

## Appendix II Time-domain cross-correlation baroreflex sensitivity: performance on the EUROBAVAR data set

B.E. Westerhof, J. Gisolf, W.J. Stok, K.H. Wesseling  
and J.M. Karemaker, *J Hypertens* 2004 Jul;22(7):1371-80

The following chapter explains a method, developed by Wesseling and Karemaker, for computing baroreflex sensitivity, using time-domain cross-correlation of inter-beat interval and systolic blood pressure series. The method is applied to the Eurobavar database, allowing comparison with existing, established methods for determining baroreflex sensitivity.

### Introduction

Baroreflex sensitivity (BRS) is now a prognostic factor in cardiology<sup>74; 80; 82</sup>. It is the amount of response in heart beat interval to a change in blood pressure, expressed in ms/mmHg. A blood pressure increment must lead to an increment in interval within 3 or 4 s, and similarly a blood pressure decrement must lead to an interval decrement within 3 or 4 s, for the changes to be considered to be baroreflex action. Since the concept was proposed in 1969<sup>112</sup>, a number of methods have been developed for the assessment of BRS, some using a circulatory challenge such as injections of vasoconstrictor or vasodilator agents<sup>112</sup>, neck suction<sup>42</sup> or a change from supine to standing<sup>53; 132</sup>, and some using spontaneous blood pressure and interval variability, studied in the time domain<sup>13; 38; 39</sup> or in the frequency domain<sup>38; 105</sup>. These various methods produce somewhat different numerical values<sup>50</sup>, although results obtained on the same data set show acceptable correlation<sup>82</sup>. Before the cross-correlation method described below, we developed a sequential method (sBRS) based on and comparable to the well known method of Di Rienzo *et al.*<sup>39</sup>. During the development of that technique, when spontaneous fluctuations in pressure and interval were plotted against each other, we often noticed open Lissajous loops, which indicated that allowance should be made for any delay between pressure and interval, as was suggested at an early stage by Karemaker<sup>72</sup>. As the amount of delay for each patient and patient state is not known in advance, we decided to compute BRS as a cross-correlation function of blood pressure and pulse interval and call this method cross-correlation baroreflex sensitivity, or xBRS.

Recently, the European Society of Hypertension working group on baroreflex and cardiovascular variability, in which 11 centres participate, has produced a comprehensive database which is available for the testing and comparison of methods<sup>82</sup>. We tested the xBRS method on that data set, comparing the results obtained by xBRS using our local

Amsterdam sequence and spectral algorithms with the 21 results obtained with various methods returned by the 11 centres participating in EUROBAVAR<sup>82</sup>.

## Methods

The xBRS, sBRS and spectral methods described below we will refer to as Amsterdam ‘local’ methods and results, to distinguish them from those in the EUROBAVAR study.

### *The EUROBAVAR data set*

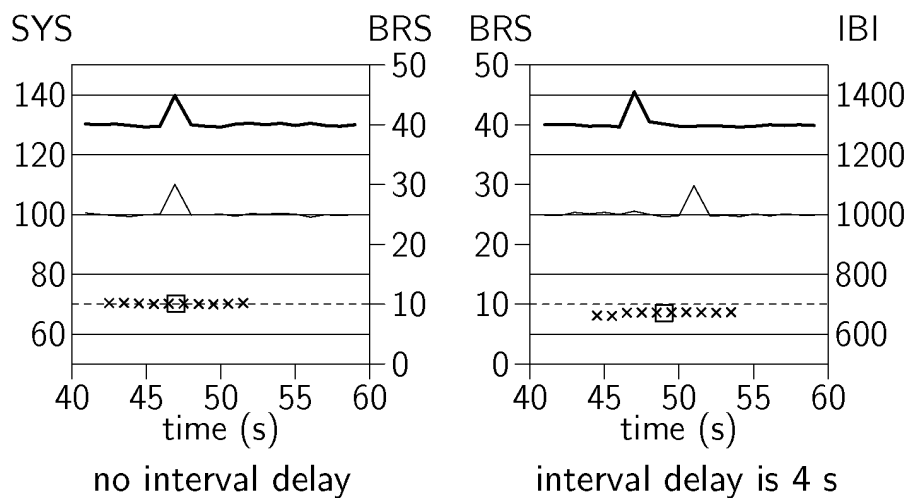
The EUROBAVAR data set consists of 10–12 min recordings obtained in 21 patients (four men and 17 women) who were monitored non-invasively with a Finapres 2300 (Ohmeda, Louisville, Colorado, USA) and a Cardiocap II (Datex Engstrom, Helsinki, Finland) in both the supine (henceforth referred to as ‘lying’) and the standing positions. Their ages ranged from 20 to 68 years. One patient had diabetes with evident cardiac autonomic neuropathy, one was a recent recipient of a heart transplant, one had diabetes without cardiac neuropathy, eight were normotensive patients, one had hypertension, two had hypertension that was treated, two had hypercholesterolaemia that was treated, one woman was pregnant in her first term, and four were healthy volunteers. (For further details see Laude *et al.*<sup>82</sup>.) The EUROBAVAR data set is available from the internet as beat-to-beat systolic and interval values. A set (a) consists of 16 files from eight patients, identified as a0011 for lying and a001s for standing, and so on. A set (b) consists of 30 files identified as b0011 and b001s and so on; these were from 13 new patients and two copied from the previous (a) set to test repeatability.

