Resonance in a mathematical model of baroreflex control: arterial blood pressure waves accompanying postural stress

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Hammer, Peter E., and J. Philip Saul. Resonance in a mathematical model of baroreflex control: arterial blood pressure waves accompanying postural stress. \textit{Am J Physiol Regul Integr Comp Physiol} 288: R1637–R1648, 2005. First published February 17, 2005; \textit{doi}:10.1152/ajpregu.00050.2004.—A mathematical model of the arterial baroreflex was developed and used to assess the stability of the reflex and its potential role in producing the low-frequency arterial blood pressure oscillations called Mayer waves that are commonly seen in humans and animals in response to decreased central blood volume. The model consists of an arrangement of discrete-time filters derived from published physiological studies, which is reduced to a numerical expression for the baroreflex open-loop frequency response. Model stability was assessed for two states: normal and decreased central blood volume. The state of decreased central blood volume was simulated by decreasing baroreflex parasympathetic heart rate gain and by increasing baroreflex sympathetic vaso/venomotor gains as occurs with the unloading of cardiopulmonary baroreceptors. For the normal state, the feedback system was stable by the Nyquist criterion (gain margin = 0.6), but in the hypovolemic state, the gain margin was small (0.07), and the closed-loop frequency response exhibited a sharp peak (gain of 11) at 0.07 Hz, the same frequency as that observed for arterial pressure fluctuations in a group of healthy standing subjects. These findings support the theory that stresses affecting central blood volume, including upright posture, can reduce the stability of the normally stable arterial baroreflex feedback, leading to resonance and low-frequency blood pressure waves.

arterial baroreflex model; Mayer waves; arterial baroreflex stability; control systems

OSCILLATIONS IN ARTERIAL BLOOD pressure (ABP) at frequencies slightly lower than respiratory frequencies are commonly observed in humans and animals in response to low central blood volume (27, 56). Common stresses causing decreased central blood volume include hemorrhage and orthostasis due to sitting or standing. The ABP waves, referred to as Mayer waves, are accompanied by oscillations of sympathetic nerve activity. In humans, the frequency of the waves is near 0.1 Hz, although it is thought to vary considerably about this frequency (57) and may range from 0.05 Hz to 0.15 Hz (35, 57).

More than 50 years ago, Guyton and Harris (19) elicited nearly constant frequency ABP oscillations at 0.05 to 0.09 Hz (11 to 40-s period) with a variety of physiological stresses in dogs. The oscillations were disrupted by total baroreceptor denervation, suggesting that the arterial baroreflex played a critical role in producing them. A number of groups have used mathematical control system analysis to assess the role of the arterial baroreflex in producing sustained oscillations of ABP (14, 24, 29, 44, 48) and have reached different conclusions. Some have agreed with Guyton, attributing the oscillations to baroreflex instabilities (1, 14, 24, 33), while others have attributed ABP oscillations to mechanisms other than the arterial baroreflex, such as a central oscillator (9, 11, 41), peripheral chemoreflexes (15), or the cerebral ischemic response (27).

The arterial baroreflex can be considered a feedback control system because it maintains mean arterial blood pressure near a target value through the use of sensors and effectors. The sensors are the arterial baroreceptors located in the carotid sinuses and aortic arch, and the effectors include the physiological mechanisms capable of changing vascular resistance, venous capacity, heart rate and cardiac contractility. It is well known that control systems exhibiting powerful responses and containing time delays can become unstable, that is, can cause the controlled variable to exhibit oscillations that grow in an unbounded fashion. It is possible for such an unstable control system to produce sustained, constant amplitude oscillations if the feedback control system contains nonlinear elements that limit the swings in the controlled variable. Alternatively, a stable linear feedback system can produce sustained, constant-amplitude oscillations of the controlled variable if the system exhibits frequency-selective behavior with certain characteristics and if there is a source of broadband random fluctuations of the controlled variable in the system. This phenomenon is called resonance. To determine whether either of these feedback control phenomena characterizes the arterial baroreflex and is responsible for the low-frequency ABP oscillations, the frequency-selective behavior, or open-loop frequency response, of the arterial baroreflex system must be quantified. Many studies have tried to assess the stability of the baroreflex by delivering perturbations at a range of frequencies to the intact system, while measuring ABP response (5, 24). However, the presence of multiple, interacting branches of the reflex responding with different speeds makes the results difficult to interpret.

Some groups have tried to characterize the arterial baroreflex open-loop frequency response by attempting to open the reflex loop without disturbing the behavior of system components and then performing measurements on the entire feedback control loop. It is possible to isolate the carotid sinus from ABP in animal models, exposing carotid baroreceptors to an input pressure that can be independently controlled and not subject to corrective action (8, 29, 48). However, this experimental design probably changes the system from its physiological state so drastically that it is difficult to assess the accuracy of the
resulting analysis. Alternatively, the arterial baroreflex open-loop frequency response has been modeled by measuring the responses of individual components of the reflex, then combining the component responses appropriately. Although baroreflex-based oscillations are widely believed to be the cause of the ABP waves, published studies have failed to present definitive evidence (44), and attempts at quantifying arterial baroreflex stability have led to widely varying conclusions. In fact, several studies have used linear control systems analysis of the arterial baroreflex to show that the system properties indicate stability (17, 29, 48).

The goal of this study was to evaluate arterial baroreflex stability and its role in producing sustained ABP oscillations using a feedback control model of the arterial baroreflex. The model was based on experimentally derived data and analyzed for stability by applying feedback control system stability criteria. Specifically, the impulse responses of all model components were combined and transformed to the frequency domain, resulting in a single expression for model open-loop frequency response, to which the Nyquist stability criterion was applied. From this expression, the closed-loop frequency response was computed and used to assess the ability of the system to support feedback-based oscillations due to resonance.

