Assessment of Baroreflex Sensitivity by the Closed-Loop Blood Pressure to Interbeat Interval Transfer Function

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Abstract

Noninvasive baroreflex sensitivity (BRS) measurements in humans — by computation of the transfer function from systolic blood pressure to interbeat interval — are basically assessments, because they are made under closed-loop blood pressure control. Our study aims to compare such closed-loop BRS assessments with true open-loop BRS values by means of a simulation model of the human blood pressure control system.

Simulations were done with the TenVoorde model, modified by removing respiration and by adding a pressure probe, adjustable autonomic and hemodynamic conditions, and a switch to open/close the loop. True, open-loop BRS values ranged from 1 to 23 ms/mmHg. Closed-loop BRS assessments differed between –5 to +4.0% from the open-loop values. Our results demonstrate that, under physiological and pathological conditions, noninvasive closed-loop BRS measurements assess true open-loop BRS with virtually no bias.

1. Introduction

Noninvasive baroreflex sensitivity (BRS, the reflex-induced increase in the interval between heartbeats per mmHg arterial blood pressure rise) assessment relies on the spontaneous fluctuations in blood pressure and heart rate. By using spectral analysis, i.e, computation of the systolic blood pressure to interbeat interval transfer function, the confounding influence of respiration can effectively be removed by applying high frequency, 0.25 Hz, metronome respiration, well above the frequency band of interest, namely, the low-frequency band (LF, 0.05-0.15 Hz). In the LF band both the orthosympathetic and the parasympathetic limbs of the baroreflex to the heart are operational [1]. BRS is expressed as one number, representing the averaged modulus of the transfer function in this band. [2]

Whether or not the modulus of the blood-pressure-to-interbeat-interval transfer function really represents baroreflex vigor is not obvious. Baroreflex induced changes in heart rate, cardiac contractility and peripheral vasoconstriction are fed back to the baroreceptors in the form of blood pressure changes. Hence, all clinical measurements are inherently made in a *closed-loop* control system. If the open-loop transfer function is thought to represent true BRS, the closed-loop transfer function can at best be regarded as an estimator of BRS. Clinical applicability of noninvasive BRS assessment depends on the error thus made.

To our knowledge, only two groups have investigated this topic [3,4], with different results. Our study aims to contribute to this unresolved issue by means of simulations with a mathematical model, in open-loop and closed-loop conditions, for low and high baroreflex gains and for physiological and pathological hemodynamic and autonomic conditions.

2. Methods

For our study we elaborated a simulation model on the basis of the TenVoorde model as recently published by TenVoorde and Kingma [5]. The here used model is outlined in Figure 1, and will henceforth be called the "modified TenVoorde model". Like the original model, the modified TenVoorde model of the human cardiovascular control system consists of a beat-to-beat hemodynamic part — Starling heart, Windkessel — and a continuous neural control part with different dynamics for the sympathetic and vagal branches.

At the baroreceptors, the systolic blood pressure (SBP) is compared with a reference value. This results in an error signal. In the model, this signal — denoted as 'Effective SBP' — is a pressure signal, but it actually represents the afferent neural traffic that provides the autonomic nervous system with blood pressure information.

After some delay, the autonomic nervous system reacts with modulating autonomic signals that are proportional to the incoming effective SBP. These autonomic signals are added to the sympathetic and vagal tones. The resulting autonomic outflow is fed to the sinus node (where the interbeat interval IBI is generated), and to the

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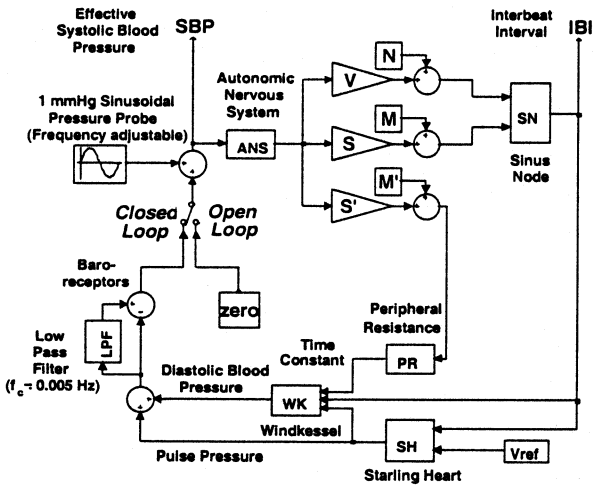

