Spontaneous Indices Are Inconsistent With Arterial Baroreflex Gain

Ruth D. Lipman, Julie K. Salisbury, J. Andrew Taylor

Abstract—Spontaneously occurring, parallel fluctuations in arterial pressure and heart period are frequently used as indices of baroreflex function. Despite the convenience of spontaneous indices, their relation to the arterial baroreflex remains unclear. Therefore, in 97 volunteers, we derived 5 proposed indices (sequence method, α-index, transfer function, low-frequency transfer function, and impulse response function), compared them with arterial baroreflex gain (by the modified Oxford pharmacologic technique), and examined their relation to carotid distensibility and respiratory sinus arrhythmia. The subjects comprised men and women (n=41) aged 25 to 86 years, 30% of whom had established coronary artery disease. Generally, the indices were correlated with each other (except α-index and low-frequency transfer function) and with baroreflex gain. However, the Bland-Altman method demonstrated that the spontaneous indices had limits of agreement as large as the baroreflex gain itself. Even in individuals within the lowest tertile of baroreflex gain for whom baroreflex gain appears to be the most clinically relevant, spontaneous indices failed to relate to baroreflex gain. In fact, for these individuals, there was no correlation between any index and baroreflex gain. Forward stepwise linear regression showed that all spontaneous indices and baroreflex gain were related to respiratory sinus arrhythmia, but only baroreflex gain was related to carotid distensibility. Therefore, these data suggest that spontaneous indices are inadequate estimates of gain and are inconsistent with arterial baroreflex function. (Hypertension. 2003;42:481-487.)

Key Words: baroreceptors • carotid sinus • elasticity • arrhythmia • baroreflex

The arterial baroreflex is a key mechanism for blood pressure homeostasis, is clinically relevant as a predictor of cardiovascular mortality,1 and is physiologically relevant as an indicator of autonomic control.2 The sensitivity, or gain, of the arterial baroreflex is calculated routinely from the relation of bradycardic and/or tachycardic responses to increases and/or decreases in systemic arterial pressure.3 These responses encompass both mechanical and neural aspects of the system. Changes in pressure result in stretch of the aortic arch and the carotid sinus, wherein stretch-sensitive receptors reside. These afferent baroreceptive neurons terminate in the dorsomedial medulla, which in turn signals the neurons composing the efferent autonomic limb of the baroreflex. The resultant cardiac vagal adjustments appropriately regulate heart period to buffer against pressure rises and falls.2

Arterial baroreflex physiology dictates that both barosensory vessel distensibility and cardiac vagal function critically determine reflex sensitivity. Indeed, a relation between baroreflex gain and carotid stiffness has been shown in healthy young and middle-aged subjects,4 as well as in hypertensive individuals.5 Additionally, in patients with coronary disease6,7 and diabetes,8,9 both gain and carotid distensibility are prognostically relevant, reflecting their close association. However, cardiac vagal neural function is also a potent determinant of baroreflex gain. For example, a generalized vagal deficit with increasing age reduces resting vagal tone but also has an independent effect on baroreflex sensitivity compromising baroreflex-mediated responses.10

The classic assessment of baroreflex gain by Smyth et al11 used a venous bolus of angiotensin to generate a pressoreceptor stimulus. Subsequent studies induced pressure rises with phenylephrine,12 pressure falls with nitroprusside,13 and pressure falls and rises with sequential nitroprusside and phenylephrine.14 These pharmacologic techniques were designed to perturb the system and assess reflex gain. This approach is based on the fact that baroreceptor responses are greatest and most apparent with rapidly changing pressures, as opposed to stationary or minimally changing pressures.15 Thus, these techniques represent a “gold standard,” because there is a clear cause for baroreceptor engagement and a clear effect in baroreflex-mediated cardiac chronotropy. In fact, baroreflex gain derived from actively engaging the system provides the strongest evidence that reflex function is related to cardiovascular mortality.1,16

In recent years, investigators have exploited spontaneous fluctuations in blood pressure and heart period to index...
cardiovascular control\textsuperscript{17} and have proposed that these spontaneous oscillations provide a less-invasive route to assess baroreflex gain.\textsuperscript{18} However, it is unclear whether cardiovascular variances arise from fluctuations in central neural activity, extracardiovascular inputs (eg, mechanical and neural effects of respiration), and/or baroreflex engagement.\textsuperscript{19} Although spontaneous indices for baroreflex gain might have some prognostic utility,\textsuperscript{20,21} it remains unclear whether they broadly represent arterial baroreflex function or merely recapitulate vagally mediated heart rate variability.