**ARTERIAL BAROREFLEX MODEL**

**Glossary**

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>ABP</td>
<td>Arterial blood pressure</td>
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<tr>
<td>ZPV</td>
<td>Zero-pressure volume (unstressed volume)</td>
</tr>
<tr>
<td>H_b(z)</td>
<td>Discrete-time filter: sensitivity of arterial baroreceptors to rate of change of ABP</td>
</tr>
<tr>
<td>z^{-k1}</td>
<td>Nerve transmission time: arterial baroreceptors to peripheral vasculature (via sympathetic nerves)</td>
</tr>
<tr>
<td>z^{-k2}</td>
<td>Nerve transmission time: arterial baroreceptors to sinoatrial node (via sympathetic nerves)</td>
</tr>
<tr>
<td>z^{-k3}</td>
<td>Nerve transmission time: arterial baroreceptors to sinoatrial node (via vagus nerve)</td>
</tr>
<tr>
<td>H_s(z)</td>
<td>Discrete-time filter: sympathetic receptor response</td>
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A discrete-time filter model (Fig. 1), which allows for application of the Nyquist stability criterion, was developed on the basis of published physiological characteristics of the baroreflexes. Variable abbreviations are defined in the caption of Fig. 1. The model consists of discrete-time filters, time delays, and gain constants that describe each physiological component.

The model has one input, ABP_{OL} (open-loop arterial blood pressure), representing the level that arterial blood pressure would assume in the absence of baroreflex feedback, one output, ABP, which is compared with a set point (ABP_{SET}), and a feedback controller which produces corrective action based on ABP – ABP_{SET}. The feedback controller contains five effector pathways, which act on ABP. The effectors are 1) peripheral vascular resistance, 2) the zero-pressure volume (ZPV), or unstressed volume, of the systemic veins, 3) the contractility of the left ventricle, 4) the contractility of the right ventricle, and 5) the heartbeat period. Specifically, the difference between ABP and ABP_{SET} is input to the filter H_b(z), which represents the sensitivity of the baroreceptors to the rate of change of ABP. Because this model is not used to simulate temporal ABP patterns but rather to quantify stability at fixed operating points, the well-described nonlinear saturation of arterial baroreceptor firing rate with large ABP deviations is not included. From the baroreceptor rate response filter, the signals pass through time delays z^{-k}, representing neural transmission times from the arterial baroreceptors to the receptors at the respective end-organs, and are then inputs to the autonomic receptor filters H_s(z) and H_p(z). These receptor filters describe the transfer functions relating efferent sympathetic and parasympathetic nervous activity to effector organ responses. Outputs from the receptor filters go to gain blocks...

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**Fig. 1.** This diagram shows the structure of the model developed to assess arterial baroreflex stability. The difference between ABP and the arterial baroreceptor setpoint, ABP_{SET}, passes through a filter representing the rate-sensitive response of the receptors, H_b(z). The z^{-k} terms represent neural transmission delays, and H_s(z) and H_p(z) are filters that describe end-organ responses to sympathetic and parasympathetic stimulation. G_{1} through G_{5}, are, in order, gains influencing peripheral resistance (G_{1}), venous zero-pressure volume (G_{2}), systolic compliance of the left ventricle (G_{3}), systolic compliance of the right ventricle (G_{4}), heartbeat period through the sympathetic branch (G_{5}), and heartbeat period through the parasympathetic branch (G_{SP}). The left-most column of blocks H(z) through H(z) are filters relating changes in peripheral resistance, venous zero-pressure volume, LV and RV systolic compliances, and heartbeat period to changes in ABP. ABP_{OL} is the open-loop ABP, that is, ABP in the absence of feedback control.
(G₁, G₂, G₃, G₄, G₅S, and G₅P) that represent the sensitivities of the effectors. The outputs of the gain blocks are then summed, if appropriate, and input to the transfer functions from the effector organs to ABP corrective action [H₁(z), H₂(z), H₃(z), H₄(z), and H₅(z)]. In terms of model variables, the effector organs respond to a decrease in ABP by 1) increasing the peripheral vascular resistance, 2) decreasing the zero-pressure volume of the systemic veins, 3) decreasing the compliance of the left ventricle during systole, 4) decreasing the compliance of the right ventricle during systole, and 5) decreasing the heartbeat period. The corrective actions are then summed and subtracted from ABPOL to yield the corrected value of ABP.

The sensitivities G, time delays z⁻ᵏ, baroreceptor rate response filter Hₛ(z), and receptor filters H₃(z) and H₄(z) used in this formulation are taken from previously reported studies. Sensitivities and time delays are given in Table 1, and the model filter blocks are described below.

**Baroreceptor rate response.** The arterial baroreceptors are known to respond to both ABP and the rate of change of ABP. The transfer function describing this rate response is the same used by Wesseling and Settels (60), which was based on prior animal studies. Specifically, the following continuous-time filter is used:

\[ H_{\text{RATE}}(s) = \frac{8s + 1}{4s + 1} \]  

(1)

where s is the Laplace variable describing complex frequency. The impulse response of this filter was sampled to yield the corresponding discrete-time filter, Hₛ(z), where z = e⁻jΩ and Ω is discrete-time frequency. The frequency response magnitude of this filter approaches 1.0 for frequencies less than 0.01 Hz and approaches 2.0 for frequencies greater than 0.10 Hz.

