Estimation of arterial and cardiopulmonary total peripheral resistance baroreflex gain values: validation by chronic arterial baroreceptor denervation

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The technique has been shown to respond to an increase in central venous transmural pressure (CVTP) by decreasing TPR (21).

Almost all existing techniques for characterizing this autonomically mediated TPR baroreflex mechanism involve perturbing blood pressure with an external stimulus, measuring the steady-state TPR response, and constructing a stimulus–response curve whose slope indicates the system gain value. The external stimuli that have been employed may be broadly classified as selective or nonselective (18). Selective stimuli (e.g., variable pressure neck chamber) are intended to excite, and permit the study of, one baroreflex system. Although selective stimuli have provided much insight into TPR baroreflex functioning, they open the feedback loop between the baroreflex and circulation and thereby preclude its study during normal physiological conditions. Moreover, the tenet that only one set of baroreceptors has been perturbed may not always be valid. In contrast, nonselective stimuli (e.g., upright tilting) excite both baroreflex systems simultaneously and can preserve normal closed-loop conditions. However, the individual contribution of each baroreflex system to the measured TPR response cannot be distinguished from a simple stimulus–response curve analysis.

Raymundo et al. (21) introduced a more sophisticated, multiple-regression analysis to distinguish the individual gain values of each TPR baroreflex. With this analysis, these investigators demonstrated in five conscious dogs laying quietly that 1) the arterial and cardiopulmonary TPR baroreflex systems both contribute significantly to TPR control during relatively normal physiological conditions, and 2) chronic arterial baroreceptor denervation causes the gain value of the arterial TPR baroreflex (G_A) to reduce to zero (as expected) and the gain value of the cardiopulmonary TPR baroreflex (G_C) to increase by about a factor of three (perhaps due to a central compensatory mechanism). However, their analysis requires a complex experimental preparation in which invasive hemodynamic measurements are obtained during large, nonselective perturbations to the ventricular pacing rate (after atroventricular block) and blood volume and has not been repeated. Thus a more simple technique to elucidate the normal, integrated functioning of arterial and cardiopulmonary baroreflex control of TPR could be of significant value.

To this end, we have previously proposed a technique for estimating G_A and G_C under closed-loop conditions by mathematical analysis of beat-to-beat fluctuations in ABP, cardiac output (CO), and stroke volume (SV) (19). Thus the technique...
may not require the application of any external stimuli and could be employed in humans with totally noninvasive measurement methods [e.g., Doppler ultrasound (9) and finger-cuff photoplethysmography (14)]. We have also demonstrated the theoretical validity of the technique with respect to realistic beat-to-beat variability generated by a cardiovascular simulator in which the actual TPR baroreflex gain values were exactly controlled (19).

In this paper, we review the technique with additional details and present its experimental evaluation with respect to spontaneous beat-to-beat hemodynamic variability measured from seven conscious dogs before and after chronic arterial baroreceptor denervation. The specific aim of this study was to determine whether the technique could correctly predict the changes in $G_A$ and $G_C$ that are expected to occur following the chronic arterial baroreceptor denervation.

**METHODS**

**Mathematical Analysis Technique**

Assumption 1: **TPR baroreflex systems are defined as in the block diagram.** The technique, which was initially presented in Ref. 19, mathematically analyzes beat-to-beat hemodynamic fluctuations to quantitatively characterize the arterial and cardiopulmonary TPR baroreflex systems, as defined in the block diagram of Fig. 1. This block diagram is based on the work of Raymundo et al. (21) and specifically defines the arterial TPR baroreflex as the system that couples ABP fluctuations to TPR fluctuations and the cardiopulmonary TPR baroreflex as the system that couples CVTP fluctuations to TPR fluctuations. Because Raymundo et al. found no statistical evidence of nonlinear baroreflex behaviors (over a wider hemodynamic range than that attained by spontaneous beat-to-beat fluctuations) from their multiple-regression analysis, the two baroreflex systems are considered here to be linear as well as time invariant (LTI). The block diagram also includes a noise source $N_{TPR}$, which is unmeasured and reflects the residual variability in TPR that is not accounted for by the baroreflex systems. Such variability may be due to, for example, local vascular control mechanisms (see Ref. 11).

