varying-elastance concept. Gravity affects not only the systemic, but also the pulmonary, circulation. In accordance with the experimental results, model simulations do not show a BP dip on HUT; the tilt-back response is also realistic. If it is assumed that venous capacities are steady-state values, the introduction of stress-relaxation initially reduces venous pooling. The resulting time course of venous pooling is comparable to measured impedance changes. When venous pressure-volume dynamics are neglected, rapid (completed within 30 s) venous pooling leads to a drop in BP. The direct effect of gravity on the pulmonary circulation influences the BP response in the first ~5 s after HUT and tilt back. In conclusion, the initial BP response to HUT is mainly determined by the response of the venous system. The time course of lower body pooling is essential in understanding the response to passive HUT.

baroreflex; cardiovascular system; modeling; tilt table

A MODELING APPROACH to the study of the blood circulation and its response to postural changes can provide insight into the underlying physiology. Existing models approximate certain aspects of the circulation and its response to orthostatic stress, but the transients seen on passive head-up tilt (HUT) have proven difficult to capture.

Transient response of the cardiovascular system to active standing and passive HUT has been the focus of various studies (3, 34, 45, 47, 51, 59). The steady-state response to active standing and HUT is usually comparable, but there is a difference in the blood pressure (BP) and heart rate (HR) responses in the first 30 s (Fig. 1). On passive HUT, Rossberg and Martinez (34) found initial increases in HR comparable to the response to active standing. In later studies, however, a BP dip on active standing was reduced (3, 47) or absent (45, 51, 59) in passive HUT responses. The initial BP dip on standing is thought to be due to a decrease in peripheral resistance resulting from the active part of the maneuver (45). Sprangers et al. (45) point out two mechanisms: 1) the central (autonomic) command that accompanies active muscle contraction and 2) the displacement of large amounts of venous blood to the right atrium by the massive muscle action induced by active standing, eliciting a cardiopulmonary (CP) reflex effect on the systemic circulation. In passive tilt, if abrupt muscle contraction in response to sudden tilt maneuvers is avoided, peripheral resistance increases gradually, and there is little or no pressure dip. This explanation of the immediate response to active and passive posture change implies that venous return and, consequently, cardiac output (CO) are not sufficiently reduced to induce a BP dip. Experimental studies, including measurements or estimations of CO during tilt (45, 51), indeed, report only a gradual decrease toward upright values, sometimes preceded by an initial increase.

Several published models have been designed to simulate the cardiovascular response to passive tilt or active standing (1, 21, 22, 28, 29, 32, 44). The simulated BP response of a recent model, including a detailed circulation and reflex model (21), shows a major BP dip in the first 10–20 s after HUT (20). This, in fact, resembles active standing, rather than passive HUT, although the model was designed to simulate passive tilt and does not include any effect of the active part of the maneuver on peripheral resistance. A transient decrease in BP in response to HUT can result from rapid filling of the veins (and, thus, a reduction in preload) or arterial dilation related to muscle activation (and, thus, a reduction in afterload). In the present study, we focus on the transient response to passive HUT (during which peripheral resistance is assumed to be unaffected by muscular activity). We hypothesized that the pressure dip produced by previous models simulating HUT, even though arterial dilation in response to muscle activation is not incorporated, is related to the time course of the filling of the veins. A proper simulation of a response to passive HUT requires a realistic time course of resultant transients.

We therefore developed a cardiovascular model that combines aspects of existing models but focuses on features affecting the preload to the heart during posture change. Venous pressure-volume dynamics are modeled as viscoelastic properties (37), and the effects of gravity on the pulmonary circulation (1) are included; blood flow redistribution as a result of (de)recruitment of capillary vessels is taken into account (24, 30, 58). The systemic circulation is divided in branches above and below heart level (1), since we expect a large amount of
blood to flow from the upper body toward the atrium immediately after HUT.

To develop the model, a data set of cardiovascular measurements (BP, HR, and electric impedance) during supine baseline posture and HUT in 20 healthy subjects was used (14). These tilts were conducted on a specially designed tilt table for smooth, rapid postural changes to obtain a hemodynamic response without involuntary muscle tensing and additional disturbances associated with active standing. These data do not show a transient dip in BP after HUT.

