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Comparison of various techniques used to estimate spontaneous baroreflex sensitivity (the EuroBaVar study)

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Laude, Dominique, Jean-Luc Elghozi, Arlette Girard, Elisabeth Bellard, Malika Bouhaddi, Paolo Castiglioni, Catherine Cerutti, Andrei Cividjian, Marco Di Rienzo, Jacques-Olivier Fortrat, Ben Janssen, John M. Karemaker, Georges Lefthériotis, Gianfranco Parati, Pontus B. Persson, Alberto Porta, Luc Quintin, Jacques Regnard, Heinz Rüdiger, and Harald M. Stauss. Comparison of various techniques used to estimate spontaneous baroreflex sensitivity (the EuroBaVar study). *Am J Physiol Regul Integr Comp Physiol* 286: R226–R231, 2004. First published September 18, 2003; 10.1152/ajpregu.00709.2002.—This study compared spontaneous baroreflex sensitivity (BRS) estimates obtained from an identical set of data by 11 European centers using different methods and procedures. Noninvasive blood pressure (BP) and ECG recordings were obtained in 21 subjects, including 2 subjects with established baroreflex failure. Twenty-one estimates of BRS were obtained by methods including the two main techniques of BRS estimates, i.e., the spectral analysis (11 procedures) and the sequence method (7 procedures) but also one trigonometric regressive spectral analysis method (TRS), one exogenous model with autoregressive input method (X-AR), and one Z method. With subjects in a supine position, BRS estimates obtained with calculations of α-coefficient or gain of the transfer function in both the low-frequency band or high-frequency band, TRS, and sequence methods gave strongly related results. Conversely, weighted gain, X-AR, and Z exhibited lower agreement with all the other techniques. In addition, the use of mean BP instead of systolic BP in the sequence method decreased the relationships with the other estimates. Some procedures were unable to provide results when BRS estimates were expected to be very low in data sets (in patients with established baroreflex failure). The failure to provide BRS values was due to setting of algorithmic parameters too strictly. The discrepancies between procedures show that the choice of parameters and data handling should be considered before BRS estimation. These data are available on the web site (http://www.cbi.polimi.it/glossary/eurobavar.html) to allow the comparison of new techniques with this set of results.

baroreceptor reflex; autonomic nervous system; spectral analysis; sequence technique

INDEXES OF BAROREFLEX SENSITIVITY (BRS) of heart rate (HR) have emerged as a prognostic factor in cardiology (8, 9). BRS has often been quantified by vasoactive drug administration (16) or by direct stimulation of carotid baroreceptors with neck chamber devices (7). These methods are not appropriate in all clinical situations. Over the last 15 years, other methods have been developed to estimate BRS from the computer analysis of spontaneous fluctuations of cardiovascular variables, recorded with noninvasive equipment (3). Although each of these "modern" techniques has been demonstrated to provide a BRS estimate somewhat related to values obtained by the classic drug injection method, important differences may be observed in the BRS estimates obtained from these modern methods. Furthermore, over the years, methods have evolved, and now various procedures exist for each method.

The aim of this study was to quantify the differences in the BRS estimates obtained by these modern techniques and to test for the effect of the different procedures implementing each technique. This was done by comparing BRS estimates obtained from an identical set of data by different research laboratories, each using its own software. The data set included recordings obtained in a nonhomogenous population of subjects characterized by a relatively large range of BRS. Thus it has been possible *1*) to compare the BRS values obtained by the different procedures, *2*) to evaluate, for each technique, how different implementations influence the BRS estimate, *3*) to evaluate the ability of each procedure to detect BRS in the case of baroreflex failure, and *4*) to test the reproducibility of the procedures. The study was not designed to assess the best method for estimating BRS (this would not be

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possible because a gold standard for the estimation of the true BRS does not exist), but rather to evaluate the individual performance of each technique, investigate the effects of the different implementations, and identify which procedures could be interpreted as equivalent.

By applying most of the currently available methods to estimate spontaneous BRS, this study provides a unique opportunity to apply newly developed methods to an identical set of data (via the web site: http://www.cbi.polimi.it/glossary/eurobavar.html) and to compare the results obtained with the procedures used in this study.

