Baroreflex sensitivity, an elusive number

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Baroreflex sensitivity (BRS) was coined as a term for the regression of pulse interval on simultaneous blood pressure upon an injection of phenylephrine (a vasoconstrictor). This technique was developed and advocated by the 'Oxford group'. The phenomena were clearly visible. The idea was that the sudden blood pressure increase was counteracted by the baroreflex reducing heart rate. This baroreflex action, for constant stroke volume, reduces cardiac output, and thus counteracts the blood pressure increase. Note that the heart rate response is evoked and is obtained in a closed baroreflex.

1 Evoked BRS

It would have been best if the term BRS had been reserved for both the technique and the resultant number for BRS. Why? The baroreflex is a complex blood pressure control system and not only has several sensor areas (receptors) but also several effector organs and mechanisms and the reflex on heart rate is only one of those. Principal sensors for this reflex are the carotid baroreceptors, effectors are the fast vagus and the slower sympathetic control of pulse interval. Only because this reflex is so fast can it be separated from other blood pressure control actions.

To label the sensitivity of the reflex on heart rate the baroreflex sensitivity is strictly speaking a misnomer unless this reflex would be representative for the other reflexes. This is not at all clear and decided, thus possibilities are created for confusion. In fact, it is known that in aging people the baroreflex on heart rate via the vagus nerve reduces progressively in sensitivity. Heart rate when modulated vagally begins within the same heart beat in which the increased blood pressure is sensed,

but certainly in the next beat; when modulated sympathetically there is a small delay and an integrating time constant and the reflex comes to full effect only after a few seconds.

Thus, although in the first few seconds of the development of the reflex the regression slope (the baroreflex pulse interval sensitivity as measured with phenylephrine) is determined by the vagal response, after some 3 seconds the sympathetic response augments the vagal response making it less clear what is measured. Even so, one can always *define* BRS as the number that is evoked by an injection of x kg/kg of body weight of phenylephrine.

Other techniques of changing blood pressure were subsequently explored.

1. An obvious one is *lowering* blood pressure pharmacologically by administering a vasodilator. This was done with sodium nitroprusside (SNP) and the 'Milan group' reported lower numbers for BRS than under vasoconstriction with phenylephrine. If the baroreflex responses are equally powerful in either direction, and when the reflex is linear, i.e. has the same sensitivity at lower and at higher blood pressures, and SNP has the exact opposite effect of phenylephrine, the numbers should have been identical. This is apparently not the case. The number was still called BRS.
2. Neck suction causes a local carotid baroreceptor change in transmural pressure. The choking sensation caused by the suction device disturbs many a subject and thus probably the state of his or her baroreflex. Only one sensor area (the carotid) is affected and the unaffected but less effective aortic receptors should oppose any induced blood pressure decrease. Neck cuff pressure is not transferred unattenuated to the tissues at the carotid receptors and although the attenuation factor has been estimated it is not known with certainty. For these three reasons it cannot be assumed that this ingenious technique produces similar numbers.
3. Goedhard et alii evaluated the noninvasively measured mean finger blood pressure - pulse interval response upon the maneuver of standing up from supine.

They used healthy subjects from a laboratory population over a wide age range. It is still uncertain in which way the blood pressure drop is produced by the circulatory system at stand up. Total systemic peripheral resistance, however, is measurably reduced. When the baroreflex takes corrective action the blood pressure returns to normal at least by raising heart rate, and the pulse interval response is measured. Although this casts doubt on the numbers to truly represent 'Oxford' BRS, agreeable quantification was obtained of a measure called "autonomic reflex sensitivity" (ARS) by Goedhard, to not suggest that numbers should be the same as those obtained the Oxford way.

In the group of 131 subjects in which a good response was obtained it turned out that ARS in ms/mmHg regressed significantly upon, in order of importance, control heart rate (f) in BPM, control blood pressure (p) in mmHg, and age (A) in years as follows:

$$ARS = 51 - 0.33f - 0.088p - 0.15A$$

with r=0.683, N=131, P<0.001, over the age range [20...60]. Between rate, pressure and age partial correlation is negligible and thus they are statistically independent parameters. Exactly the same age dependency was found later by Steptoe with another technique.