**Glossary**

- **C, R, V** Arterial capacity, arterial resistance, and change in circulating volume (used in optimization)
- **ρ** Density of blood
- **α** Tilt angle
- **β** Factor determining influence of $t_{\text{diast}}$ on $B_{\text{symp}}$
- **α_{\text{int}}** Gain; sensitivity of baroreflex to $f_{\text{Pd}}$
- **α_{\text{syst}}** Gain; sensitivity of baroreflex to $P_{\text{syst}}$
- **A** Constant used to calculate elastance
- **$B_{\text{afferent}}$** Afferent barosignal
- **$B_{\text{symp}}$** Sympathetic efferent activity
- **$B_{\text{vagal}}$** Vagal efferent activity
- **C** Constant used in impedance scaling
- **CO** Cardiac output
- **CO_{\text{ref}}** Reference value for CO (used in optimization), based on subject’s weight
- **C_{\text{static}}** Static capacities (used in the venous part of the systemic circulation model)
- **$E_{\text{max}}$** Maximal elastance
- **$E_0(t)$** Normalized elastance at time $t$
- **Error** Error in optimization algorithm
- **$g$** Gravitational acceleration
- **$G_{\text{CP}}$** Gain of CP reflex on resistance
- **$G_{\text{E}}$** Gain of reflex on contractility ($E_{\text{max}}$)
- **$G_{\text{HR symp}}$** Gain of sympathetic reflex on HR
- **$G_{\text{HR vagal}}$** Gain of vagal reflex on HR
- **$G_{\text{R}}$** Gain of resistance reflex
- **$G_{\text{V}}$** Gain of unstressed volume reflex
- **HR** Heart rate
- **HR_{0}$** Constant added to the sympathetic reflex on HR
- **HR_{\text{symp}}** Influence of sympathetic efferents on $m(t)$
- **HR_{\text{vagal}}** Influence of vagal efferents on $m(t)$
- **IBI** Interbeat interval
- **Imp** Measure of impedance signal
- **$\text{Imp}_{\text{scaled}}$** Scaled impedance signal
- **IPFM** Integral pulse frequency modulation
- **$k$** Constant used to calculate elastance for $P_{\text{diast}}$
- **$k_{\text{nonuniform}}$** Multiplication factor (used in impedance scaling)
- **$l_{\text{column}}$** Length of the column forming the hydrostatic column
- **LV** Left ventricle
- **m(t)** Integrated signal of the IPFM model
- **NonSpl** Compartments outside the splanchnic area (used in volume reflex)
- **P, P(t), P(s)** Pressure, pressure at time $t$, Laplace transform of pressure
- **$P_{\text{diast}}$** Diastolic pressure
- **$P_{\text{diast Ref}}$** Reference value for $P_{\text{diast}}$ (used in optimization), based on subject’s supine pressure
- **P_{\text{endo}}** End-diastolic pressure
- **$P_{\text{hydro}}$** Hydrostatic pressure
- **$P_{\text{mean}}$** Mean pressure
- **$P_{\text{min}}$** Minimal pressure, as defined for some compartments in the circulation model
- **$P_{\text{perfusion}}$** Perfusion pressure of pulmonary capillary vessels
- **$P_{\text{pulse}}$** Pulse pressure
- **$P_{\text{syst}}$** Systolic pressure
- **$P_{\text{syst Ref}}$** Reference value for $P_{\text{syst}}$ (used in optimization), based on subject’s supine pressure
- **PRU** Peripheral resistance unit
- **R** Resistance
- **$R_{\text{CP}}$** Resistance change as a result of CP reflex
- **$R_N$** Normalized nonlinear pulmonary resistance
- **RV** Right ventricle
- **Spl** Compartments in the splanchnic area (used in volume reflex)
- **Supine** Supine steady-state value
MODELING GRAVITATIONAL EFFECTS ON THE CIRCULATION

METHODS

Procedure and Measurements

Data were obtained from 20 test subjects (40 ± 8 yr of age, 176 ± 9 cm height, 71 ± 11 kg body wt; 4 women). The study was approved by the Medical Ethics Committee of the Academic Medical Center at the University of Amsterdam (MEC00/069) (14). Procedures are described elsewhere (14); in summary, the subjects were instrumented on a computer-controlled tilt table in the supine position and subjected to changes in volume in this part of the circulation have significant effects on arterial BP and the circulating blood volume. This volume, however, will not be available immediately; it will first have to pass the liver. Modeling the intestinal and the liver vasculature separately allows the delay to be taken into account and also introduces possible volume changes due to changes in the resistance ratio \( R_{\text{intestine}}/R_{\text{liver}} \).

The compartments of the systemic circulation are shown in Fig. 2. All capacities and resistances in the systemic circulation are linear. In the systemic veins, stress-relaxation [viscoelasticity or creep (17)] is included. Stress-relaxation refers to the intrinsic ability of the vascular walls to stretch slowly when the pressure rises and to contract slowly when the pressure falls (17). In humans, the effect of stress-relaxation on the vascular pressure-volume relation has been shown (11, 25), but the results of these studies are not suitable for quantification. We therefore use the results of experiments conducted in dogs (41).

We consider the capacity of the veins, as used in existing models, to be steady-state values subsequent to the effects of stress-relaxation. This implies that stress-relaxation initially reduces the volume needed to form the hydrostatic column. Because of the relaxation of the veins, the venous volume increases slowly to maintain the hydrostatic pressure. It is therefore not surprising that most models accurately simulate steady-state pressure, rather than pressure transients, after HUT. Stress-relaxation is represented by a first-order transfer function based on fitting of the pressure-volume relation found by Shoukas and Sagawa (41) (Eq. 1). The static (low-frequency) compliance values (35, 36) can be found in Table 1

\[
P(t) = (V/C_{\text{sys}})(1 + 5/3e^{-t/T})
\]

(1)

The pumping action of the heart is modeled using the varying-elasticity concept (10, 39, 46). We used the normalized elastance curve, as described by Heldt et al. (21), adjusted with a nonlinear diastolic elastance (52). Two valves complete the ventricular model; closure of both valves when the pressure difference is reversed allows no backflow.

Parameter values of the systemic circulation and the ventricles. The model is designed to be applicable for data-fitting procedures in future work. In the present study, no fitting to experimentally obtained data has been done, but the structure of the model and the way in which the values are assigned to the various parameters allow individualization of the model. Supine steady-state hemodynamic parameters are used as the starting point.

Pressures in the model are derived from reported resistance distribution (35, 36) and pressure levels (5) (Table 1). Capacities, CO, and blood volumes in the different compartments are dependent on body weight (35, 36). Resistance values, as well as the unstressed volumes, in the different compartments can be calculated using the CO and pressure levels. The following resistance values are used around the ventricles (22): \( R_{\text{pulmonary aorta}} = 0.008 \text{mmHg}\cdot\text{s}\cdot\text{ml}^{-1} \), \( R_{\text{RV}} = 0.003 \text{mmHg}\cdot\text{s}\cdot\text{ml}^{-1} \), and \( R_{\text{LV}} = 0.003 \text{mmHg}\cdot\text{s}\cdot\text{ml}^{-1} \).

In our simple, linear arterial model, the resulting \( P_{\text{pulse}} \) range is limited when values are used for the arterial compartment. We use a least-squares optimization algorithm minimizing error in \( P_{\text{sys}} \), \( P_{\text{diast}} \), and CO to find values for arterial capacity, peripheral resistance, and circulating volume to reproduce supine steady-state values of pressure and CO.