We reasoned that estimates of barosensory vessel mechanical function would allow us to test which of the proposed spontaneous indices encompasses this important aspect of the arterial baroreflex system. Moreover, because both mechanical and neural functions are powerful baroreflex determinants, we reasoned that cardiac vagal tone would be equally related to baroreflex gain when examined across a broadly heterogenous population. Indeed, both carotid distensibility and respiratory sinus arrhythmia were related to pharmacologically derived baroreflex gain. Although each index was correlated with baroreflex gain, all had limits of agreement that were unreasonable; no index evidenced a relation to barosensory vessel distensibility; and they primarily reflected vagally mediated heart rate variability. In addition, among individuals with decreased baroreflex sensitivity (which is related to greater cardiovascular risk\textsuperscript{1}), the indices did not even demonstrate a correlation to baroreflex gain. Thus, using these indices as simple surrogates for baroreflex gain is neither statistically nor physiologically sound, and more important, these indices are not clinically relevant measures of autonomic cardiovascular control.

Methods

Subjects

The study was approved by the Hebrew Rehabilitation Center for Aged Institutional Review Board. Written, informed consent was obtained from all subjects. We sought the strongest approach to test whether the purported spontaneous indices agree with a direct measure of baroreflex gain and whether they have a reasonable relation to carotid distensibility. Therefore, because the correlation might not be observed in small, homogenous samples, we used a heterogenous population to provide a broad range of oscillation amplitude, baroreflex gain, and distensibility. Accordingly, we studied 97 (41 female) subjects aged 25 to 86 years, including individuals with (n=30) and without documented coronary artery disease. Individuals with diabetes, nervous system disease, cancer, body mass index >30, or high blood pressure (140/90, systolic/diastolic) were excluded. All prospective subjects were screened with a full carotid ultrasound examination to exclude carotid vascular disease. Individuals without established coronary artery disease (previous myocardial infarction or angiography) were screened with a graded exercise test using the Bruce protocol.\textsuperscript{25} Subjects with coronary disease were studied 72 hours after withdrawal of all cardioactive medications.

Protocol and Measurements

Subjects were instrumented with a 3-lead electrocardiograph (ECG) for determination of heart period, finger photoplethysmograph (Finapres model 2300, Ohmeda) for beat-by-beat arterial pressures, oscillometric arm cuff (Dinamap, Critikon) for standard measure of brachial arterial pressure, elastic respiratory transducer bands (Respitrace, NIMS) for breathing depth and frequency, and an antecubital venous catheter for drug infusions. Subjects were allowed to acclimate for at least 10 minutes, and then all waveforms were recorded for 15 minutes of quiet rest. Data collected during this period were used for calculation of the various spontaneous indices and respiratory sinus arrhythmia. Subsequently, longitudinal common carotid artery B-mode ultrasound images (7.5 MHz, Hewlett-Packard) were collected at a rate of 15 consecutive images per ECG R-wave (PCI DT3152 frame grabber board, Data Translation, Inc). These were obtained for 1 minute concurrent with beat-by-beat arterial pressures to derive carotid distensibility. For the modified Oxford baroreflex gain assessment,\textsuperscript{14} the ECG and beat-by-beat arterial pressures were recorded during sequential venous boluses of 100 μg nitroprusside and 150 phenylephrine, separated by 60 seconds. This was repeated twice, with at least 15 minutes between each trial.

Analysis

All waveforms were digitized throughout at 500 Hz and stored on a computer for signal processing and subsequent analysis (CODAS, Dataq Instruments, Inc). R-R intervals were calculated from the time difference of successive R-wave peaks, and systolic and diastolic pressures were taken as the maxima and minima of the pressure waveform.