**Neural time delays.** The time that the nervous impulses take to travel from the arterial baroreceptors to the appropriate receptors at the heart and vasculature are based on the work of Borst and Karemaker (7). They reported the time from increased carotid sinus pressure to increased nerve activity as 20 ms, conduction to the brain as 5 ms, and a typical central delay of 300 ms. Conduction along the vagus to the sinoatrial node they reported as 55 ms (~0.4 m at 7 m/s). Sympathetic cardiac control is also subject to the first three delays above (325 ms), plus the time for conduction along the sympathetic fibers to the heart of ~400 ms (~0.4 m at 1 m/s). Sympathetic vasomotor control consists of the same 325 ms initial delay above plus the time for conduction along the sympathetic fibers to peripheral vascular beds of 600 to 800 ms (0.6 to 0.8 m at 1 m/s). It is important to note that these values do not include the time delays due to the sympathetic and parasympathetic receptors, which are included in the receptor filters.

**Responses of heart and vasculature to sympathetic and parasympathetic efferent activity.** Changes in vagus and sympathetic nerve firing rates are transduced into changes in heart rate, myocardial contractility, peripheral vascular resistance, and venous ZPV by neurochemical receptors. Two types of receptors are believed to play primary roles in mediating these changes: the muscarinic receptor, which mediates parasympathetic activity and the adrenergic receptor, which mediates sympathetic activity. Previous studies have reported quantitative descriptions of responses mediated by these receptors. Berger et al. (3) applied frequency-modulated pulse trains to the right vagus and the cardiac sympathetic nerve in dogs and computed transfer functions between nerve stimulation rate and the evoked atrial rate. They described the parasympathetic heart rate response using a low-pass filter with a corner frequency of ~0.3 Hz, in fairly close agreement with the earlier work of Warner and Cox (59).

Berger et al. (3) also described the sympathetic heart rate response as a low-pass filter, but with a corner frequency of 0.01 to 0.02 Hz. Again, this is in close agreement with Warner and Cox who fit their recorded responses using a model with a time constant near 10 s (corner frequency of ~0.016 Hz). Mokrane and Nadeau (38) reported that removal of norepinephrine at the neuroeffector junction dominates the response of the adrenergic receptor and estimated a time constant of ~9 s for this removal process.

The adrenergic receptor also mediates the vasconstrictor response to sympathetic activity. The properties of this response are thought to play a critical role in determining the stability of the baroreflex at low frequencies (14). Many animal studies have tried to quantify this response (4, 18, 25, 31, 43, 45), although the methods used in these studies vary considerably. Rosenbaum and Race (43) clearly showed that the time constant of the vascular response decreases as nerve stimulation rate increases; thus it is important that physiological rates of sympathetic nerve stimulation be used if the data are used to model physiological phenomena. Janig (26) gives a range of 0.5 to 3.0 spikes/s for postganglionic sympathetic neurons innervating muscle vasculature, and Malpas (35) gives a maximum firing rate of 2–2.5 spikes/s for individual neurons and 1–6 spikes/s for synchronized bursts of discharges from bundles of nerves.

To compare the published sympathetic vascular responses, we plotted normalized step responses in Fig. 2, plots A–E. The response that appears in plot A is markedly faster than the others, but this may be due to the high rate of sympathetic nerve stimulation (20 Hz) used in the study. Plots B–E exhibit time constants of ~7 to 14 s, with a mean of about 10, and plot F shows the sympathetically mediated heart rate response published by Berger et al. (3).

We chose to use the adrenergic receptor heart rate response reported by Berger et al. to represent the adrenergic receptor vasoconstrictor response for several reasons. First, it exhibited low-pass characteristics with a time constant very close to the

Table 1. Gains and delays used to characterize components of the discrete-time arterial baroreflex model shown in Figure 1

<table>
<thead>
<tr>
<th>Parameter Name</th>
<th>Symbol</th>
<th>Value</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td>Peripheral resistance gain</td>
<td>G₁</td>
<td>–11 mmHg/ml/s mmHg⁻¹</td>
<td>(13), (14)</td>
</tr>
<tr>
<td>Venous ZPV gain</td>
<td>G₂</td>
<td>0.03 l/mmHg</td>
<td>(13), (23)</td>
</tr>
<tr>
<td>LV compliance gain</td>
<td>G₃</td>
<td>7.0 × 10⁻⁶ l/mmHg²</td>
<td>(13)</td>
</tr>
<tr>
<td>RV compliance gain</td>
<td>G₄</td>
<td>2.1 × 10⁻⁶ l/mmHg²</td>
<td>(13)</td>
</tr>
<tr>
<td>Parasympathetic heartbeat</td>
<td>G₅</td>
<td>0.009 s/mmHg</td>
<td>(14)</td>
</tr>
<tr>
<td>period gain</td>
<td>G₅S</td>
<td>0.009 s/mmHg</td>
<td>(14)</td>
</tr>
<tr>
<td>Peripheral sympathetic delay</td>
<td>k₁</td>
<td>1.0 s</td>
<td>(7)</td>
</tr>
<tr>
<td>Cardiac sympathetic delay</td>
<td>k₂</td>
<td>0.7 s</td>
<td>(7)</td>
</tr>
<tr>
<td>Parasympathetic delay</td>
<td>k₃</td>
<td>0.4 s</td>
<td>(7)</td>
</tr>
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mean for the studies cited here. Second, by using the samples of an actual response, rather than the parameters of a best-fit model, subtleties of the actual response that might affect model stability are not lost through parameterization.

The transfer functions computed by Berger et al. describing the dynamic response of the adrenergic receptor to sympathetic, $H_s(z)$, and of the muscarinic receptor to parasympathetic activity, $H_p(z)$ were inverse Fourier-transformed to compute impulse responses (Fig. 3). These filters are normalized, that is, the areas under their respective impulse responses equal 1.

**Responses of ABP effectors.** Arterial blood pressure response to changes in each of the five effectors, $H_s(z)$ through $H_p(z)$, are difficult or impossible to measure experimentally. For example, trying to measure the isolated effect of a disturbance to venous ZPV on ABP in the absence of all central and local control mechanisms would involve devising a method of producing the disturbance, while completely suppressing all branches of the baroreflexes, the myogenic response of vessels throughout the circulation, the local flow control due to endothelium-derived relaxation factor, and any chemical or humoral-based control mechanisms affecting ABP during the transient portion of the ABP response.