METHODS

Subjects

Twenty-one subjects (17 women, 4 men) underwent continuous noninvasive blood pressure (BP) recording using a Finapres 2300 device (Ohmeda, Helsinki, Finland, continued as Finometer supplied by FMS, Arnheim, The Netherlands) together with an ECG recording using a Datex cardiocap II monitor (Datex Engstrom, Helsinki, Finland). Subjects were recorded 10–12 min in supine position and 10–12 min in standing position. Demographic data are summarized in Table 1.

One subject was a diabetic patient with evident cardiac autonomic neuropathy, and one subject was a patient who recently underwent heart transplantation. The conventional tests (Ewing's score) documented the inadequate HR responses in these two patients considered as subjects with cardiac baroreflex failure (5). The other subjects were 12 normotensive outpatients (including 1 diabetic patient without cardiac neuropathy, 2 treated hypercholesterolemic subjects, and 1 3-mo pregnant woman), one untreated hypertensive, and two treated hypertensive subjects. Four subjects were healthy volunteers.

Informed consent was obtained, and the study was approved by the Paris-Necker committee for the protection of human subjects in biomedical research.

Recordings

Data were provided as the BP and ECG signals sampled at 500 Hz with a 16-bit resolution or resampled beat by beat: systolic BP (SBP), diastolic BP (DBP), mean BP (MBP), and R-R interval.

The first set of data contained 16 files obtained from 8 subjects in supine and standing position. The second set of data contained 30 files: 13 subjects in supine and standing position, and in addition four duplicates (the recording of 2 subjects in supine and standing position) were incorporated to test the reproducibility of the BRS procedures. Distribution of the data set occurred over 12 mo. A total of 46 files were analyzed by the 11 centers listed in the author's list. Each contributing team was asked to provide an estimation of BRS using their respective laboratory procedures, with a full description of their technique(s). Twenty-one estimates of BRS were obtained from the 11 centers. The study was performed as a blind analysis, i.e., the participating centers had no information on the subjects from which data had been recorded.

Table 1. *Demographic data of the 21 subjects*

Age, yr	38.4±3.3
Height, m	1.65±0.02
Weight, kg	64.1±2.4
Body mass index, kg/m^2	23.3±0.8
HR supine, beats/min	70.7±3.0
SBP supine, mmHg	121.1±4.0
DBP supine, mmHg	61.8±2.6
HR standing, beats/min	83.0±3.3
SBP standing, mmHg	121.2±4.7
DBP standing, mmHg	67.9±2.5

Values are means ± SE. HR, heart rate; SBP and DBP, systolic and diastolic blood pressure, respectively.

Estimates of BRS

The 21 BRS estimates included 7 procedures based on the sequence method, 11 procedures based on spectral analysis, 1 Z method, 1 trigonometric regressive spectral analysis (TRS) method, and 1 causal exogenous autoregressive (X-AR) method. Most of these procedures used the SBP and R-R interval (18 of 21). One estimation used SBP and pulse interval (PI), i.e., the interval between two systoles, and another used MBP and PI. These 20 BRS estimates have units of milliseconds per millimeters mercury. One estimation used MBP and HR with units of beats per minute per millimeters mercury.

Procedures derived from spectral analysis. Eleven procedures used spectral analysis. Five provided the α-coefficient in the low-frequency (LF) or high-frequency (HF) bands (10). Five estimates used the calculation of the gain of the transfer function between BP and R-R interval in the LF or HF bands (14). One estimation was calculated as: BRS = LF gain × (LF of PI/HF of PI), and this composite index was defined throughout this paper as a "weighted gain" (WG). All of these estimates used SBP and R-R interval. Specifications are summarized in Table 2.

Sequence method. Seven procedures used the sequence method. All of these estimates considered the slope between changes in heart rhythm and changes in BP as the index of BRS (1, 11, 12). Four of these procedures used SBP and R-R interval, one used SBP and PI, one used MBP and PI, and one used MBP and HR. Four of seven procedures applied a lag of one beat for considering a sequence, four fixed minimal changes in BP and R-R interval to validate a sequence (up to 1 mmHg between 2 BP values and 5 ms for R-R interval), four procedures required a minimal coefficient of correlation between changes in BP and R-R interval to validate a sequence ($r > 0.7$ or 0.8 or 0.85), and two procedures required a minimum number of sequences (n min = 2 or 5) to validate a BRS estimate. Six procedures required ramps with three beats to validate sequences, and one procedure required four beats.