Five spontaneous indices were calculated from the 15 minutes of resting data; these represent the range of mathematical approaches to index baroreflex function. These proposed methods to assess baroreflex gain seem reasonable because the naturally occurring oscillations in blood pressure and heart rate appear to be causally related, and a more observational approach could dispense with invasive techniques. The sequence method relates sequences of 3 or more consecutive heartbeats in which both systolic pressure and the following R-R interval either increase or decrease. As routinely done, we calculated the linear regressions of each individual sequence and derived a mean for each subject.\textsuperscript{23-25} The α-index uses the simple ratio between R-R interval spectral power and systolic pressure spectral power at low (0.1 Hz) and high (0.25 Hz) frequencies. The square roots of the ratios were derived and averaged for this index.\textsuperscript{26,27} The transfer function index uses R-R interval and systolic pressure cross-spectral magnitude in the frequency range of 0.05 to 0.3 Hz where coherence is >0.5. Cross-spectral magnitudes were averaged across these frequencies for this index.\textsuperscript{28} The low-frequency transfer function index is a modification of the transfer function. The average R-R interval and systolic pressure cross-spectral magnitude within the 0.05- to 0.15-Hz frequency band, where coherence was >0.5, provided this index.\textsuperscript{29} Last, the impulse-response function index also relies on cross-spectral analysis but employs the inverse Fourier transform. The peak value of the inverse Fourier transform of the cross-spectral transfer function between R-R interval and systolic pressure was derived for this index.\textsuperscript{29,30}

Also calculated from the 15 minutes of resting R-R interval data was respiratory sinus arrhythmia. Although cardiac vagal outflow is crucial for nearly all frequencies of heart rate variability,\textsuperscript{31} phasic vagal modulation with respiration produces an oscillation proportional to the mean level of cardiac vagal outflow.\textsuperscript{32} Therefore, respiratory sinus arrhythmia is commonly used as an index of resting vagal tone. We estimated respiratory sinus arrhythmia from the average spectral power content of the R-R interval at frequencies >0.20 Hz.\textsuperscript{33}

There are convincing data that carotid arterial distensibility is directly related to\textsuperscript{34} and determines\textsuperscript{35} arterial baroreflex gain. This derives from the fact that afferent, stretch-sensitive nerves embedded in the carotid walls determine baroreflex responses that buffer arterial pressure changes.\textsuperscript{36-38} We calculated distensibility of the carotid artery from concurrently measured diameters and pressures. Beat-by-beat common carotid internal diameters were determined from B-mode images with a Viterbi search routine with custom software (Matlab, Mathworks, Inc). For distensibility, we used the calculation (2×ΔD/DIA)/ΔP, where ΔD is the change in diameter from diastole to systole, DIA is end-diastolic diameter, and ΔP is pulse (ie, systolic–diastolic) pressure.\textsuperscript{5}

The modified Oxford technique has the advantage that arterial pressure is moved through a wide range. For most subjects, pressure
dropped ∼15 mm Hg below baroreflex threshold and rose ∼15 mm Hg above baseline, usually into the saturation region of the response. Therefore, the entire sigmoid nature of arterial baroreflex function is revealed during the phenylephrine-induced rise in pressure, allowing for a robust estimation of linear gain. Additionally, values from the nitroprusside-induced pressure fall can be excluded to avoid confounding by hysteresis; cardiac vagal gain derived from the pressure fall is usually lower but is strongly correlated.39 (In our subjects, it was insignificantly lower, by 12%, and was correlated at 0.64.) We associated the R-R intervals with systolic pressure after appropriately accounting for baroreflex delays: the concurrent R-R interval at heart periods of 800 ms and the subsequent R-R interval at heart periods between 500 and 800 ms.40 Beat-by-beat values of R-R interval were averaged across 3 mm Hg pressure increments to account for respiration-related variations.14 (Beat-by-beat finger systolic and diastolic blood pressures are similar to those measured intra-arterially during intravenous injections of phenylephrine.41) Saturation and threshold regions were excluded, and the linear relation between R-R interval and systolic pressure was extracted. Only trials with $r^2>0.60$ were used as valid measures of baroreflex gain. All subjects had at least 2 valid trials (intraindividual coefficient of variation equaled 22.7%), and all trials within each subject were averaged to provide a single baroreflex gain measure.