### *Cross-correlation baroreflex sensitivity*

The xBRS method differs from the original<sup>39</sup> time-domain sequential method in that it observes blood pressure and heart interval variability over a fixed time period rather than over a variable number of beats. Cross-correlation and regression between systolic blood pressure and R–R interval are computed over 10 s sliding windows, a time-span sufficient to accommodate fully a 10 s variability in rhythm, or several cycles at ventilatory frequencies. The method thus may observe two or more slopes simultaneously. Often, the interval variability is delayed with respect to systolic pressure variability. Steptoe and Vögele<sup>117</sup> found a 0-, 1- or 2-beat delay to be adequate in young men. Delays in the baroreflex, however, are measured in seconds of time, not beats<sup>17</sup>. We therefore programmed delays in the pulse interval series to compensate for physiological delays by applying time shifts of 0–5 s to interval, thereby correlating current pressure with later interval values. A 5 s delay should suffice for sympathetically mediated reflexes on pulse interval.

Systolic pressure and heart interval series were taken from the EUROBAVAR files. Beat events were spaced on the time axis by distances equal to heart interval. Cubic splines were fitted to the blood pressure and interval event series and the splines were resampled at 1 Hz. For each window, the correlation coefficient was computed six times. The first computation was for zero delay and was executed between the first 10 pressure and interval value pairs ( $t = 1-10$  s). The next computation was for a delay of 1 s and was carried out between the same 10 pressures, but with interval values at  $t = 2-11$  s. Computations continued until the 10 pressure values ( $t = 1-10$  s) were correlated with

interval values at  $t = 6-15$  s. The cross-correlation with the greatest value was selected, and the corresponding regression slope was taken as a determination of BRS, provided it was positive and its probability of being a random regression was less than 1% ( $P < 0.01$ ). When these conditions were not met, there was no result for this time segment. The accepted regression slope was divided by the correlation coefficient to obtain a slope fitting pressure and interval variability simultaneously<sup>114</sup>; this was done because the pressure and the interval values are both disturbed by random variability in excess of that explained by baroreflex variability. The corresponding delay was recorded as best delay  $\tau$ . There were no thresholds for pressure or interval changes within a segment. The timing point of a valid xBRS was the middle position of the pressure and possibly time-shifted interval windows. A simulated spike of short duration demonstrates timing in Figure II.1. Such short events cause clusters of BRS detection, 1 s apart. In the software, such clusters are detected as contiguous values not more than 1.5 s apart; the BRS values in a cluster are averaged and timed at the cluster midposition, thus indicating the joint event. Spiked events are rare, however, and approximately sinusoidal events of limited duration are more probable. These may also cause clusters. Values within clusters were usually not as stable as in the simulation example, but were seen to vary over a 2:1 range in amplitude. The results presented are based on individual determinations, not on clusters. With each new determination, the window was advanced 1 s, cumulative means and ranges were updated, and histograms were formed of xBRS and best delay  $\tau$ , for inspection.



**Figure II.1**

**Simulated pressure and interval plots to demonstrate timing.**

The upper line is pressure; the lower line is interval. X, Time of a cross-correlation determination of baroreflex sensitivity (BRS); □, cluster midpoint. SBP, systolic blood pressure.

*Sequential baroreflex sensitivity*

For comparison, we include results obtained with the sBRS method, programmed previously in consultation with Di Rienzo and colleagues<sup>39</sup>. This method detects sequences of beats with simultaneously increasing or decreasing pressure and interval. A minimum of three sequential beats (three intervals, four R-waves) is required, and a pulse interval delay

of 0 is taken – that is, systolic pressure falls within the R–R interval considered. The method requires a systolic pressure variation of at least 2.5 mmHg over the beats in the sequence, but has no threshold for interval. The estimate is accepted when correlation is significant at  $P = 0.05$ . At the occurrence of the next beat, the direction of the changes in interval and pressure are compared with those of the previous beats. If directions are the same, then correlation and regression are again computed over the longer sequence and evaluated for significance. This leads to clusters of sBRS values similar to the clusters that the xBRS method produces. Our results are based on the individual values.

### *Spectral method*

Our spectral method computes baroreflex sensitivity as the transfer gain of the cross-spectra between pressure and interval. Their coherence is usually high in the 10 s rhythm band taken from 0.06 to 0.15 Hz and at ventilatory frequencies in the spectra between 0.15 and 0.5 Hz.