Other methods. Three other BRS estimates were tested: the TRS, the X-AR, and the Z coefficient. These three methods compared SBP and R-R interval fluctuations (4, 13, 15).

Statistical Analysis

Results are expressed as means ± SE.

The agreement between methods was calculated using the intraclass correlation coefficient (ICC). The ICC evaluates the level of agreement between raters in measurements, when the measurements are parametric (6). The ICC was calculated using absolute values and also using standardized variables. The standardized variables were calculated using $(x-\text{m})/\text{s}$, where x was the variable, m was the mean of the procedure, and s was the standard deviation of the procedure. This standardization allows the comparison of procedures with different levels or different units, and therefore allows comparisons between individual procedures. ICCs were estimated as low when $0 < r < 0.4$, medium when $0.4 < r < 0.75$, and high when $r > 0.75$.

Different procedures were applied for the following three methods: the sequence method, the spectral analysis in the LF band, and the spectral analysis in the HF band (for both the α-coefficient and gain). Within each of these three methods, the ICC were calculated between individual procedures ($n = 7$ for the sequence method, $n = 6$ for the spectral analysis in the LF band, and $n = 4$ for the spectral analysis in the HF band).

For each method, BRS values obtained with the different procedures were averaged, leading to data from nine methods, namely *1*) the mean of the procedures using LF band, *2*) the mean of the procedures using HF band, *3*) the mean of the procedures using the sequence method with SBP, *4*) the procedure using the sequence

Table 2. *Characteristics of the techniques*

No.	Technique	Data Length	Overlapping	Frequency Band	Thresholds	%Responses	CV
1	α-LF	whole record	>50%	0.05–0.15 Hz	coherence > 0.5	83	3
2	α-LF	256 beats	no	0.04–0.15 Hz	coherence > 0.5	100	0
3	α-LF	part	no	0.05–0.15 Hz	coherence > 0.5	93	35
4	α-HF	whole record	>50%	0.15–0.5 Hz	coherence > 0.5	100	8
5	α-HF	part	no	visual determination	coherence > 0.5	98	34
6	Gain LF	whole record	>50%	0.05–0.15 Hz	coherence > 0.2	98	5
7	Gain LF	600 s	50%	0.07–0.141 Hz	coherence > 0.5	100	0
8	Gain LF	204.8 s	no	0.06–0.13 Hz	no	100	27
9	Gain HF	whole record	>50%	0.15–0.5 Hz	coherence > 0.2	100	12
10	Gain HF	204.8 s	no	visual determination	no	100	17
11	Weighted gain	200 s	50%	0.05–0.15 Hz; 0.15–0.4 Hz	no	100	79

No.	Data Length	Parameters	Heartbeats, n	Lag	Thresholds	%Responses	CV
12	300 s	SBP, R-R int	3	1	1 mmHg, 1 ms, n min: 2	93	0
13	whole record	SBP, R-R int	3	1	1 mmHg, 4 ms, $r > 0.7$	93	0
14	296 beats	SBP, R-R int	3	1	1 mmHg, 1 ms, n min: 5	78	0
15	whole record	SBP, R-R int	3	1	$r > 0.85$	100	0
16	whole record	MBP, PI	3	0	$r > 0.8$	98	0
17	whole record	MBP, HR	3	0	$r > 0.8$	98	0
18	whole record	SBP, PI	4	0	1 mmHg, 5 ms	83	8

No.	Data Length	Description	%Responses	CV
19	120 s	TRS: trigonometric regressive spectral analysis	100	5
20	300 beats	X-AR: causal exogenous autoregressive model	100	40
21	600 s	Z: statistical dependence	61	17

CV, coefficient of variation in % derived from the baroreflex sensitivity (BRS) estimates of the duplicates. *Top:* techniques derived from spectral analysis. *Middle:* techniques derived from the sequence method. n min: Minimum number of sequences for validating a spontaneous BRS estimate. *Bottom:* characteristics of the other techniques. MBP, mean blood pressure; PI, pulse interval; LF, low frequency; HF, high frequency; int, interval.

method with MBP and PI, *5*) the procedure using the sequence method with MBP and HR, *6*) the WG, *7*) the X-AR, *8*) the TRS, and *9*) the Z method. These nine estimates were used for the comparison between methods.

