

Dynamic regulation of heart rate during acute hypotension: new insight into baroreflex function

RONG ZHANG, KHOSROW BEHBEHANI, CRAIG G. CRANDALL,
JULIE H. ZUCKERMAN, AND BENJAMIN D. LEVINE

*Institute for Exercise and Environmental Medicine, Presbyterian Hospital of Dallas,
and University of Texas Southwestern Medical Center Dallas, Dallas, Texas 75231*

Received 22 February 2000; accepted in final form 23 August 2000

Zhang, Rong, Khosrow Behbehani, Craig G. Crandall, Julie H. Zuckerman, and Benjamin D. Levine. Dynamic regulation of heart rate during acute hypotension: new insight into baroreflex function. *Am J Physiol Heart Circ Physiol* 280: H407–H419, 2001.—To examine the dynamic properties of baroreflex function, we measured beat-to-beat changes in arterial blood pressure (ABP) and heart rate (HR) during acute hypotension induced by thigh cuff deflation in 10 healthy subjects under supine resting conditions and during progressive lower body negative pressure (LBNP). The quantitative, temporal relationship between ABP and HR was fitted by a second-order autoregressive (AR) model. The frequency response was evaluated by transfer function analysis. Results: HR changes during acute hypotension appear to be controlled by an ABP error signal between baseline and induced hypotension. The quantitative relationship between changes in ABP and HR is characterized by a second-order AR model with a pure time delay of 0.75 s containing low-pass filter properties. During LBNP, the change in HR/change in ABP during induced hypotension significantly decreased, as did the numerator coefficients of the AR model and transfer function gain. Conclusions: 1) Beat-to-beat HR responses to dynamic changes in ABP may be controlled by an error signal rather than directional changes in pressure, suggesting a “set point” mechanism in short-term ABP control. 2) The quantitative relationship between dynamic changes in ABP and HR can be described by a second-order AR model with a pure time delay. 3) The ability of the baroreflex to evoke a HR response to transient changes in pressure was reduced during LBNP, which was due primarily to a reduction of the static gain of the baroreflex.

blood pressure; mathematical modeling

THE HEART RATE LIMB of the baroreflex plays an important role in short-term regulation of blood pressure (15, 31). By its nature, the underlying control mechanisms must be dynamic. However, evaluation of dynamic baroreflex function has been difficult in humans. This difficulty arises not only because of the limitations in studying humans per se but also because of the complexity of the baroreflex system. The baroreflex functions through a complicated feedback control system with multiple inputs and outputs and has intrinsic

nonlinearity (12, 27, 43). Thus it is not surprising that analyzing such a complex system has been a great challenge to both physiologists and medical scientists.

Traditionally, baroreflex control of heart rate has been described by a sigmoid-shaped curve relating R-R interval or heart rate to arterial pressure (15, 31). This relationship implies that stimulation of baroreceptors with increases in pressure leads only to decreases in heart rate (increases in R-R interval) and unloading of the baroreceptors with decreases in pressure leads only to increases in heart rate.

Although this model may correctly reflect steady-state heart rate responses to steady-state changes in arterial pressure (24), the fundamental assumption underlying this description implies a static baroreflex with one pressure stimulus associated with one heart rate response, which may not be suitable to describe how heart rate responds to dynamic changes in pressure.

Moreover, it has been shown that the baroreflex may reset rapidly with sustained changes in pressure (8, 10). Shifting of multiple sigmoid baroreflex curves along the pressure and/or heart rate axes has been observed both in human and animal studies (10, 39). These findings demonstrate that baroreflex function is not static even when described by static techniques.

However, the limitations implicit in the static description of the baroreflex appear to be ignored in recent studies using spontaneous variations in arterial pressure and heart rate to quantify baroreflex function (6, 30, 34). For example, in one proposed method, spontaneous beat-to-beat variations in arterial pressure and cardiac period have been classified either as “baroreflex”- or “nonbaroreflex”-mediated sequences based on whether changes in R-R intervals were directionally similar or different from those of simultaneous variations in pressure (6). This classification suggests that increases in heart rate associated with simultaneous increases in pressure could not be mediated by the baroreflex (6, 30, 34). However, because spontaneous variations in heart rate are most likely mediated by dynamic changes in pressure (1, 45), this assump-

Address for reprint requests and other correspondence: B. D. Levine, Director, Institute for Exercise and Environmental Medicine, Presbyterian Hospital of Dallas, 7232 Greenville Ave., Dallas, TX 75231 (E-mail: benjaminlevine@texashealth.org).

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

tion may not be entirely valid. Also, recent observations in our laboratory during the recovery from acute hypotension have raised the possibility that, under certain conditions, increases in beat-to-beat heart rate associated with increases in arterial pressure may still be under baroreflex control.

In this study, we present a new method for the evaluation of baroreflex function in humans. The baroreflex was perturbed by acute hypotension induced by rapid thigh cuff deflation. The time course of changes in heart rate and arterial pressure was examined to determine how heart rate would respond to a dynamic change in pressure. The relationship between the transient changes in pressure and heart rate was quantified by dynamic system analysis. With the use of this method, baroreflex function under orthostatic stress was then evaluated during progressive lower body negative pressure (LBNP) designed to alter stimulation to baroreceptors and background autonomic activity.

METHODS

Subjects. Ten healthy men and women with a mean age of 33 ± 7 yr, height of 171 ± 12 cm, and weight 70 ± 14 kg voluntarily participated in the study. All were nonsmokers and free of known cardiovascular and pulmonary disorders. Each subject was informed of the experimental procedures and signed a written consent form approved by the Institutional Review Boards of the University of Texas Southwestern Medical Center and the Presbyterian Hospital of Dallas.

Instrumentation and procedures. Heart rate was monitored continuously by electrocardiogram (ECG). Arterial pressure was measured continuously in the finger using photoplethysmography (Finapres, Ohmeda) and intermittently in the arm by electrospphygmomanometry (Suntech). Respiratory frequency was monitored by using a piezoelectric pneumograph (Protech).

All experiments were performed in the morning at least 2 h postprandial. The subjects were constrained from using caffeinated or alcoholic beverages at least 12 h before the tests. The experiments were conducted in a quiet, environmentally controlled laboratory with an ambient temperature of 25°C .

After at least 30 min of supine rest, 6 min of data of ECG and arterial pressure were recorded during spontaneous breathing as a baseline steady state. Immediately after the steady-state data collection, two thigh cuffs were inflated to a pressure of at least 30 mmHg higher than each subject's systolic pressure (D. E. Hokanson) for 3 min to produce temporary ischemia in the lower limbs. The thigh cuffs were then rapidly deflated to induce a sudden decrease in arterial pressure and a transient response in heart rate. In previous studies, it has been conclusively shown that circulatory occlusion of resting skeletal muscle with thigh cuff inflation does not evoke either cardiovascular metaboreflexes or mechanoreflexes, suggesting that the cuff inflation used in the present study caused no interference with baroreflex function (41, 42, 58).

The above protocols were repeated during progressive LBNP. Subjects were placed in a Plexiglas box, which was sealed at the level of the iliac crests. Suction was provided by a vacuum pump and controlled with a variable autotransformer. The pressure difference between the LBNP chamber and the atmosphere was measured with a mercury manometer. LBNP was applied with the subjects in the supine

position. After the baseline data collection, we immediately applied -15 mmHg LBNP. After 2 min of stabilization, 6 min of data were recorded for steady state, and 5 min of data were then recorded for the transient response (3 min for the cuff inflation, 2 min for deflation) at this level of LBNP. The magnitude of LBNP was then increased to -30 mmHg followed by stepwise increments at -10 mmHg up to the subject's maximal tolerance. LBNP was terminated if the subject developed signs and/or symptoms of presyncope: sudden onset of nausea, sweating, light headedness, bradycardia, or hypotension (sustained systolic blood pressure < 80 mmHg). In the present study, all subjects completed the experimental protocol through at least -40 mmHg LBNP. However, only five subjects completed the experimental protocol at -50 mmHg. Because more subjects dropped off at high levels of LBNP, the data presented here include only those from baseline to -50 mmHg.

Data acquisition and analysis. Instantaneous heart rate was derived from the ECG signal (Cardiotachometer, Quinton). Arterial pressure waveforms were sampled at 100 Hz and digitized at 12 bits to obtain beat-to-beat values of systolic and diastolic pressure. For each cardiac cycle, defined as a time interval between the sequential maximal upstrokes of arterial pressure, the systolic and diastolic pressure were detected as the maximal and minimal values within the interval. The beat-to-beat heart rate and systolic and diastolic pressure were then linearly interpolated and resampled simultaneously at 4 Hz to construct equally spaced time series for the modeling and data analysis.

For steady-state data analysis, arterial pressure and heart rate were averaged over the 6-min time interval before the cuff inflation and over the 3-min time interval during the cuff inflation. For transient data analysis, the maximal decrease in pressure after the thigh cuff deflation was calculated as a systolic pressure difference between an average of 10 s of data immediately before the cuff release and a minimal value after the cuff release. Correspondingly, the maximal heart rate response to the acute hypotension was calculated as a heart rate difference between an average of 10 s of data immediately before the thigh cuff release and a maximal heart rate after the cuff release. All the measurements were conducted under baseline conditions and at each level of LBNP.

Mathematical modeling. Systolic pressure and heart rate from 10 s before through 30 s after the thigh cuff release were used for identification of baroreflex function. To obtain a mathematical model relating the changes in heart rate to the changes in pressure, the autoregressive moving average model (ARMA) was used (28). The basic assumption of the ARMA approach is that the response of heart rate at a time point can be represented as a linear function of the present and past values of changes in pressure as well as previously observed heart rate. A general form of an ARMA model is proposed as follows

$$\sum_{i=0}^n a_i \Delta r_m(k-i) = \sum_{j=0}^m b_j \Delta p_m(k-j-q) \quad (1)$$

where $\Delta r_m(k)$ signifies the measured change in the heart rate at sample instant k , $\Delta p_m(k)$ is the measured change in blood pressure at sample instant k , i and j represent the sample instants preceding k , a_i and b_j are the weighting coefficients, and q is an integer multiple of the sampling interval and represents the pure time delay involved in the process. n and m represent the model order, reflecting the number of previous sample values of heart rate and blood pressure that are

included in the model. It is noted that, without loss of generality, $a_0 = 1$.