LV supine maximal elastance, as well as unstressed volumes, are based on previous reports (\( E_{\text{max}} \), \( V_{\text{LV}} \), \( V_{\text{unstressed}} \), \( V_{\text{max}} \)) (19, 39). RV elastance and unstressed volume have been measured using techniques that probably overestimate these values (4, 10): \( E_{\text{max}} \sim 1.3 \text{mmHg/ml} \) and \( V_{\text{unstressed}} \sim 30–40 \text{ml} \).
adjusted the experimental values and used $E_{\text{max RV}} = 0.6 \text{ mmHg/ml}$ and $V_{\text{unstressed RV}} = 10 \text{ ml}$. End-systolic volume can be calculated using systolic pressure, $E_{\text{max}}$, and $V_{\text{unstressed}}$. Together with the stroke volume, this determines the end-diastolic volume. Diastolic elastance is nonlinear according to the following equation: $P(t) = A(t) e^{k(e^{kt} - 1)}$ (52). $k_{LV} = 0.014 \text{ ml}^{-1}$ and $k_{RV} = 0.011 \text{ ml}^{-1}$ (52); $A_{LV}$ and $A_{RV}$ are calculated as follows: $A = P_{\text{EDV}} / (e^{k_{LV}} - 1)$, where $P_{\text{EDV}}$ is the atrial pressure adjusted from Table 1.

**Pulmonary circulation.** The effect of gravity on the pulmonary circulation is important in tilt responses, because posture changes influence the total blood volume in the lungs via vascular distensibility and (de)recruitment of capillary vessels (30). (De)recruitment of capillary vessels with changes in perfusion pressure (24, 26) also influences the flow distribution in the lungs (58). The structure of the pulmonary model is shown in Fig. 3. The pulmonary capillary resistances in the model are nonlinear. In this way, resistance changes as a result of recruitment are taken into account, allowing changes in flow distribution on tilt. The dynamics of the (de)recruitment of capillary vessels (24) are included in the model using a first-order transfer function.

**Parameter values of the pulmonary circulation.** Pulmonary pressures are based on reported measurements (31). The division between pulmonary veins above and below heart level is based on the segmental division introduced by West (58) and measurements of pulmonary dimensions (30) (2 segments are placed below heart level). Capacities and volumes are listed in Table 1.

Pulmonary arterial resistance is defined as 15% of total pulmonary resistance [experimental values vary from 5 to 50% (31)]. We combined previously reported pressure and CO measurements (30) with flow distributions (58) to quantify the nonlinearity and normalized this nonlinear capillary resistance curve. The calculated normalized resistances were fitted by an exponential curve: $R_N = 0.6178(\text{P}_{\text{perfusion}} + 3)^{-0.9786}$, which is scaled to match the supine resistances as calculated elsewhere (24). The dynamic effect on resistance is included in the model by use of a first-order transfer function with a time constant of 0.5 s.

**Introduction of gravity.** The effects of gravity are introduced into the systemic and pulmonary circulation by pressure sources (22, 29, 44). Hydrostatic pressure $P_{\text{hydro}} = l_{\text{column}} \cdot \rho \cdot g \cdot \sin(\alpha)$ is added to/subtracted from the arterial pressure perfusing each compartment; on the venous side of the model, the outflow pressure of the compartments is adjusted with the hydrostatic pressure. Pulmonary dimensions are based on reported values (30). We measured the distances in the systemic circulation in a live-sized anatomic model (Table 1).

The baroreceptors in the aortic arch and the carotid sinuses are located above heart level. In the model, the input pressure to the receptors is the aortic pressure at heart level adjusted with a hydrostatic column.

**Reflex Model**

The reflex model includes a baroreflex on HR (vagally and sympathetically mediated), peripheral resistance, cardiac contractility, and venous unstressed volume, as well as a CP reflex on peripheral resistance. Figure 4 is a schematic representation of the model; the various building blocks are explained below.

**Baroreflex.** The input to the baroreflex in our model is based on observations after hemorrhage reported previously (18) as well as our own measurements. Although HR increased after HUT for all subjects in our data set ($n = 20$), the corresponding $P_{\text{mean}}$ and $P_{\text{diast}}$ at carotid level did not always decrease. Only when $P_{\text{pul}}$ was taken into account could the increase in HR be related to the decreased input (1). The role of changes in $P_{\text{pul}}$ in the baroreflex has been reported previously (18, 48). The input to our baroreflex model is a combination of the systolic pressure and the integral of the pressure at the level of the receptors over the time of opening of the aortic valve (Eq. 2). In this way, pressure level, $P_{\text{pul}}$, and stroke volume are taken into account. The afferent barosignal, $B_{\text{affer}}$, is normalized. Thresholds are introduced to produce an afferent gain independent of the supine pressure level; these gains depend on the size of this threshold.

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**Fig. 2. Schematic representation of compartments of the circulation model. Distances used to determine the hydrostatic column for each compartment are indicated at left (not scaled). Arrows, blood flow between compartments.**
The vagal effect on HR is rapid and can occur within one beat; therefore, the vagal efferent activity in the model is pulsatile (Eq. 3).

A threshold ensures no efferent signal at low pressures; consequently, there is no vagal influence on HR at low pressure levels. We included the inhibitory effect of the afferent baroactivity on the sympathetic efferent activity and took into account the time of the afferent and efferent activity within the beat (7, 56). The sympathetic efferent activity is defined at the end of the diastolic phase of each beat (Eq. 4).