Figure 1. The modified TenVoorde model. Parameters marked with '*' are adjustable. M* = sysmpathetic tone (heart); M'* = sympathetic tone (peripheral resistance); N* = vagal tone; S* = sympathetic gain (heart); S'* = sympathetic gain (peripheral resistance); V* = parasympathetic gain; Vref = stroke volume at 1 s filling time.

peripheral resistance. The Starling heart fills throughout the interbeat interval: a larger IBI value causes a larger stroke volume. Stroke volume determines the Starling heart's pulse pressure.

Diastolic blood pressure is controlled by the Windkessel time constant τ (under influence of the dynamically changing peripheral resistance), by IBI, and by the pulse pressure. Finally, the systolic blood pressure (SBP) is computed by adding the diastolic blood pressure and the pulse pressure. For a complete description of TenVoorde model, we refer to [5].

We removed some complexity of the original TenVoorde model: respiration (irrelevant when in clinical practice high frequency metronome respiration is applied), the contractility branch and the orthosympathetic influence on venous return (marginal effects on variability in stroke volume). A pressure probe signal at the baroreceptors was substituted for the noise source. This sinusoid signal with a 1 mmHg amplitude that is superimposed on SBP allows for generation of IBI and SBP variability at different frequencies, the quotient of which constitutes the transfer function [6].

To simulate different physiological and pathological conditions, we placed baroreflex gains (V, S and S'), and autonomic tones (N, M, M') were made explicit and adjustable. By replacing the constant blood pressure set point by a low-pass filtered value of SBP, we achieved that different settings of the sympathovagal balance result in different average heart rate and systolic blood pressure values. This baroreceptor resetting mechanism greatly increases the dynamics of the model.

Finally, a switch was incorporated, to open or close the feedback loop. In the open loop state the pressure probe fluctuations constitute the sole input for the arterial baroreflex arc. This switch thus facilitates the open- and closed-loop simulations needed for the computation of the SBP-to-IBI gain for the feed-back branch alone, and for the (real-life) intact situation, respectively.

The three autonomic tone parameters M, N, M' and cardiac stroke volume Vref, were set as two fixed combinations to represent either normal, physiological, or abnormal, pathological resting conditions. (see Table 1). The pathological parameter settings assumably represent a serious condition that resembles congestive heart failure, as the parameter values yield a heart rate of 90 bpm (instead of 60 bpm for the normal parameter settings) and also yield a decreased stroke volume. The three baroreflex gains S, S', and V were set at nine different combinations (see Table 1).

For the so defined eighteen combinations, both the open- and closed-loop transfer functions were computed. For each transfer function 100 simulations of 500 s duration were run, at pressure probe frequencies of 0.003-0.3 Hz, step 0.003 Hz.

3. Results

As opposed to open-loop conditions, closed-loop simulations have reduced SBP and IBI fluctuations for the lowest (<0.05 Hz) frequencies, while there is resonance with higher amplitudes in the LF band.

Figure 2 depicts the results for three situations (i.e., normal baroreflex, strong baroreflex, and sympathetic predominance to the peripheral resistance), under physiological and pathological conditions. A high gain to the periphery is a prerequisite for strong resonance (Fig. 2, panels B1, C1, B2, C2). SBP variability is not sensitive to the gains to the heart (Fig. 2, panels B1 and C1), while IBI varibility increases over the whole frequency band with higher baroreflex gain to the heart (Fig. 2, panels B2 and C2). Closed-loop transfer functions are larger than the open-loop transfer functions in the lowest frequencies, and cross the open-loop transfer functions near the resonance frequency (Fig. 2, panels A3, B3 and C3).