Spectral estimates of the entire recording were computed with in-house developed software (Graphical User Interface For Fourier Transform), providing an easy-to-use interface on top of proven Matlab signal analysis procedures. Signals were de-trended and a von Hann window<sup>54</sup> applied. A discrete Fourier transform was used that needed no interpolation or zero padding. Triangular spectral smoothing was set at a width of 10 for this study, in view of the 10 min duration of the records. Spectral density, coherence, pressure–interval transfer gain and phase plots are shown on a computer screen and in addition a cursor allows manual selection of bands in which coherence and spectral power are high. An output program lists the resultant data and all the choices made for later analysis.

### *Statistics*

Histograms of xBRS values per patient file most often conformed to a log-normal distribution. For log-normally distributed variables, the geometric average is a better estimate of central tendency than the arithmetic average. To obtain the geometric average, we took the logarithm of the numbers, computed their arithmetic average, and exponentiated the resultant mean. The numbers were required to be positive or the logarithm could not be taken. BRS values were positive. Values of xBRS best delay  $\tau$  were averaged arithmetically per patient file, as were values for sBRS. In addition, the distributions of best delay  $\tau$  per patient file were pooled separately for the lying and standing positions and compared using the  $\chi^2$  test<sup>114</sup>. Multiple regression was used in an attempt to correlate xBRS to patient parameters, to explain variability between patients. When grouped data were compared, non-parametric statistics were used. To maintain comparability with the results of the EUROBAVAR study, we present the pooled arithmetic mean, SD and range. For goodness of fit to a distribution, we used the Kolmogorov–Smirnov one-sample test. For correlation, we used Spearman rank correlation. For significance of differences we used the Mann–Whitney U-test or the Wilcoxon matched pair signed ranks test where appropriate.

## **Results**

### *Duplicates*

The duplicate files were b014 and b015. They gave results identical to their twins (a003 and a008) with our local methods. Identical results were expected, because no manual selection

of data was made and the same algorithms were applied to the same data files. In the case of the overall statistics, we removed these duplicates, 21 patients and 42 records thus remaining <sup>82</sup>.

### *Distribution types*

The Kolmogorov–Smirnov test on xBRS rejected 25 (12 lying and 13 standing) files as normally distributed ( $P = 0.05$ ). The same test rejected no lying and one standing distribution as log-normal. The xBRS distribution for patient a002s was not accepted as either normal or log-normal. The assumption of log-normal distributions, therefore, was acceptable in 41 of the 42 cases, and the assumption of normal xBRS distributions per file must be rejected. For sBRS, similarly, normality was rejected 12 times, accepted 23 times and undecided seven times because of a very small number of values. Log-normality was rejected in no case and undecided eight times. The assumption of log-normal sBRS distributions per file was the safer one, but the picture was less clear.

For grouped data, neither the normal nor the lognormal distribution hypothesis was rejected for any method (xBRS, sequential or spectral), and arithmetic averages were taken.

**Table II.1**  
**Number of estimates and variance for sequential (sBRS) and cross-correlation (xBRS) baroreflex sensitivity**

	Number of estimates		Variance	
	sBRS	xBRS	sBRS <sup>a</sup>	xBRS
Lying	(n=20)	(n=21)	(n=18)	(n=18)
Mean	50	185	83	39
SD	63	84	129	53
Range	2 – 174	18 – 418	0 – 545	4 – 179
Standing	(n=21)	(n=21)	(n=18)	(n=18)
Mean	76	214	23	12
SD	78	106	34	17
Range	1 – 279	11 – 423	1 – 139	0 – 71

<sup>a</sup>Data from patients for whom there was no value for sBRS have been removed.

### *Ability to provide baroreflex sensitivity estimates*

The xBRS method provided BRS values for all patient files of both sets (Table II.1). The smallest number of determinations was 11 on patient b010 in the standing position. The sBRS method did not provide a result for patient a003 in the lying position (note that the number in the sample for sBRS was 20, not 21); for patients b005 and b010 in the standing position, only a single sBRS value was obtained; on both records for patient b004, and for patients b0051 and b0131, only two sBRS values were obtained over the entire 11 min patient record. sBRS produced fewer than 22 determinations for 22 of the 42 patient records, or fewer than two per minute. The number of xBRS estimates was three times greater on average than for sBRS. The average period of time between xBRS estimates was

**Table II.2**  
**Baroreflex sensitivity assessed by various methods**

	EUROBAVAR				Local		
	Sequential	Spectral-LF	Spectral-HF	sBRS	TG-LF	TG-HF	xBRS
Lying	(n=6 <sup>a</sup> )	(n=6 <sup>a</sup> )	(n=4 <sup>a</sup> )	(n=20)	(n=21)	(n=21)	(n=21)
Mean	16.2	11.2	16.9	13.4	9.5	14.6	12.4
SD				9.8	10.7	12.3	12.1
Range				2.1-46	0.2-51	1.5-54	2.0-60
Standing		(n=20 <sup>a</sup> )		(n=21)	(n=21)	(n=21)	(n=21)
Mean		6.7		6.8	5.2	5.9	6.2
SD				3.9	3.8	4.3	3.9
Range				1.2-15.7	0.1-14.7	0.4-16.6	0.8-16.3
Ratio lying/standing	(n=6 <sup>a</sup> )	(n=6 <sup>a</sup> )	(n=4 <sup>a</sup> )	(n=20)	(n=21)	(n=21)	(n=21)
Mean	2.10	1.70	2.63	2.01	1.87	2.68	1.96
SD				0.97	1.02	1.43	0.92
Range				0.80-4.54	0.70-3.82	0.85-6.31	0.85-4.20