RESULTS

Duplicates

The nine procedures using the entire record gave similar results for the duplicates, with a coefficient of variation (CV) of 0 for four procedures and a CV ranging from 3 to 12% for five procedures. The 12 procedures depending on a selected part of the records had CV ranging from 0 to 79%. These CV are shown in Table 2.

Sensitivity for Providing BRS Estimates

Most of the techniques used thresholds to calculate the BRS estimates. For the spectral analysis, the threshold was set at the level of the coherence between BP and R-R interval spectral estimates: only bands in which a certain level of coherence (>0.2 or >0.5) was reached were used in the calculation of the gain or the α-coefficient. Only common oscillations (heart period and SBP) with a cross-correlation coefficient >0.7 were used for computation of BRS on the based TRS method. For the sequence method, some criteria for validating a sequence could lead to a smaller number of sequences (see METHODS). The Z method selected SBP and R-R interval pairs of values with Z estimates higher than 0.01, and it required a $P < 0.05$ for the correlation between R-R interval and SBP.

The above thresholds were set to increase the reliability of the BRS estimate. However, their use might also reduce the ability of the procedures to provide an individual estimate, particularly in the case of subjects with a poor baroreflex response. Indeed, some procedures (9 of 21) did not identify a baroreflex pattern for at least one recording. This was considered as missing data. The percentage of BRS determinations was indicated in Table 2 (% of responses).

Standing and Supine BRS Estimates

BRS estimates were consistent among subjects in standing position, whatever the method: 6.7 ± 0.5 ms/mmHg for the 20 procedures expressing BRS in units of milliseconds per millimeters mercury.

The BRS values increased when the subject was in a supine position: 13.0 ± 1.1 ms/mmHg for the same 20 procedures. The average BRS obtained with the six procedures using LF analysis was 11.2 ± 0.8 ms/mmHg, and the four procedures using HF analysis indicated higher values with an average BRS of 16.9 ± 0.7 ms/mmHg, close to the BRS obtained with the six procedures using the sequence method: 16.2 ± 1.9 ms/mmHg. The WG, TRS, X-AR, and Z procedures had values of BRS of 4.5, 12.5, 5.1, and 5.8 ms/mmHg, respectively, for the supine position (Fig. 1).

The averaged supine-to-standing BRS ratio was 2.11 ± 0.10 for the 21 procedures.

Relationships Within Methods

Agreement between techniques using the sequence method. In the supine position, baroreflex estimates using SBP were in high agreement when standardized values were used (r = 0.78 ± 0.09, range 0.62–0.93), but baroreflex estimated with MBP and PI were less correlated to the other procedures (mean r = 0.52 ± 0.07, range 0.34–0.79). The use of MBP and HR