To obtain an ARMA model, the values of n , m , and the corresponding a_i for $i = 1, 2, \dots, n$ and for $j = 0, 1, \dots, m$ should be determined. Although there are some systematic trial and error approaches to estimating n and m (28), the step response of a system of interest often provides a good initial estimate for these parameters. In this study, the changes in arterial pressure were induced by rapid thigh cuff deflation. Hence, the changes in pressure approximated a step input, and the changes in heart rate approximated a step response. Examination of a representative heart rate response to the changes in pressure revealed that the response is underdamped with a slight overshoot (Fig. 1). Furthermore, it indicates that from the time that blood pressure decreased until the heart rate began to respond, there was a latency of ~ 0.75 s (i.e., $q = 3$). Hence, it is reasonable to use a second-order model (i.e., $n = 2$) as an initial estimate. We initially selected $m = 1$ to simplify the model structure, and the analysis of the experimental data showed that this value of m was adequate. Equation 2 below shows the resulting second-order system

$$\Delta r_m(k) + a_1 \Delta r_m(k-1) + a_2 \Delta r_m(k-2) = b_0 \Delta p_m(k-3) \quad (2)$$

For a sampling interval of 0.25 s used in the present study, $k-3$ in argument of Δp_m above reflects the effect of 0.75 pure time delay. With the use of system identification techniques, the values of a_i and b_0 were obtained by application of a least-square estimation technique. Moreover, validation of model identification was conducted by autocorrelation analysis of the model residuals. Theoretically, if the input-output relationship of a dynamic system can be described well by an ARMA model, time series of the model residuals is white noise, and autocorrelation of the model residuals is a δ function (29).

In analyzing the model in Eq. 2, it is helpful to obtain the transfer function between the pressure and heart rate by taking the z -transform of Eq. 2. A transfer function can be obtained as

$$G(z) = \frac{\Delta R_m(z)}{\Delta P_m(z)} = \frac{b_0 z^{-3}}{(1 + a_1 z^{-1} + a_2 z^{-2})} \quad (3)$$

where $\Delta R_m(z)$ and $\Delta P_m(z)$ represent the z -transform of changes in heart rate $[\Delta r_m(k)]$ and pressure $[\Delta p_m(k)]$, respectively.

Equation 3 provides a means to examine the frequency response of the system by letting $z = e^{j2\pi fT}$, where j is the complex operator, f is the frequency, and T is the sampling interval. In the present study, the transfer function gain (G) between the changes in pressure and heart rate was calculated as a magnitude of $G(z)$, and the phase spectrum was estimated from real and imaginary parts of $G(z)$ (25).

An advantage of transfer function analysis is that it allows the examination of both the transient and steady-state response of a system to a given input. In APPENDIX A, we show that for a step change in the blood pressure, the steady-state value of the heart rate is predicted to be

$$\Delta r_{ss} = \lim_{k \rightarrow \infty} \Delta r_m(k) = \frac{p_0 b_0}{(1 + a_1 + a_2)} \quad (4)$$

where p_0 is the magnitude of the step input and Δr_{ss} signifies the steady-state value of the heart rate. Thus it is important to note that the term $b_0/(1 + a_1 + a_2)$ reflects the static gain (i.e., zero frequency) of the system. It represents how the magnitude of the input affects the magnitude of the output

after the transient response has diminished. From Eq. 4, it is clear that the static transfer function gain is determined by the coefficients of both the numerator and denominator polynomials of Eq. 3. However, the shape of the frequency distribution of the transfer function and, therefore, the transient response of the system is determined only by the coefficients of the denominator polynomials of Eq. 3 (see APPENDIX A).

Statistical analysis. The parameters of the autoregressive (AR) model were identified for each individual subject at baseline and at each level of LBNP and then averaged to obtain the group mean values. In addition, the time course of pressure and heart rate for each individual subject during the acute hypotension were aligned at the time point of thigh cuff deflation and then averaged to obtain group-averaged changes. The group-averaged pressure and heart rate were also fitted by the second AR model at the baseline and at each level of LBNP. Transfer function gain [i.e., $|G(z)|$ for $z = e^{j2\pi fT}$] was averaged in low (0.0156–0.15 Hz)-, high (0.15–0.50 Hz)-, and very high-frequency ranges (0.50–2.00 Hz), first for each individual subject and then group averaged for statistical analysis. The selection of frequency ranges was arbitrary in this study to facilitate the data analysis. However, the low- and high-frequency ranges were selected based on the consideration that a consistency between the present study and those in the study of spontaneous changes in arterial pressure and heart rate may facilitate further comparisons regarding the frequency domain properties of baroreflex function (9, 45). The steady-state and transient changes in pressure and heart rate, and the AR model parameters as well as the transfer function gain at baseline and at each level of LBNP, were compared by using one-way ANOVA with Duncan's post hoc tests for multiple comparisons. The effects of thigh cuff inflation on blood pressure and heart rate at baseline and during LBNP were evaluated by two-way ANOVA with cuff inflation and magnitude of LBNP as intervention factors. A P value < 0.05 was considered statistically significant, and all data were represented as means \pm SE. Statistics were performed by using a PC-based software program (ABstat, AndersonBell, Arvada, CO).

RESULTS

Heart rate response to acute hypotension. The thigh cuff inflation alone had no effects on blood pressure or heart rate at baseline (Table 1). A representative thigh cuff deflation, with its consequent induced acute hypotension, and the heart rate response are shown in Fig. 1. Three phases with different characteristics can be identified. In *phase 1*, after the cuff deflation (Fig. 1, *point A*), arterial pressure decreased quickly to a nadir with a magnitude about 16 ± 2 mmHg under supine rest (Figs. 1 and 2 and Table 1). In response to this reduction in pressure, heart rate increased after a slight time delay, suggesting a typical baroreflex mediated cardioacceleration (Figs. 1 and 2). In *phase 2*, in association with the restoration of pressure from the nadir to the level before the cuff release (Fig. 1, *point B*), heart rate continuously increased with simultaneous increases in pressure, which is in contrast to what might be expected from a static model of baroreflex function. In *phase 3*, with the overshoot of pressure (Fig. 1, from *point B* to *C*), heart rate decreased from the maximal response and recovered to the level before the cuff release in association with the recovery of pressure. These data suggest that beat-to-beat heart

Table 1. *Hemodynamics during LBNP*

	LBNP, mmHg				
	0	-15	-30	-40	-50
SBP, mmHg	123 ± 6	124 ± 6	122 ± 5	119 ± 5	118 ± 5
DBP, mmHg	70 ± 5	71 ± 5	73 ± 4	74 ± 4	77 ± 6*
PBP, mmHg	53 ± 3	52 ± 4	49 ± 3	45 ± 3*	41 ± 2*
HR, beats/min	63 ± 4	64 ± 4	70 ± 5*	79 ± 5*	86 ± 7*
SBP _C , mmHg	121 ± 6	120 ± 5	121 ± 6	118 ± 4	122 ± 6
DBP _C , mmHg	69 ± 4	69 ± 4	70 ± 4	76 ± 4*†	80 ± 4*
PBP _C , mmHg	52 ± 4	51 ± 4	51 ± 4	43 ± 2*	43 ± 3*
HR _C , beats/min	62 ± 4	63 ± 4	67 ± 4	75 ± 5*	80 ± 7*
<i>f</i> , breaths/min	12 ± 1	11 ± 1	11 ± 1	11 ± 1	12 ± 2
ΔSBP, mmHg	16 ± 2	15 ± 3	23 ± 4*	25 ± 4*	34 ± 7*
ΔHR, bpm	17 ± 2	20 ± 2	25 ± 3*	21 ± 4	16 ± 2
ΔHR/ΔSBP, beats·min ⁻¹ ·mmHg ⁻¹	1.25 ± 0.32	1.95 ± 0.77	1.22 ± 0.18	1.00 ± 0.23	0.55 ± 0.12

Values are means ± SE; *n* = 10 subjects. LBNP, lower body negative pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; PBP, pulse pressure; HR, heart rate; SBP_C, DBP_C, PBP_C, and HR_C, SBP, DBP, PBP, and HR obtained during thigh cuff inflation, respectively; *f*, respiratory frequency; ΔSBP, maximum SBP drop induced by thigh cuff deflation; ΔHR, maximal HR response. **P* < 0.05 vs. pre-LBNP; †*P* < 0.05 vs. prethigh cuff inflation at same level of LBNP.

rate response to transient changes in pressure are likely controlled by an error signal in the pressure generated by the difference between the pressure level before and after the thigh cuff release. Specifically, it appears that heart rate increased when the pressure was below the level attained before the cuff release and decreased when pressure was above the level.