LF, HF, Low- and high-frequency; sBRS, sequential baroreflex sensitivity; TG, spectral transfer gain; xBRS, cross-correlation baroreflex sensitivity. n, Number of patients having at least one BRS estimate, or <sup>a</sup> number of procedures of that type returned by participating centres. EUROBAVAR pools the estimates obtained with the various techniques for the standing position because they differed little. Values for SD and range are between patients.

3.0 s; between sBRS estimates it was 7.7 s. A total of 0.2% of xBRS values were obtained at intervals longer than 60 s, compared with 1.8% of sBRS values, not including the three patients in whom no or only single estimates were obtained. Excluding both patients with impaired baroreflexes, xBRS provided 20 values per minute, sBRS just six. With the spectral methods, occasionally, we had to accept bands without significant coherence.

#### *Lying and standing baroreflex sensitivity values*

Table II.2 provides a comparison between the EUROBAVAR results averaged over the various centres and techniques, results from our local sequential and spectral techniques, and those from the new xBRS method. Values for the lying and standing positions and their ratio (which is also considered an important statistic) are listed separately. Note that the number in the sample is 20 for sBRS in the lying position, because no value was obtained for patient record a003l. There was a clear difference between results for lying and standing, with lying values for baroreflex sensitivity approximately two times greater than standing values for all techniques. The SD and range for the local techniques are for the group of 21 patients. The greater value for xBRS SD in the lying position is accounted for by patient b013l, treated separately below (Outlier patient). The differences between the xBRS and sBRS methods were small and not significant (U-test), and rank correlation at 0.95 (Spearman) was highly significant ( $P < 0.0001$ ).

#### *Within-patient variance in baroreflex sensitivity*

The within-patient stability of BRS values was analysed by computing the variance (SD squared) for each method. In three cases, no sBRS variance was available because no, or only a single, BRS value was obtained; the results from these patients were removed from the averages of both methods. Table II.1 gives the variances. For xBRS, the average variance per patient file and position was approximately 50% of that for sBRS. The variance ratio became 2.2 when the lying and standing data for each method were combined. All differences were significant (Wilcoxon at  $P = 0.0001$ ). The coefficient of variation (SD in % of the mean per patient record) was on average 41% for xBRS (range 19–62%) and 52% for sBRS (range 3–96%); in both cases it was nearly proportional to the BRS – that is, large and small values of sensitivity had approximately the same percentage scatter.

**Table II.3**  
**Sequential (sBRS) and cross-correlation (xBRS) baroreflex sensitivity in patients with impaired baroreflex**

File	sBRS		xBRS	
	Value	n	Value	n
b005s	1.2	1	0.8 ± 0.3	46
b005l	2.1 ± 0.6	2	2.3 ± 0.8	82
b010s	2.5	1	1.3 ± 0.4	11
b010l	2.2 ± 0.7	3	2.0 ± 1.8	18

Values are mean ± SD. n, Number of values obtained per record. Note that the number of sBRS estimates was so small that it was not always possible to establish a value for SD.

### *Ability to detect baroreflex impairment*

The smallest BRS values were obtained for patients b005 and b010 in both positions, with lying values greater than those for standing (Table II.3). The value was also small in the case of patient a005, but only for the standing position. In these patients, xBRS yielded values similar to those from sBRS, but the xBRS method gave more values per patient file. Figure II.2 shows a plot of systolic pressure and R–R interval of the patient who had recently received a heart transplant. There was a gradual down-drift of the R–R interval, possibly as a result of increases in circulating (nor)adrenaline after standing up. The interval oscillations looked like noise; enlarged, they were almost sinusoidal in the rhythm of ventilation at one oscillation per 3 or 4 s, and the enlarged systolic oscillations seemed to be synchronous. Thus the xBRS algorithm produced an occasional value, and so did sBRS, even though fluctuations probably had a nonbaroreflex origin <sup>12</sup>.

### *Outlier patient*

In the (b) set files there was one patient (b013) with a very high value for xBRS in the lying position: 59.7 ms/mmHg (SD 13.3 ms/mmHg). The sBRS value was 45.5 ms/mmHg, the spectral low-frequency transfer gain value 51.2 ms/mmHg and the spectral high-frequency transfer gain value 54.0 ms/mmHg. For the standing position, values were more normal. Figure II.3 shows 20 s (two windows wide) sections of the records for both positions. For the lying position, the mean of the pressure range per xBRS determination was 3.93 mmHg and that of the interval range was 236 ms, a very high ratio. It can thus be argued that the high xBRS value is not unreasonable.