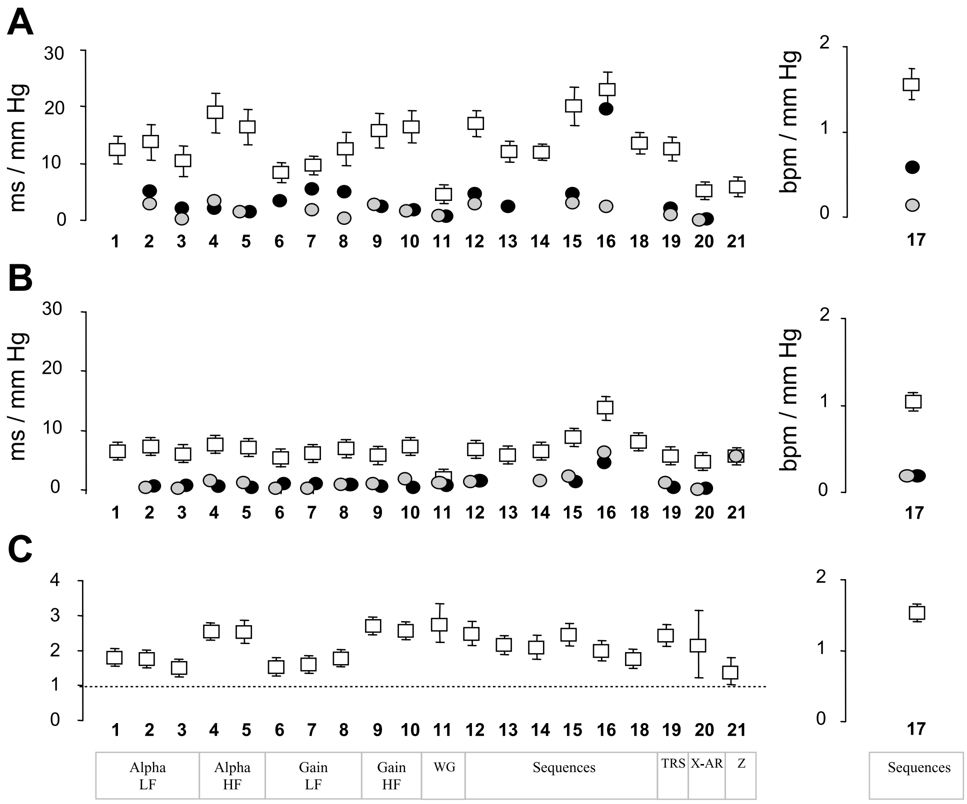

Fig. 1. Mean ± SE of the baroreflex sensitivity (BRS) estimates. Numbers on the *x*-axis refer to the procedures labeled in Table 2. ●, Established diabetic autonomic neuropathy. Shaded circles, heart transplant recipient. *A*: supine; *B*: standing; *C*: supine-to-standing ratio. Notice that some techniques do not detect the cardiac baroreflex impairment. bpm, beats/min; LF, low frequency; HF, high frequency; WG, weighted gain; TRS, trigonometric regressive spectral analysis; X-AR, causal exogenous autoregressive.

(expressed in beats/min) diminished the ICC (r = 0.39 ± 0.06, range 0.25–0.60). Estimates were highly correlated with subjects in the standing position (r = 0.80 ± 0.02, range 0.63–0.95). The two estimates using MBP were related (r = 0.83, supine; r = 0.86, standing). When absolute values were used, the ICC was decreased in both standing and supine positions, exemplifying some differences in absolute values or units for the procedure using HR.

Agreement between techniques using spectral analysis. All indexes derived from spectral analysis (α-coefficient and gain of the transfer function) calculated in the LF band were highly correlated for both the supine (r = 0.95 ± 0.006; range 0.90–0.98) and standing positions (r = 0.93 ± 0.011, range 0.87–0.99).

Baroreflex estimates using HF band were highly correlated for the standing (r = 0.95 ± 0.007, range 0.93–0.98) and supine position (r = 0.97 ± 0.007, range 0.95–0.99). It is noteworthy that ICC remained high even when the absolute values were used, showing few discrepancies in the absolute values between procedures using the spectral analysis.

Relationships Between Methods

The ICC between methods are summarized in Table 3. We compared the sequence methods using SBP or MBP, spectral analysis (α-coefficient and gain) in the LF and HF band, WG, Z technique, X-AR, and TRS as described in *Statistical Analysis*.

With subjects in the supine position, and when standardized values were used, the spectral techniques using LF or HF bands, sequence methods, and TRS were strongly correlated. The WG and X-AR were not significantly correlated to the other techniques. In addition, Z was related to estimates using LF bands and TRS and to a lesser extent to estimates using HF bands. The sequence procedure using MBP and PI was related to TRS and to a lesser extent to procedures using LF bands, HF bands, and to the sequence method using SBP. The ICC values fell when absolute values were used.

In standing position, and when standardized values were used, the spectral estimates using LF and HF bands, sequence methods (including SBP and MBP), TRS, and X-AR were significantly correlated. Z was correlated to a lesser extent to methods using LF band, HF band, sequence method using SBP, TRS, and X-AR. Weighted gain was not correlated to the other methods.

The ICC were lowered when absolute values were used.