The block diagram of Fig. 1 suggests that the transfer functions or impulse responses (i.e., time-domain representation of transfer functions) characterizing the arterial and cardiopulmonary TPR baroreflex systems as well as the power spectrum of $N_{TPR}$ can be estimated by applying standard system identification methods (17, 24) to beat-to-beat measurements of ABP, CVTP, and TPR. However, techniques for directly measuring beat-to-beat fluctuations in TPR are unavailable. Furthermore, invasive procedures are required to measure CVTP. The technique, therefore, considers only continuous measurements of ABP and CO to be available for analysis, since, as discussed above, these measurements could be obtained noninvasively in humans. With this limited information, the technique aims to estimate $G_A$ and $G_C$ rather than the entire TPR baroreflex impulse responses. (Note that $G_A$ and $G_C$ are equivalent to the areas of the corresponding TPR baroreflex impulse responses.) To do so, the technique utilizes physiological knowledge and assumes that the spontaneous fluctuations in all of the involved signals are sufficiently small and stationary, such that they may be coupled via an LTI system (see Discussion).

Assumption 2: **TPR fluctuations are reflected in the coupling between CO and ABP fluctuations.** The most obvious approach to account for the unobserved TPR fluctuations is to directly estimate them from the measured signals. However, in Ref. 19, we showed how this approach can preclude reliable estimation of $G_A$ and $G_C$. The technique, therefore, exploits the concept that the dynamic couplings between the measured fluctuations reflect the fluctuations in TPR that are caused by the baroreflex. For example, consider the ABP response to a step change in CO under a simpler scenario in which the cardiopulmonary TPR baroreflex is inactive (i.e., $G_C = 0$). If the arterial TPR baroreflex were also inactive (i.e., $G_A = 0$), then, by Ohm’s law, the steady-state fractional change in ABP would equal the fractional change in CO (i.e., a unity gain value; see Fig. 2). However, if the arterial TPR baroreflex were active (i.e., $G_A < 0$), then the steady-state fractional change in ABP would be less than that of CO due to the accompanying drop in TPR (see Fig. 2), with a smaller steady-state fractional ABP change indicating greater arterial TPR baroreflex functioning. Thus, by identifying the step response (integral of impulse response) relating CO fluctuations to ABP fluctuations, $G_A$ could be determined from its asymptotic value (area of impulse response). Of course, the study of Raymundo et al. (21) clearly demonstrates that the cardiopulmonary baroreflex plays a significant role in TPR control, and the technique must, therefore, account for the unmeasured CVTP fluctuations as well.

Assumption 3: **SV fluctuations are a surrogate for CVTP fluctuations.** The technique specifically assumes that the fluctuations in left ventricular (LV) SV, which may be computed from the measured CO signal, are an adequate surrogate for the unmeasured CVTP fluctuations (see Discussion). The assumption is specifically that the present SV variation is completely determined by the past fluctuations in CVTP through a LTI relationship. The impulse response that precisely couples the CVTP fluctuations to the SV fluctuations characterizes the input-output relationship of the heart-lung unit (12). The gain value of the heart-lung unit is equal to the right ventricular (RV) diastolic compliance (12). With this impulse response inverted, the CVTP fluctuations may then be completely specified by the SV fluctuations convolved with an impulse response, which may be thought of as characterizing the inverse dynamic properties (output-input relationship) of the heart-lung unit (inverse heart-lung unit). The gain value of the inverse heart-lung unit is, therefore, equal to the reciprocal of the RV diastolic compliance. Importantly, however, when the fluctuations in the SV and CVTP signals are normalized by their respective mean values (which will be the case, henceforth, for all considered signals $X$, as indicated by $\bar{X}$), the gain value of the inverse heart-lung unit is always equal to one and is no longer dependent on the RV diastolic properties.

