Assessing the Sensitivity of Spontaneous Baroreflex Control of the Heart: Deeper Insight Into Complex Physiology

To the Editor:

While several papers support the physiological and clinical relevance of indices quantifying the sensitivity of spontaneous baroreflex control of heart rate (BRS), Lipman et al claim that they are unable to properly explore baroreflex function because spontaneous BRS was found to be quantitatively different from BRS values provided by the vasoactive drug injection technique and is unrelated to common carotid artery distensibility. We believe that this conclusion is not supported by Lipman’s data, for the following reasons.

1. The time honored (and still valuable) method for assessing BRS through vasoactive drugs injection cannot be a “gold standard” due to pharmacological alteration of baroreceptor activity through both changes in blood pressure and unquantifiable mechanical distortion of the vessel: direct drug effect on the sinus node; simultaneous stimulation of cardiopulmonary stretch receptors; and limited reproducibility of the few spot BRS estimates obtainable.

2. Pharmacological and spontaneous BRS values are significantly correlated in most instances as demonstrated by Parlow et al in a study not cited by Lipman et al. Moreover, spontaneous and drug-related BRS values display directionally similar changes under different conditions, thus reflecting virtually superimposable baroreflex physiology.

3. Both the drug injection and the spontaneous sequence technique focus on the slope of the RR interval response to progressive Systolic (S) BP changes. Whether the origin of SBP ramps is spontaneous or by pharmacological means must be immaterial to the baroreceptors, with the partial physiological exception of spontaneous BP changes due to central influences simultaneously responsible also for arterial baroreflex resetting.

4. Spontaneous BRS assessment by the sequence and spectral method was validated not only by the drug injection approach, but also by surrogate data analysis and for baroreceptor denervation in animals, which led to disappearance of baroreflex sequences and to a marked reduction in the α coefficient values.

5. The relation between carotid distensibility and BRS should be assessed in absence of diseases altering the baroreflex arch, while in some patients recruited in Lipman’s study normal carotid distensibility coexisted with disease-induced alterations of BRS. Moreover, there is evidence, in absence of drug injection, of spontaneous low frequency oscillations in carotid diameter that are related with low-frequency heart rate oscillations, further supporting the relevance of spontaneous methods to baroreflex physiology.

6. No BRS estimation technique, including drug injections, can produce stable numbers due to the physiological variability in BRS. Thus BRS estimates provided by only a few drug injections may be less reliable than spontaneous estimates assessed by averaging data over a sufficiently long time period.

7. Lipman et al’s paper also faces other methodological problems: patients selection criteria, excessive focus on subjects with low baroreflex gain in whom a decrease in the between-method correlation is mathematically expected given the larger bias of low BRS estimates; sequential performance of drug injections with insufficient time to resume baseline conditions; use of different algorithms to derive pharmacological and spontaneous BRS values and improper use of the Bland-Altman approach to assess between-method discrepancies.

The conclusions of Lipman et al should thus be carefully reconsidered and the finding of quantitative discrepancies between pharmacological and spontaneous BRS values should not be interpreted as a difference between “real” and “biased” BRS estimates but rather as the expected difference in result of methods that explore baroreflex function from different but complementary perspectives.

Gianfranco Parati
University of Milano-Bicocca and Ospedale San Luca
IRCCS, Istituto Auxologico Italiano
Milano, Italy

Marco Di Rienzo
Paolo Castiglioni
Centro di Bioingegneria FDG, IRCCS
Fondazione Don Gnocchi
Milano, Italy

Malika Bouhaddi
Physiologie-Centre Hospitalier Universitaire Besançon, France

Catherine Cerutti
Génomique Fonctionnelle dans l’Athérosclérose Faculté de Médecine Laennec
Lyon, France

Andrei Cividjian
Physiologie (CNRS UMR 5123)
Campus de la Doua
Lyon-Villeurbanne, France

Jean-Luc Elghozi
Pharmacologie Clinique / Néphrologie 2
Hôpital Necker
Paris, France

Jacques-Olivier Fortrat
Laboratoire de Physiologie
UMR CNRS 6188
Faculté de Médecine Angers, France

Arlette Girard
Pharmacologie Clinique / Néphrologie 2
Hôpital Necker
Paris, France

Ben J.A. Janssen
Department of Pharmacology & Toxicology
Cardiovascular Research Institute Maastricht
University of Maastricht
The Netherlands


**Response: Assessing the Sensitivity of Spontaneous Baroreflex Control of the Heart: Deeper Insight Into Complex Physiology**

The logical principle that underlies all scientific modeling and theory building cautions against favoring the complex explanation over the simple one (i.e., Occam’s razor, ca. 1285 to 1349). There are an infinite number of possible explanations for any scientific finding. For example, although 2 data points fall on a straight line, a variety of the most complicated curves could be construed to pass through those same 2 points and fit the data just as well. However, logic dictates choosing the linear relation as the best explanation. The simplest interpretation of our findings is that spontaneous indices do not relate adequately to baroreflex gain or to carotid distensibility.

The European Society of Hypertension Working Group on Blood Pressure and Heart Rate Variability cites a host of publications that could be construed to support their perspective that spontaneous indices can be used to reflect baroreflex gain. As a result, they are critical of our work, contending that it suffers serious methodological shortcomings and that the simple explanation of our findings is not supported by the data. Indeed, there is literature that could be interpreted to support the use of various indirect approaches to the baroreflex; we hope our work might be viewed as a comprehensive assessment of some of these approaches, adding to the literature a fair critique of the utility of spontaneous indices. We used a large, heterogeneous sample to provide the strongest test of correlations; we also examined a subset of subjects with low baroreflex gain for whom sensitive measures may be most important; we made serial measurements for each subject to provide the most representative gain value; we allowed sufficient time for return to baseline between measures based on the known half-lives of nitroprusside and phenylephrine; we used techniques for the spontaneous indices previously published in papers with high citation rates; we were exacting in our determination of the linear baroreflex gain from drug-induced blood pressure changes; and, we sought the most complete statistics to test the relationships among spontaneous indices, baroreflex gain, and carotid distensibility. Our approach was rigorous, yet simple and straightforward, allowing clear interpretation of our findings. Although there was a relation between the spontaneous indices and baroreflex gain, in all cases this existed with gross bias and an error that exceeded the mean baroreflex gain of the population studied. In addition, no spontaneous index related to carotid distensibility while pharmacologically derived baroreflex gain did. These results do not indict the prognostic utility of cardiovascular oscillations, but they are a simple caution against exploiting these oscillations for indices of baroreflex gain.

**J. Andrew Taylor**

*Laboratories for Cardiovascular Research*

*HRCA Research and Training Institute*

*Boston, Mass*

**Ruth D. Lipman**

*Division on Aging*

*Harvard Medical School*

*Boston, Mass*
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Gianfranco Parati, Marco Di Rienzo, Paolo Castiglioni, Malika Bouhaddi, Catherine Cerutti, Andrei Cividjian, Jean-Luc Elghozi, Jacques-Olivier Fortrat, Arlette Girard, Ben J.A. Janssen, Claude Julien, John M. Karemaker, Ferdinando Iellamo, Dominique Laude, Elena Lukoshkova, Massimo Pagani, Pontus B. Persson, Luc Quintin, Jacques Regnard, J. Heinz Ruediger, Philip J. Saul, Marco Vettorello, Karel H. Wesseling and Giuseppe Mancia on behalf of the European Society of Hypertension Working Group on Blood Pressure and Heart Rate Variability;

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