Table 1. Parameter values of the circulation model

<table>
<thead>
<tr>
<th>Capacity</th>
<th>Initial Volume</th>
<th>Initial Pressure, mmHg</th>
<th>Distance to Heart Level, cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>2.1 ml·mmHg(^{-1})·kg(^{-1}) (35, 36)</td>
<td>77 ml/kg (35, 36)</td>
<td>120</td>
</tr>
<tr>
<td>Systemic</td>
<td>70%</td>
<td>78%</td>
<td>3% (35, 36)</td>
</tr>
<tr>
<td>Aorta</td>
<td>Result fit(^a)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arteries</td>
<td>2% (35, 36)</td>
<td>7.50% (35, 36)</td>
<td>8</td>
</tr>
<tr>
<td>Upper body</td>
<td>3% (35, 36)</td>
<td>9% (35, 36)</td>
<td>8</td>
</tr>
<tr>
<td>Lower body</td>
<td>6% (35, 36)</td>
<td>14% (35, 36)</td>
<td>8</td>
</tr>
<tr>
<td>Liver</td>
<td>28% (35, 36)</td>
<td>12% (35, 36)</td>
<td>8</td>
</tr>
<tr>
<td>Renal</td>
<td>10% (35, 36)</td>
<td>6% (35, 36)</td>
<td>8</td>
</tr>
<tr>
<td>Intestines</td>
<td>9.50% (35, 36)</td>
<td>10.50% (35, 36)</td>
<td>5</td>
</tr>
<tr>
<td>SVC</td>
<td>4% (35, 36)</td>
<td>4.50% (35, 36)</td>
<td>5</td>
</tr>
<tr>
<td>Total large veins</td>
<td>16%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVC</td>
<td>6% (35, 36)</td>
<td>11.50% (35, 36)</td>
<td>5</td>
</tr>
<tr>
<td>Total pulmonary</td>
<td>30%</td>
<td>17% (35, 36)</td>
<td>25</td>
</tr>
<tr>
<td>Pulmonary arteries</td>
<td>6% (35, 36)</td>
<td>4.25% (35, 36)</td>
<td>15</td>
</tr>
<tr>
<td>Pulmonary veins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Above heart level</td>
<td>18% (35, 36, 58)</td>
<td>9.40% (35, 36)</td>
<td>9</td>
</tr>
<tr>
<td>Below heart level</td>
<td>6% (35, 36, 58)</td>
<td>3.30% (35, 36)</td>
<td>9</td>
</tr>
<tr>
<td>Right atrium</td>
<td>20 ml·mmHg(^{-1})·kg(^{-1}) (2)</td>
<td>Only stressed volume</td>
<td>3.5</td>
</tr>
<tr>
<td>Left atrium</td>
<td>8.33 ml·mmHg(^{-1})·kg(^{-1}) (2)</td>
<td>Only stressed volume</td>
<td>7</td>
</tr>
<tr>
<td>HR</td>
<td>70 beats/min(^d)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CO</td>
<td>75 ml·min(^{-1})·kg(^{-1}) (35, 36)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Capacity values are given for each compartment (corresponding to compartments in Figs. 2 and 3). Total amount of blood volume, initial volume distribution, and initial pressure levels used to calculate stressed volumes are also given, as well as distances used to determine the hydrostatic column to each compartment. In all simulations, weight = 70 kg. Reference numbers are shown in parentheses. SVC and AVC, superior and abdominal vena cava. \(^a\)Optimization. \(^b\)Estimate. \(^c\)Independent of weight. \(^d\)Individual values to be derived from data.

Fig. 3. Schematic representation of compartments of the pulmonary circulation model. Distances used to determine the hydrostatic column for each compartment are indicated at left (scaled). Arrows, blood flow between compartments.
Sympathetic activity thus occurs in the diastolic silence of the afferents (6) and increases when the afferent baroactivity decreases or when the silence is prolonged.

\[ B_{\text{afferent}} = \alpha_\text{symp}(P_{\text{sys}} - \text{Thres}_{\text{sys}}) + \alpha_\text{ref}(\text{intP} \cdot \text{Thres}_{\text{int}}) \]  
\[ B_{\text{afferent}} = B_{\text{afferent}} - \text{Thres}_{\text{vagal}} \cdot t_{\text{close}} < t < (t_{\text{close}} + 0.1B_{\text{afferent}}), \]  
\[ B_{\text{symp}} = B_{\text{afferent}} - \beta t_{\text{dist}} \]  

**Effectors.** The sympathetic reflexes on resistance, unstressed volume, and ventricular contractility are completed by a delay, a first-order transfer function representing the dynamics, and a gain. A constant is added to each output of the reflexes to obtain the steady-state output for each value of the gain (for different gain values, the constant is recalculated to ensure that the supine steady state of the model does not change). The effect of autoregulation of the cerebral circulation (27) is assumed to compensate the autonomic regulation of the other vessel beds in the upper body; in our model, the baroreflex does not influence the resistance of the upper body. Two different reflex gains for the reflex on venous volume are defined: one for vessels in the liver and intestines and another for the other compartments (53).

**HR reflex.** The HR is vagally and sympathetically mediated. Heartbeats are generated by an IPFM model (49), where the integrated signal is \( m \) according to Eq. 5

\[ m(t) = 1 + H R_{\text{symp}}(t) - H R_{\text{vagal}}(t) \]  

The sympathetic reflex loop on the HR is completed by a delay, a first-order transfer function, a gain, and a constant, similar to the other sympathetic reflex loops. The fast vagal influence is taken into account by use of impulses for the vagal efferent signal in combination with a third-order transfer function.

**CP reflex.** In the model, the CP reflex affects the peripheral resistance (55). Input to the CP reflex is the deviation of the right atrial pressure from its supine steady-state value (supine RCP = 0). The dynamics of the CP reflex are the same as those of the baroreflex on peripheral resistance; the effects of both are summed.