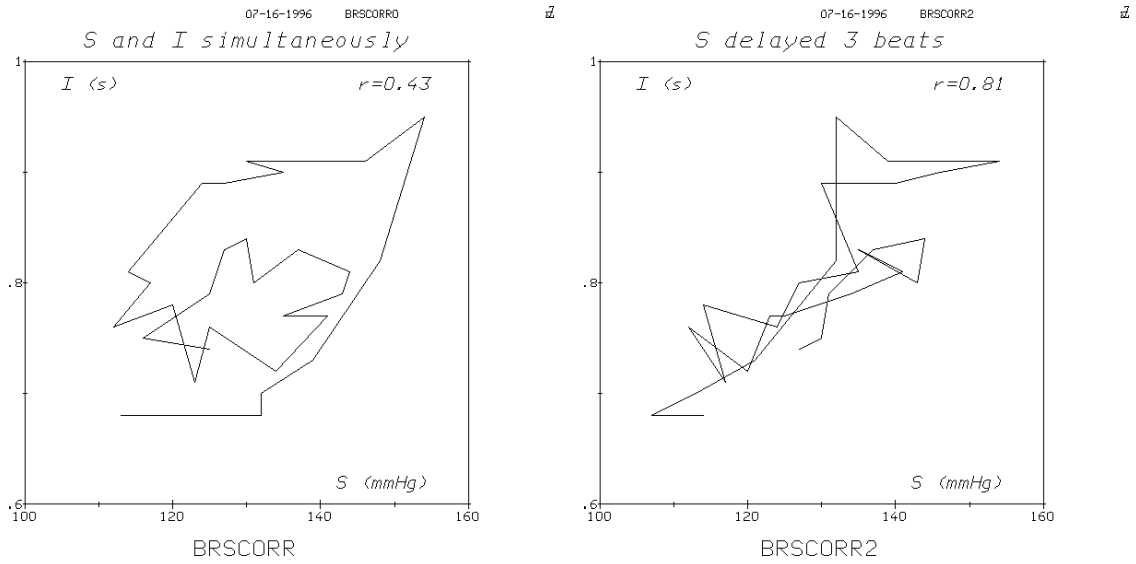
2 Spontaneous BRS

Whatever the described techniques, the results were obtained from evoked, stimulus-response experiments. Then it was reasoned that blood pressure and pulse interval changes also occur "spontaneously", and thus methods were developed to estimate 'BRS' from such spontaneous blood pressure - pulse interval variability.

1. The spontaneous pressure and interval fluctuations can be analyzed in the frequency domain by Fourier analysis. After simultaneous spectral analysis of blood pressure and pulse interval the frequency band between 0.05 and 0.15 Hz

is selected and an average spectral (transfer) ratio extracted to obtain a number in ms/mmHg. Both vagal and sympathetic responses are measured with their, possibly different, gains mixed. Furthermore, spontaneous fluctuations when pulse interval, as the stimulus, increases thereby causing a decreased blood pressure (negative correlation) and those when pulse interval increases in response to increasing blood pressures (positive correlation) both occur and in the frequency domain cannot be separated. An advantage of the chosen frequency band, however, is that it represents phenomena in time that compare acceptably to the response time of the phenylephrine test (10 s or 0.1 Hz). A further advantage is that averaging, usually over several minutes, is involved which tends to produce rather stable numbers. Numeric values, however, may be as much as a factor of two below those of the time–domain methods described earlier. This technique has been developed by Mulder's group in Groningen (Robbe et al.) and similar techniques have been used by the Milan group in their 24–hour analyses, and by Karemaker and coworkers.

2. DiRienzo et alii in Milan developed a time domain sequential technique for spontaneous blood pressure - pulse interval fluctuations which should reduce some of the problems mentioned. Whenever blood pressure and pulse interval change in the same direction for at least four beats a linear regression is computed between the pressure change and the pulse interval change of the next beat. When changes are in the same direction and statistically significant the regression slope is presented as a BRS estimate. In agreement with DiRienzo, we implemented this technique in a software program `SBRS.EXE` for sequential BRS, to work directly with the FAST system and Beatscope results files, obtained noninvasively with Finapres. The program takes care automatically that all heart beats with one or more artifact bits set, such as those obtained during a Physiocal period, are rejected from the analysis. A command line parameter specifies the blood pressure level to be taken in the analysis: systolic, diastolic, mean or mid-pressure[1]. The output file produced is an ASCII text file.



No delay Three beat delay

Figure 1 Not a linear but a phase shifted systolic pressure (S) — pulse interval (I) relationship is often seen in the beat-to-beat data, producing an approximate loop or Lissajous shaped pattern. Delaying the pulse intervals (right) tends to flatten the loop while improving cross-correlation.

During development we sometimes noted on spontaneous fluctuations that a loop is traced when blood pressure and pulse interval are plotted against each other (see Fig. 1 left side) and low (taking four or five beats at the bottom or top) and high numbers (at the steeper sides) for BRS are computed in quick succession. The scatter is such that substantial averaging on such data is needed. The presence of a loop suggests that a zero or one beat delay between the variables may not be optimal.