**Conceptual implementation of the technique.** By assuming that the linear TPR baroreflex systems are defined as in Fig. 1 (Assumption 1), ABP fluctuations are due to CO fluctuations and TPR fluctuations in a linear fashion, as implied in Fig. 2 (Assumption 2), and CVTP fluctuations are precisely specified by SV fluctuations via a linear relationship as discussed above (Assumption 3), the block diagrams in Figs. 3 and 4 follow through linear systems theory. Figure 3 illustrates the physiological systems that the technique specifically seeks to estimate from the available beat-to-beat measurements via standard system identification (step 1 of the technique). Figure 4 shows physiological models of the internal functioning of these two systems, which demonstrate that they reflect the dynamic properties of the arterial and cardiopulmonary TPR baroreflex systems (i.e., the systems that the technique is ultimately aiming to quantify). Below, we
describe the physiological models and show how the technique computes \( G_A \) and \( G_C \) from the identified impulse responses of the physiological systems in Fig. 3, based on the physiological models (step 2 of the technique).

\( CO \rightarrow ABP \) (in Fig. 3), which represents the coupling from \( CO \) fluctuations to \( ABP \) fluctuations, encompasses the dynamic properties of the arterial TPR baroreflex and the systemic arterial tree, as shown in the physiological model of Fig. 4A. The systemic arterial tree characterizes the mechanical properties of the systemic arteries and specifically couples \( CO \) fluctuations to \( ABP \) fluctuations, as well as TPR fluctuations to \( ABP \) fluctuations. The physiological model of Fig. 4A indicates that an increase in \( CO \) would initially cause \( ABP \) to increase via the systemic arterial tree. This would, in turn, excite the arterial TPR baroreflex/systemic arterial tree loop to decrease TPR so as to maintain \( ABP \). \( G_A \) may be exactly computed from the gain value of \( CO \rightarrow ABP \) (which is determined in step 1 of the technique), since the gain value of the systemic arterial tree is always equal to one due to the normalization of the analyzed signals with their respective mean values (see Fig. 2 and Eqs. 1 and 2 below). Because of the signal normalization, \( G_A \) here is a dimensionless quantity. This quantity indicates the steady-state percent change in TPR (with respect to its mean value) that would occur, if the arterial TPR baroreflex were stimulated by an \( X \% \) step change in \( ABP \) (with respect to its mean value) while the cardiopulmonary TPR baroreflex was inactive through the product of \( X \) and \( G_A \).

\( SV \rightarrow ABP \) (in Fig. 3), which represents the coupling from \( SV \) fluctuations to \( ABP \) fluctuations, encompasses the dynamic properties of the arterial TPR baroreflex and cardiopulmonary TPR baroreflex, as well as the inverse heart-lung unit and systemic arterial tree, according to the physiological model in Fig. 4B. This physiological model illustrates that an increase in \( SV \) would indicate that an increase in CVTP had occurred through the inverse heart-lung unit. This CVTP increase would excite the cardiopulmonary TPR baroreflex to decrease TPR, which would then stimulate the arterial TPR baroreflex/systemic arterial tree loop to increase TPR and maintain \( ABP \). The physiological model here may appear to be counterintuitive, since the increase in \( SV \) does not initially cause an increase in \( CO \) and thus \( ABP \) through the systemic arterial tree. The reason is that \( SV \rightarrow ABP \) is mathematically defined to represent the effects of \( SV \) fluctuations on \( ABP \) fluctuations, while \( CO \) and all other inputs to \( ABP \) are held constant. (Likewise, the physiological model of Fig. 4A does not include the cardiopulmonary TPR baroreflex, since \( SV \) is constant.) This implies that the increase in \( SV \) must be accompanied by a commensurate decrease in heart rate (HR). \( G_C \) may be exactly computed from the gain values of both \( SV \rightarrow ABP \) and \( CO \rightarrow ABP \) (which are determined in step 1 of the technique; see Eqs. 1 and 2 below) and may be interpreted analogously to \( G_A \).
Mathematical implementation of the technique. Step 1 of the technique (i.e., identification of the physiological models and noise source in Fig. 3) is achieved with the following dual-input, autoregressive exogenous input (ARX) model:

\[
\frac{\Delta \text{ABP}(t)}{\text{ABP}} = \sum_{i=1}^{m} a_i \frac{\Delta \text{ABP}(t-i)}{\text{ABP}} + \sum_{i=0}^{n} b_i \frac{\Delta \text{CO}(t-i)}{\text{CO}} + \sum_{i=0}^{p} c_i \frac{\Delta \text{SV}(t-i)}{\text{SV}} + W_{\text{ABP}}(t)
\]