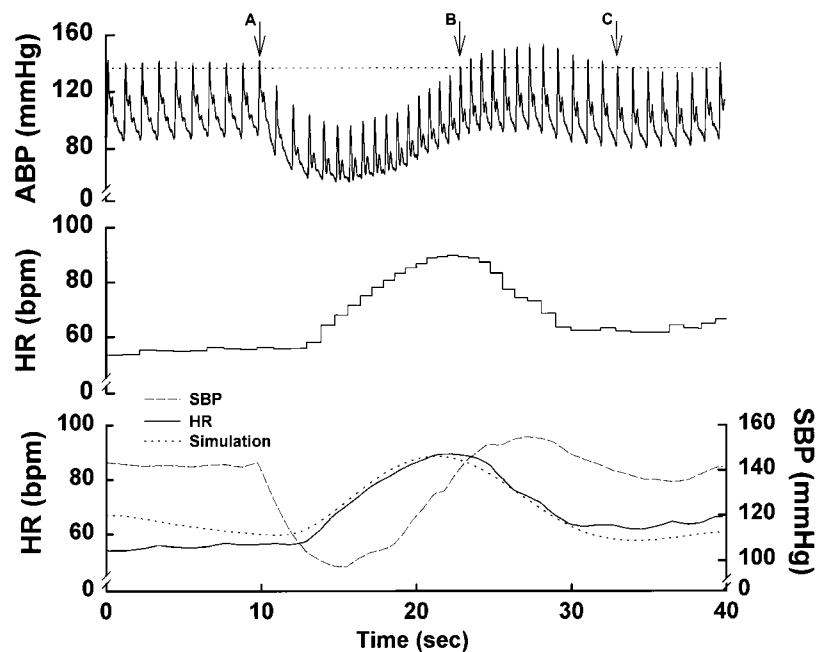
Mathematical modeling. Figures 1 and 2 show that changes in heart rate and pressure were fitted well by the second-order AR model with a pure time delay of 0.75 s. This result was obtained not only at baseline but also during LBNP and is further supported by the model residual analysis (Fig. 2).

Group-averaged transfer functions derived from the AR model are shown in Figs. 3 and 4. Examination of the gain plots reveals low-pass filter properties of the baroreflex with a corner frequency at 0.09 ± 0.01 Hz

under supine rest. The phase spectra show a degree of $\sim 180^\circ$ at the very low frequencies, suggesting that at steady state, a fall in pressure results in an increase in the heart rate and vice versa, which is consistent with the predications of static model of baroreflex. With the increase in frequency, phase fell gradually and crossed 0° at ~ 0.20 Hz (Fig. 3). At higher frequencies, the slope of the fall in phase was steeper, reflecting the pure time delay of the baroreflex, which was incorporated in the model as 0.75 s.

Lower body negative pressure. During LBNP, the thigh cuff inflation caused a slight increase in diastolic pressure at -40 mmHg LBNP (Table 1). In association with the typical changes in the steady-state hemodynamics, the maximal decreases in systolic pressure after the thigh cuff deflation were significantly augmented at -30 , -40 , and -50 mmHg LBNP. In con-

Fig. 1. *Top*: representative changes in arterial blood pressure (ABP) induced by the thigh cuff deflation. *Point A* indicates the time of cuff deflation; *point B* indicates recovery of pressure to the level before the cuff deflation; and *point C* indicates the ending of pressure overshoot. *Middle*: changes in heart rate (HR) during the acute hypotension. *Bottom*: measured and simulated HR of the second-order autoregressive (AR) model in response to the changes in systolic blood pressure (SBP). bpm, Beats per minute.



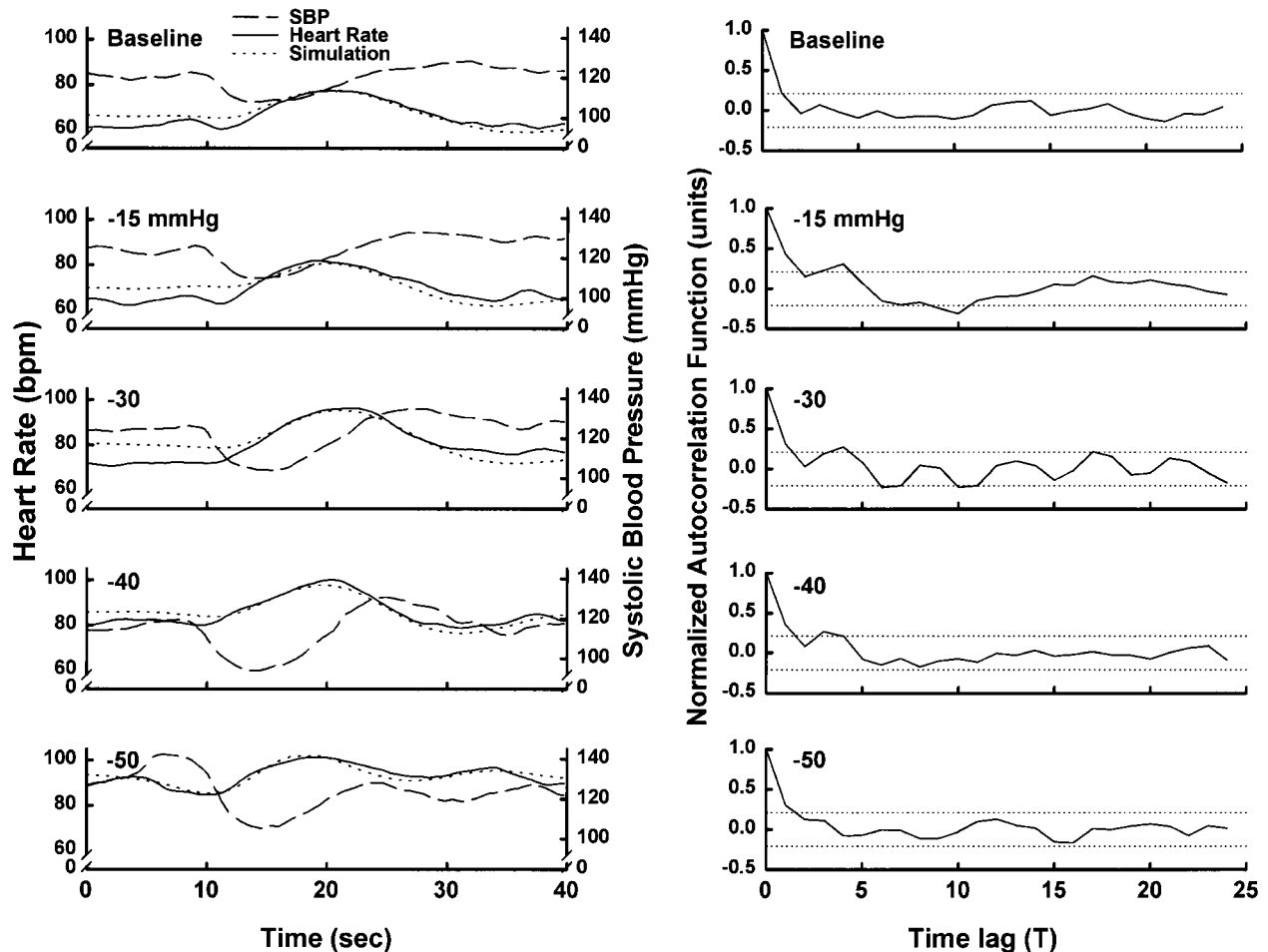


Fig. 2. *Left*: group-averaged SBP and HR as well as simulated HR during acute hypotension induced by the thigh cuff deflation at baseline and at each level of lower body negative pressure (LBNP). *Right*: estimates of autocorrelation function of the AR model residuals at the baseline and at each level of LBNP. The 99% confidence intervals for the estimated autocorrelation function were calculated and displayed as dotted lines. Note that the confidence intervals were calculated assuming that the model residuals are white noise.

trast, the maximal responses of heart rate remained unchanged (Table 1). Hence, the ratio of maximal heart rate response to the maximal pressure decrease showed a trend toward a reduction (Table 1). Moreover, the numerator coefficients of the AR model significantly decreased during LBNP (Table 2). However, the denominator coefficients of the AR model and the corner frequency of transfer function remained unchanged (Figs. 3 and 4, Table 2). Consequently, the transfer function gain in the low-, high-, and very high-frequency ranges all were significantly reduced during LBNP (Fig. 4, Table 2). Taken together, these data suggest that the ability of the baroreflex to evoke a heart rate response to transient changes in pressure was reduced during LBNP, which was primarily due to a reduction of the static gain of the baroreflex.

DISCUSSION

The primary new findings of the present study are threefold. 1) With novel application of thigh cuff deflation as a perturbation to the baroreflex, we found that beat-to-beat heart rate responses to acute hypotension

are likely controlled by an error signal rather than by directional changes in pressure. These data suggest a “set-point” mechanism in short-term beat-to-beat blood pressure control. 2) The quantitative relationship between changes in pressure and heart rate can be described well by a second-order AR model with a pure time delay of 0.75s, confirming dynamic properties of baroreflex function. 3) Dynamic baroreflex function, as reflected by the shape of the transfer function gain, was preserved during LBNP. However, the ability of the baroreflex to evoke a heart rate response to transient changes in pressure was reduced during LBNP, which was primarily due to a reduction of the static gain of baroreflex function.

