Non-Invasive Identification of the Total Peripheral Resistance Baroreflex Impulse Response from Spontaneous Hemodynamic Variability

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Abstract

We propose a novel technique for identifying the impulse response characterizing the total peripheral resistance (TPR) baroreflex by mathematical analysis of spontaneous, beat-to-beat fluctuations in arterial blood pressure, cardiac output, and stroke volume. The technique may therefore provide a complete linear dynamic characterization of the TPR baroreflex during normal, closed-loop conditions from only non-invasive measurements. We then describe a theoretical evaluation of the technique against realistic beat-to-beat variability generated by a cardiovascular simulator whose actual dynamic properties were exactly known. We report that the technique accurately estimated the TPR baroreflex impulse response as well as other key cardiovascular parameters for a range of simulator parameter values.

1. Introduction

Feedback control of total peripheral resistance (TPR) by the arterial and cardiopulmonary baroreflex systems is a well-known mechanism for short-term blood pressure regulation. The conventional approach for characterizing this TPR baroreflex mechanism involves perturbing blood pressure with an external stimulus, measuring the steady-state TPR response, and constructing a stimulus-response curve whose slope indicates the system static gain. Although the conventional approach has provided insight into TPR baroreflex functioning, it has two major limitations. One limitation stems from the application of the external stimulus, which may be regarded as either selective or non-selective [1]. Selective stimuli (*e.g.*, variable pressure neck chamber) aim to excite, and permit the study of, one baroreflex system. However, these stimuli open the feedback loop between the baroreflex and circulation and thereby preclude its study during normal physiologic conditions. In contrast, non-selective stimuli (*e.g.*, upright tilting) excite both baroreflex systems simultaneously and preserve normal closed-loop conditions. However, the contribution of each baroreflex system to the measured TPR response cannot be distinguished from a simple stimulus-response curve analysis. While Raymundo et al introduced and convincingly validated a more sophisticated multiple regression analysis to distinguish the static gains of each TPR baroreflex [2], their technique requires a complex experimental preparation in which both the ventricular rate and blood volume are perturbed and has therefore received little attention. The other limitation of the conventional approach (and the technique of Raymundo et al) is that it only provides a static characterization of the TPR baroreflex without revealing potentially useful dynamic information (*e.g.*, latencies and time constants). Thus, a practical technique is needed to elucidate the normal, integrated, and dynamic functioning of the arterial and cardiopulmonary baroreflex control of TPR.

To this end, we recently introduced a technique for estimating the static gains of the arterial TPR baroreflex (G_A) and the cardiopulmonary TPR baroreflex (G_C) by mathematical analysis of beat-to-beat fluctuations in arterial blood pressure (ABP), cardiac output (CO), and stroke volume (SV) [3]. In this paper, we propose an extension to the mathematical analysis so as to identify the TPR baroreflex impulse response. The technique may therefore provide a complete linear dynamic characterization of the TPR baroreflex without the application of any external stimuli and from totally non-invasive measurement methods (*e.g.*, Doppler ultrasound and arterial tonometry). We then describe a theoretical evaluation of the technique against realistic beat-to-beat variability generated by a cardiovascular simulator [3] whose actual dynamic properties were exactly known.

2. The mathematical analysis technique

Our previous technique for mathematically estimating G_A and G_C is described in detail in [3]. We first review this technique at the conceptual level and then describe a novel extension of the technique so as to estimate the linear dynamic properties of the TPR baroreflex.

Our previous technique quantitatively characterizes the arterial and cardiopulmonary TPR baroreflex systems as defined in the block diagram of Figure 1. This block diagram is based on the work of Raymundo et al [2] and specifically defines the arterial TPR baroreflex as the system that couples fluctuations in ABP to TPR and the

cardiopulmonary TPR baroreflex as the system that couples fluctuations in central venous transmural pressure (CVTP) to TPR. Since Raymundo et al found no statistical evidence of nonlinear baroreflex behaviors, the baroreflex systems here are considered 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.

