The following is the abstract of the article discussed in the subsequent letter:

Di Rienzo, Marco, Gianfranco Parati, Paolo Castiglioni, Roberto Tordi, Giuseppe Mancia, and Antonio Pedotti. Baroreflex effectiveness index: an additional measure of baroreflex control of heart rate in daily life. Am J Physiol Regulatory Integrative Comp Physiol 280: R744–R751, 2001.—In health subjects, progressive beat-to-beat increases or decreases in systolic blood pressure (SBP) ramps are not always accompanied by baroreflex-driven lengthening or shortening in pulse interval (PI) ramps, respectively. This phenomenon has been quantified by a new index, the baroreflex effectiveness index (BEI), defined as the ratio between the number of SBP ramps observed in a given time window. Specificity of BEI was shown in eight cats by a −89% reduction of BEI after sinoaortic denervation. In 14 healthy humans, the 24-h average BEI value was 0.21, with a marked day-night modulation (~0.25 day, ~0.15 night) in counterphase with modulation of baroreflex sensitivity (BRS). Our analysis indicates that 1) in normal subjects, arterial baroreflex can induce beat-by-beat PI changes in response to only 21% of all SBP ramps, possibly because of central inhibitory influences or of interferences at sinus node level by nonbaroreflex mechanisms and 2) BEI provides information on the baroreflex function that is complementary to BRS.

Yet Another Statistic to Index Baroreflex Function

To the Editor: Di Rienzo et al. (1) propose a new statistical index to assess baroreflex function. Although useful indexes are needed to explain physiological phenomena, this work suffers from conceptual, physiological, and mathematical shortcomings.

Conceptually, baroreflex “effectiveness” requires serious consideration. To assess “effectiveness,” one would have to know the “intended or expected result.” Baroreflex “effectiveness” might be assessed by applying a stimulus to perturb the system and subsequently measuring effective buffering of pressure. For example, low-dose nitroprusside infusions in young healthy humans generate mild tachycardia and sympathetic activation that almost perfectly buffer pressure against any fall—an effective response (5). In contrast, the proposed metric presumes without justification that spontaneously occurring sequences of unidirectional pressure changes without concomitant, parallel R-R interval changes indicate an “ineffective” baroreflex. But, without perturbing the system, it cannot be known when reflexive responses might be engaged to maintain homeostasis, and, without opening the closed loop, spontaneously occurring heart rate patterns will cause blood pressure changes.

Physiologically, this index ignores baroreflex latencies derived from experimental studies carried out under strictly controlled conditions. Both animal data [cats included (2)] and human data (4) show that only when the cardiac interval is sufficiently long, can baroreflex-mediated R-R interval changes occur within the same beat as the pressure stimulus. The authors ignore human latencies based on their data from cats showing fewer blood pressure ramps correlated with parallel R-R interval changes after sinoaortic denervation. Without convincing argument, the authors suggest this evidences a baroreflex genesis for correlated slopes with delays shorter and longer than normal baroreflex latencies. Known human latencies must be used for a metric that purports to index baroreflex function in humans.

Mathematically, their results appear artifactual and inaccurate. First, the authors never demonstrate that reduced “effectiveness” after sinoaortic denervation did not result from decreased variance of R-R interval distribution. To show this they would have to run a noise control. In addition, their finding of reduced nighttime slope of systolic blood pressure ramps is largely determined by mean heart rate. Similar blood pressure swings across the same number of beats of longer duration will reduce the slope. Finally, blood pressure was recorded at 165 Hz and interpolated. Interpolation does not negate the Nyquist sampling theorem, which implies that only frequencies <82 Hz can be resolved from the original sampling rate, corresponding to a temporal difference of 12 ms (3, 6). However, the authors construct their metric from 5-ms heart period differences; this is less than even their overall sampling rate and makes their measure unreliable.

Last, it should be remembered that “spontaneous” baroreflex gain indexes rely on very broad assumptions of arterial baroreflex function and are merely observational: they do not test the baroreflex’s power to produce a change in heart period. This new treatment of naturally occurring heart rate and arterial pressure patterns may only provide yet another mathematical manipulation that obscures true baroreflex function.