The effector responses depend primarily on the time course of blood redistribution, which is a function of the compliance and resistance to flow in the various circulatory regions. The filters representing these responses were determined with the aid of a computer-based mathematical simulator of circulatory mechanics based on previous work (13, 61). They were determined by measuring ABP response to step changes in each effector variable (e.g., peripheral resistance) in the absence of all reflexes. Computing the derivative of each step response yielded the corresponding impulse response. These discrete-time impulse responses were used as the effector filters (Fig. 4).

The effector filters have the general characteristics of low-pass filters with time delays. The low-pass shape arises from the resistance and compliance characteristics of the various compartments of the cardiovascular simulator. The time delays reflect the time required for fluid transport. Because the different effectors influence hemodynamics from different points in the cardiovascular system, the influence of each on ABP will reflect the dynamics of a particular combination of time constants and fluid transport delays. For example, the effector filter describing the response of ABP to a change in venous ZPV (Fig. 4B) shows the slowest response of the effectors as illustrated by the delay and duration of the impulse response. (The delay is the time it takes the output to begin to respond after an impulse is applied to the input. The duration of the impulse response is the time it takes the output to return to zero relative to the time of the impulse.) The large time constant and time delay result from the very high compliance of the large veins and from the fact that the blood that is displaced from the systemic veins must travel to the right heart then through the pulmonary circulation to the left heart before reaching the arteries. Right ventricular (RV) systolic compliance (Fig. 4E) exhibits similar dynamics, while the effector filters depicting the peripheral resistance (Fig. 4A) and heartbeat period (Fig. 4C) responses exhibit less delay and smaller time constants, due to their relative proximity to the systemic arteries. The impulse response of the left ventricular (LV) systolic compliance effector has a negative portion after the peak (Fig. 4D), indicating transient overshoot of the ABP step response. This results from the fact that a sudden increase in LV contractility has an immediate and strong effect on ABP because little of the high-frequency energy in the input step is absorbed by the LV and the systemic arteries. The systemic arteries store this energy until the added volume is slowly bled through the large peripheral resistance and the system achieves a new equilibrium state at a value of ABP slightly below the transient peak. Because the step response falls following the overshoot, the impulse response (its derivative) has a negative region.

**Analysis.** Open- and closed-loop frequency responses are computed under conditions of normal and decreased central blood volume to provide a quantitative assessment of stability. The open-loop frequency response is the transfer function of a feedback control system in which the feedback path is broken just before the point at which it feeds back to the input. Stability can be evaluated by examining the open-loop frequency response magnitude at the frequency where the output is out of phase with the input (i.e., phase is $-180^\circ$). If the magnitude at that frequency is less than 1.0, the system is stable; however, if the magnitude is greater than 1.0, the system is unstable. For magnitudes close to but less than 1, the system, while technically stable, will support sustained oscillations in the presence of input noise at that frequency and is said to exhibit resonance at that frequency. The open-loop frequency response at 0 Hz describes the ratio of the corrective action to the error signal (error = ABP - ABP_set) in the steady state.

A Nyquist plot is a graphical means of displaying the relationship between magnitude and phase that highlights the
The degree of stability of a system. If the curve does not encircle the point on the complex plane corresponding to a magnitude of 1.0 and phase of \(-180^\circ\) (i.e., coordinates: \(-1, 0j\)), the system is stable. The distance between where the curve intersects the real axis and the point \((-1, 0j)\) reflects the margin between the state of the system and the point of instability and is called the gain margin.

The closed-loop frequency response was computed by rearranging the control diagram such that the input became \(ABP_{OL} - ABP_{SET}\) and all of the blocks in the feedback were combined into a single block, \(H_{OL}(z)\). Blocks in series were combined by convolving the samples of the impulse responses and blocks in parallel were combined by addition. The closed-loop system could then be described by the following equation:

\[
Y(z) = R(z) - H_{OL}(z)Y(z)
\]  

where \(Y(z)\) and \(R(z)\) are the z-transforms of the output and input, respectively. The closed-loop frequency response was derived by solving for the output/input ratio as follows:

\[
H_{CL}(z) = \frac{Y(z)}{R(z)} = \frac{1}{1 + H_{OL}(z)}
\]  

The closed-loop frequency response yields further insight into the presence and amplitude of system output oscillations by quantifying the amplification that the intact reflex produces as a function of frequency.

**Implementation.** Two cardiovascular states were studied, specifically: 1) a baseline condition corresponding to a normotensive, supine adult human, and 2) a stress condition of decreased central blood volume (hypovolemia) corresponding to a mild hemorrhage or to upright posture. Several components of the model (Fig. 1) were changed to reflect the stress of decreased central blood volume. First, the five effector filters, \(H_1(z)\) through \(H_5(z)\) were recomputed using the cardiovascular simulator that was used to derive those in the baseline state, this time decreasing total blood volume by 0.5 liters. The recomputed responses quantify how ABP responds to small changes in heartbeat period and peripheral resistance from this new operating state of decreased central blood volume.

Several gain blocks were changed to reflect the condition of hypovolemia. These gain changes are based on the reported interaction of cardiopulmonary receptors with the arterial baroreflex (40, 62). It is believed that with relatively high levels of central venous volume, as during supine posture, the
cardiopulmonary receptors are stimulated, partially inhibiting some branches of the arterial baroreflex and enhancing others. During periods of decreased central venous volume, this inhibitory signal from the cardiopulmonary receptors is reduced, resulting in significant changes to the gains of the various branches of the arterial baroreflex.