Table 1 shows the closed-loop (assessed) and open-loop (true) BRS values and the errors for all simulated combinations. The closed-loop BRS assessment is almost equal to the true BRS: the largest difference was 5.2% underestimation. The averaged absolute error is larger (the maximal error was 13.1%). Obviously, the larger absolute errors are not specifically associated with larger BRS over- or underestimations.

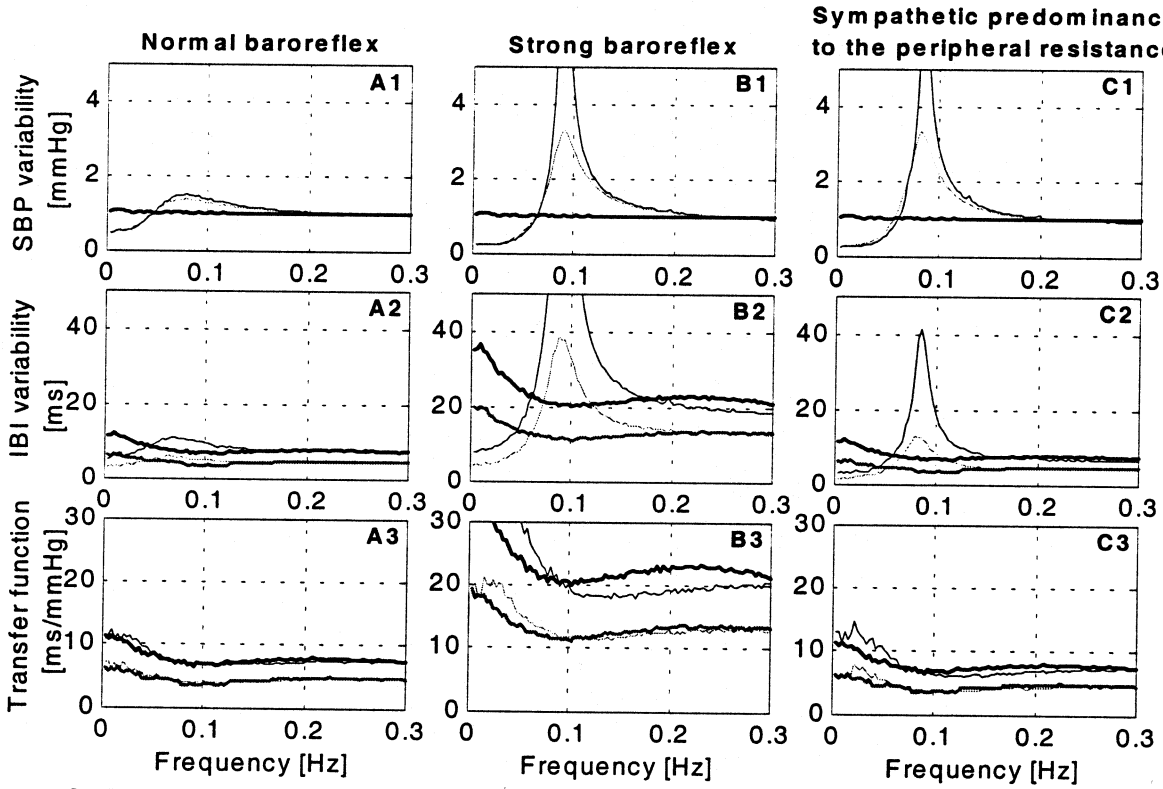

Figure 2. Results for normal baroreflex (panels A1-A3), strong baroreflex (panels B1-B3) and sympathetic predominance to the peripheral resistance (panels C1-C3). Thick black lines: physiological conditions, open loop. Thick grey lines: pathological conditions, open loop. Thin lines are the closed loop variants. When thin lines are not visible, they are close to the thick curves. Nota bene: Due to the properties of the simulation model open-loop SBP variability has ever a 1 mmHg amplitude (panels A1, B1 and C1).