Baroreflex Impairment

Small BRS values were expected for the four recordings obtained in the two subjects with an established cardiac baroreflex failure. Only 15 of 21 procedures were able to give a value of BRS in such conditions. One method could not provide a value for one of the four recordings, three methods could not provide three values, and two methods were unable to give any of the four values expected from these four recordings. When the BRS estimates were available, the data were in the lower quartile of the BRS distribution for 15 procedures (see Fig. 1).

DISCUSSION

The main features of this study can be summarized as follows.

Differences Between Methods

When subjects were supine, BRS estimates obtained with calculations of α-coefficient or gain of the transfer function

Table 3. *Matrix of ICC between procedures of estimates of BRS in supine position*

		LF	HF	WG	SEQ	SEQ (PI & MBP)	SEQ (HR & MBP)	TRS	X-AR
HF	a	0.77							
	s	0.88							
	n	21							
WG	a	0.08	0.11						
	s	0.13	0.27						
	n	21	21						
SEQ	a	0.77	0.91	0.14					
	s	0.84	0.97	0.31					
	n	21	21	21					
SEQ (PI & MBP)	a	0.47	0.63	0.04	0.49				
	s	0.73	0.70	0.16	0.65				
	n	21	21	21	21				
SEQ (HR & MBP)	a	0.05	0.03	0.07	0.03	0.03			
	s	0.50	0.51	0.26	0.50	0.83			
	n	21	21	21	21	21			
TRS	a	0.91	0.82	0.16	0.83	0.53	0.05		
	s	0.92	0.92	0.28	0.87	0.81	0.61		
	n	21	21	21	21	21	21		
X-AR	a	0.09	0.008	0.22	0.03	0.04	0.09	0.06	
	s	0.14	0.02	0.22	0.08	0.17	0.36	0.11	
	n	21	21	21	21	21	21	21	
Z	a	0.53	0.24	0.03	0.26	0.18	0.11	0.43	−0.14
	s	0.87	0.65	0.03	0.57	0.73	0.47	0.79	−0.18
	n	10	10	10	10	10	10	10	10

a, intraclass correlation coefficient (ICC) calculated with absolute values; s, ICC calculated with standardized variables, *n*, number of couples of points; WG, weighted gain.

(both in the LF band or HF band), TRS, and sequence methods gave strongly related results. More precisely, estimates by the sequence method using SBP, spectral technique using HF, and TRS formed a cluster at a distance from those of spectral techniques using LF. It is noteworthy that the new technique TRS appeared in good agreement with many techniques, such as methods derived from spectral analysis using the LF and HF bands and the sequence method (Fig. 2). The use of MBP led to a decrease in the relationship with the other estimates (Fig. 2). Statistical dependence Z, WG, and X-AR were not related to the other techniques. The Z method was previously applied to longer recordings of 1 h but was tested on shorter recordings in the present study, and the poor correlation with the other estimates could result from this inappropriate use (4).

Comparison of the Ability to Detect Impairment of Baroreflex

Some procedures did not detect a baroreflex pattern for the two subjects who exhibited BRS impairment. A too strict setting of mathematical parameters in algorithms or a combination of parameters could explain why these procedures were unsuitable for detecting BRS impairment. Missing values could indirectly reflect small BRS, but the contributors preferred not to give a BRS value (or limit) when the procedure was unable to detect any baroreflex activity. A lack of values could be considered as a low BRS, but only if the procedure was able to discriminate normal subjects from impaired BRS subjects. In such a case, a precise