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Conceptual aspects: Dr. Taylor and Dr. Cohen correctly recall that the ultimate goal of the arterial baroreflex is blood pressure control. Unfortunately, at present this function can hardly be assessed in humans in the context of a dynamic analysis throughout the 24 h. For this reason evaluation of baroreflex function over prolonged time periods is usually limited to reflex heart rate control, also considering that the diagnostic and prognostic importance of this measurement has been documented in several cardiovascular diseases (2). We, of course, made it clear (beginning from the title) that in our study we only referred to measurements of the baroreceptor-heart rate reflex. Accordingly, “effectiveness” and “expected response” correctly targeted reflex heart rate modulation.

We also acknowledged in the discussion (page R749, second column, lines 4–18) that baroreflex influences on the heart may differ from those on the peripheral circulation and blood pressure and that in healthy subjects, blood pressure homeostasis is not jeopardized by the occasional absence of the expected reflex R-R interval changes. We could hardly be unaware of this problem because our group has in the past largely contributed to current knowledge on this matter in animals and humans (3–5).

Physiological aspects: Concerning the latencies in reflex pulse interval responses to spontaneous alterations in systolic blood pressure, Dr. Taylor and Dr. Cohen missed that we indeed based our procedure on available knowledge collected in humans (page R745, first column, lines 11–16), showing that in any given subject spontaneous sequences with lag 0, 1, and 2 can all be observed in the frame of the same experimental session and without any apparent correlation with the subject’s heart rate. These findings clearly indicate the presence of intra- and intersubject variability in baroreflex latency. On the other hand, a certain individual variability was also observed in studies where the latency was more directly assessed (8). Our lag analysis in cats before and after sinoaortic denervation was ancillary to these findings. Additionally, we wish to mention a paper by our group in which the latency of the pulse interval responses to injections of vasodilator drugs was thoroughly investigated (1). The results of this study are entirely in line with our present approach.

Mathematical aspects: One, the virtual disappearance of blood pressure-pulse interval spontaneous sequences and the decrease in pulse interval variability after sinoaortic denervation is exactly what should be expected because of removal of the pro-oscillatory baroreflex influences on heart rate (5–7). Two, the slope of the systolic blood pressure ramps is expressed in millimeters Hg per second and thus is by definition normalized for the time duration of the ramp independently from the number of beats included. Three, the comments on time resolution uncover a major confusion on some basic concepts of signal processing. The Nyquist sampling frequency (i.e., twice the maximal frequency content of the original signal) determines the minimal sampling frequency at which a signal can be digitized without losing the information contained in the original waveform. Once correctly digitized, the signal can be perfectly reconstructed by proper interpolation, and any feature of the original waveform can be localized over time with a resolution which may, in principle, be infinite and which is not any more related to the original sampling rate nor to the frequency content of the signal. Obviously this does not apply if the localization of a given waveform fiducial point is made directly on the sampled signal and not on the interpolated curve. Thus, the authors of the letter can be reassured, our procedure was appropriate and correctly followed the theoretical requirements. Indeed, we sampled our blood pressure tracing at 165 Hz (i.e., more than twice the Nyquist frequency, which for blood pressure is lower than 60 Hz), and we localized the systolic peaks after data interpolation. This procedure thus allowed the blood pressure peaks to be detected with a high resolution, independently from the original sampling rate.

Our study provided a quantification of the baroreflex ability to modulate heart rate in response to a specific baroreceptor stimulus (the SBP ramp). Such a quantification offers an additional means to characterize baroreflex function in daily life. It seems that the concerns raised by these authors are based on an irrational bias against the dynamical analysis of cardiovascular phenomena outside the laboratory environment. This might have led them to regard “spontaneous” baroreflex gain indexes as “mathematical manipulations.” The huge amount of literature so far produced on this topic by hundreds of independent scientists is clearly against such a drastic position. Needless to say that our view, as well as that of many other researchers working in this field, is totally different.

Marco Di Rienzo
Paolo Castiglioni
Giuseppe Mancia
Gianfranco Parati
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