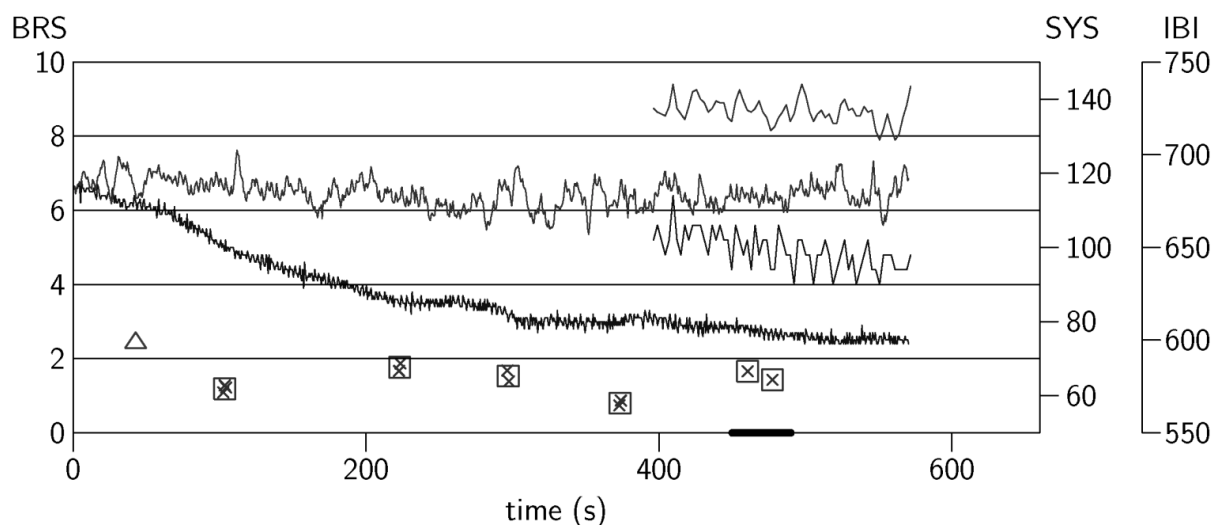
### *Correlations between methods*

To compute correlation coefficients, first the data for patient a003, for whom there was no sBRS value for the lying position, were removed. In Table II.4, we present the non-parametric (Spearman) rank coefficients, ranking being insensitive to the very high value of patient b013. xBRS had the greatest correlation with sBRS; next best was xBRS on spectral high-frequency transfer gain value, and finally xBRS on spectral low-frequency transfer gain value. The significance of these correlations ( $P = 0.0001$ ) was very high.

### *Correlations and differences between lying and standing results*

The coefficient of determination  $R^2$  (Table II.5) was the same for both positions, implying that lying and standing xBRS were determined with the same precision, even though the pressure and interval ranges differed according to position. xBRS values (Table II.2) were correlated at  $P = 0.0004$ , meaning that a patient with a high or low sensitivity in the standing position has a high or low sensitivity when lying down. Best delay  $\tau$  was similarly correlated at  $P = 0.0002$ , meaning that a patient with a short or long delay in the standing position had a short or long delay when lying down. The paired difference for xBRS (lying – standing) was 6.14 ms/mmHg (SD 9.3 ms/mmHg) and was significant ( $P \approx 0.0001$ ). The paired difference for  $\tau$  (lying – standing) was –102 ms and was not significant. Although the mean difference between  $\tau$  for both body positions was not significant, the cumulative distributions of  $\tau$  showed a clear shift towards greater values for the standing position (Fig. II.4). Comparing these distributions by computing  $\chi^2$ , the difference was highly significant ( $P < 0.0001$ ).