**Parameter Values of the Reflex Model**

We assume that delays in the reflex system, inasmuch as they are the result of nervous transport times and the dynamics of the effector response, differ relatively little between individuals but that the sensitivities and resulting gains differ much more. We therefore use constant delays and dynamic characteristics of the baroreflex and the CP reflex but variable gains.

**Model constants: dynamics and delays.** The distance from heart level to the receptors is initially 12 cm, representing an intermediate influence between carotid and aortic arch receptors (cf. Fig. 4). Sympathetic activity is generated at end diastole. This already takes into account the delay between afferents and efferents. The delay of the resistance reflex is 1.5 s; 0.7 s for delay between sympathetic activity and the response of the effectors (15) and 0.8 s for transport over the sympathetic nerves [with the assumption that average conduction velocity is \( \sim 1 \text{ m/s} \) and average distance to the effectors is 0.8 m (12)]. The dynamics of the reflex are based on those presented by Sato et al. (38). The CP reflex on resistance has the same dynamics.
but the delay is 2 s; 0.5 s is added to the delay of the baroreflex to compensate for delay between afferent and efferent activity in the CR reflex loop.

The dynamics of the contractility reflex are represented by a first-order transfer function with a time constant of 8 s; the delay is 1.5 s (52). The (much slower) reflex on unstressed volume is within the range of delays previously reported (52, 57).

Because the input, the vagal efferent activity, is pulsatile, the dynamics are represented by a third-order transfer function with two poles in $-2.5$ and one in $-20$ and a constant gain of 1,200 (the adjustable parameter $G_{HR vagal}$ is multiplied by this constant gain).

The thresholds in Eq. 2 determine the gain of the reflex model ($\text{Thres}_\text{syst} = P_{\text{syst supine}} - 70$ and $\text{Thres}_\text{int} = P_{\text{syst supine}} - 15$). The threshold in Eq. 3 is 0.4. The threshold of the IPPM model is 0.6, which results in an intrinsic HR of 100 beats/min.

The values for the constants added to each sympathetic reflex loop ($X_x$) are dependent on the gain and calculated using Eqs. 6 or 7. In this way, the resulting supine reflex values are equal to the steady-state values of the circulation model.

\begin{equation}
X_x = X_{\text{supine}} - G_B \text{symp supine}
\end{equation}

\begin{equation}
\text{HR}_R = \text{HR}_{\text{supine}}(0.6/60) - 1 + \text{HR}_{\text{symp supine}} + \text{HR}_{\text{vagal supine}}
\end{equation}

Variables. The variables that can be used to fit individual responses are the gains of the six reflex loops as well as the ratio of $\alpha_\text{sys}$ to $\alpha_\text{int}$ and $\beta$ (Eqs. 2 and 4). Initially, we chose $\alpha_\text{sys}/\alpha_\text{int} = 1.3$ and $\beta = 0.2$.

The overall gain of the different reflex loops is the combination of the efferent gain.

The resistance reflex is nonuniform. The overall gain is approximately 0.01 mmHg/s·ml⁻¹·mmHg (57), with $G_\text{R} = 1.0$. Because there is no reflex on the upper body resistance, the gain of the other compartments must be adjusted with a factor $k_{\text{nonuniform}} = 1.3929$. The reflex gain for compartment $x$ becomes $G_{\text{R}_x} = G_{\text{R supine}}G_{\text{R supine}}k_{\text{nonuniform}}$

The reflex on unstressed volume is nonuniform: the reflex is stronger in the liver and the intestines (52). $G_V$ is defined using the total amount of volume change, $G_V = 12$ ml/kg; 54% of which is assumed to originate from the splanchnic bed and the remaining 46% from the other areas. The amount of blood originating from each compartment is assumed to be related to the total amount of unstressed volume in that compartment: $G_{\text{Spl}} = 0.54G_V(V_{\text{Un Spl}}/V_{\text{n Spl}})$ and $G_{\text{R nonSpl}} = 0.46G_V(V_{\text{Un Spl}}/V_{\text{n Spl}})$. This reflex has an effect on all capacities in the venous part of the systemic circulation model, except the right atrium.

The reflex on contractility is defined as a percent change compared with the supine values: $G_{\text{ELV}} = G_{\text{R supine}}E_{\text{max supine}}, G_{\text{ERV}} = G_{\text{R supine}}E_{\text{max supine}}$. The overall gain of the afferent path and $G_{\text{ER}}$ is 50% of the supine $E_{\text{max supine}}$ over 100-mmHg pressure change, with $G_{\text{ER}} = 0.35$ [slightly stronger than the ~30% change used in previous models (52, 57)].

The gain of the CP reflex on peripheral resistance ($G_{\text{CP}}$) is 0.06 PRU/mmHg (33). This reflex does not affect the resistance of the upper body: $G_{\text{CP}_x} = G_{\text{R supine}}G_{\text{CP supine}}k_{\text{nonuniform}}$.

The reflex on HR is linear in HR because of the use of an IPPM model. A gain of 9 ms/mmHg for the sympathetic and vagal reflex (9), linear in IBI, is used in various published models. The HR of our circulation model is 70 beats/min in the supine position; at this HR, a gain of 9 ms/mmHg agrees with ~0.7 beats-min⁻¹·mmHg, which has been used for most of the simulations in this study.

RESULTS

Human Data

The results of BP, IBI, thoracic impedance, and leg impedance measurements in 20 subjects during HUT and tilt back are shown in Fig. 5. During the first 30 s after HUT, neither systolic nor diastolic BP shows a transient decrease. The group average response and individual recordings are used to develop and tune the model. There is a wide interindividual range in calf impedance, whereas impedance variation due to postural changes is of a smaller magnitude. Scaling of impedance signals is discussed below.