### Statistics

The first step in comparing a proposed measure to an established measure is to assess whether the 2 have any relation. Agreement can only be assessed if there exists a significant correlation. Subsequently, bias in the proposed measure can be assessed by regression analysis and the method of differences. Accordingly, we computed the correlation coefficients between the various calculated indices and baroreflex gain with the modified Oxford technique. When the correlation was significant, the data were assessed with least-products regression analysis42 and the method of differences described by Bland and Altman.43 Least-products regression analysis was used because it allows both measures to be attended by random error. The Bland-Altman method plots the difference between the proposed and established measures against the mean of the 2. If a least-squares regression fitted to this plot has a slope significantly greater than zero, a proportional (or changing) bias exists. However, if a proportional bias exists, the Bland-Altman method can overdiagnose or underdiagnose a fixed (or unchanging) bias. Therefore, 95% confidence intervals of the y intercept from the least-products regression were used to determine fixed bias.44 When only fixed bias was present, limits of agreement were calculated from $d ± 1.96(SD)$, where $d$ is the mean difference, 1.96 is the standardized normal deviate corresponding to a 2-sided $P=0.05$, and SD is the standard deviation of the mean difference. This provides the range of disagreement present across the full scope of observed baroreflex gain. When a proportional bias was present, the 95% confidence interval of the bias slope was used to determine the range of bias. The greatest probable bias slope and the lowest and highest mean gains were used in the regression equation to derive the disagreement across the observed baroreflex gains.

Prior work has demonstrated the direct relation between carotid distensibility and baroreflex gain5,45 and the association of vagal function with both respiratory sinus arrhythmia and baroreflex gain.9 Therefore, we applied forward, stepwise, multiple linear-regression analysis (SigmaStat, SPSS Science) to determine the variance in each index and in gain explained by carotid distensibility and respiratory sinus arrhythmia. Because $\beta$-coefficients are metric dependent, this was performed with variables expressed as z scores. This provides $\beta$-coefficients that accurately reflect the relative importance of each input variable in explaining the indices and baroreflex gain. Significance for all tests was set a priori at $P<0.05$. All data are presented as mean±SD.

### Results

The average baroreflex gain measured with the modified Oxford technique was 7.62±4.42 ms/mm Hg. The average for the indices was comparable only for the low-frequency transfer function (7.54±2.31 ms/mm Hg); the other indices were from 13% to 46% higher (8.60±2.40 ms/mm Hg, transfer function; 10.44±6.98 ms/mm Hg, sequence; and 11.10±4.37, $\alpha$-index) or 44% lower (4.27±5.13 ms/mm Hg, impulse-response function). Among the various indices, there were strong, positive correlations ($P<0.05$), with the exception of the $\alpha$-index and the low-frequency transfer function (Table). Correlations of the various indices to the modified Oxford baroreflex gain ranged from 0.19 to 0.55.

Figure 1 depicts the least-products regression of the values from each index to baroreflex gain. In all cases, there was a statistically significant relation. Because a significant relation can coexist with gross bias,44 the agreement of these indices to baroreflex gain was determined by the Bland-Altman analyses shown in Figure 2. Proportional bias obviates the utility of fixed-bias estimates. According to both least-products regression and Bland-Altman analysis, proportional bias was present in the sequence index, $\alpha$-index, transfer function, and low-frequency transfer function. The confidence interval around the proportional bias slope can provide the minimal and maximal bias across the observed baroreflex gains. In each case, the range exceeded the estimated mean baroreflex gain of the population; the ranges of bias were 4.74 to 26.93 for sequence, 4.32 to 19.90 for $\alpha$-index, −6.72 to 5.31 for transfer function, and −8.19 to 5.31 for low-frequency transfer function. Fixed bias alone was present in only the impulse-response function. For this index, the fixed bias was −3.10, and limits of agreement were −12.12 to 5.92. In summary, true baroreflex gain could be as much as 12 ms/mm Hg higher than the impulse-response function to almost 27 ms/mm Hg lower than the sequence index. Thus, the limits of agreement for all indices were larger than the