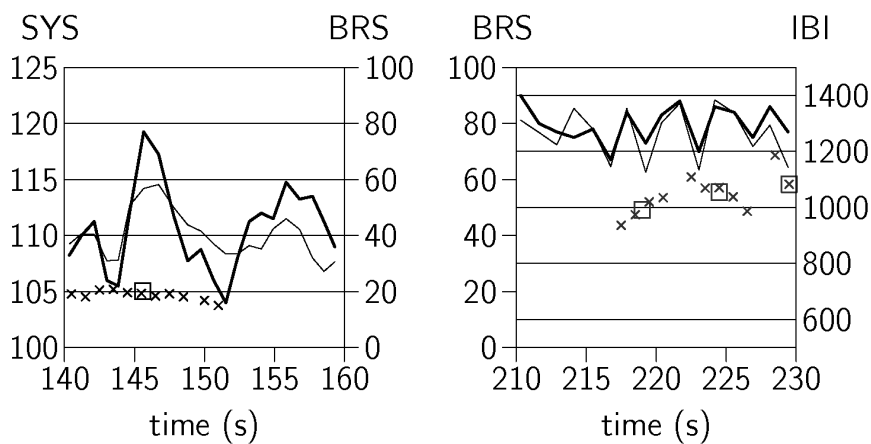




**Figure II.2**

**Recording in the heart transplant patient in the standing position.**

Upper trace: systolic blood pressure (SBP); lower trace: R–R interval. Sequential baroreflex sensitivity ( $\Delta$ ), cross-correlation baroreflex sensitivity (xBRS, X) and xBRS cluster ( $\square$ ) are marked. The full time scale is 660 s (11 min). An sBRS value occurs near  $t = 40$  s reading 2.5 ms/mmHg; xBRS is 1.31 ms/mmHg (SD 0.4 ms/mmHg) averaged over 11 estimates. To show details of variability, the period marked by a thick bar on the time axis between 450 and 490 s is also shown enlarged: X4.4 with respect to the time, x4 with respect to the R–R interval and X2 with respect to the pressure.



**Figure II.3**

**Section of the standing (left) and the lying (right) recordings in patient b013, who had the highest BRS values in the group.**

The bold line is pressure; the thin line is interval. X, Time of cross-correlation determination of baroreflex sensitivity (BRS);  $\square$ , cluster midpoint. SBP, systolic blood pressure. Both diagrams have the same vertical scales, with the common pressure scale at the left and the interval scale at the far right. In this figure, standing BRS is about 20 ms/mmHg, and lying BRS ranges between 45 and 70 ms/mmHg.

*Regression of cross-correlation baroreflex sensitivity upon interval, delay and age*

The between-patient SD for xBRS in the lying position was almost as great as the mean; for the standing position it was about two-thirds of the mean (Table II.2). Was this just estimation error or was it patient specific? It appeared that 73% of the scatter in xBRS values between patients and positions could be explained for by variations in interval, delay and patient age. The multiple regressions of xBRS on these parameters were:

$$\begin{aligned}x &= -18.2 + 0.0616I - 4.82\tau - 0.431A \text{ (lying)} \\x &= -7.8 + 0.0299I - 1.56\tau - 0.158A \text{ (standing)} \\x &= -14.1 + 0.0509I - 3.77\tau - 0.323A \text{ (combined)}\end{aligned}$$

where  $x$  is the xBRS geometric mean value per patient,  $I$  is the mean interval,  $\tau$  is best delay and  $A$  is patient age. Regressions on pressure were not significant. The regression on  $\tau$  and the strong lying–standing correlation (see paragraph above) suggest that best delay  $\tau$  with the xBRS method was more than simply a methodological parameter with which to obtain greatest correlation, but also had physiological significance. Clearly and significantly, xBRS decreased with shorter interbeat interval (greater heart rate), with longer delay and with greater patient age.

*Scatter plots*

With xBRS plotted against the three other local results (Fig. II.5) the scattergrams appeared to be similar, but they differed in detail. For the lying position, xBRS tended towards lower values than sBRS and spectral high-frequency transfer gain. The plot of xBRS against low-frequency transfer gain had a wider scatter in the lower range of values than that of xBRS against the other methods.

**Table II.4**  
**Spearman rank correlation between local methods of estimating baroreflex sensitivity**

	sBRS	TG-LF	TG-HF
Lying			
TG-LF	0.783***		
TG-HF	0.912***	0.689	
xBRS	0.931***	0.808***	0.901***
Standing			
TG-LF	0.442	0.442	
TG-HF	0.916***	0.697	0.853***
xBRS	0.884***		
Combined			
TG-LF	0.711***		
TG-HF	0.938***	0.598***	
xBRS	0.943***	0.764***	0.903***

sBRS, sequential and baroreflex sensitivity; TG-LF, TG-HF, low- and high-frequency spectral transfer gains; xBRS, cross-correlation baroreflex sensitivity. All correlations are significant at  $P = 0.05$ ; \*\*\*significant at  $P = 0.0001$ .

**Table II.5**  
**Miscellaneous parameters detected by cross-correlation baroreflex sensitivity**

	$\tau$ (s)	$R^2$	$\Delta p$ (mmHg)	$\Delta I$ (ms)
Lying				
Mean	1.45	0.71	8.7	93
SD		0.02	3.1	53
Range	0.51 – 2.63	0.68 – 0.75	4.0 – 15.8	10 – 237
Standing				
Mean	1.55	0.72	13.5	81
SD		0.03	4.1	45
Range	0.86 – 2.87	0.64 – 0.78	5.6 – 19.0	5 – 215

For each patient record:  $\tau$ , best delay;  $\Delta p$ , systolic blood pressure range;  $\Delta I$ , R-R interval range.