For hypovolemia, the gain of the parasympathetic branch of the baroreflex, $G_{SP}$, was reduced based on data from several studies. One study quantified changes in baroreflex heart rate gain accompanying orthostatic challenge in humans and found an average decrease in high frequency (parasympathetic) gain of 57% associated with upright posture (2). Another study found a nearly identical decrease in baroreflex gain accompanying standing (49). A third study reported a decrease in parasympathetic gain of 40% with upright tilt (52). For our stability calculations, we used a parasympathetic gain decrease of 50% for our state of decreased central blood volume, based on the average of these reported values.

The gain of the branch representing sympathetic control of peripheral resistance was also changed to simulate decreased central blood volume. Victor and Mark (58) have shown that reductions in central venous volume induced by nonhypotensive lower-body negative pressure (LBNP) enhance arterial baroreflex control of vascular resistance in humans (58). They found arterial baroreflex/peripheral resistance gain to increase by a factor of $10^{1.5}$ with 10 mmHg LBNP. We estimated the effect of LBNP on central venous volume based on

$$P_{EV} = \frac{V_{EV} - ZP_{EV}}{C_{EV}} + LBNP$$

where $P_{EV}$, $V_{EV}$, $ZP_{EV}$, and $C_{EV}$ are pressure (mmHg), volume (liters), zero-pressure volume (liters), and compliance (l/mmHg) in the extrathoracic veins and LBNP is the value of lower-body negative pressure (mmHg). Values for $P_{EV}$, $ZP_{EV}$, and $C_{EV}$ were taken to be 6 mmHg, 2.5 l, and 0.1 l/mmHg (61), and $V_{EV}$ was solved for the two cases, where LBNP was equal to zero and 10 mmHg. This resulted in a difference in $V_{EV}$ of 1.0 l, a volume which we assumed to come from the central venous supply since this level of LBNP did not result in hypotension. The reflex effect on vascular resistance is believed to increase linearly with decreasing central venous volume (32). On the basis of Victor and Mark’s result, a 0.5-l decrease in central venous volume corresponds to a baroreflex peripheral resistance gain increase of 1.5 times.

The gain of the branch representing sympathetic control of venous ZPV was also increased to simulate upright posture. Decreases in central volume induced by nonhypotensive LBNP have also been shown to affect venoarterial activity in humans, and although no explicit values for gain changes could be found, investigators suggest that it is likely that resistance and venous capacitance vessels respond similarly to increasing sympathetic stimulation with increasing levels of LBNP (53). Accordingly, we chose the baroreflex/venous ZPV gain increase to be also equal to 1.5.

RESULTS

Baseline condition: supine posture. The open-loop frequency response in the supine posture has the characteristics of a low-pass filter with a corner frequency of about 0.03 Hz (Fig. 5A). The frequency where the phase equals $-180^\circ$ is $0.3$ Hz, where the magnitude plot is much less than 1.0, indicating a stable control system. The closed-loop frequency response magnitude is small (0.2) at frequencies less than the corner frequency of 0.03 Hz, indicating that very low-frequency disturbances are about 80% corrected by the reflex and corresponding to a static open-loop gain of $\sim 4$. This is consistent with values of static open-loop gain averaging about 3.5 reported by Burattinni et al. (9) and ranging from 2 to 4 in dogs reported by McRitchie et al. (36). At the higher frequencies, near the point of $-180^\circ$ open-loop phase, there is no evidence of significant resonance. At the highest frequencies evaluated ($>0.3$ Hz), where the open-loop magnitude approaches 0, the closed-loop magnitude approaches a value of 1.0, indicating that the reflex has minimal to no effect on ABP at those frequencies. The Nyquist diagram (Fig. 5B) does not encircle the point $(-1, 0)$ and has a gain margin of 0.6, again indicating that the closed-loop system is stable.

Hypovolemic condition: upright posture. The open-loop frequency response in the hypovolemic state also has the charac-
teristics of a low-pass filter, again with a corner frequency of about 0.03 Hz (Fig. 6, top). The open-loop frequency response magnitude is 0.93 at 0.073 Hz, the frequency at which the phase equals $-180^\circ$. Thus in the hypovolemic state, the arterial baroreflex is stable but very close to instability. In contrast to the normal state, the closed-loop frequency response during hypovolemia shows a peak, with a magnitude equal to 11, at 0.073 Hz. This indicates that the closed-loop system exhibits resonance at 0.073 Hz, amplifying any system noise that is present near this frequency by a factor of 11. The Nyquist plot depicting this condition confirms that the system is approaching instability, almost encompassing the point $(-1, 0)$ and with a gain margin of 0.07.

**Sensitivity.** To understand how model parameter changes affect stability, a sensitivity analysis was performed. A general expression for the sensitivity of a function, $F$, to parameter, $X$, can be written:

$$\text{Sensitivity} = \lim_{\Delta X \to 0} \frac{\Delta F}{\Delta X}$$  \hfill (5)

The gain margin was chosen as the measure of system stability and is represented by $F$ in Eq. 5. If gain margin equals zero, the frequency response magnitude at the critical frequency is 1.0, and the control system will produce undamped oscillations. Behavior at frequencies where the phase equals odd multiples of $-180^\circ$ is not analyzed here because these frequencies prove to be above the range of interest for the study of low frequency (<0.15 Hz) oscillations. Choices for parameters $X$ include model gains and time delays, receptor filter durations (i.e., the time for the receptor to completely respond to a sudden change in nerve firing rate), and the baroreceptor rate response filter shape. Sensitivity to the chosen parameter was computed by subjecting the parameter to a small (<5%) positive and negative change, and quantifying the subsequent change in gain margin produced by the system model (Fig. 7). A high value of sensitivity for a given parameter indicates that relatively small changes in that parameter lead to large changes in gain margin.