Baroreflex regulation of heart rate: methodological considerations. The regulatory mechanisms and the properties of the baroreflex have been extensively studied over the last several decades (15, 31). Two basic methods have been developed for evaluation of the heart rate limb of the baroreflex in humans (14, 24, 38, 48). First, by using vasoactive drugs to alter arterial pressure, baroreflex function has been described either

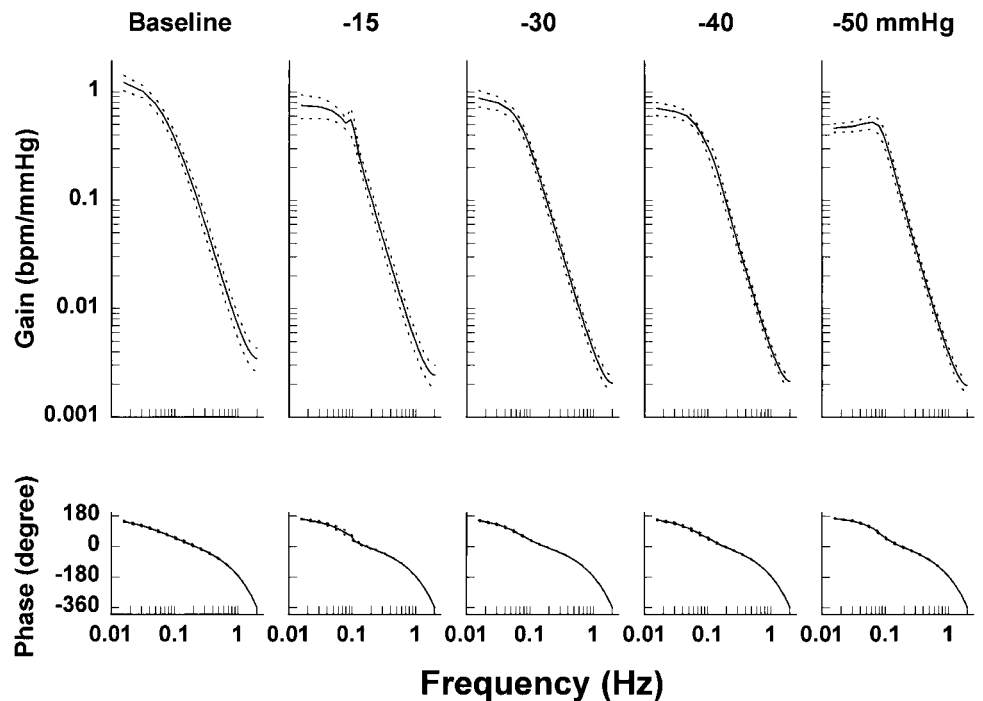


Fig. 3. Group-averaged transfer function gain (*top*) and phase (*bottom*) at baseline and each level of LBNP. Solid lines, averaged estimates; dotted lines, SE.

as a linear or sigmoid curve relating changes in heart rate to changes in pressure (24, 38, 48). Second, by using a specially designed neck chamber, the carotid baroreceptor can be unloaded or stretched by a sequence of stepwise pressure changes in the neck chamber (14). Heart rate responses to the pressure stimuli have been quantified by a sigmoid curve (15). The slope of the linear or the maximal slope of the sigmoid curve, obtained with either infusion of vasoactive drugs or application of the neck chamber, has been calculated to reflect the baroreflex gain for heart rate control (15, 38).

Although modeling of the baroreflex with these methods has provided valuable insights into cardiovascular control mechanisms, a fundamental limitation with these methods is that these descriptions imply a static baroreflex. That is, either the linear or the sigmoid curve is constructed from “one-to-one” pressure-heart rate mapping, suggesting that one stimulus induces only one response. Thus these curves are static in nature, containing relatively little information regarding the dynamic properties of baroreflex function.

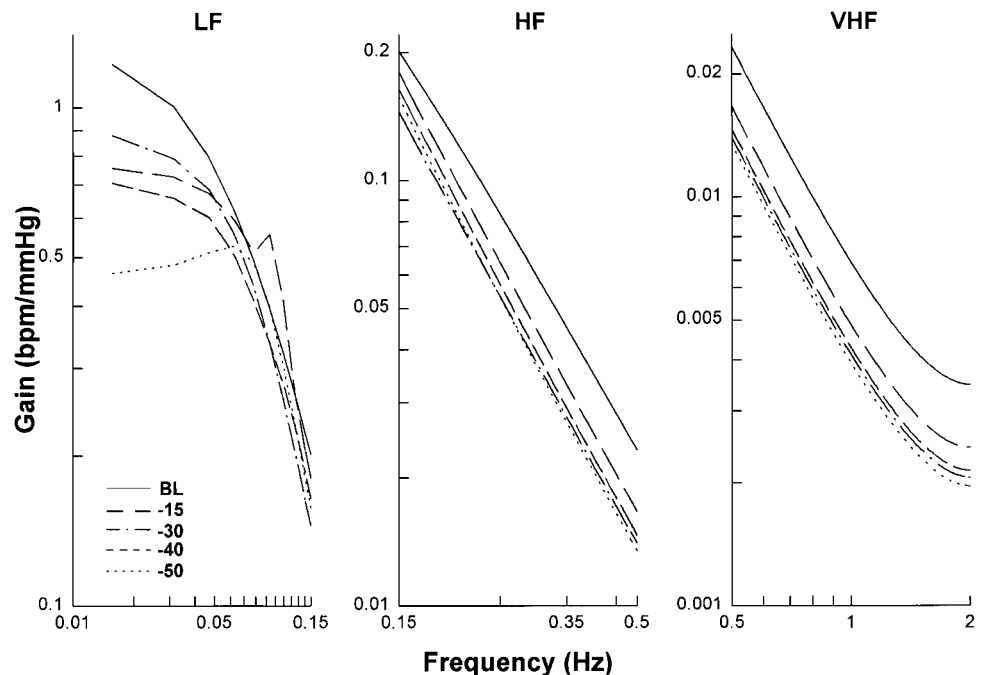


Fig. 4. Overlap of averaged transfer function gain at baseline (BL) with those obtained at each level of LBNP in zoomed scales. *Left*: low-frequency (LF) range (0.0156–0.15 Hz); *middle*: high-frequency (HF) range (0.15–0.50 Hz); *right*: very high-frequency (VHF) range (0.50–2.00 Hz).

Table 2. *Model parameters and transfer function gain during LBNP*

	LBNP, mmHg				
	0	-15	-30	-40	-50
a_1	-1.83 ± 0.01	-1.87 ± 0.02	-1.85 ± 0.01	-1.84 ± 0.02	-1.85 ± 0.03
a_2	0.85 ± 0.01	0.88 ± 0.02	0.86 ± 0.01	0.85 ± 0.02	0.87 ± 0.03
b_0	-0.014 ± 0.002	$-0.009 \pm 0.002^*$	$-0.009 \pm 0.002^*$	$-0.008 \pm 0.001^*$	$-0.005 \pm 0.003^*$
f_c	0.09 ± 0.01	0.08 ± 0.01	0.06 ± 0.01	0.08 ± 0.01	0.10 ± 0.01
LF, $\text{beats} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$	0.624 ± 0.098	0.486 ± 0.069	0.486 ± 0.066	$0.406 \pm 0.029^*$	$0.373 \pm 0.048^*$
HF, $\text{beats} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$	0.084 ± 0.015	$0.053 \pm 0.011^*$	$0.050 \pm 0.008^*$	$0.048 \pm 0.007^*$	$0.045 \pm 0.007^*$
VHF, $\text{beats} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$	0.008 ± 0.001	$0.005 \pm 0.001^*$	$0.005 \pm 0.001^*$	$0.004 \pm 0.001^*$	$0.004 \pm 0.001^*$

Values are means \pm SE; $n = 10$ subjects. a_1 and a_2 , denominator coefficients of the second-order autoregressive model; b_0 , numerator coefficient of the second-order autoregressive model; f_c , corner frequency of transfer function gain; LF, mean value of transfer function gain in the low-frequency range of 0.0156–0.15 Hz; HF, mean value of transfer function gain in the high-frequency range of 0.15–0.50 Hz; VHF, mean value of transfer function gain in the very high-frequency range of 0.50–2.00 Hz. * $P < 0.05$ vs. pre-LBNP.

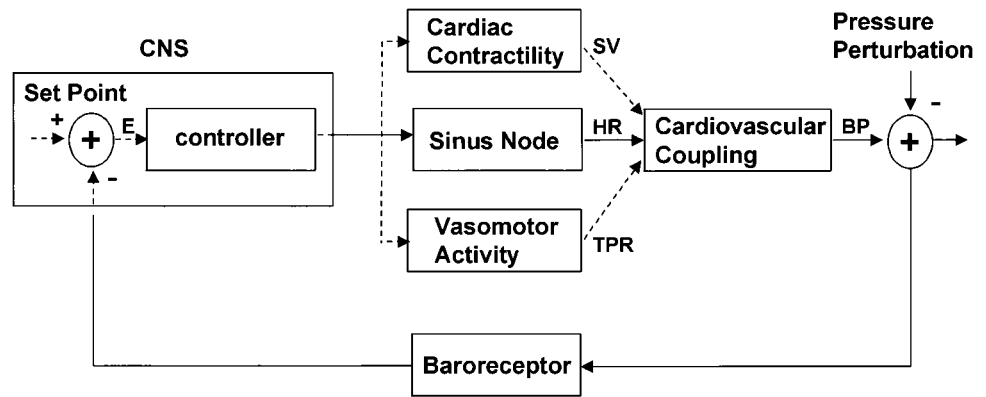
The concepts of dynamic system analysis deserve a brief comment here. First, on the basis of engineering principles and common sense, it is not difficult to appreciate that the output of a dynamic system at any given moment is determined not only by the current input to the system but also by the preceding inputs and outputs of the system (25). This fact emphasizes the importance of history and memory properties of a dynamic system in determining its behavior. Mathematically, contributions of the preceding inputs and outputs to the current output of the system are characterized by the impulse response function of the system in the time domain, which is equivalent to the transfer function of the system in the frequency domain (25). Second, as shown in APPENDIX A, responses of a dynamic system to a step function input include two components. One is the transient response; the other is the steady-state response. Specifically, the transient response contains multiple frequencies, whereas the steady-state response is determined only by the frequency response of the system at the zero frequency. Hence, a proper system analysis must reflect both the steady state and transient characteristics of the system.