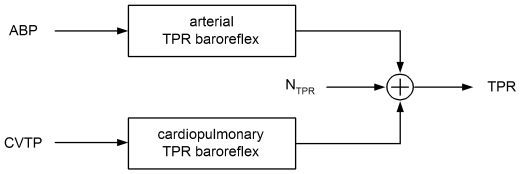

Figure 1. Short-term TPR control mechanisms [2].

The block diagram here suggests that the impulse responses characterizing the arterial and cardiopulmonary TPR baroreflex systems (and the power spectrum of N_{TPR}) can be determined by applying standard system identification analysis [4] to beat-to-beat measurements of ABP, CVTP, and TPR. However, techniques for directly measuring beat-to-beat fluctuations in TPR are not available. 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 these measurements may be obtained non-invasively in humans.

To account for the unobserved TPR fluctuations, the technique exploits the concept that the dynamic coupling between fluctuations in CO and ABP reflects the fluctuations in TPR that are caused by the baroreflex. To understand this concept, consider the ABP response to a step change in CO under a simpler scenario in which the cardiopulmonary TPR baroreflex is inactive. If the arterial TPR baroreflex were also inactive, then, by Ohm's law, the steady-state fractional change in ABP would equal the fractional change in CO (*i.e.*, a unity static gain; see Figure 2). However, if the arterial TPR baroreflex were active, then the steady-state fractional change in ABP would be less than that of CO due to the accompanying drop in TPR (see Figure 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 fluctuations in CO to ABP, G_A may be determined from its asymptotic value (area of impulse response).

Since the cardiopulmonary baroreflex also plays a major role in short-term TPR control, the technique must account for the unmeasured CVTP fluctuations as well. To do so, the technique assumes that the past, present, and future fluctuations in left ventricular SV, which may be derived from the measured CO, are an adequate surrogate for the present fluctuation in CVTP. This assumption is supported by the following experimental evidence: 1) steady-state SV changes are exclusively determined by steady-state CVTP changes provided that mean ABP<~180 mmHg [5]; 2) ventricular contractility changes little at rest [6]; and 3) pulmonary ABP is relatively constant due to recruitment and distension [5].

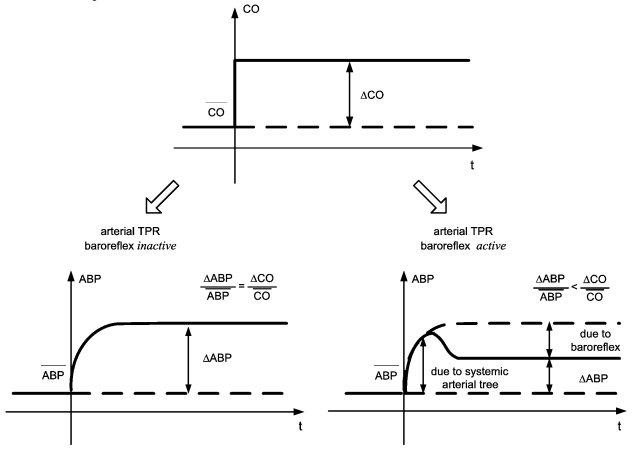

Figure 2. Conceptual basis of the technique.

By accounting for the unobserved TPR and CVTP fluctuations as described above (and assuming that the involved fluctuations are sufficiently small and stationary to be coupled by LTI systems), the block diagrams in Figures 3 and 4 may be derived. Figure 3 shows the physiologic systems that the technique specifically seeks to identify from the observed signals via a standard autoregressive exogenous input method [4] (step 1). Figure 4 illustrates physiologic models of the internal functioning of these two systems, which show that they reflect the dynamic properties of the arterial and cardiopulmonary TPR baroreflex systems. We now describe these physiologic models and how the technique computes G_A and G_C from the identified impulse responses of the physiologic systems in Figure 3 (step 2).

CO→ABP, which represents the coupling from fluctuations in CO to ABP, encompasses the dynamic properties of the arterial TPR baroreflex and the systemic arterial tree as shown in the physiologic model of Figure 4a. The systemic arterial tree characterizes the mechanical properties of the systemic arteries and specifically couples fluctuations in CO to ABP and fluctuations in TPR to ABP. The physiologic model here 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. Importantly, when the fluctuations in ABP and CO are

normalized with respect to their mean values (as will be the case for all considered variables), the static gain of systemic arterial tree is always equal to one (see Figure 2). Thus, G_A may be computed from the static gain of CO→ABP (determined in step 1) according to Figure 4a.

