Identification of Open-loop Transfer Functions in Closed-loop Baroreflex System using Random Breathing in Humans

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Abstract

The existence of feedback loop in the baroreflex system makes it difficult to determine the open-loop transfer function characteristic of the central arc by which blood pressure (BP) modulates sympathetic nerve activity (SNA) and the peripheral arc by which SNA modulates BP. Random aortic pressure perturbation and electrical stimulation of aortic depressor nerve have been proposed to identify these open-loop characteristics under closed-loop conditions in animals, but are limited of application in humans. We explored the random breathing technique to identify open-loop characteristics under closed-loop condition in 14 healthy subjects (10m/4f, 27±2years, mean±S.E.). Random interval breathing (RB) can perturb BP with white noise characteristics over the physiologically relevant frequency range of 0.01-0.3 Hz. We measured the muscle SNA of the peroneal nerve and the continuous BP. The peripheral arc transfer function (SNA→BP) could be approximated by a second-order low-pass filter and the fitted parameters of dynamic gain, natural frequency, damping ratio, and lag time were 1.12±0.35, 0.06±0.01 Hz, 0.49±0.14, and 1.05±0.26 s, respectively. The central arc transfer function (BP→SNA) could be approximated by a first-order high-pass filter and the fitted parameters of dynamic gain, corner frequency, and lag time were 1.75±0.28, 0.17±0.04 Hz, and 0.57±0.18 s, respectively. In conclusion, the proposed random breathing technique is an useful tool of assessment in human autonomic nervous system for identification of open-loop transfer functions in the closed-loop baroreflex system.

1. Introduction

In the circulatory system, a change in carotid sinus pressure causes a carotid sinus baroreflex control mediated alteration of efferent sympathetic nerve activity. This also modulates arterial pressure [1]. The existence of this feedback loop in the baroreflex system makes its open-loop transfer function difficult to be determined by means of conventional frequency domain approaches based on the Fourier transformation. The broad-band respiratory perturbation is one of the most extensively studied influences on human autonomic nervous system [5]. The characteristics of baroreflex system can be noninvasively determined over a wide range of physiologically relevant frequencies. The closed feedback loop of carotid sinus baroreflex system can be generally decomposed into two major arcs, central arc and peripheral arc. The estimated transfer function from carotid sinus pressure to efferent sympathetic nerve activity would represent the frequency response characteristic of central arc. The estimated transfer function from efferent sympathetic nerve activity to arterial pressure would represent the frequency response characteristic of peripheral arc.

This study was proposed to estimate the open-loop transfer function characteristics of human carotid sinus baroreflex system under closed-loop condition by using random breathing as an exogenous perturbation. This perturbation technique makes it possible to identify the open-loop transfer function characteristics of baroreflex control with the closed-loop identification method [8].

2. Methods

We studied fourteen volunteers (10males/4females, 27±2years, mean±S.E.) in resting supine position. Instantaneous lung volume, muscle sympathetic nerve activity, and blood pressure were measured during a period of random breathing perturbation for at least six minutes after recording base line. Broad-band respiration activity is elicited by instructing volunteers to follow triangular waveforms with their inspiration and expiration. The dept and duration of respiration are randomly selected on the IBM laptop screen. In the closed-loop identification protocol, we perturbed the carotid sinus baroreflex according to random breathing with the broadened frequencies between 0.01 Hz and 0.3 Hz [5]. Signals were digitized by a 14-bit analog-to-digital converter with a sampling rate of 500 Hz per channel. The muscle sympathetic nerve activity was measured using a pair of tungsten microelectrodes inserted percutaneously into the peroneal nerve at the fibular head. Details regarding of this technique has been published previously [6]. The pre-amplified nerve signal was full-wave rectified and then was integrated by a resistance-capacitor circuit with a time constant of 0.1 s. The smoothed envelope of nerve signal was referred as integrated muscle sympathetic nerve activity (IMSNA). Since the absolute voltage of nerve activity depends on various physiological conditions such as positioning of the electrodes and size of the nerves, we expressed the amplitude of IMSNA in arbitrary unit (a.u.).

2.1. Data analysis

The recorded data were normalized to reduce the difference of amplitude scale. The normalized data were analyzed starting at 1 minute after the onset of the perturbation. We then resampled the data at 10 Hz with an anti-aliasing filter. The 6-min resampled data were then subdivided into 50% overlapping bins of 1,024 data points (102.4 s) per segment [8]. The linear trend removal and Hanning window were applied to each segment before subsequent calculation of the open-loop transfer functions. We applied Fourier transformation and obtained power spectra of blood pressure [BP(f)], integrated muscle sympathetic nerve activity [SNA(f)], and random breathing [RB(f)]. The crosspower spectra between signals were calculated for each segment and then ensemble-averaged over segments to reduce spectral variance [7]. The coherence between BP and SNA was also estimated.