Simulation Results

The supine steady state of the controlled model is realistic; results are listed in Table 2. The complete model, including stress-relaxation, which takes into account the effect of gravity on the pulmonary circulation and allows fast volume shifts via the atria, does not show a dip in arterial pressure on HUT (Fig. 6). The diastolic pressure increases slowly; the systolic pressure initially increases before it returns to a value slightly below that in the supine position. HR increases from 70 to 86 beats/min in ~15 s. The pressure response on tilt back shows an initial decrease followed by an overshoot before return to values in the supine position. HR remains constant in the first seconds after tilt back. After ~4 s, HR decreases, showing a small overshoot after ~12 s before reaching the value in the supine position. Values of other parameters in the system are given in Table 2.

The BP response of the complete model reproduces the most important characteristics of passive HUT responses. The pattern of the HR response also resembles experimental results.

Hypothesis Testing

In this study, we developed a model of the circulation and its control system that should be able to reproduce realistic responses to passive HUT. We hypothesized that an initial dip in BP in previous models was the result of a dip in venous return as a result of rapid filling of the veins. To prevent this initial dip in the BP response of the model, we included stress-relaxation as well as several other aspects affecting venous return on HUT. Tilt responses of different model configurations showing the effect on CO and BP are shown in Fig. 7.

Effect of stress-relaxation. When stress-relaxation is removed from the model (Fig. 7, row 3), diastolic pressure is maintained, but systolic pressure shows a dip after ~20 s and P pulse decreases ~50%. CO shows a fast decrease (corresponding to the pressure dip) followed by a slow increase. With stress-relaxation, the decrease in CO is smaller and is followed by a further decrease. Systolic pressure, as well as CO, shows an initial increase as a result of the emptying of the lungs. When the direct effect of gravity on the lungs is removed, the initial increase in systolic pressure disappears and the overshoot in CO decreases (Fig. 7, row 4).

The strong influence of stress-relaxation on CO and, consequently, arterial pressure can be appreciated when we look at the filling pattern of the systemic veins below heart level. Volume increases are a result of gravity, introduced in the model using pressure sources. On HUT, the venous pressure below heart level must increase to form the venous hydrostatic column. The amount of blood needed to form this column is dependent on the capacity assigned to the venous compartment. In the case of the model without stress-relaxation, this capacity is constant, and pooling progresses rapidly (Fig. 8).
until the hydrostatic column is formed. In the model including stress-relaxation, the capacity is initially smaller and increases slowly as a result of relaxation. The initial volume increase necessary to form the hydrostatic column is smaller (Fig. 8), but a slow increase in volume is necessary to maintain this pressure.

Figure 8 (also see Fig. 5, bottom) shows measured impedance signals. The impedance signals are then scaled to match the volume change of the simulation, according to \( \text{Imp}_{\text{scaled}} = K/\text{Imp} - c \). (The scaled impedance signal cannot be seen as a quantitative representation of the volume change in the subject’s leg or thorax, but the shape of the transients does reflect the time course of the variations.) The resulting time course of filling in the model with relaxation matches the average of 17 measurements almost perfectly for the first 3 min of HUT. The four individual responses given in Fig. 8 are typical examples showing the individual differences. For comparison of the time course of changes after HUT, similar values are given for the pulmonary volume (simulated volumes are averaged per beat). Thoracic impedance measurements show a much faster volume increase after HUT.
H2160

MODELING GRAVITATIONAL EFFECTS ON THE CIRCULATION

Table 2. Summary of simulation results, supine and after 70° HUT

<table>
<thead>
<tr>
<th>Hemodynamic Parameters</th>
<th>Simulation Results</th>
<th>Reference Values</th>
<th>Conversion of Reference Values</th>
</tr>
</thead>
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<tr>
<td></td>
<td>Supine steady state</td>
<td>30 s</td>
<td>60 s</td>
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<tr>
<td></td>
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<td></td>
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</tr>
<tr>
<td>IBI, s</td>
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<td>0.704</td>
<td>0.696</td>
</tr>
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<td></td>
<td></td>
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</tr>
<tr>
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</tr>
<tr>
<td>Pdias, mmHg</td>
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<td>88</td>
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<tr>
<td>CO, l/min</td>
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<td>4.14</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<td>Blood volume, %</td>
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<td></td>
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<td></td>
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</tr>
<tr>
<td>Pressure, mmHg</td>
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<td>1.6–2.9</td>
<td>1.6–2.8</td>
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<td>Right atrium</td>
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<td>−3.9</td>
<td>−4</td>
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<tr>
<td>Upper body</td>
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<td>21.6</td>
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<tr>
<td>Renal</td>
<td>9.5–9.7</td>
<td>20.3</td>
<td>20.1</td>
</tr>
<tr>
<td>Intestine</td>
<td>7.5–7.8</td>
<td>52.5</td>
<td>52.4</td>
</tr>
<tr>
<td>Lower body</td>
<td>7.6–7.7</td>
<td>9.3</td>
<td>9.1</td>
</tr>
<tr>
<td>Liver</td>
<td>4.2–5.3</td>
<td>6.8</td>
<td>6.8</td>
</tr>
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<td>−7.3</td>
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<td>3.0–5.8</td>
<td>2.9–5.6</td>
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<td>Pulmonary veins</td>
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<td>18.9–10.4</td>
<td>18.5–10.2</td>
</tr>
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<td>Above heart</td>
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<td>−0.3</td>
<td>−0.6</td>
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<tr>
<td>Below heart</td>
<td>7.8–8.6</td>
<td>8.3</td>
<td>6.8</td>
</tr>
<tr>
<td>Blood volume, %</td>
<td></td>
<td></td>
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<tr>
<td>Pulmonary veins</td>
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</tr>
<tr>
<td>Above heart</td>
<td>74</td>
<td>64</td>
<td>64</td>
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<tr>
<td>Below heart</td>
<td>26</td>
<td>36</td>
<td>36</td>
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<tr>
<td>Volume, ml</td>
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<tr>
<td>Pulmonary</td>
<td>2,897</td>
<td>3,250</td>
<td>3,287</td>
</tr>
<tr>
<td>Total below heart</td>
<td>752</td>
<td>959</td>
<td>1,000</td>
</tr>
<tr>
<td>Lower body</td>
<td>638</td>
<td>654</td>
<td>644</td>
</tr>
<tr>
<td>Liver</td>
<td>563</td>
<td>623</td>
<td>621</td>
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<tr>
<td>Intestine</td>
<td>530</td>
<td>388</td>
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<tr>
<td>Renal</td>
<td>624</td>
<td>626</td>
<td>620</td>
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<tr>
<td>SVC + upper body</td>
<td>729</td>
<td>651</td>
<td>624</td>
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</tbody>
</table>