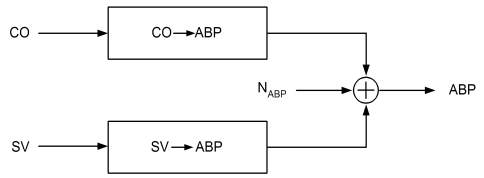

Figure 3. Block diagram for step 1 of the technique. (N_{ABP} is residual ABP variability not due to CO and SV.)

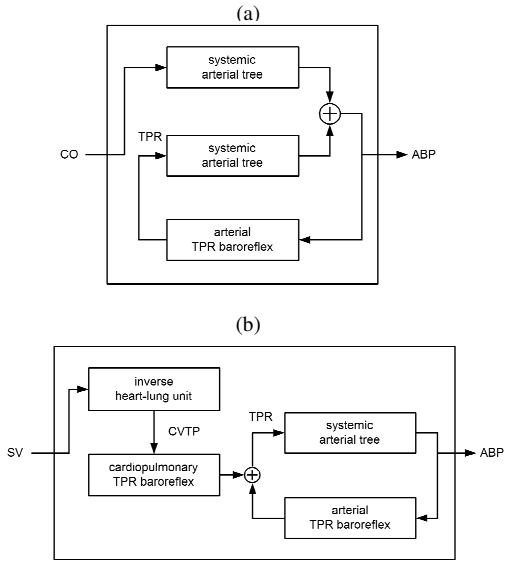

Figure 4. Block diagrams for step 2 of the technique.

SV→ABP, which represents the coupling from fluctuations in SV to ABP, encompasses the dynamic properties of the arterial and cardiopulmonary TPR baroreflex systems as well as the systemic arterial tree and inverse heart-lung unit according to the physiologic model of Figure 4b. The inverse heart-lung unit characterizes what may be thought of as the inverse dynamic properties of the heart-lung unit [5] and is assumed to precisely couple fluctuations in SV to CVTP (see above). The physiologic model here illustrates that an increase in SV would indicate that an increase in CVTP had occurred through this inverse heart-lung unit. The CVTP increase would excite the cardiopulmonary TPR baroreflex to decrease TPR, which would then stimulate the arterial TPR baroreflex/systemic arterial tree loop in order to increase TPR and maintain ABP. Because of the signal normalization, the inverse heart-lung unit static gain is also always equal to one. Thus, G_C may be computed from the static gains of SV→ABP and CO→ABP (determined in step 1) according to Figure 4.

To extend this technique so as to estimate the TPR baroreflex impulse response, we revisit the physiologic model of Figure 4a. This model suggests that the arterial TPR baroreflex impulse response may be computed from the identified CO→ABP impulse response, if the systemic arterial tree impulse response were known. While the static gain of the systemic arterial tree is always unity, its system dynamics are generally unknown. We therefore specifically propose to extend the technique by also estimating the systemic arterial tree impulse response from the observed signals. To do so, we draw upon the following physiologic knowledge: 1) the distributed systemic arterial tree may be regarded as a lumped system governed by a single time constant τ equal to the product of TPR and the lumped arterial compliance (AC) *for the slow, beat-to-beat fluctuations considered here* [7] and 2) TPR baroreflex dynamics are delayed with respect to, and slower than, systemic arterial tree dynamics [3]. Thus, the extended technique estimates τ and the systemic arterial tree impulse response via $(1/\tau)\exp(-t/\tau)u(t)$ (where $u(t)$ is the unit step function) by least squares fitting of $(1-\exp(-t/\tau))u(t)$ to the first three seconds of the CO→ABP step response in which the TPR baroreflex has yet to be activated (see Figure 2). Since we do not propose a method to estimate the inverse heart-lung unit impulse response, the extended technique does not provide a direct estimate of the cardiopulmonary TPR baroreflex impulse response (see Figure 4b). However, since each TPR baroreflex system is governed by the α-sympathetic nervous system, it may be reasonable to assume that their dynamics are the same (*i.e.*, the TPR baroreflex impulse responses differ only by a scale factor.)