where \( t \) is discrete time, and \( W_{\text{ABP}} \) is the unmeasured residual error. The three sets of unknown parameters \( (a_i, b_i, c_i) \) fully define the power spectrum of \( W_{\text{ABP}} \) (17). The terms \( m, n, \) and \( p \) limit the number of parameters (model order). The parameter values are estimated from 5- to 10-min intervals of beat-to-beat fluctuations in \( \text{CO}, \text{SV}, \) and \( \text{ABP} \) signals, normalized by their respective mean values and resampled to 0.5 Hz (19) by minimizing the variance of the residual error in conjunction with a model order reduction algorithm (20). Then, according to the physiological models in Fig. 4, step 2 of the technique (i.e., computation of \( G_A \) and \( G_C \)) is achieved with the parameter sets estimated from step 1 as follows:

\[
G_A = \left( \sum_{i=0}^{n} b_i + \sum_{i=1}^{m} a_i - 1 \right) \sum_{i=0}^{n} b_i, \quad G_C = \sum_{i=0}^{p} c_i \sum_{i=0}^{n} b_i
\]

Experimental Procedures

The hemodynamic data utilized in the present study were originally collected to address different specific aims, and the materials and surgical methods are presented in substantial detail elsewhere (15). We briefly describe here the most basic aspects of the experimental procedures that were relevant to the present study. All procedures were reviewed and approved by the Wayne State University Animal Investigation Committee.

Seven conscious dogs (20–25 kg) of either sex were studied. Through a series of aseptic surgeries, chronic instrumentation was installed in each dog to measure continuous \( \text{ABP} \) (via a catheter positioned in the side branch of the aorta and attached to an external transducer; Transpac IV, Abbott Laboratories), \( \text{CO} \) (via a 20-mm blood flow probe placed around the ascending aorta; Transonic Systems), HR (via a cardiotachometer triggered by the CO signal), and other hemodynamic variables. After recovery from the instrumentation surgeries, the beat-to-beat hemodynamic data were recorded (WindaqPro, Datag Instruments) for approximately 10 min while the dog was standing quietly. Then, baroreceptor denervation was accomplished by transection of the aortic depressor and the carotid sinus nerves. Completeness of the baroreceptor denervation was confirmed by observing the lack of any HR response to an intravenous bolus infusion of phenylephrine, which increased mean \( \text{ABP} \) by \( \approx 40 \) mmHg. Finally, \( \approx 2 \) wk after the completion of the arterial baroreceptor denervation surgeries, the beat-to-beat hemodynamic data were again recorded for \( \approx 10 \) min while the dog was standing quietly.

Data Analysis

The mean, standard deviation (SD), and power spectra of the beat-to-beat \( \text{ABP}, \text{CO}, \) and \( \text{SV} \) data were first computed for each of the two conditions of each animal. Then, the mathematical analysis technique was applied to these data sets. Finally, paired \( t \)-tests were performed to determine whether the estimated \( G_A \) and \( G_C \) values were significantly altered from the control condition to the chronic arterial baroreceptor denervation condition. A \( P < 0.05 \) was considered to be statistically significant.

RESULTS

Table 1 and Fig. 5, respectively, illustrate the group average (mean ± SD over the seven dogs) of the mean and SD of the beat-to-beat \( \text{ABP}, \text{CO}, \) and \( \text{SV} \) data and sample power spectra (from a single dog) of these same data before and after chronic arterial baroreceptor denervation. These results indicate that the baroreceptor denervation had hardly any effect on the mean hemodynamic values but did alter the variability characteristics about the mean values, with the most prominent change being a large increase in \( \text{ABP} \) variability.

Table 6 illustrates the group average estimates (mean ± SD) of \( G_A \) and \( G_C \) before and after chronic arterial barorece-

### Table 1. Group average of the mean and SD of the beat-to-beat variability

<table>
<thead>
<tr>
<th>Hemodynamic Variability</th>
<th>Mean Before (SD)</th>
<th>Mean After (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{ABP}, \text{mmHg} )</td>
<td>105.9 ± 12.3</td>
<td>117.2 ± 14.0</td>
</tr>
<tr>
<td>( \text{CO}, \text{l/min} )</td>
<td>4.8 ± 0.6</td>
<td>4.8 ± 0.8</td>
</tr>
<tr>
<td>( \text{SV}, \text{ml} )</td>
<td>46.1 ± 6.0</td>
<td>37.7 ± 4.9</td>
</tr>
<tr>
<td>( \text{HR}, \text{beats/min} )</td>
<td>108.4 ± 11.8</td>
<td>127.1 ± 15.3</td>
</tr>
</tbody>
</table>