Dynamic properties of baroreflex function in humans have been recognized in a previous study (4), which indicated that the heart rate response to a brief baroreceptor stimulation could last for several seconds. More recently, dynamic properties of baroreflex function have been studied by using spontaneous variations in arterial pressure and heart rate (45). Estimation of the transfer function between these two variables confirms the frequency-dependent properties of the baroreflex (9, 30, 34, 45). However, because the underlying mechanisms for generating the rhythmic variations in pressure and heart rate are not always clear, the physiological significance of the transfer function estimated under these conditions has yet to be elucidated (1, 45, 51). For example, an estimated phase between the spontaneous changes in pressure and heart rate at most frequencies below 0.5 Hz has been found neither near 0° nor near 180° (45, 54). This result has been interpreted to reflect both a feedforward effect of heart rate on arterial pressure and a feedback effect of pressure on heart rate (45, 51, 53, 54). However, this

interpretation is derived from the static model of the baroreflex, which assumes that baroreflex mediated changes in heart rate occur only as a consequence of those directionally opposite from changes in arterial pressure (45). On the basis of similar assumptions, a “sequence method” has been proposed to classify the spontaneous variations in pressure and heart rate into either baroreflex or nonbaroreflex mediated sequences (6, 30, 34). However, if spontaneous variations in arterial pressure and heart rate truly reflect a dynamic process, then why should these changes be dictated by the rules derived from the static model of baroreflex function?

In the present study, by using thigh cuff deflation, a moderate acute hypotensive stimulus was generated to perturb the baroreflex without “clamping” or restricting the physiological responses by injection of vasoactive drugs (16). Heart rate responses to the changes in pressure are consistent with a baroreflex-mediated stimulus-response relationship. Identification of this relationship with an AR process confirmed the dynamic properties of the baroreflex. Most importantly, we have observed that the beat-to-beat heart rate response to transient changes in pressure is not always controlled by directional changes in pressure, as would be expected from a static model of baroreflex function (15, 38). Rather, the heart rate response to changes in pressure appears to be controlled by an error signal in the pressure generated by the differences between the pressure values before and after the thigh cuff deflation. These data suggest a “set-point” mechanism for beat-to-beat blood pressure control in a time scale of <1 min. On the basis of previous studies (23, 46), we speculate the following chain of events (Fig. 5): 1) a disturbance to the systemic pressure would cause the baroreceptors to signal the central nervous system; 2) a deviation between the set point (which may reflect the steady-state value of arterial pressure) and the actual pressure occurs; 3) the error signal generated will then control the heart rate response as well as other cardiovascular variables (e.g., vascular resistance and stroke volume) to restore the pressure back to the set-point level before the perturbations. On the basis of this hypothesis, a simplified mathematical model has been developed in APPENDIX B for deriving the transfer func-

Fig. 5. Schematic representation of baroreflex control system. CNS, central nervous system; BP, blood pressure; SV, stroke volume; TPR, total peripheral resistance.



tion relationship between the changes in the pressure and the heart rate.

The concept of a set point for blood pressure control is not new. A previous study (23) indicated that autonomic neural activity, which controls blood pressure and heart rate, is reflexively regulated by an error signal in pressure in reference to its set point. Furthermore, it has been proposed that the set point for blood pressure control may reset centrally and/or peripherally to accommodate steady-state changes in pressure and heart rate (23). However, recent studies (8, 10) suggest that, instead of a single set point, the whole sigmoid curve of the baroreflex may reset rapidly within 20 to 30 s under sustained changes in arterial pressure. These findings have raised doubts about whether an absolute set point exists in the blood pressure control system (10, 41).

Moreover, for long-term time scales over hours and days, it has been well known that blood pressure is controlled by the balance of body fluid volume regulated by the kidney (17, 18). A pressure higher than the set point will cause loss of body fluid, whereas a pressure lower than the set point will cause retention of body fluid. Thus an error signal in pressure plays an essential role in the control of body fluid volume, which in turn buffers the changes in the steady-state pressure.

The present study extends these previous studies by demonstrating that even during short-term intervals of seconds to minutes, a set-point regulatory mechanism may still play an essential role in beat-to-beat blood pressure and heart rate control. We cannot exclude the possibility that a rapid resetting of the baroreflex curves may explain the simultaneous increases in pressure and heart rate observed in the present study. However, recent carefully performed animal studies (8, 32) have shown that rapid baroreflex resetting does not occur or is attenuated when changes in pressure are transient and pulsatile. We hypothesize that a set-point regulatory scheme across different time scales may contribute to an overall homeostasis in blood pressure control even though the regulatory mechanisms for short- versus long-term blood pressure control may be distinctly different.

Interestingly, although the static model of the baroreflex may not be completely accurate when heart

rate or R-R interval is used as the dependent variable during acute changes in pressure, the behavior of the baroreflex does appear to be modeled accurately by a sigmoid curve if baroreceptor afferent nerve activity is used as the dependent variable and the frequency of changes in pressure is low (<1 Hz) (36, 44). Thus whenever baroreceptor afferent nerve activity deviates from its own operating point by a perturbation in pressure, continuous compensatory responses of pressure and heart rate will be elicited until the stimulus to the baroreceptors is diminished. Thus increases or decreases in arterial pressure always lead to directionally similar increases or decreases in baroreceptor afferent nerve activity regardless of the absolute value of heart rate or pressure (36). This speculation is consistent with the characteristics of dynamic changes in pressure and heart rate observed in the present study.

It is important to note, however, that the set point in short-term blood pressure control may reset to a new level if the steady-state arterial pressure has been altered (10). Consequently, heart rate responses to changes in pressure would be controlled by the new set point. The transient heart rate response to acute hypotension during progressive LBNP suggests this possibility. During LBNP, a similar pattern of heart rate responses was observed as that at baseline (Fig. 2). These data suggest a "resetting" of the set point associated with gradual decreases of cardiac filling, stroke volume, and steady-state systolic pressure (26). However, we have also observed that the transient changes in pressure and heart rate did not always follow the set-point predictions precisely at the highest levels of LBNP, suggesting either an interference from the enhanced spontaneous variations in arterial pressure or a degradation of blood pressure control during high degrees of orthostatic stress (59).

Limitations. Two limitations of the present study should be emphasized. First, the specific regulatory mechanisms underlying the transient changes in pressure and heart rate cannot be determined from the data collected. However, on the basis of reported differences in the latency of vagal and sympathetic responses to a sudden change in pressure (11, 12, 57), it is likely that the initial cardioacceleration associated with the rapid fall in pressure after the thigh cuff deflation was mediated primarily by vagal withdrawal.

However, the continuous augmentation of heart rate that follows, associated with the simultaneous increases in pressure, was more likely mediated by both vagal withdrawal and/or concurrent activation of cardiac sympathetic nerve activity (56). Direct recording of sympathetic nerve activity or pharmacological blockade might provide additional insight into these specific mechanisms.

Second, because the magnitude, direction, and rate of pressure changes induced by the thigh cuff deflation could not be controlled in the present study, baroreflex function was not evaluated over a large range of pressure changes in both directions, as might be obtained with other conventional methods (14, 48). Considering the well-known nonlinear properties of baroreceptors in response to transient changes in pressure (12, 27), we are cautious about extending the results obtained in the present study to other situations where changes in blood pressure may have different magnitudes, rates, and directions. However, it should be noted that the thigh cuff deflation-induced changes in pressure were biphasic rather than unidirectional (Fig. 1). Moreover, the transient changes in pressure and heart rate were fitted very well by the linear AR model not only at baseline but also during LBNP and associated with significantly augmented changes in pressure. These data suggest that the method used in the present study for baroreflex identification may be efficacious even when changes in pressure are of different magnitudes, as induced by the thigh cuff deflation.

Mathematical modeling of baroreflex function. In the present study, we demonstrated that the dynamic changes in pressure and heart rate during thigh cuff deflation can be fitted well by a second-order AR model with a pure time delay of 0.75 s. Moreover, the frequency response of the baroreflex showed properties of a low-pass filter with a gradual phase decline from $\sim 180^\circ$ at the very low frequencies. The low-pass filter properties of the baroreflex with a gradual phase decline is intuitive in that as the frequency of changes in pressure rises, the heart rate response to the pressure stimuli will lag more and diminish in amplitude.

However, two limitations should be addressed regarding the modeling strategies in the present study. First, it has been shown that heart rate responses to brief stimuli to baroreceptors are asymmetrical, and, second, adaptation occurs with sustained changes in pressure (12, 27). In addition, the baroreflex saturates with large variations in pressure and has thresholds with small variations in pressure (15, 31). These data suggest intrinsic nonlinearity of the baroreflex in the regulation of heart rate. An important question then arises, Is the linear model assumption of the baroreflex suitable in the present study?

Theoretically, the linearity of a system can be tested according to the principle of superposition. That is, if two or more stimuli are acting on a system, the responses of a linear system are the sum of the effects of each individual stimuli on the system (25). Direct testing of linearity of the baroreflex is difficult to conduct under the current experimental conditions. However,

the efficacy of using linear system analysis methods in the evaluation of baroreflex function has been shown by other investigators (3, 33, 44). For example, in animal studies (22, 44), with open-loop control of the baroreflex, linear properties have been demonstrated in both the afferent traffic of carotid and aortic baroreceptors and in the efferent sympathetic nerve activity in response to dynamic changes in pressure. Additionally, linearity has been shown in the responses of the sinus node to vagal and sympathetic nerve stimuli (5). In humans, under closed-loop conditions, evaluation of baroreflex function using spontaneous variations in arterial pressure and heart rate also has revealed linear properties of baroreflex function (3, 33).

In the present study, we found that heart rate responses to acute hypotension can be fitted well by a second-order AR model, as evidenced by the randomness of the model residuals. These findings support the efficacy of using linear system methods in the present study. Although we caution that a nonlinear relationship between steady-state changes in pressure and heart rate may modulate temporal responses of heart rate to dynamic changes in pressure (2, 15), it is possible that, for a given steady state, when transient changes in pressure are in the physiological range, contribution of nonlinearities may not be significant for the baroreflex control of heart rate. In the present study, the maximal pressure fall induced by the thigh cuff deflation was ~ 16 mmHg at baseline and ~ 34 mmHg at -50 mmHg LBNP. Hence, as a first approximation, linear system analysis should be applicable under the current experimental conditions.

Second, in the present study, for model identification, the transient changes in pressure and heart rate were considered as the input and output of the baroreflex system respectively. This strategy was implemented as if the system performed under open-loop conditions (49). However, we caution that the baroreflex by nature is a proprioceptive reflex (43). Thus, in normal situations, the system must operate under closed-loop conditions.