### Correlation Coefficients Among Baroreflex Gain and the Various Indices

<table>
<thead>
<tr>
<th>Variables</th>
<th>Sequence Method Index</th>
<th>$\alpha$-Index</th>
<th>Low-Frequency Transfer Function</th>
<th>Impulse-Response Function Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified Oxford baroreflex gain</td>
<td>0.50*</td>
<td>0.19*</td>
<td>0.39*</td>
<td>0.54*</td>
</tr>
<tr>
<td>Sequence method index</td>
<td>0.64*</td>
<td>0.72*</td>
<td>0.47*</td>
<td>0.81*</td>
</tr>
<tr>
<td>$\alpha$-Index</td>
<td>0.45*</td>
<td>0.07</td>
<td>0.51*</td>
<td></td>
</tr>
<tr>
<td>Transfer function magnitude</td>
<td>0.77*</td>
<td></td>
<td>0.60*</td>
<td></td>
</tr>
<tr>
<td>Low-frequency transfer function magnitude</td>
<td></td>
<td></td>
<td></td>
<td>0.37*</td>
</tr>
</tbody>
</table>

*P<0.05.
estimated mean baroreflex gain of the population, indicating weak agreement.43 It has previously been proposed that differences in agreement between pharmacologic assessment of baroreflex gain and spectral indices might depend on the population studied.45 For example, individuals with low baroreflex gain are at the greatest risk in terms of cardiovascular mortality1 and the group for whom sensitive measures of baroreflex gain are most important. Therefore, we examined the correlation for subjects in the lowest tertile of baroreflex gain. Within this group of subjects, there was absolutely no correlation between baroreflex gain as measured by the modified Oxford technique and any of the calculated indices (Figure 3). The lack of correlation indicates there is no agreement between the indices and baroreflex gain in this population, so applying regression analysis and the method of differences is invalid. Despite the discrepancy between the indices and the modified Oxford baroreflex gain, there might be some phys-

Figure 1. Least-products regression of each index to baroreflex gain.

Figure 2. Bland-Altman plots of differences between baroreflex gain and each index (y axis) and mean of baroreflex gain and each index (x axis; open circles). Lines indicate proportional bias, and filled square indicates fixed bias.

Figure 3. Correlations of each index to baroreflex gain for individuals in the lowest tertile of baroreflex gain.
Spontaneous and Direct Estimates of Baroreflex Gain

There are several methods to directly assess baroreflex gain. Historically, these have involved some perturbation that directly engages the system: the Valsalva maneuver,\(^50\) carotid occlusion,\(^51\) neck suction,\(^52\) vasodilators and/or vasoconstrictors,\(^11–14\) and postural changes.\(^53\) Recent research has made use of the spontaneous oscillations in blood pressure and heart rate. These fluctuations can be linked through the baroreflex\(^59\); thus, it might be reasonable to exploit them to quantify baroreflex-mediated control of arterial pressure. If valid, these indices would have the advantage that they can be calculated without perturbing the system and might provide gain around the set point during a given physiologic state. Rapid resetting of the baroreflex during induced blood pressure changes\(^54\) could conceivably confound measured gain. This has, in fact, been used previously as an explanation for the poor relation between spontaneous indices and directly assessed gain.\(^28\) However, there are major assumptions in this observational approach to baroreflex physiology. Although assessing gain of a closed-loop system can be achieved by observing spontaneously occurring input and output fluctuations, the system must encompass only feedback relations, the fluctuations must be sufficiently large, and the gain must be linear across all ranges. Yet heart rate fluctuations represent both feedback and feedforward aspects of the cardiovascular system,\(^55\) spontaneous fluctuations can at times be immeasurably small (eg, Gulli et al\(^56\)), and baroreflex gain is characteristically nonlinear across its range.\(^49\)