To further characterize the influences of model parameters on resonance, the value of each parameter $X$ was increased or decreased until the gain margin approached 0. The parameter change required to bring the system to the brink of instability, along with the resonant frequency of the model for that parameter change, appears in Table 2. This information quantifies the resonant behavior of the model in response to relatively large parameter changes.

To summarize the results of Fig. 7, the gain margin of the system exhibited the highest sensitivity to gain of the venous ZPV branch of the arterial baroreflex ($G_2$), indicating that a change in the value of venous ZPV gain had a greater effect on gain margin than a proportional change in any other parameter. Gain margin was almost equally sensitive to changes in parasympathetic gain. Table 2 shows that either an increase in venous ZPV gain or a decrease in parasympathetic gain alone can result in model instability in the 0.07 to 0.08 Hz range, although in both cases, the requisite gain changes are larger than values derived from published studies. Reducing parasympathetic filter duration by 50% (from 30 to 15 s) causes unstable oscillations at 0.08 Hz, and decreasing parasympathetic filter duration by 96% (from 1.3 to 0.05 s) causes unstable oscillations at 0.07 Hz. In fact, more than half of the parameters in Table 2, when changed to the point of system instability, result in system oscillations in the range of 0.07 to 0.11 Hz.

**Human Studies of Low-Frequency ABP Oscillations**

ABP signals from a prior study of 14 healthy young subjects (median 21 years of age) in the standing posture during random interval breathing (46) were analyzed to investigate the presence of a preferential low-frequency ABP oscillation. The power spectrum of systolic blood pressure from each subject was normalized so that the total power from 0.05 to 0.15 Hz equaled 1, and the power spectra were summed (Fig. 8). The frequency at which the spectrum peaked was 0.074 Hz.

**DISCUSSION**

The most important findings from this modeling study are 1) the model of the arterial baroreflex is characterized by stable behavior at baseline and 2) simulated upright posture decreases...
the stability of the normally stable arterial baroreflex leading to resonance and low-frequency ABP waves at frequencies between 0.07 and 0.08 Hz.

Model parameters and stability. The model demonstrated a strong tendency to support oscillations at frequencies near 0.07–0.08 Hz, where changes in many model parameters resulted in a feedback system with resonance near this frequency. Model stability was most sensitive to changes in venous ZPV gain, and it is the change in venous ZPV gain with hemorrhage that plays a large role in the reflex enhancement leading to decreased stability. This agrees with the results of a modeling study by Ursino (54), who reported that control of venous ZPV plays the major role in rapid cardiovascular response to acute hemorrhage.

Table 2. Resonant behavior of the model in response to relatively large parameter changes

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ΔXX/X</th>
<th>Frequency (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral resistance gain, G₁</td>
<td>9.0</td>
<td>0.10</td>
</tr>
<tr>
<td>Venous ZPV gain, G₂</td>
<td>2.5</td>
<td>0.08</td>
</tr>
<tr>
<td>LV compliance gain, G₃</td>
<td>16.0</td>
<td>0.13</td>
</tr>
<tr>
<td>RV compliance gain, G₄</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sympathetic heartbeat period gain, G₅₇</td>
<td>9.0</td>
<td>0.10</td>
</tr>
<tr>
<td>Parasympathetic heartbeat period gain, G₅₉</td>
<td>−0.9</td>
<td>0.07</td>
</tr>
<tr>
<td>Peripheral sympathetic transmission delay, k₁</td>
<td>21.0</td>
<td>0.02</td>
</tr>
<tr>
<td>Cardiac sympathetic transmission delay, k₂</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parasympathetic transmission delay, k₃</td>
<td>4.0</td>
<td>0.11</td>
</tr>
<tr>
<td>Sympathetic filter duration</td>
<td>−0.5</td>
<td>0.08</td>
</tr>
<tr>
<td>Parasympathetic filter duration</td>
<td>−0.96</td>
<td>0.07</td>
</tr>
<tr>
<td>Baroreceptor rate response HF gain</td>
<td>1.2</td>
<td>0.28</td>
</tr>
</tbody>
</table>

These results quantify the resonant behavior of the model in response to relatively large parameter changes—those that bring the system to the brink of stability (gain-margin approaching). The columns, from left to right, contain the name of the model parameter, the fractional change in model parameter (ΔXX) required to evoke instability, and the resonant frequency at the point of instability. For right ventricle (RV) compliance gain and cardiac sympathetic transmission delay, neither large increases nor decreases evoked instability. ZPV, zero pressure volume; LV, left ventricle; HF, high frequency.

Fig. 7. Sensitivity of the gain margin to changes in model parameters.

Fig. 8. Average normalized power spectrum of systolic blood pressure from 14 healthy subjects in the standing posture during random interval breathing. The peak in spectral power is at 0.074 Hz.

Autonomic gains. Sensitivity analysis results revealed relatively high model sensitivity to parasympathetic gain, such that a decrease in parasympathetic gain played a role in producing the large peak in closed-loop gain between 0.07 and 0.08 Hz accompanying hypovolemia. Reducing parasympathetic gain further (to 0.10 times its baseline value), in the absence of changes in venous ZPV gain and peripheral resistance gain, causes the gain margin to approach 0 and also produces a strong resonance near 0.07 Hz. This destabilizing effect of decreasing parasympathetic gain is supported by studies showing that parasympathetic blockade can produce sustained low-frequency ABP oscillations in dogs (34, 47). Further, the model is able to simulate the Mayer waves seen after cardiac denervation in animals (33) or after cardiac transplant in humans (56) by setting sympathetic and parasympathetic heart rate gains, and sympathetic LV and RV systolic compliance gains, to 0.