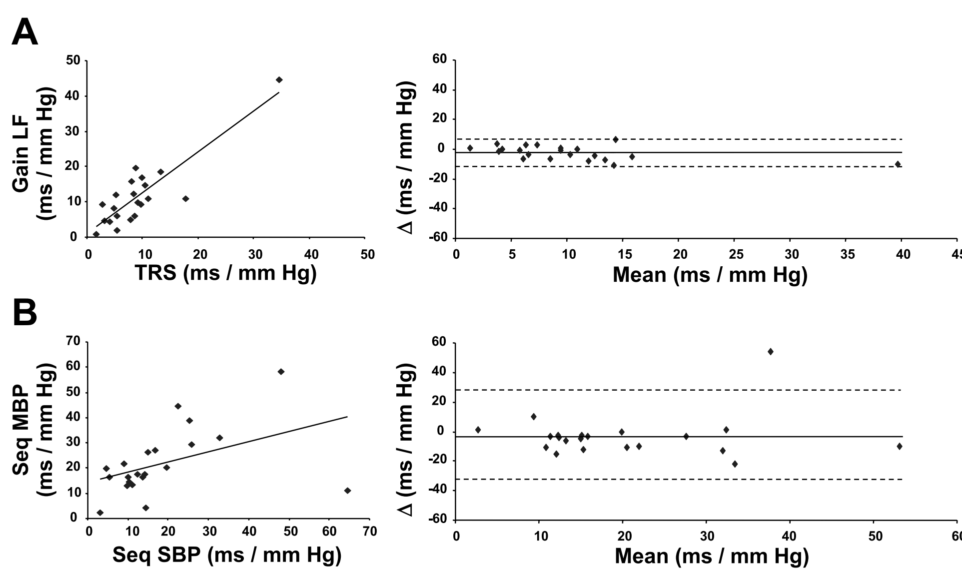

Fig. 2. Examples of correlation between 2 techniques of estimation of BRS using a Bland and Altman's representation. *A*: gain of the transfer function in the LF band (*procedure 7*) vs. TRS (*procedure 19*); *B*: sequence method using systolic blood pressure (SBP; *procedure 15*) vs. method using mean blood pressure (MBP; *procedure 17*). Solid lines indicate the averaged discrepancies, and dashed lines indicated the ±2 standard deviation interval. Δ, Change.

indication of the impairment (such as "low BRS") should be clearly indicated.

For the sequence methods, a good detection of the two cases of baroreflex impairment was achieved when three beats were used for validating a sequence, without any thresholds in terms of pressure or R-R interval changes, or in terms of the minimal number of sequences required for validating a BRS estimate. One sequence procedure using MBP indicated an unexpectedly high BRS value for the subject with diabetic autonomic neuropathy. However, it is noteworthy that this estimate was based on only one single sequence detected in the 990 heartbeats of this time series. It is likely that this particular sequence was not driven by the baroreceptor reflex. This effect points out the problem of the validity of BRS values obtained from few sequences.

Reproducibility

Reproducibility of BRS was higher when the whole length of the recording was analyzed, and it declined when part of the recording was selected for the subsequent analysis. This was caused by the fact that most methods require stationary segments (with the exception of the sequence method) and stationarity was tested by visual inspection. This procedure led to a selection of different periods between the originals and the duplicates, and this resulted in different BRS estimates.

Effects of Setting Parameters

The repetition of procedures using the same techniques allows a comparison within methods for the spectral analysis and the sequence technique. It is remarkable that the various filters, smoothing procedures, bandwidth selected for the LF or HF region, and coherence threshold had minimal influence on the BRS estimates obtained using the spectral procedures. For the sequence method, the minimum coefficient of the correlation between R-R interval (or PI) and SBP to validate a sequence affected the agreement between procedures only marginally. Similarly, a lag of 0 or 1 beat or the choice of ramps with 3 or 4 beats did not affect the agreement between procedures. In this study, the data were provided beat to beat, and a zero-beat delay refers to the R-R interval surrounding the systolic peak. Another source of differences between subjects could be the resting HR, which could influence the optimal HR latency. Further estimates could be made by varying the latency according to the resting HR.

The unit used to estimate heart rhythm fluctuations was R-R interval or its surrogate PI for 20 procedures. It has been shown previously that these two estimates of heart rhythm are similar (2). Only one procedure used HR. The possible bias due to the heart rhythm unit was, therefore, not involved in the differences between or within the methods.

In conclusion, this study clearly shows that the various BRS estimates are not interchangeable and are not always able to detect baroreflex impairment. Future estimates should optimize the setting of parameters to provide a robust estimate, even in the cases of low BRS. To extend the comparison to other methods or procedures, access to the present set of data, the full description of the methods used, and the complete results can be obtained from the following web address: http://www.cbi.polimi.it/glossary/eurobavar.html.

GRANTS

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