## Discussion

This study has shown that the xBRS method produced results comparable to those achieved with pre-existing time-domain and spectral methods<sup>82</sup>. On average, xBRS determinations of baroreflex sensitivity were approximately equally close to those obtained with sBRS and with local spectral low-frequency and high-frequency transfer gain. The number of determinations per minute of time was high for all patients except the one who had a recent heart transplant. xBRS was sensitive to fluctuations in the low-frequency and high-frequency bands. This is shown clearly in Figure II.3, which shows values for 10 s rhythm (left panel) and ventilatory frequency fluctuations (right panel) corresponding roughly to their low-frequency transfer gain and high-frequency transfer gain values. xBRS values were highly significantly correlated between the lying and standing positions within patients, and more than 70% of the variance between patients was explained by R-R interval, best delay  $\tau$  and patient age.

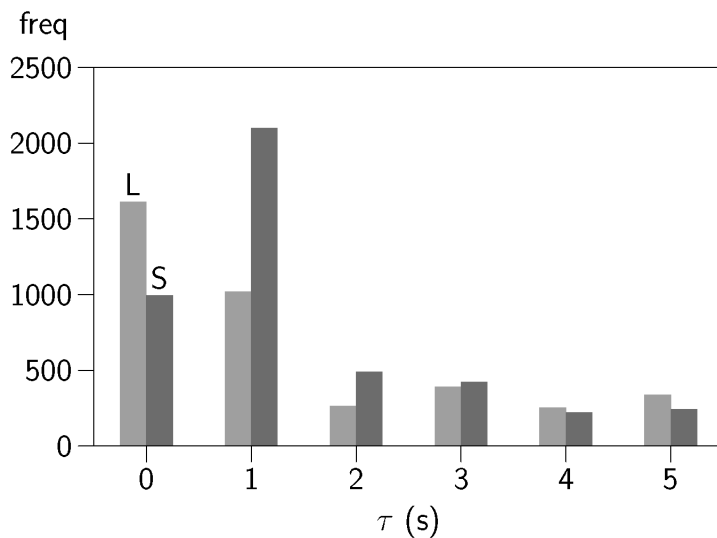
With clinical interest in baroreflex sensitivity mounting, it is important to have reliable, simple to use, well researched methods for BRS computation. The time-honoured sequential method<sup>39</sup> is such a method giving accurate results<sup>97</sup>. The cross-correlation method proposed in this study gave smaller within-patient scatter and a greater number of values per minute than the sBRS method. It removed uncertainty as to the number of beats of interval delay that should be implemented in common sequential methods by computing regression for all reasonable delays. Thresholds were avoided, to improve frequency of detection in patients with impaired baroreflexes. Nevertheless, the method provided results comparable to and correlated with those obtained with sBRS in the EUROBAVAR data set. The effects of algorithmic differences between the sBRS and xBRS methods are that

- (1) within-patient variance is reduced using a fixed 10 s wide window, which allows computation of complete oscillations, not just their slopes;
- (2) improved correlation and increased number of detections follow from a search for greatest crosscorrelation by varying the time delay between pressure and interval;

- (3) application to young and old patients, in the supine, standing or head-up tilted position, or under any other influence that may alter the delay between pressure and interval, is possible by the automatic selection of best delay  $\tau$ ;
- (4) a better estimator of central tendency on the within-patient log-normally distributed values is provided by geometric averaging, which is traditionally not used with the common sequential techniques;
- (5) detection reliability is increased by a low  $P$  value ( $P = 0.01$ , compared with  $P = 0.05$  for most sequential implementations);
- (6) determination of BRS in patients with low baroreflex sensitivity is facilitated by the absence of thresholds for pressure and interval variation (range).

Time-domain sequential BRS methods can pinpoint the instant of activity of the baroreflex better than frequency domain methods, but only when a large number of determinations are available. The xBRS method, on average, produced three times as many values as our implementation of the sequential method, sBRS, and the determinations were more uniformly distributed over time.

The advantage of a high number of determinations per minute is evident when a statistically reliable BRS estimate is to be obtained in a stationary patient in the smallest possible period of time. It is also obvious when tracking changes in BRS in non-stationary patients, for example during tilt and mental or physical exercise procedures. When patients are monitored in the supine position, the low number of sBRS determinations (fewer than two per minute in 12 of the 21 patients) in the EUROBAVAR data set seems problematic. xBRS had such a low frequency of determination only in the heart transplant patient.