In our model, the ability of the parasympathetic branch to enhance the stability of the arterial baroreflex under normal (supine) conditions results from the parallel nature of the actions of the two autonomic branches and from their distinct dynamics. The frequency response of the parallel combination of the sympathetic and parasympathetic branches is equal to the complex sum of the frequency responses of the two branches. The additive effect of the parasympathetic branch essentially raises the phase of the combined reflex for frequencies between 0.05 and 0.1 Hz so that it does not approach −180° until higher frequencies, at which the frequency response magnitude is significantly below 1.0. As the gain of the parasympathetic branch decreases (with hypovolemia), this effect is reduced, and the phase of the combined response (the open-loop frequency response) falls more quickly with frequency, reaching −180° at a lower frequency, where the magnitude is higher. The higher frequency response magnitude at the frequency where phase is −180° means smaller gain margin and decreased stability.

The stabilizing effect of the parasympathetic branch of the baroreflex can also be explained in more physical terms. The very rapid parasympathetic response time enables buffering of low-frequency ABP oscillations by parasympathetically mediated heart rate changes, with heart rate increasing in response to decreases in ABP and decreasing in response to increases in ABP. Consequently, a decrease in parasympathetic gain diminishes this buffering effect and lets ABP oscillate unopposed.

Sympathetic filter characteristics. It was of interest that, using experimentally derived autonomic filters, the current...
model produced no oscillations at baseline and 0.07–0.08 Hz oscillations during mild hypovolemia. We have previously studied effects of the sympathetic receptor filter shape and duration on the stability of baroreflex models (22). When filters used in previously published baroreflex models (14, 33) were substituted into a model simulating cardiovascular control (61), the normally stable simulator produced oscillations very similar to those reported for the previous models. However, when the sympathetic filter used here and derived experimentally by Berger et al. (3) was substituted into the same simulator, the system was stable, as was the case for the model in this report, analyzed in baseline conditions.

Our results show that decreasing the duration of the sympathetic filter (Fig. 3A) causes the system to move toward a state of decreased stability (Table 2). This effect derives from the low-pass shape of the open-loop frequency response and from the frequency response of the sympathetic filter, which dominates the shape of the open-loop frequency response of the model. Narrowing the impulse response of the sympathetic filter corresponds to widening its frequency response, so the open-loop frequency response gains will be higher throughout the spectrum, including at the frequency where the phase equals −180°. Thus accurate description of the sympathetic receptor filter is critical when baroreflex models are constructed and used to assess stability.

Baroreflex stability and the frequency of oscillation are highly dependent upon the phase properties of the sympathetic filter. If low-pass filter models are used to represent the response of the sympathetic filter, careful attention must be paid to the order of the model, which strongly influences the phase. For example, a first-order low-pass filter will undergo a phase shift of −90° near the corner frequency, while a second-order low-pass filter will undergo a −180° shift. The size of this shift in phase in the vicinity of the corner frequency (typically 0.01 to 0.02 Hz) will have a strong effect on the frequency at which the response of the entire baroreflex loop reaches negative 180°, with the higher-order filter reaching this phase at a much lower frequency. If the filter order is chosen based on features of the magnitude response (e.g., roll-off rate), then phase may be poorly approximated by the model. The relatively poor ability of simple low-pass filter models to capture details of the sympathetic response compelled us to use the actual measured response in this model.

Other baroreflex models. Other groups have used mathematical models to assess baroreflex stability, but results have varied widely. A model developed by deBoer et al. (14) exhibited a strong resonance (gain of ~10) at 0.12 Hz. The real baroreflex, however, does not exhibit such a resonance under normal conditions, and several unrealistic features of their model underlie the enhanced instability. First, the duration of the sympathetic filter influencing peripheral resistance was only 4 s, much shorter than the ~30-s filter derived experimentally (5). Second, the model does not explicitly close the circulatory loop for venous return, excluding a powerful pressure-buffering mechanism intrinsic to arterial pressure control. In vivo, a change in peripheral resistance directly changes arterial pressure, but also causes a change in venous return and cardiac output in the opposite direction, which, according to Guyton, “almost completely nullifies the effect on arterial pressure that the change in resistance would otherwise cause” (20). Failure to model this phenomenon results in an unrealistically powerful baroreflex.

A model by Madwed et al. (33) demonstrated low-frequency ABP oscillations with hemorrhage, but a long delay (5 s) and a short filter (15 s) were chosen to describe the sympathetic control of peripheral resistance. Their model also lacked the powerful stabilizing influence of a closed-loop circulatory system. Interestingly, hemorrhage was simulated by changing the relative influences of the sympathetic and parasympathetic branches, effectively decreasing the gain of the parasympathetic branch.

TenVoorde et al. (51) were able to get a slight baroreflex resonance at 0.09 Hz in their model but did so by fine tuning model parameters, noting that the dynamic parameters of resistance control were most influential. The time constant of the filter from sympathetic activity to peripheral resistance was very short (2 s). This model also lacked a closed-loop circulatory system.

Abbiw-Jackson and Langford published a mathematical model of baroreflex control and concluded that an increase in the feedback gain controlling venous volume can lead to oscillations while changes in other parameters do not (1). Perhaps their model did not explain the sensitivity of oscillations to other parameters because their baroreflex model assumed instantaneous responses of sympathetic and parasympathetic receptors and of all effectors of blood pressure change. A baroreflex model by Wesseling and Settels (60), which included a closed circulatory loop and first-order filter descriptions of the sympathetic and parasympathetic receptor filters, exhibited a high degree of stability and did not produce low-frequency ABP oscillations. Oscillations could be induced by cutting all reflex branches except that controlling peripheral resistance or by increasing the gain of the peripheral resistance branch by a factor of 3. Sensitivity of oscillations to changes in venous ZPV gain were not observed, probably because of the extremely long time delay and filter duration used to describe that branch.