2.2. Closed-loop identification

Figure1 schematizes the closed-loop system where the aortic pressure is directly propagated to the carotid sinus baroreceptors. This system identification relies on an exogenous perturbation. This approach has been popularly used to demonstrate in animal model study [8] and in humans [3]. In this framework, the equations of sympathetic nerve activity and blood pressure can be written as

$$SNA(f) = H_1(f) \cdot BP(f) + U(f) \qquad (1)$$

$$BP(f) = H_2(f) \cdot SNA(f) + V(f) + H_x(f) \cdot RB(f) \qquad (2)$$

Calculating the ensemble average of crosspower spectra between terms of equation 1 and RB(f). We have,

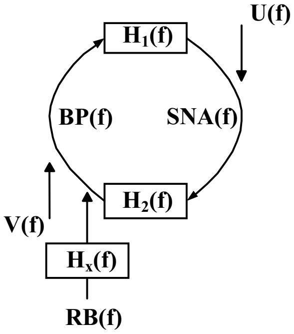

Fig. 1. Closed-loop identification in frequency domain. $H_1(f)$ and $H_2(f)$ represent the central and peripheral arc transfer functions, respectively. SNA(f), BP(f), and RB(f) represent Fourier transforms of sympathetic nerve activity, blood pressure, and random respiration, respectively. U(f) and V(f) represent unknown internal noises in SNA(f) and BP(f), respectively. $H_x(f)$ denotes transfer function from perturbation RB(f) to BP(f).

$$E[S_{SNA \cdot RB}(f)] = H_1(f) \cdot E[S_{BP \cdot RB}(f)] + E[S_{U \cdot RB}(f)] \qquad (3)$$

Because $E[S_{U.RB}(f)]$ converges to zero by virtue of the white-noise nature of RB(f), we can obtain an unbiased estimate of $H_1(f)$ as follow.

$$H_1(f) = \frac{E[S_{SNA \cdot RB}(f)]}{E[S_{BP \cdot RB}(f)]} \qquad (4)$$

Once we obtain $H_1(f)$, we can estimate U(f) from equation 1 and $H_2(f)$ can be estimated as the following equation.

$$H_2(f) = \frac{E[S_{BP \cdot U}(f)]}{E[S_{SNA \cdot U}(f)]} \qquad (5)$$

3. Results

The actual recordings obtained from one volunteer are shown in Figure 2. The magnitudes of power spectral density of random respiratory signal were fairly constant up to 0.3 Hz and diminished to noise level at higher frequencies as shown in Figure 3. So, we estimated the open-loop transfer functions of the baroreflex system up to 0.3 Hz. In Figure 4, the mean coherence is above 0.5 along frequency range from 0.02 Hz to 0.25 Hz, indicating that the changes in integrated muscle SNA were highly linearly dependent on those in BP. Contrary to this finding, at higher frequencies than 0.25 Hz the coherence values were lower than 0.5, indicating that the changes in integrated muscle SNA and BP did not linearly depend on each other.

As observed in Figure 5, the peripheral arc transfer function has a peak at 0.25 Hz. It might be related to a resonance frequency close to the normal breathing

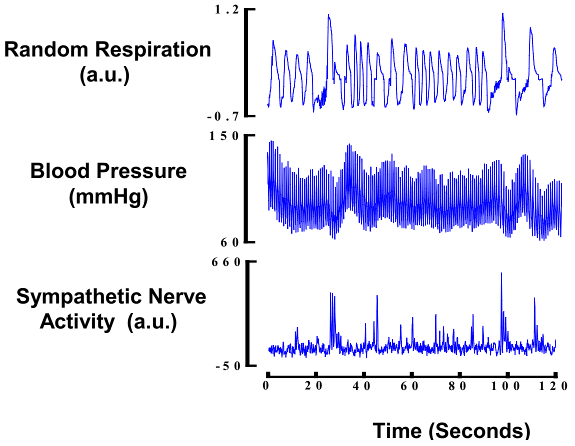

Fig. 2. Measured random respiration (*top*), blood pressure (*middle*), and integrated muscle sympathetic nerve activity (*bottom*) under closed-loop condition during random breathing perturbation.

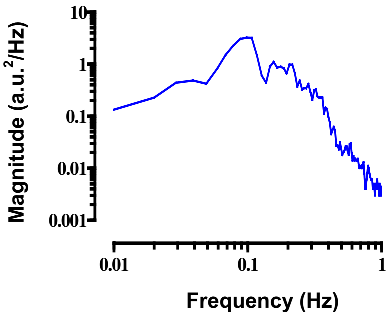

Fig. 3. Mean power spectra of the random respiration from fourteen healthy volunteers.

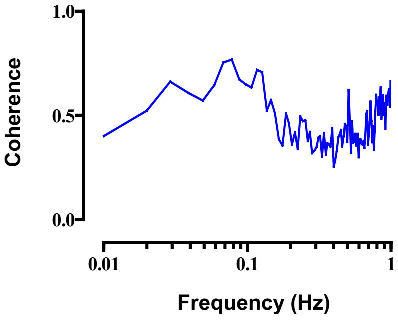

Fig. 4. Mean coherence between the sympathetic nerve activity and the blood pressure under closed-loop condition.

frequency. For the transfer function of central arc, the S.E. values seemed to be very small along the interested frequency range of 0.01-0.3 Hz. However, the S.E. values seemed to disperse around the lower frequency range from 0.01 Hz to 0.05 Hz which were physiologically very low breathing frequencies and difficult to follow for volunteers. The peripheral arc transfer characteristic also shows some variations in the very low frequency range from 0.01 Hz to 0.1 Hz. It was less for higher frequencies above 0.1 Hz.