Supine steady-state results of the controlled model were used as the starting point (see Table 1 for references). Parameter values after head-up tilt (HUT) are given for 30, 60, and 120 s as well as available head up tilt results from literature. Reference values are approximately steady-state HUT values; however, exact time after HUT is not reported in most studies. Therefore, values are best compared with changes in the model after 120 s. Converted reference values are given for direct comparison with our simulation results. SV, stroke volume.

change than lower body impedance; our model shows similar rapid changes.

In the model without stress-relaxation, arterial pressure could possibly be maintained when the increase in resistance is more pronounced. To test this, we adjusted the reflex model parameter values (Fig. 7, row 7). In the resulting HUT response, the arterial pressure, both systolic and diastolic, is maintained, without changes in the time course of the CO. The tilt-back response, however, shows that the reflex gains must be increased to unrealistic values, because of large oscillations not seen in measured responses.

**Tilt-back responses.** On tilt back, the pooled blood is returned to the heart more gradually in the model, including stress-relaxation, than when constant capacities are assumed. The resulting overshoot is larger in the model without stress-relaxation than in the model with stress-relaxation (Fig. 7). The volume responses in Fig. 8 show the slowed emptying of the veins; again, the measured impedance signals show the same time course as the model, including stress-relaxation.

The tilt-back response also shows a direct influence of gravity on the pulmonary circulation. The complete model shows an initial pressure dip followed by an overshoot. When the direct influence of gravity in the lungs is removed, this initial dip does not occur. The overshoot occurs earlier in the response and earlier than in the average of the measured responses.

**DISCUSSION**

We developed a model of the cardiovascular system to simulate tilt experiments. We hypothesized that, to simulate a realistic tilt response, factors affecting preload are essential; to reproduce the time course of filling of the veins, venous viscoelastic properties must be taken into account. Our model, based on experimental results, can reproduce the most important characteristics of the tilt response. It includes stress-relaxation, as well as a division between compartments above and below heart level, the influence of gravity on the pulmonary circulation, a nonlinear diastolic ventricular elastance, and a detailed venous model.

**Factors Affecting Preload During HUT**

This modeling study shows that the maintenance of CO is essential to prevent a BP dip on passive HUT. In ideal passive...
HUT without muscle activation, factors affecting preload, rather than those affecting afterload, determine CO during the first 30 s. Stress-relaxation slows initial pooling of blood in the lower body. The volume needed to form the hydrostatic column is initially reduced compared with the model without stress-relaxation.

Venous pressure-volume dynamics. The venous pressure-volume relation is affected by three major mechanisms: the baroreflex (16), viscoelastic vessel properties referred to as stress relaxation (also named “creep” or “delayed compliance”) (11, 25, 42), and transcapillary fluid transfer (37). The combined effect of these mechanisms defines the pressure-volume relation in time, making it difficult to experimentally distinguish the individual contribution of each. Filtration increases tissue fluid pressure, reducing venous transmural pressure and effectively decreasing the amount of blood distending the veins (37). Although the baroreflex may limit volume increase, stress-relaxation and transcapillary fluid transfer progressively increase the lower body volume and, subsequently, reduce circulating blood volume. Stress-relaxation in our model is based on the findings of Shoukas and Sagawa (41), who stated that, with the method used, “the assumption of no fluid shift across the capillary is certainly unjustifiable” (40). The pressure change in the central veins in this experiment was only \( \Delta P \approx 2 \) mmHg, but the quantitative importance of filtration could not be determined. Possibly, the neglect of fluid filtration in our model or, rather, the inclusion of fast effects of fluid filtration in the definition of stress-relaxation affects the model response to tilt back. If we assume that fluid filtration outward is fast and affects the response in the first 30 s, we should assume that filtration inward also affects the response in the first 30 s. The resulting dynamics during tilt back are similar to the effect of stress-relaxation as implemented in the model, although we consider a fast inward filtration physiologically much more improbable than the proven effects of stress-relaxation.

Overall, the time course of the simulated volume response is comparable to measured impedance signals. The model is therefore applicable for simulation of fast hemodynamic changes, as seen in HUT and tilt back. Further support for the adequacy of the venous model dynamics can be found in comparing the response to tilt of the uncontrolled model with tilt responses in patients with autonomic failure (59) (removal of all reflexes in the model approximates the lack of reflex adjustments in these patients). On the basis of these observations, the gradual pooling as a result of stress-relaxation seems to be realistic. In autonomic failure patients, BP decreases gradually, not within \( \Delta \approx 20 \) s, as in our model without stress-relaxation.

Other aspects affecting venous return on HUT. The level of detail in this model allows us to analyze the effect of other physiological aspects that could influence the venous return and, consequently, CO on HUT. The direct influence of gravity on the pulmonary circulation, introduced as the formation of a hydrostatic column in the pulmonary veins, influences LV filling pressure. This introduces an initial overshoot in systolic pressure in the modeled HUT and, also, an increase in the CO overshoot. However, this influences the pressure response mainly in the first 5 s after HUT and cannot prevent the subsequent pressure dip. The nonlinearity of the pulmonary resistances does not affect the tilt responses appreciably; it does introduce flow redistribution in the lungs as a result of posture changes.