Values are mean over the seven dogs ± SD over the seven dogs. \( \text{ABP} \), arterial blood pressure; \( \text{CO} \), cardiac output; \( \text{SV} \), stroke volume; \( \text{HR} \), heart rate.
tor denervation. These results indicate that the technique predicted that chronic arterial baroreceptor denervation caused the magnitude of GA to reduce to nearly zero (i.e., arterial TPR baroreflex functioning was lost) and the magnitude of GC to more than double (i.e., cardiopulmonary TPR baroreflex functioning was enhanced). Moreover, Fig. 6 indicates that these GA and GC changes were both statistically significant.

DISCUSSION

Experimental Results

In our experiments, the mean hemodynamic values did not change after the chronic arterial baroreceptor denervation (see Table 1), which is consistent with the notion that the baroreflex is not important in long-term blood pressure regulation (see Fig. 18-8 in Ref. 11). Thus the mean hemodynamic values here are “blind” to baroreflex functioning. In contrast, the fluctuations in the hemodynamic variables about their mean values were altered by the chronic arterial baroreceptor denervation (see Table 1 and Fig. 5). These alterations were especially apparent in ABP, in which there was a substantial increase in variability due to the reduced ability to maintain blood pressure. However, with conventional analyses of beat-to-beat variability (e.g., SD, power spectra), it is virtually impossible to “see” the effects of the baroreceptor denervation specifically on TPR baroreflex functioning (see Table 1 and Fig. 5).

Our technique mathematically analyzed the couplings between the beat-to-beat fluctuations in ABP, CO, and SV to predict that chronic arterial baroreceptor denervation abolished arterial TPR baroreflex functioning (as expected) while enhancing cardiopulmonary TPR baroreflex functioning (perhaps due to a central compensatory mechanism). Although the numerical gain values reported by Raymundo et al. (21) are different (due to, for example, differences in signal normalization schemes), these predictions are entirely consistent with the pattern of findings of Raymundo et al. However, as discussed above, these investigators employed a multiple-regression analysis method to measure the gain values, which required a more complex experimental preparation and large hemodynamic perturbations.

Assumptions of the Mathematical Analysis Technique

SV as a surrogate for CVTP. To be able to determine GC from potentially noninvasive measurements, our technique assumes that LV SV fluctuations are an adequate surrogate for CVTP fluctuations. In general, beat-to-beat changes in LV SV are caused by changes in LV preload (left atrial transmural pressure), LV afterload (ABP), and ventricular contractility (VC). However, Sagawa et al. showed that spontaneous fluctuations in VC are very small at rest (see Ref. 22 and references therein). By accordingly regarding the contribution of resting VC changes to SV changes to be negligible and based on the experimental data of Herndon and Sagawa (12) (also see Fig. 9-8 in Ref. 11), steady-state SV changes may be regarded as proportional to steady-state CVTP changes, provided that mean ABP and CVTP are not excessively high. Note that the preceding point is most critical to our technique for estimating TPR baroreflex gain values.

On the other hand, as just indicated, beat-to-beat LV SV changes are not determined by just CVTP changes. However, our assumption is specifically that the present CVTP fluctuation is determined by a future LV SV fluctuation as well as present and past LV SV fluctuations. Note that, by inversion, this assumption may be interpreted as the present LV SV fluctuation is determined by the past CVTP fluctuations. Thus all of these CVTP fluctuations may at least partly account for LV preload and afterload variability. Actually, the ARX for-
mulation that we have utilized to estimate CO→ABP and SV→ABP (see Eq. 1) may be interpreted such that the assumption is that the present LV SV fluctuation is determined by the past ABP and CVTP fluctuations. Thus these past fluctuations may fully account for afterload variability and partially account for preload variability. Finally, while this assumption may not be entirely correct, the experimental results we present here (see Fig. 6) indicate that the assumption may be sufficiently valid to at least detect large changes in TPR baroreflex functioning.