Burgess et al. (10) devised a baroreflex model consisting of a proportional-derivative controller, a delay and a first-order low-pass sympathetic filter to predict 0.4-Hz blood pressure oscillations in rats. The delay and first-order time constant were based on experimental studies, but the proportional and derivative gains were not and instead were chosen deliberately to reproduce a marginally stable reflex loop. Ringwood and Malpas (42) modified that model to include a nonlinearity that effectively allowed the model to produce sustained arterial pressure oscillations over a much wider range of model parameters. Their model is very similar to a nonlinear model proposed much earlier by Kitney (28), which showed the ability of respiration to entrain baroreflex-mediated blood pressure waves. Like Burgess et al., they used a simple first-order low-pass filter with a pure time delay to model the composite effects of the response of the vasculature to sympathetic stimulation and the response of arterial pressure to vasculature changes. Furthermore, both models used a differentiator to describe the rate sensitivity of the baroreceptors. In terms of the open-loop frequency response, the differentiator adds 90° of positive phase across all frequencies, raising the frequency at which the phase plot crosses negative 180° (i.e., the oscillation frequency). Both models also ignore the influence of the parasympathetic control of heart rate on the stability of the
baroreflex, an influence that our model suggests plays a role in maintaining baroreflex stability under normal conditions.

In order for the baroreflex system to produce ABP oscillations due to resonance, small-amplitude ABP variation due to some other factor must be present. In this study, we did not specifically model such disturbances, but they can arise from several sources. Spontaneous respiration is known to contain considerable spectral power at frequencies below 0.10 Hz, leading to periodic changes in pleural pressure and oscillations in venous and arterial pressures. Furthermore, ABP fluctuates spontaneously with 1-over-f characteristics (spectral power inversely related to frequency) in animals on heart-lung machines with completely severed reflex control (60). In our baroreflex model, ABP fluctuations like these would be selectively amplified by the bandpass characteristics of the closed-loop baroreflex, producing 0.07–0.08 Hz ABP oscillations under conditions of hypovolemic stress.

Frequency of LF oscillations. Our model demonstrated the potential of arterial pressure to oscillate at 0.07–0.08 Hz, a period of about 12–14 s. These low-frequency ABP oscillations observed in humans are commonly referred to as “10-s waves” (0.10 Hz), but many human studies, including the experimental portion of this study, actually report ABP oscillations at frequencies ranging from 0.07 to 0.10 Hz (6, 12, 16, 39, 50). Although our clinical observations support the notion that the exact frequency of these ABP waves varies among individuals and even within the same individual over time, the oscillatory frequency of our model was not so labile, as most model parameter changes influenced the degree of stability but not the oscillation frequency. Changes in some model parameters directly increase the frequency at which the open-loop frequency response phase equals −180° (i.e., the frequency at which positive feedback occurs). Decreasing any time delays in the feedback loop would increase this frequency, increasing the stability of the system as a result of the low-pass shape of the open-loop frequency response. Decreasing the time constant of the adrenergic filter raises the frequency at which its frequency response magnitude starts to fall and its phase undergoes a sharp decrease. Like the time-delay decrease, this change would raise the frequency at which positive feedback occurs; however, in this case, the magnitude will be higher at this frequency, possibly high enough to cause instability. Although our sensitivity analysis was limited to changes in single parameters at a time, it is possible to simultaneously change two or more parameters to produce resonance at any frequency. A systematic analysis of sensitivity of stability to simultaneous changes in two or more parameters might provide additional insights.

Limitations. Errors in model parameters could be due to the fact that many of the values and response characteristics of model components were derived from animal studies. It is noteworthy that dogs tend to exhibit slower ABP waves than humans, with oscillation frequencies near 0.05 Hz commonly reported (19, 27, 34). Mechanisms other than the arterial baroreflex could play a role in ABP oscillations. Automatical regulatory mechanisms are thought to respond in as little as 10–15 s in the brain, heart, and kidneys (55) and could thus affect ABP within the frequency range of 0.06 to 0.10 Hz.

The model of the arterial baroreflex presented here was linear, and the assessment of stability was based on linear control system theory; however, many elements of the baroreflex are known to behave nonlinearly. The curve describing baroreceptor afferent firing rate in response to arterial pressure is sigmoid, not linear. Representing its response by a linear gain term is certainly not accurate over the full physiological range of ABP, but it is valid for assessing properties of the reflex within a narrow range about a given operating point. We also assumed that the influences of the effectors on ABP can be summed in a linear fashion, that is, the net effect of corrective action through two different effector branches is the same as the sum of the effects of the individual branches. Model simulations support this assumption (21), but it has not been validated experimentally. With respect to heart period, investigators disagree on the importance of nonlinear effects between the sympathetic and parasympathetic branches (30, 37, 54).

Regardless, this interaction would be unlikely to affect the model results significantly because of the relative insensitivity of model stability to changes in sympathetic heart rate gain. Consequently, the linear assumptions of the model are probably reasonable for the limited physiological conditions examined here. Finally, the vessels controlling peripheral resistance and venous ZPV are distributed throughout the body, but for simplicity we have lumped them into a single model component characterized by a single value of neural time delay. It would be interesting to model the effect of the distributed nature of these vessels on baroreflex stability.

Conclusions. The model of the arterial baroreflex presented here is characterized by stable behavior at baseline. Simulating the condition of upright posture decreases the stability of the normally stable arterial baroreflex, leading to strong resonance between 0.07 and 0.08 Hz. Parasympathetic control of heart beat period seems to help maintain stability of the reflex under supine conditions, and the control of venous ZPV appears to play an important role in the baroreflex resonance. A realistic description of the effect of sympathetic stimulation on the vasculature is crucial to models of baroreflex stability.

REFERENCES

10. Burgess DE, Hundley JC, Li SG, Randall DC, and Brown DR. First-order differential-delay equation for the baroreflex predicts the