Identifiability of a system under closed-loop conditions is determined by the specific features of the feedback loop of the system and the properties of external inputs to the system (49). It has been shown that identifiability of a closed-loop system based on input-output data cannot be guaranteed if the input is determined through a linear low-order noise-free feedback from the output (49). Because effects of baroreflex-mediated changes in heart rate (output) on arterial pressure (input) are likely determined through the "triple product" of heart rate, stroke volume, and total peripheral resistance (Fig. 5), it appears unlikely that the effects of heart rate on arterial pressure could be modeled by a linear low-order noise-free system (26). Thus the aforementioned unidentifiable condition may not be applicable in the present study. Furthermore, in the present study, an external perturbation to the arterial pressure was generated by the thigh cuff deflation. A typical baroreflex mediated response in heart rate was observed. We speculate that the identifiability

of baroreflex function may be enhanced by the external perturbations used in the present study (49). In the simplified model of Fig. 5, under linear assumptions, with the presence of external perturbations, it is possible to show that the transfer function between the dynamic changes in pressure and heart rate will reflect the fundamental operating properties of baroreflex function even under closed-loop conditions (see APPENDIX B).

Attempts have been made to quantify baroreflex function under closed-loop conditions from spontaneous changes in arterial pressure and heart rate (1, 3, 33). While the interpretation of these results has been controversial (3, 45), the usefulness of this technique for the evaluation of baroreflex function has been demonstrated in many recent studies (9, 30, 34). Furthermore, with the application of external perturbations to the carotid transmural pressure, it has been shown that the transfer function between the changes in pressure and efferent sympathetic nerve activity identified under closed-loop conditions did not significantly differ from those identified under open-loop conditions (22).

Taken together, although perfect applicability of the modeling strategy for the system identification cannot be demonstrated under the conditions of the present study, considering the remarkable fit of the stimulus-response data with the second-order AR model, the proposed methods appear able to evaluate well the dynamic properties of baroreflex function in humans.

Baroreflex function during LBNP. LBNP has been used extensively to simulate the effects of orthostatic stress on the cardiovascular system (26). Typical cardiovascular responses, including augmented sympathetic nerve activity with LBNP, have been consistently reported in the literature (21, 26, 55). However, findings regarding baroreflex regulation of heart rate during orthostatic stress are much more controversial (13, 35, 37, 50). Earlier work showed that prolongation of R-R intervals provoked with neck suction or infusion of vasoactive drugs either did not change or was diminished with changes in either posture or application of LBNP (13, 37, 50). However, these reports have been challenged by data using both neck pressure and neck suction during LBNP (35). The results of the latter study showed that maximal baroreflex gain calculated from the steep portion of the sigmoidal baroreflex curve significantly increased during LBNP, suggesting a reduction of inhibitory effects from "cardiopulmonary receptors" on the arterial baroreflex regulation of heart rate (35). However, recent studies (9, 19, 20) evaluating baroreflex function using spontaneous changes in arterial pressure and heart rate showed that baroreflex gain significantly decreased during LBNP and with head-up tilt.

One explanation for this discrepancy may be that the stimulation of different baroreceptor populations (i.e., carotid vs. aortic) and different methods used for estimating the baroreflex gain may result in different conclusions, particularly if the operating point has shifted closer to the threshold for baroreceptor stimu-

lation associated with the significant increases in heart rate during orthostatic stress.

In the present study, we found that the heart response to acute hypotension induced by thigh cuff deflation was attenuated at high levels of LBNP. We also found, consistently, that the numerator coefficients of the AR model significantly decreased during LBNP and associated with an overall reduction of transfer function gain. These data suggest that the ability of the baroreflex to regulate heart rate was reduced during LBNP.

However, further analysis showed that the denominator coefficients of the AR model and the curve shape of the transfer function gain remained unchanged during LBNP. These data suggest that the reduced ability of the baroreflex to buffer changes in pressure was due primarily to a reduction of the static gain rather than changes in the dynamic properties of baroreflex function. In other words, these data suggest that the heart rate response to dynamic changes in pressure are preserved during LBNP, whereas the magnitude of steady-state heart rate responses to the steady-state changes in pressure is diminished with the orthostatic stress.

We speculate that, during LBNP, a reduction in pulsatile pressure and/or flow associated with the fall in stroke volume may modulate transduction properties of baroreceptors and therefore attenuate its responsiveness to the maximal changes in pressure (7, 26). However, it is also possible that an augmented sympathetic nerve activity and/or a diminished vagal reserve (i.e., nearly complete vagal withdrawal and therefore limited capacity to shorten R-R interval with further unloading of the baroreceptors) in control of heart rate may contribute to the static gain reduction (37, 40, 47).

Interestingly, the significant reduction in the transfer function gain also occurred at -15 mmHg LBNP and are associated with no significant changes in steady-state arterial pressure and heart rate. Whether the arterial baroreflex is provoked at this low level of LBNP is controversial, even though recent evidence clearly shows changes in aortic dimension making unloading of arterial baroreceptors very likely (52). These data support our findings that the arterial baroreflex may be altered even at low levels of LBNP.

In summary, we have presented a new noninvasive method for the evaluation of baroreflex function in humans. The primary findings are that beat-to-beat heart rate responses to dynamic changes in arterial pressure appear to be controlled by an error signal rather than by directional changes in pressure, suggesting a set-point mechanism in short-term beat-to-beat blood pressure control. Furthermore, we found that dynamic changes in pressure and heart rate during acute hypotension induced by thigh cuff deflation can be fitted well by a second-order AR model, confirming dynamic properties of baroreflex function. Moreover, the frequency response of the baroreflex demonstrated low-pass filter properties. Finally, in applying this method for the evaluation of baroreflex function

during LBNP, we found that the ability of the baroreflex to evoke a heart rate response to transient changes in arterial pressure was reduced during orthostatic stress and this reduction was due primarily to a reduction of the static gain of the baroreflex.

APPENDIX A

Assuming that changes in arterial pressure (i.e., the input) is a step function, the change in heart rate can be obtained from

$$\Delta R_m(z) = \Delta P_m(z)G(z) \quad (1a)$$

where $\Delta R_m(z)$ is the z -transform of changes in heart rate, $\Delta P_m(z)$ is the z -transform of changes in pressure, and $G(z)$ represents the transfer function of the system. Equation 1a provides the total response of the baroreflex function with respect to heart rate. That is, it contains both the transient and steady-state response. To explore this, assume that $G(z)$ is a second-order system with a pure time delay of 0.75 s, as we have shown previously in Eq. 3. Allowing the input, $\Delta P_m(z)$, to be a step function with a magnitude of p_0 , the expression for $\Delta P_m(z)$ becomes

$$\Delta P_m(z) = \frac{p_0}{1 - z^{-1}} \quad (2a)$$

Hence, the total change in heart rate, $\Delta R_m(z)$, is given by

$$\Delta R_m(z) = \frac{z^{-3}b_0p_0}{(1 + a_1z^{-1} + a_2z^{-2})(1 - z^{-1})} \quad (3a)$$

Taking the inverse z -transform of $\Delta R_m(z)$, we get

$$\Delta r_m(k) = [(\beta e^{-j\theta})^{(k-3)} + (\gamma e^{j\theta})^{(k-3)} + \alpha]u(k-3) \quad (4a)$$

where $\Delta r_m(k)$ is the total change in heart rate in time domain; β , θ , γ , and α are functions of b_0 , p_0 , a_1 , and a_2 , respectively; and $[u(k-3)]$ is the discrete unit step function delayed by three sampling intervals (0.75 s). For a stable system, $|\beta| < 1$ and $|\gamma| < 1$.

It is noted that after the input, $\Delta p_m(k)$, is applied to the system, the total response of the system is determined by all the terms in Eq. 4a. However, as time elapses (i.e., $k \rightarrow \infty$), the first two terms inside the bracket in Eq. 4a will diminish

for a stable system (because $|\beta| < 1$ and $|\gamma| < 1$) and only α remains, which reflects the steady-state response. It can be shown that α is given by

$$\alpha = \Delta r_{ss} = \frac{p_0 b_0}{(1 + a_1 + a_2)} \quad (5a)$$

which is the same as shown in Eq. 4.

The first two terms inside the parentheses in Eq. 4a [i.e., $(\beta e^{-j\theta})^{(k-3)}$ and $(\gamma e^{j\theta})^{(k-3)}$] reflect the transient response of the system because they diminish over an extended time horizon. These two terms are functions of the roots of the denominator polynomial of the transfer function $G(z)$ in Eq. 3 [i.e., poles of $G(z)$]. Here, the poles are $\beta e^{-j\theta}$ and $\gamma e^{j\theta}$. It is well established in the linear control system theory that the poles determine the dynamic (i.e., transient) response of a linear system. That is, the position of the poles in the complex z -plane determines whether the system is stable, underdamped (overshoots present in the response), or overdamped (no overshoot present). Furthermore, the poles determine the frequency response characteristics of the system. Specifically, the transfer function poles determine whether the system acts as a low- or high-pass filter.

APPENDIX B

To gain insight into the experimental results obtained in this study, a simplified model of changes in the heart rate and arterial pressure after the thigh cuff deflation is proposed. Figure 6 shows the block diagram of the proposed model.

It is important to note that the model in Fig. 6 is intended to reflect the control process for changes in the arterial pressure and heart rate with respect to their respective levels before the cuff deflation. It does not represent the absolute value of the pressure and the heart rate. Although it is likely that the system governing the changes in pressure and heart rate is more complicated than what is shown in Fig. 6, however, the model in this figure can provide useful insight.