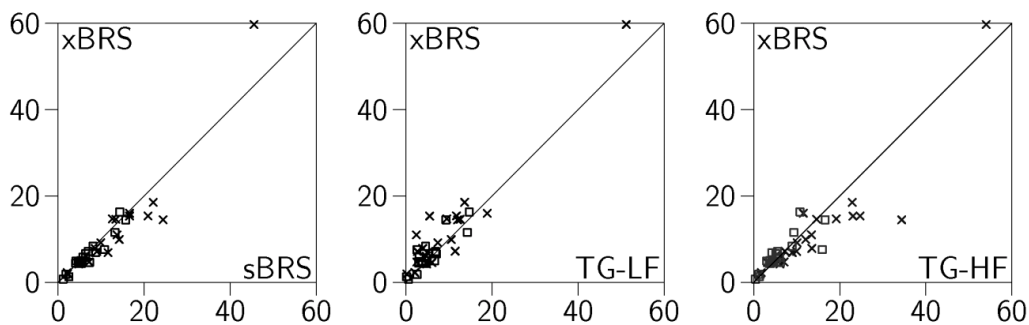


**Figure II.4**  
**Distributions of best delay  $\tau$  for lying and standing positions pooled for all patients.**  
 □, Lying; ■, standing. With the change from lying to standing, a shift towards greater values of  $\tau$  is apparent.

As was shown by Laude *et al.*<sup>82</sup> in their Figure II.1, common sequential determinations seemed to have greater difficulty than spectral techniques in providing (the low) values in the two autonomically impaired patients. The six centres that returned sequential data had estimates for only 14 of the 24 patients. xBRS produced the low values reliably in both cases and both body positions. One could argue that the failure to provide data in these cases of low to zero BRS is actually correct, as we know that a baroreflex is absent or

ineffective. Leaving an observer with no data, however, could have other implications. For example, in patients under atropine, the vagal reflex is suppressed but a sympathetic reflex may still be present. This reflex has a longer delay and for that reason may be overlooked by the common fixed-delay sequential technique, whereas an algorithm that searches for best delay might provide useful data values, as do spectral methods that compute rather than assume the phase shift between pressure and interval and therefore are also successful in such difficult cases.

The scatter in the values of individual BRS determinations with both time-domain methods was substantial and is puzzling. Within-patient variance for xBRS is 50% that of sBRS, a statistically significant improvement. Is it likely that, with improved methodology, the scatter would be reduced to zero? Probably not. The present scatter was proportional to baroreflex sensitivity and proportionality was closer for xBRS, which had lower within-patient variance. This suggests a physiological cause for part of the within-patient scatter. Blood pressure and R–R interval variability are known to show ‘one-over-f’ behaviour – that is, spectral intensity increases with decreasing frequency<sup>28</sup>. It is thus not surprising that BRS was not constant even in stationary patients, and it is questionable whether averaging over progressively longer periods would provide a true value of BRS. A certain amount of scatter observed in BRS values, in addition to variability caused by mental and physical exercise, day–night difference, and body position change, should be regarded as an essential aspect of baroreflex blood pressure control.



**Figure II.5**

**Scatter plot of cross-correlation baroreflex sensitivity (xBRS) against the three local BRS estimates.**

X, Lying position; □, standing values; TG-LF, TG-HF, low- and high frequency spectral transfer gains. The line of identity is drawn in each plot.

Best delay  $\tau$  varies per determination within a patient record and its mean value per patient differs between patients. For the lying position, delays of 0 s occur most frequently, whereas for the standing position a 1 s delay occurs most often (Fig. II.4). This finding casts doubt on any fixed delay of 0 or 1 beat in common sequential BRS methods, and supports the findings of Steptoe and Vögele<sup>117</sup>. The automatic selection of a best delay removes an uncertainty of those sequential methods that have a fixed 0 or 1 beat delay that may be less suitable in certain patient conditions.

Frequency-domain methods distinguish between low-frequency (partly sympathetic) and high-frequency (vagal) baroreflex activity, whereas time-domain methods would require a filter stage preceding the BRS computation to achieve the same distinction.

A limitation of the xBRS method in its present form is that it does not discriminate between oscillations in ventilatory and 10 s rhythm bands. In a recent review<sup>41</sup>, Eckberg concluded that ventilatory pressure and interval variability had little to do with baroreflex action, because there is a common cause: the human respiratory gate. This limitation might not be too serious in practice if it is argued that respiratory gating suppresses the baroreflex to a degree depending on ventilatory rate, and is therefore responsible for the lower BRS values found in exercise. BRS determinations on spontaneous fluctuations are, indeed, highly correlated between both spectral bands and between spectral and time-domain estimates, and produce similar values. However, there is no guarantee that such correlation and similarity would be maintained under all circumstances met clinically.

In conclusion, the proposed time-domain, cross-correlation computation of BRS (xBRS) yielded values for BRS to spontaneous systolic pressure and R–R interval variability that were close to those achieved with earlier methods, and including those for the lying to standing ratio, the values of which tended to show less scatter within patients compared with those obtained from the sequential method. xBRS is able to deal with situations in which changes in R–R interval lag behind pressure changes – in the elderly, at high heart rates, or when the baroreflex tends towards sympathetic – because it searches for best delay. Statistically unbiased estimates of central tendency on the log-normal distributions of xBRS values result from geometric averaging. Time resolution is good, with 20 xBRS determinations per minute on average. In autonomically impaired patients with low interval variability and thus baroreflex sensitivity, the absence of thresholds for pressure and interval changes is probably responsible for the ability of the method to provide acceptable results.