The alternative to observation is to drive the system; ie, to open the loop and observe the gain. This derives a more robust estimate that represents only feedback relations, that spans a large range to reliably estimate gain, and that directly assesses linearity rather than assumes it. The open-loop approach that we used is a standard pharmacologic intervention, modified from the “Oxford” pressor-infusion technique. Infusion of a pressor agent alone creates an increase in arterial pressure that results in vagal activation.\(^57\) Although there is clear cause and effect, it remains unclear whether the derived open-loop gain equals the closed-loop gain on which the system depends.\(^57,58\)

The addition of nitroprusside does not obviate the limitations of open-loop gain, but it does have the advantage that pressure is moved through a wider range, thereby allowing more complete examination of the sigmoid relation and more robust determination of linear gain. The additional drawback of this approach might be the effect of exogenous nitric oxide on baroreflex function. Both in vivo and in vitro, rabbits demonstrate a non–baroreflex-mediated positive chronotropic response to sodium nitroprusside.\(^59\) However, this takes minutes to develop and might not confound rapid, neurally mediated responses. In humans, simultaneous infusions of nitroprusside and phenylephrine at a steady rate that does not produce obvious changes in pressure result in a 12% increase in heart rate but no change in baroreflex gain.\(^60\) Thus, pharmacologically derived baroreflex gain appears most confounded when estimated from continuous nitroprusside infusions made over several minutes. One additional consideration is the role of cardiac effects; sympathetic activation might decrease both baroreflex gain\(^61\) and heart rate variability.\(^31\) Nonetheless, direct engagement of baroreceptors through rapid, bolus injections of nitroprusside and phenylephrine should be sufficiently robust to accurately reflect baroreflex gain.

Ignoring the lack of agreement in and limitations of spontaneous indices, the argument has been made that they provide complementary information to direct assessments.\(^52,63\) One represents a robust estimate across the range

**Figure 4.** Graphical representation of the contribution of respiratory sinus arrhythmia and carotid distensibility to each index and baroreflex gain.
of baroreflex function, and the other represents a closed-loop estimate without the possible confounding of resetting. However, if this is the case, then the 2 should be related; reset baroreflex gains are closely correlated in humans, and directly assessed open- and closed-loop gains can be essentially the same. Our comparison across a heterogeneous population showed that spontaneous indices lack any correspondence to baroreflex gain. In fact, restricting our comparison to those with the lowest baroreflex gain resulted in the disappearance of even simple correlation. It is surprising, considering their broad use, that others before us have reported poor agreement of these purported indices with classic measures of baroreflex gain. Moreover, it appears that the agreement progressively worsens from healthy individuals to those with mild and more severe cardiovascular disease.

The other primary determinant of baroreflex gain is cardiac vagal function; eg, a vagal deficit is the primary mechanism by which baroreflex function declines with human aging. Although in supine subjects the baroreflex role in generating respiratory sinus arrhythmia appears to be minimal, their common vagal effector is reflected in their correlation. Our results reflect this physiology: carotid distensibility and respiratory sinus arrhythmia were equally predictive of arterial baroreflex gain in our broadly heterogenous population.

When the relations of both respiratory sinus arrhythmia and carotid distensibility to the spontaneous indices were considered, only the vagally mediated heart period variability contributed significantly. This suggests that the indices merely recapitulate the magnitude of heart rate variability and explain the modest correlations that they have with arterial baroreflex gain. For example, lower spectral and sequence indices mirror the reduced heart rate variability seen with increasing autonomic neuropathy. Although a significant relation between a spontaneous index and barosensory vessel distensibility has been demonstrated, this likely reflects parallel declines in arterial distensibility and vagally mediated heart period variability.

Perspective

Fluctuations in blood pressure and heart period can have clinical relevance as prognostic indicators of cardiovascular morbidity and mortality. However, our results show that their various mathematical ratios do not clearly and unarguably reflect arterial baroreflex gain. Moreover, they most strongly mirror the vagally mediated heart period oscillations whence they derive and do not reflect barosensory vessel distensibility. Without clear, consistent relations to a key component of the reflex or to baroreflex gain itself, we can only conclude that spontaneous baroreflex indices do not have utility as surrogates for baroreflex gain.

Acknowledgments

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