For this model, it is assumed that components are linear. Specifically, it is assumed that $B(z)$, $G_1(z)$, and $G_2(z)$ are linear transfer functions of the baroreceptor, heart rate regulator, and blood pressure regulator, respectively. In this regard, the following parameters are defined: $\Delta P_s(z)$, physi-

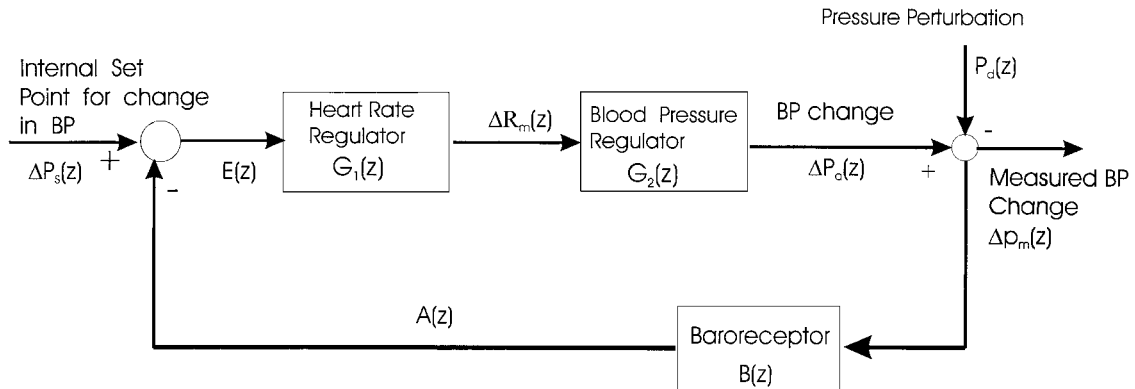


Fig. 6. Simplified model of baroreflex control system with perturbations in arterial pressure induced by thigh cuff deflation. $\Delta P_s(z)$, physiological set point (or desired value) of change in ABP; $A(z)$, change in the afferent signal of baroreceptors, reflecting changes in ABP sensed by the baroreceptors; $E(z)$, difference between $\Delta P_s(z)$ and $A(z)$; $B(z)$, $G_1(z)$, and $G_2(z)$, linear transform functions of the baroreceptor, HR regulator, and ABP regulator, respectively; $\Delta R_m(z)$, change in HR in response to $E(z)$; $\Delta P_d(z)$, change in ABP relating to changes in HR; $P_d(z)$, change in ABP induced by thigh cuff deflation; $\Delta P_m(z)$, change in measured ABP determined by the combined effects of $\Delta P_d(z)$ and $\Delta P_s(z)$.

ological set point (or desired value) of change in arterial pressure; $A(z)$, change in the afferent signal of baroreceptors, reflecting changes in arterial pressure sensed by the baroreceptors; $E(z)$, difference between $\Delta P_s(z)$ and $A(z)$; $\Delta R_m(z)$, change in heart rate in response to $E(z)$; and $\Delta P_a(z)$, change in arterial pressure relating to the changes in the heart rate. It is important to note that $\Delta P_a(z)$ depends not only on $\Delta R_m(z)$ but also on the change in the stroke volume (SV) and the total peripheral resistance (TPR), as we have shown in the Fig. 5. However, for the sake of simplicity, it is assumed that the effects of changes in SV and TPR on $\Delta P_a(z)$ could be integrated into the transfer function of pressure regulator. $P_d(z)$ is the change in the blood pressure induced by the thigh cuff deflation, and $\Delta P_m(z)$ is the change in the measured blood pressure determined by the combined effects of $\Delta P_d(z)$ and $\Delta P_a(z)$.

With the use of the model in Fig. 6, it can be shown that the changes in the heart rate, $\Delta R_m(z)$, is related to the changes in the internal set point, $\Delta P_s(z)$, and pressure perturbation induced by the thigh cuff deflation, $P_d(z)$, in the following manner

$$\Delta R_m(z) = \frac{G_1(z)\Delta P_s(z) + B(z)G_1(z)P_d(z)}{1 + B(z)G_1(z)G_2(z)} \quad (1b)$$

Likewise, the measured changes in blood pressure, $\Delta P_m(z)$, can be expressed in terms of $\Delta P_s(z)$ and $P_d(z)$ as

$$\Delta P_m(z) = \frac{G_1(z)G_2(z)\Delta P_s(z) - P_d(z)}{1 + B(z)G_1(z)G_2(z)} \quad (2b)$$

Hence, the relationship between the measured changes in the heart rate, $\Delta R_m(z)$, and the measured changes in the pressure, $\Delta P_m(z)$, can be obtained from the following equation

$$\frac{\Delta R_m(z)}{\Delta P_m(z)} = \frac{G_1(z)\Delta P_s(z) + B(z)G_1(z)P_d(z)}{G_1(z)G_2(z)\Delta P_s(z) - P_d(z)} \quad (3b)$$

Equations 1b and 2b provide that when there is no perturbation [i.e., $P_d(z) = 0$] and $\Delta P_s(z)$ is nonzero, the $\Delta R_m(z)$ and $\Delta P_m(z)$ are then affected by $\Delta P_s(z)$ as follows

$$\Delta R_m(z) = \frac{G_1(z)\Delta P_s(z)}{1 + B(z)G_1(z)G_2(z)} \quad (4b)$$

$$\Delta P_m(z) = \frac{G_1(z)G_2(z)\Delta P_s(z)}{1 + B(z)G_1(z)G_2(z)} \quad (5b)$$

Alternatively, when $\Delta P_s(z) = 0$, that is, assuming that the physiological set point of changes in pressure remains constant for the short-term blood pressure control and $P_d(z) \neq 0$, the changes in the heart rate and blood pressure are related as (from Eq. 3b)

$$\frac{\Delta R_m(z)}{\Delta P_m(z)} = -B(z)G_1(z) \quad (6b)$$

Equation 6b is of particular interest because it shows that the transfer function between the dynamic changes in pressure and heart rate reflect properties of baroreflex function even under a closed-loop condition. Moreover, it suggests that at the steady state (i.e., $f \rightarrow 0$ in $z = e^{j2\pi fT}$; hence, $z \rightarrow 1$), a rise in the measured blood pressure (i.e., $p_0 > 0$) may yield a drop in the heart rate. Particularly, let

$$\Delta P_m(z) = \frac{p_0}{1 - z^{-1}} \quad (7b)$$

where $p_0 > 0$, reflecting a positive step change in the measured pressure. Note that the resulting change in the heart rate, $\Delta R_m(z)$, can be obtained from the following equation

$$\Delta R_m(z) = -B(z)G_1(z)\Delta P_m(z) = \frac{-p_0B(z)G_1(z)}{1 - z^{-1}} \quad (8b)$$

At the steady state, we have

$$\begin{aligned} \Delta r_{ss} &= \lim_{k \rightarrow \infty} \Delta r_m(k) = \lim_{z \rightarrow 1} (z - 1)\Delta R_m(z) \\ &= \lim_{z \rightarrow 1} \{z[-p_0B(z)G_1(z)]\} = -p_0B(1)G_1(1) \end{aligned} \quad (9b)$$

Hence, if $B(1)G_1(1) > 0$, then the change in the heart rate will be negative, which implies that at the steady state the heart rate will decrease. This is consistent with the expectations from a static baroreflex function.

We thank Dr. Dwain L. Eckberg for constructive comments on the study and manuscript.

This study was supported by American Heart Association Texas Affiliate Grant-In-Aid 98BG058 and National Heart, Lung, and Blood Institute Neurolab Grant HL-53206-03.

REFERENCES

1. **Akselrod S, Gordon D, Madweb JB, Snidman NC, Shannon DC, and Cohen RJ.** Hemodynamic regulation: investigation by spectral analysis. *Am J Physiol Heart Circ Physiol* 249: H867–H875, 1985.
2. **Arndt JO, Dorrenhaus A, and Wiecken H.** The aortic arch baroreceptor response to static and dynamic stretches in an isolated aorta-depressor nerve preparation of cats in vitro. *J Physiol (Lond)* 252: 59–78, 1975.
3. **Baselli G, Cerutti S, Civardi S, Malliani A, and Pagani M.** Cardiovascular variability signals: towards the identification of a closed-loop model of the neural control mechanisms. *IEEE Trans Biomed Eng* 35: 1033–1046, 1988.
4. **Baskerville AL, Eckberg DL, and Thompson MA.** Arterial pressure and pulse interval responses to repetitive carotid baroreceptor stimuli in man. *J Physiol (Lond)* 297: 61–71, 1979.
5. **Berger RD, Saul JP, and Cohen RJ.** Transfer function analysis of autonomic regulation. I. Canine atrial rate response. *Am J Physiol Heart Circ Physiol* 256: H142–H152, 1989.
6. **Bertinieri G, Di Rienzo M, Cavallazzi A, Ferrari AU, Pedotti A, and Mancia G.** Evaluation of baroreceptor reflex by blood pressure monitoring in unanesthetized cats. *Am J Physiol Heart Circ Physiol* 254: H377–H383, 1988.
7. **Chapleau MW and Abboud FM.** Determinants of sensitization of carotid baroreceptors by pulsatile pressure in dogs. *Circ Res* 65: 566–577, 1989.
8. **Chapleau MW, Hajduczuk G, and Abboud FM.** Peripheral and central mechanisms of baroreflex resetting. *Clin Exp Pharmacol Physiol Suppl* 15: 31–43, 1989.
9. **Cooke WH, Hoag JB, Crossman AA, Kuusela TA, Tahvanainen KU, and Eckberg DL.** Human responses to upright tilt: a window on central autonomic integration. *J Physiol (Lond)* 517: 617–628, 1999.
10. **Dorward PK and Korner PI.** Does the brain “remember” the absolute blood pressure? *News Physiol Sci* 2: 10–13, 1987.
11. **Eckberg DL.** Temporal response patterns of the human sinus node to brief carotid baroreceptor stimuli. *J Physiol (Lond)* 258: 769–782, 1976.
12. **Eckberg DL.** Nonlinearities of the human carotid baroreceptor-cardiac reflex. *Circ Res* 47: 208–216, 1980.
13. **Eckberg DL, Abboud FM, and Mark AL.** Modulation of carotid baroreflex responsiveness in man: effects of posture and propranolol. *J Appl Physiol* 41: 383–387, 1976.
14. **Eckberg DL, Cavanaugh MS, Mark AL, and Abboud FM.** A simplified neck suction device for activation of carotid baroreceptors. *J Lab Clin Med* 85: 167–173, 1975.
15. **Eckberg DL and Sleight P.** *Human Baroreflexes in Health and Disease.* Oxford: Clarendon, 1992.