Linearity. Our technique also assumes that spontaneous fluctuations in hemodynamic signals measured at rest are sufficiently small, such that they may be related by linear models. Indeed, Chon et al. (6) demonstrated that second-order nonlinear couplings accounted for only a small fraction of human beat-to-beat HR fluctuations, whereas, as discussed above, Raymundo et al. (21) showed that nonlinear TPR baroreflex effects were insignificant in conscious dogs over an even wider physiological range. We appreciate the important previous investigations concerning nonlinear baroreflex behaviors such as cross talk between the two baroreflex systems (e.g., Refs. 5, 26). However, many nonlinear baroreflex behaviors that have been observed were elicited with larger perturbations. Moreover, many studies demonstrating nonlinearity give results consistent with linear responses for small perturbations (e.g., Refs. 4, 13). However, we note that linear models are only valid around the system’s current operating point (e.g., mean hemodynamic values). That is, they cannot be assumed to be indicative of small signal system behavior around a significantly different operating point. Thus, when the mean hemodynamic values are significantly altered, the technique must be reapplied to the observed spontaneous hemodynamic variability so as to determine $G_A$ and $G_C$ under the new system operating point.

Sufficiently informative inputs. To be able to estimate both linear TPR baroreflex gain values, our technique further assumes that the fluctuations in the measured signals are sufficiently informative. Mathematically speaking, this means that the spectral density matrix of CO and SV is positively definite for at least as many frequency components as the number of parameters that are utilized to represent CO→ABP and SV→ABP (24). Practically speaking, this means that 1) the beat-to-beat fluctuations in both CO and SV contain sufficient spectral content, and 2) significant HR variability is present (to preclude a trivial relationship between CO and SV fluctuations). Our technique specifically assumes that naturally occurring, beat-to-beat hemodynamic fluctuations usually satisfy each of these conditions. This assumption is based on numerous studies showing that the spectral content of HR variability is usually present at and below the respiratory frequency (e.g., Refs. 1, 2), as well as recent studies showing similar spectral characteristics for SV and CO fluctuations (e.g., Refs. 23, 25). Other than respiration, the ultimate sources of spontaneous hemodynamic fluctuations are not well understood. As proposed in Refs. 1 and 2, vasomotor activity perturbing TPR (e.g., the autoregulation of local vascular beds) may be an important source of low-frequency fluctuations (<0.15 Hz). Note that, in the present study, HR variability following chronic arterial baroreceptor denervation may have been sufficiently preserved (see Table 1) via a central compensatory mechanism.

Fig. 6. Experimental evaluation results of the mathematical analysis technique depicted in Figs. 3 and 4. The bar graphs illustrate the resulting group average (mean ± SD) arterial TPR baroreflex gain values ($G_A$) and cardiopulmonary TPR baroreflex gain values ($G_C$) over seven conscious dogs before and after chronic arterial baroreceptor denervation. These results indicate that the technique predicted that the baroreceptor denervation abolished arterial TPR baroreflex functioning (as expected) and enhanced cardiopulmonary TPR baroreflex functioning (perhaps due to a central compensatory mechanism). These results are consistent with the multiple regression analysis method for quantifying $G_A$ and $G_C$, which requires a more complex experimental preparation and large hemodynamic perturbations (21).
Validated by the model of this physiological system becomes the sum identified (via a single-input ARX equation). However, in this follows:

\[ G_L = \frac{1 + G_C}{1 - G_A} \]

Thus, when HR variability is insignificant, the technique estimates \( G_L \) and therefore cannot distinguish between the functioning of the arterial and cardiopulmonary TPR baroreflex systems. However, note that \( G_L \) provides a quantitative measure of the lumped functioning of the two TPR baroreflex systems.

In conclusion, the present experimental validation study demonstrates that our mathematical analysis technique with its underlying assumptions can indeed detect large changes in the functioning of both the arterial and cardiopulmonary TPR baroreflex systems induced by chronic arterial baroreceptor denervation from only spontaneous, beat-to-beat information in ABP, CO, and SV. With further successful testing, the technique may ultimately be employed to advance the basic understanding of integrated functioning of both TPR baroreflex systems in humans and animals during physiological and pathological conditions, such as peripheral autonomic neuropathy due to diabetes mellitus and congestive heart failure.

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