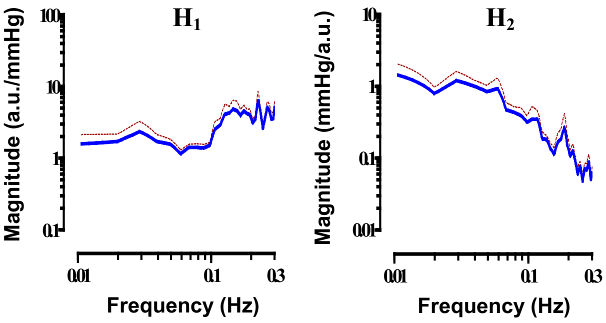

Fig. 5. Mean open-loop transfer functions of central arc (left) and peripheral arc (right) show the high-pass filter characteristic and low-pass filter characteristic, respectively. Solid lines and dash lines indicate mean and S.E. values, respectively.

3.1. Model fitting

The estimated central arc transfer function was fitted to a first-order high-pass filter and the estimated peripheral arc transfer function was fitted to a second-order low-pass filter with the iterative nonlinear least-square regression [9]. For the peripheral arc characteristic, the estimated gain, corner frequency, damping ratio, and lag time determined by fitting were 1.12±0.35, 0.06±0.01 Hz, 0.49±0.14, and 1.05±0.26 s, respectively. The estimated gain, corner frequency, and lag time for the central arc characteristic determined by fitting were 1.75±0.28, 0.17±0.04 Hz, and 0.57±0.18 s, respectively.

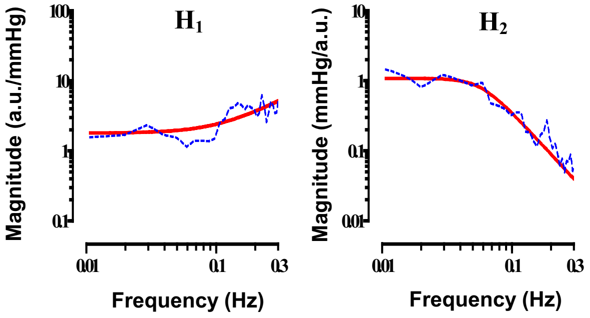

Fig. 6. Model Fittings of central (left) and peripheral (right) arc transfer function. Dashed lines and solid lines indicate estimated open-loop transfer functions and the best fitted model functions, respectively.

3.2. Validation of estimation

The correlation factor between the calculated power spectra (from estimated transfer function of central arc) and the power spectra of measured SNA was determined. The calculated power spectra of SNA can be found by multiplying the squared open-loop transfer function of central arc with the power spectra of measured BP. We also determined the correlation factor for BP from the peripheral arc. The coefficients of correlation (0.92 and 0.94 for SNA and BP, respectively) were found to be significant at level 0.001 for all fourteen volunteers.

4. Discussion

It has been shown that the closed-loop nonparametric method with an exogenous perturbation of random breathing could identify the open-loop transfer functions reasonably well. The central and peripheral arc transfer functions represent the high-pass and low-pass filter characteristics, respectively. The coherence values were less than unity for all frequencies. This implies that substantially internal noise was present in sympathetic nerve activity in term of linear system relationship. This noise consists of physiological internal fluctuations, nonlinear system responses, and physical noise associated with the recording process itself. The exogenous perturbation increased variations both in blood pressure and sympathetic nerve activity, while not affecting the magnitude of unknown internal noise. The conventional estimation of open-loop transfer functions under closed-loop condition is biased by feedback effect of internal noises on SNA and BP. Identification of the peripheral transfer function with the closed-loop identification approach is dependent on the magnitude of unknown internal noise in sympathetic nerve activity. It should be noted that any nonlinear responses of the sympathetic nerve activity to the baroreceptor pressure input can be mathematically treated as the unknown internal noise. Therefore, increasing the magnitude of exogenous perturbation might be expected to improve the system identification.

Several noninvasive techniques have been applied to perturb the baroreflex system: neck suction [2] and lower body negative pressure [4]. Although neck suction causes excitation of the carotid sinus baroreceptors, other baroreflex systems such as the aortic arc baroreflex would oppose the action of the carotid sinus baroreflex. The method of lower body negative pressure is promising as a means of blood pressure perturbation. However, with the lower body negative pressure, the pressure perturbation is imposed on the venous side rather than the arterial side. We should investigate the question of identification of arterial baroreflex function using venous perturbations before extrapolating to its utility in the framework of closed-loop system identification.

5. Conclusion

The application of the random breathing perturbation is useful to identify open-loop transfer functions of central and peripheral arc. This nonparametric frequency domain approach allows for investigation of the baroreflex control not only under normal conditions, but also under pathophysiological conditions.

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