3. Theoretical evaluation

We theoretically evaluated the technique based on a human cardiovascular simulator that we previously developed and demonstrated to generate realistic short-term, beat-to-beat variability [3]. Briefly, the major components of the simulator are a circulatory system, a short-term regulatory system, and resting perturbations. The circulatory system consists of contracting left and right ventricles, systemic arteries and veins, and pulmonary arteries and veins. The systemic arteries are specifically modeled as a third-order system accounting for viscous, compliant, and inertial effects. The regulatory system comprises arterial and cardiopulmonary baroreflex control of heart rate (HR), TPR, systemic venous unstressed volume (SVUV), and ventricular contractility as well as a direct neural coupling between respiration and HR. Each baroreflex effector system is

specifically modeled as a static non-linearity to account for saturation followed by linear dynamics. The resting perturbations include respiratory activity, stochastic disturbances to TPR and SVUV, and *1/f* HR fluctuations.

Our specific aim was to determine if the technique could accurately estimate, and detect changes in, the arterial TPR baroreflex impulse response, G_C, and τ. To address this aim, we conducted a series of simulations under different sets of parameter values. For each set of parameter values, we repeated the simulation 50 times to determine the mean and 95% confidence intervals of the estimates. To evaluate the estimates, we established the corresponding actual τ value by taking the product of the total AC and the mean TPR and the actual arterial and cardiopulmonary TPR baroreflex impulse responses by isolating these systems from the simulator, applying an impulse input to each system, and measuring the TPR response. The areas of these impulse responses were then computed so as to establish the actual G_A and G_C values.

4. Results

Figure 5 illustrates the actual and estimated arterial TPR baroreflex impulse responses for different simulator G_A values, while the Table shows the actual and estimated G_C for different simulator G_C values as well as the actual and estimated τ for different simulator total AC values. These results show that the technique was able to accurately estimate, and detect changes in, the arterial TPR baroreflex impulse response and τ. Because SV fluctuations do not perfectly represent CVTP fluctuation, the results also indicate that the technique consistently underestimated $|G_C|$. Importantly however, the technique was able to detect changes in the simulator G_C value.

5. Summary and conclusions

In summary, we have proposed a novel, non-invasive technique to estimate the arterial and cardiopulmonary TPR baroreflex impulse responses and the dominant time constant of the systemic arterial tree by mathematical analysis of spontaneous, beat-to-beat fluctuations in ABP, CO, and SV. We have also validated the technique with respect to realistic beat-to-beat variability generated by a cardiovascular simulator whose actual system dynamics were exactly determined. Importantly, such a precise evaluation could not have been achieved with an experimental model in which the actual system dynamics would be virtually impossible to ascertain. In the future, we plan to experimentally evaluate the technique using interventions with known baroreflex effects.

Acknowledgements

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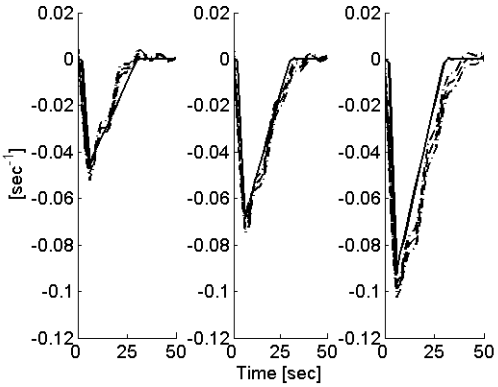

Figure 5. Actual (solid) and estimated (mean (dash) ± 95% confidence intervals (dash-dot)) arterial TPR baroreflex impulse responses.

Table. Actual and estimated (mean±95% confidence intervals) G_C and τ values.

G_C [unitless]		τ [sec]	
actual	estimate	actual	estimate
-0.37	-0.15±0.02	1.06	1.13±0.02
-0.55	-0.29±0.02	1.56	1.64±0.03
-0.74	-0.50±0.03	2.08	2.19±0.05

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