16. Franz GW. On blood pressure control. *Physiologist* 17: 73–86, 1974.
17. Guyton AC. Long-term arterial pressure control: an analysis from animal experiments and computer and graphic models. *Am J Physiol Regulatory Integrative Comp Physiol* 259: R865–R877, 1990.
18. Guyton AC. Blood pressure control—special role of the kidneys and body fluids. *Science* 252: 1813–1816, 1991.
19. Hughson RI, Maillet A, Gharib C, Fortrat JO, Yamamoto Y, Pavy-le Traon A, Riviere D, and Guell A. Reduced spontaneous baroreflex response slope during lower body negative pressure after 28 days of head-down bed rest. *J Appl Physiol* 77: 69–77, 1994.
20. Iwasaki K, Hirayanagi K, and Yajima K. Comparison between the spontaneous baroreceptor reflex sensitivity by the spectral analysis and the sequence method in human during lower body negative pressure. *Jpn J Aero Env Med* 33: 143–150, 1996.
21. Joyner MJ, Shepherd JT, and Seals DR. Sustained increases in sympathetic outflow during prolonged lower body negative pressure in humans. *J Appl Physiol* 68: 1004–1009, 1990.
22. Kawada T, Sugimachi M, Sato T, Miyano H, Shishido T, Miyashita H, Yoshimura R, Takaki H, Alexander J Jr, and Sunagawa K. Closed-loop identification of carotid sinus baroreflex open-loop transfer characteristics in rabbits. *Am J Physiol Heart Circ Physiol* 273: H1024–H1031, 1997.
23. Korner PI. Integrative neural cardiovascular control. *Physiol Rev* 51: 312–367, 1971.
24. Korner PI, West MJ, Shaw J, and Uther JB. “Steady-state” properties of the baroreceptor-heart rate reflex in essential hypertension in man. *Clin Exp Pharmacol Physiol* 1: 65–76, 1974.
25. Lathi BP. *Linear systems and Signals*. Carmichael, CA: Berkeley-Cambridge Press, 1992, p. 249–352.
26. Levine BD, Buckley JC, Fritsch JM, Yancy CW Jr, Watenpugh DE, Snell PG, Lane LD, Eckberg DL, and Blomqvist CG. Physical fitness and cardiovascular regulation: mechanisms of orthostatic intolerance. *J Appl Physiol* 70: 112–122, 1991.
27. Levison WH, Barnett GO, and Jackson WD. Nonlinear analysis of the baroreceptor reflex system. *Circ Res* 28: 673–682, 1966.
28. Liang G, Wikes MD, and Cadzow JA. ARMA identifier with automatic order estimation based on the eigenvalues of the covariance matrix. *IEEE Trans Sign Process* 41: 3003–3009, 1993.
29. Ljung L. Model structure selection and model validation. In: *System Identification*. Upper Saddle River, NJ: Prentice-Hall, 1987, p. 408–431.
30. Mancina G, Groppeli A, Di Rienzo M, Gastiglioni P, and Parati G. Smoking impairs baroreflex sensitivity in humans. *Am J Physiol Heart Circ Physiol* 273: H1555–H1560, 1997.
31. Mancina G and Mark AL. Arterial baroreflex in humans. In: *Handbook of Physiology. Cardiovascular system. Peripheral Circulation and Organ Blood Flow*. Bethesda, MD: Am. Physiol. Soc., 1983, sect. 2, vol. III, pt. 2, chapt. 20, p. 755–793.
32. Mendelowitz D and Scher AM. Pulsatile pressure can prevent rapid baroreflex resetting. *Am J Physiol Heart Circ Physiol* 258: H92–H100, 1990.
33. Mullen TJ, Appel ML, Mukkamala R, Mathias JM, and Cohen RJ. System identification of closed-loop cardiovascular control: effects of posture and autonomic blockade. *Am J Physiol Heart Circ Physiol* 272: H448–H461, 1997.
34. Parati G, Frattola A, Di Rienzo M, Gastiglioni P, Pedotti A, and Mancina G. Effects of aging on 24-h dynamic baroreceptor control of heart rate in ambulant subjects. *Am J Physiol Heart Circ Physiol* 268: H1606–H1612, 1995.
35. Pawelczyk JA and Raven PB. Reductions in central venous pressure improve carotid baroreflex responses in conscious men. *Am J Physiol Heart Circ Physiol* 257: H1389–H1395, 1989.
36. Pelletier CL, Clement DL, and Shepherd JT. Comparison of afferent activity of canine aortic and sinus nerves. *Circ Res* 31: 557–568, 1972.
37. Pickering TG, Gribbin B, Petersen ES, Gunningham JC, and Sleight P. Effects of autonomic blockade on the baroreflex in man at rest and during exercise. *Circ Res* 30: 177–185, 1972.
38. Pickering GW, Gribbin B, and Sleight P. Comparison of the reflex heart rate response to rising and falling arterial pressure in man. *Cardiovasc Res* 6: 277–283, 1972.
39. Potts JT, Shi XR, and Raven PB. Carotid baroreflex responsiveness during dynamic exercise in humans. *Am J Physiol Heart Circ Physiol* 265: H1928–H1938, 1993.
40. Robinson BF, Epstein SE, Beiser GD, and Braunwald E. Control of heart rate by the autonomic nervous system. *Circ Res* 19: 400–411, 1966.
41. Rowell LB. Arterial baroreflexes, central command, and muscle chemoreflexes: a synthesis. In: *Human Cardiovascular Control*. New York: Oxford University Press, 1993, p. 441–483.
42. Rowell LB, Hermansen L, and Blackman JR. Human cardiovascular and respiratory responses to graded muscle ischemia. *J Appl Physiol* 41: 693–701, 1976.
43. Sagawa K. Baroreflex control of systemic arterial pressure and vascular bed. In: *Handbook of Physiology. The Cardiovascular System. Peripheral Circulation and Organ Blood Flow*. Bethesda, MD: Am. Physiol. Soc., 1983, sect. 2, vol. III, pt. 2, chapt. 14, p. 453–496.
44. Sato T, Kawada T, Shishido T, Miyano H, Inagaki M, Miyashita H, Sugimachi M, Knuepfer MM, and Sunagawa K. Dynamic transduction properties of in situ baroreceptors of rabbit aortic depressor nerve. *Am J Physiol Heart Circ Physiol* 274: H358–H365, 1998.
45. Saul JP, Berger RD, Albrecht P, Stein SP, Chen MH, and Cohen RJ. Transfer function analysis of the circulation: unique insights into cardiovascular regulation. *Am J Physiol Heart Circ Physiol* 261: H1231–H1245, 1991.
46. Scher AM. Carotid and aortic regulation of arterial blood pressure. *Circulation* 56: 521–528, 1977.
47. Schobel HP, Oren RM, Mark AL, and Ferguson DW. Influence of resting sympathetic activity on reflex sympathetic responses in normal man. *Clin Auton Res* 5: 71–80, 1995.
48. Smyth HS, Sleight P, and Pickering GW. Reflex regulation or arterial pressure during sleep in man. *Circ Res* 24: 109–120, 1969.
49. Soderstrom T and Stocia P. Identification of systems operating in closed loop. In: *System Identification*. Hertfordshire, UK: Prentice Hall, 1989, p. 381–406.
50. Takeshita A, Mark AL, Eckberg DL, and Abboud FM. Effect of central venous pressure on arterial baroreflex control of heart rate. *Am J Physiol Heart Circ Physiol* 236: H42–H47, 1979.
51. Taylor JA and Eckberg DL. Fundamental relations between short-term RR interval and arterial pressure oscillations in humans. *Circulation* 93: 1527–1532, 1996.
52. Taylor JA, Halliwill JR, Brown TE, Hayano J, and Eckberg DL. “Nonhypotensive” hypovolaemia reduces ascending aortic dimensions in humans. *J Physiol (Lond)* 483: 289–298, 1995.
53. Toska K and Eriksen M. Respiration-synchronous fluctuations in stroke volume, heart rate and arterial pressure in humans. *J Physiol (Lond)* 472: 501–512, 1993.
54. Triedman JK, Cohen RJ, and Saul JP. Mild hypovolemic stress alters autonomic modulation of heart rate. *Hypertension* 21: 236–247, 1993.
55. Victor RG and Leimbach WNJ. Effects of lower body negative pressure on sympathetic discharge to leg muscles in humans. *J Appl Physiol* 63: 2258–2262, 1987.
56. Wallin BG and Nerhed C. Relationship between spontaneous variations of muscle sympathetic activity and succeeding changes of blood pressure in man. *J Auton Nerv Syst* 6: 293–302, 1982.
57. Warner HR and Russell RO Jr. Effect of combined sympathetic and vagal stimulation on heart rate in the dog. *Circ Res* 24: 567–573, 1969.
58. Williamson JW, Mitchell JH, Olesen HL, Raven PB, and Secher NH. Reflex increase in blood pressure induced by leg compression in man. *J Physiol (Lond)* 475: 351–357, 1994.
59. Zhang R, Zuckerman JH, and Levine BD. Deterioration of cerebral autoregulation during orthostatic stress: insights from the frequency domain. *J Appl Physiol* 85: 1113–1122, 1998.