The effect of a nonlinear diastolic ventricular elastance is strongly related to the effect of gravity on the ventricular filling
The steady-state situation of the model is mainly determined by the systemic circulation. The nonlinearities do have a pronounced effect on the first seconds of the transient response, when, because of the direct influence of hydrostatic pressure, the ventricular filling pressure shows large variations. A stronger ventricular nonlinearity reduces the overshoot in the HUT response. The initial overshoot in arterial pressure is always present in our model simulations, but in measured tilt responses, this is not always the case. Both effects influencing the overshoot in our model (nonlinear ventricular diastolic elastance and effect of gravity in the lungs) are difficult to quantify. Large variations between individual ventricular diastolic elastances are also affected by the circumstances (13). Measurements of pressures in the pulmonary circulation during tilt are scarce. Refinement of the model requires more extensive measurements.

The division of the systemic circulation model into a part above and a part below heart level, both influenced by gravity, and the detailed venous model are also expected to influence the CO immediately after HUT. The model does show an initial increase in venous return from the upper body, but only for \( t \approx 5 \) s. The amount of blood that is returned to the ventricle is not enough to prevent the decline in arterial pressure (without stress-relaxation). Because of the detailed venous model, backflow to the abdomen is also possible and occurs immediately after HUT.

In summary, this model indicates that the rate of filling of the systemic veins below heart level is responsible for venous return and the resulting arterial pressure response. To slow this filling of the veins and maintain venous return in this model, stress-relaxation is essential. The rate and amount of venous pooling, as well as the resulting venous flows, are difficult to

<table>
<thead>
<tr>
<th>Tilt Up</th>
<th>Tilt Down</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP</td>
<td>CO</td>
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</tbody>
</table>

Fig. 7. Systolic and diastolic blood pressure (BP) and cardiac output (CO) responses to 70° HUT and tilt back. Use of different model configurations from 15 s before to 60 s after tilt allows comparison with tilt response in 20 healthy subjects (top). Scale of BP y-axes is 0–150 mmHg; y-axes of all CO responses are scaled to 0–7 l/min. g, Gravity.
validate. In this model, venous flows are derived from compliance values reported in the literature, hydrostatic pressures, stress relaxation, and reflex on venous return, all of which introduce uncertainties. We may conclude that the venous part of the systemic circulation is essential for an understanding of the pressure response to passive HUT, but this part of the system is difficult to quantify.

**Reflex Model**

The most important differences between our model and existing models can be found in the baroreceptor model and in the definition of vagal and sympathetic efferent nervous activity. To introduce the fast vagal effects seen in tilt back, vagal efference is pulsatile, allowing a possible large effect within the same beat. Our baroreflex model is not only sensitive to the pressure level but also to \( P_{\text{pulse}} \). Sympathetic activity occurs in the diastolic silence of the baroreceptors \((7, 56)\). In the definition of the sympathetic activity, a new factor is introduced, \( \beta \). This factor has a strong influence on the damping of the system and seems to influence the exact frequency of the 10-s rhythm, making the oscillation frequency dependent on the sensitivity of the sympathetic reflex loop.

**Model Limitations**

Several possibly important mechanisms affecting venous return have not been included in our model. We have not taken into account possible nonlinear resistance effects around the diaphragm. In the steady-state tilt position, nonlinear effects have been observed in monkeys \((50)\). Such effects in a dynamic situation (e.g., HUT, where large changes in flow are likely around the right atrium) are not unlikely, but we are not familiar with any studies on this subject. The effect of the respiratory pump \((37)\) has also been neglected. Extravascular pressure changes within the thorax may well affect venous return during posture change; these are not included in the model. The possible effects of muscle tension \((37)\) are not modeled; this is justifiable only when considering measurements during passive tilt maneuvers. The possible importance of nonuniform reflex resistances is not included; the effect of these is difficult to predict but is not likely to be substantial.

![Figure 8](http://ajpheart.physiology.org/)

**Fig. 8.** Volume changes after 70° HUT and tilt back. Time course of the model response is compared with measured impedance signals (scaled). **A**: HUT. Volume in the lower body compartment is compared with (scaled) measured leg impedances. **B**: tilt back. Volume in the lower body compartment is compared with individual leg impedance signals (average response to tilt back is not shown, because this was scaled on the HUT response). **C**: HUT. Summed volume in the 4 pulmonary compartments is compared with (scaled) measured thorax impedances. The 4 individual responses are from subjects used for measurements in **A** and **B**. **D**: tilt back. Signals are the same as in **C**.
However, the neglect of nonuniform resistance reflexes and autoregulation (27, 36) might have considerable significance. The resistance in the upper body compartment in our model is constant to account for cerebral autoregulation, increasing the relative blood flow when the resistance in the lower body increases. This has only a minor effect on the venous return immediately after HUT. However, the effect of nonuniform reflexes below heart level might be much larger. Nonuniform changes in peripheral resistance influence the flow distribution. Changes in flow influence the venous pressure levels, which will have a large influence on the volume in the compartments with a large compliance [passive volume redistribution (36)]. The effect of nonuniform resistances on this passive volume redistribution is difficult to quantify, as is the nonuniformity of the reflexes.

In conclusion, the results of this modeling study indicate that an understanding of the venous part of the systemic circulation is essential in understanding the BP response to passive HUT. The arterial BP response in the first ~30 s after HUT is mainly determined by the time course of the pooling in the lower body and the emptying of the lungs, not by the reflexes. Viscoelastic stress-relaxation is included in this model to slow pooling in the lower body, maintain venous return and, consequently, CO, and reproduce realistic responses to HUT.

**GRANTS**

This study was partly supported by Space Research Organization Netherlands Projects MG-052 and MG-020.

**REFERENCES**