4. Discussion

It appears that closed-loop BRS assessment is quite accurate. It's obvious that the resonance phenomenon in the LF band, generally known as Mayer waves [7], is strongly under influence of the baroreflex. The only situation in which Mayer waves handly appear is when the orthosympathetic baroreflex gain to the peripheral resistance is small.

We have no explanation for the striking fact that the closed-loop transfer function overestimates the open-loop transfer function below the resonance frequency, and underestimates it above this frequency. Because of this systematic effect, the spectral errors made during closed-loop BRS assessment cancel out, and the resulting error in BRS is very low.

Barbieri and colleagues [3] reported much larger differences between the closed-loop and open-loop values than we have found. Admittedly, their model-based analysis was applied on human real-life data. However, this implied the need for a parameter identification procedure that may lead to errors; also, in the low frequencies the authors report problems of low-coherence.

Kawada and colleagues [4] were able to measure open-loop transfer functions in rabbits, and found little difference with closed-loop transfer functions. This parallels our results, but it has to be taken into account that the animals were surgically prepared, heavily instrumented and artificially ventilated, and under anaesthesia. Such conditioning is known to influence the state of the autonomic nervous system, which limits the value of this type of studies.

In conclusion, our study demonstrates that, under all investigated conditions, closed-loop BRS assessment by computation of the SBP to IBI transfer function leads to results with nearly no bias. In clinical practice this BRS assessment method is to be preferred because the measurements are noninvasive and cause no burden to the patient. In our opinion, the major problem in noninvasive BRS assessment is a low signal-to-noise-ratio (that becomes apparent in the form of low coherence in cross-spectral transfer function assessment [8]) rather than bias caused by the open-loop-closed-loop issue.

Baroreflex gains			Physiologic Conditions: M = 1.2, N = 0.5, M' = 1.2, Vref = 80 ml				Pathologic Conditions: M = 1.5, N = 0.6, M' = 1.25, Vref = 60 ml			
S	V	S'	Assessed BRS [mmHg]	True BRS [mmHg]	BRS Error [%]	Abs. Error [%]	Assessed BRS [mmHg]	True BRS [mmHg]	BRS Error [%]	Abs. Error [%]
partial β-adrenergic blockade:			7.75	7.80	-0.7	4.0	4.52	4.65	-2.8	4.0
0.33	1.0	1.0								
partial cholinergic blockade:			2.08	2.09	-0.7	9.0	1.25	1.28	-2.7	13.1
1.0	0.33	1.0								
partial α-adrenergic blockade:			7.21	7.22	-0.2	3.1	4.19	4.07	2.9	6.9
1.0	1.0	0.33								
weak baroreflex:			2.56	2.70	-5.1	7.8	1.67	1.76	-5.2	5.6
0.33	0.33	0.33								
normal baroreflex:			7.16	7.22	-0.9	3.6	4.21	4.07	3.5	6.5
1.0	1.0	1.0								
strong baroreflex:			21.02	21.15	-0.6	11.3	12.31	11.98	2.7	6.2
3.0	3.0	3.0								
cardiac sympathetic predominance:			5.76	5.83	-1.1	4.1	3.37	3.37	0.0	5.7
3.0	1.0	1.0								
cardiac para-symp. predominance:			23.28	22.99	1.2	5.7	13.48	12.96	4.0	4.5
1.0	3.0	1.0								
symp. predominance to the p. resist.:			6.98	7.22	-3.4	10.4	4.11	4.07	1.0	6.5
1.0	1.0	3.0								

Table 1. Assessed (closed loop) and true (open loop) BRS values for all simulated combinations of baroreflex gains under physiologic or pathologic conditions. Absolute error: averaged percentual absolute differences between the frequency-components of the closed- and open-loop transfer functions in the LF band; BRS = baroreflex sensitivity; BRS error: percentual difference between the means of the closed- and open-loop transfer functions, averaged over the LF band; M = sympathetic tone (heart); M' = sympathetic tone (peripheral resistance); N = vagal tone; S = sympathetic gain (heart); S' = sympathetic gain (peripheral resistance); V = parasympathetic gain; Vref = stroke volume at 1 s filling time.

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