3. Upon the discovery of these loops we decided to compute the cross-correlation function (see Fig. 2) over a sufficient number of beats at various delays, τ, between blood pressure and pulse interval. In the older adult subject represented in the figure it appears that a broad maximum is present for delays of 2, 3, and

[1] Mid-pressure is the pressure half way between systolic and diastolic, which has been recognized by some as the blood pressure level most directly responsible for baroreflex action

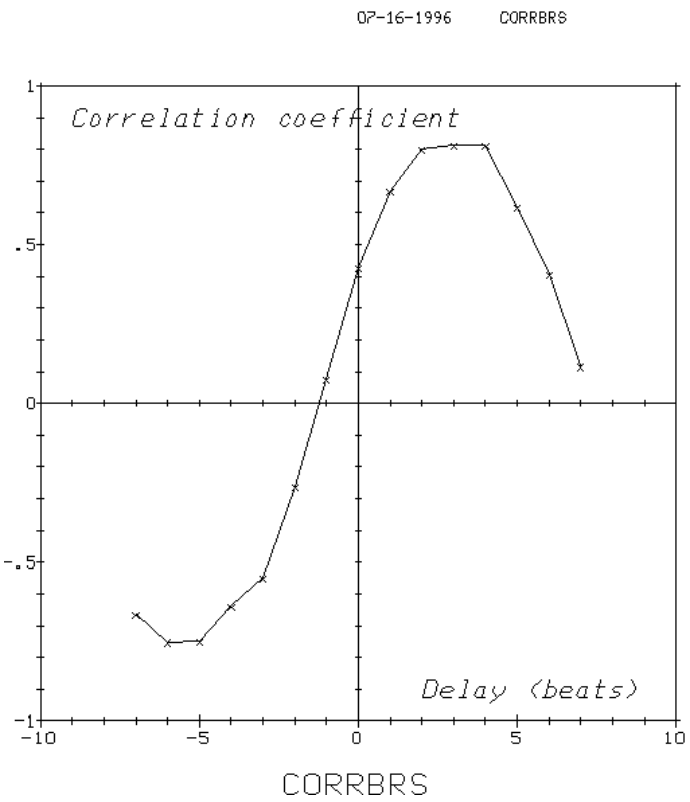


Figure 2 Partial cross-correlation function between blood pressure and pulse interval. Its sinusoidal shape suggests that sinusoidal fluctuations are present. The phase shift between pressure and pulse interval is obvious.

4 beats. In Fig. 1 at the right observe that applying a delay of 3 beats to the pulse interval data substantially flattens the loop and improves the coefficient of cross-correlation, r, from 0.43 to 0.81. Acceptable correlations are also present for negative delays, as if pulse interval leads the blood pressure change. Since this cannot be due to baroreflex action it is ignored. Since it is believed that the delay is caused by the baroreflex and is measured in seconds of time and not in heart beats, we decided to compute a running cross-correlation with each new beat available, over a time span of 12 seconds, slightly longer than the 10 s or 0.1 Hz taken in Robbe's analysis.

For this purpose heart beats are spline interpolated on a time scale having 1 s intervals using a sufficiently long start up period of the interpolation. Time delays range from 0 to 5 s. We then select the delay with highest correlation. When its coefficient of determination, r^2, is significant at P=0.01 it is accepted as a BRS estimate. We implemented this technique in a program `XBRS.EXE` for cross-correlation BRS. As before, we remove all beats with artifact bits set. Whenever a beat with an artifact bit set is met the data arrays are emptied and filling is restarted from zero. As a result, no XBRS data is obtained in the startup periods of a Finapres measurement when the number of beats between Physiocal periods is only 10 or 20 beats. Numbers obtained with this technique show a smaller scatter than those from the original DiRienzo algorithm. Delays found in young subjects typically are 0 and 1 s. Delays in elderly subjects, however, tend to scatter between 0 and 5 s, to average at 3 s. This suggests that both vagal and sympathetic responses are evaluated in these older persons with vagal responses not dominant.

Since BRS estimates with the different techniques differ and may not have any relation with the evoked BRS measures, in particular with the phenylephrine technique, and since spontaneous blood pressure changes measured at the finger are not necessarily also present to the same extent in the baroreflex sensory areas, it appears that a substantial evaluation of the spontaneous fluctuation techniques is in order.

3 A new version software: PRVBRS.EXE

Heart rate variability (HRV) measures have, more than baroreflex sensitivity (BRS), received much attention in the past. HRV can be derived from a noninvasively measured ECG which is more readily available than continuous blood pressure whose noninvasive measurement has become available only recently. HRV involves only one signal, not the relationship between two as for BRS. Very little is needed in the form

of physiological models. Most importantly, clinical significance has been attached to the computed numbers.

HRV is based on the variability of heart rate or interbeat interval detected from an ECG. Both time–domain sequential and frequency–domain measures have been proposed for HRV. A Task Force published standards for both types measures in 1996. With somewhat relaxed precision HRV can also be derived from the pressure pulse. Pressure pulsations do not have the high frequency content of an ECG. Whereas in an ECG the R–wave is characterized by a steep up swing immediately followed by an equally steep down swing, the instant of the begin of the upstroke of the pressure pulse is only marked by an up swing which is also less steep. Still, with adequate detection algorithms the begin upstroke can be determined with precision. A confounding factor is the time lapse between the begin of the Q–wave and the R–top in the ECG which is variable. Similarly, there is a variable time lapse between the begin of Q and the begin of ejection which marks the pulsation's begin upstroke. Unfortunately, the latter so–called "preejection" period is quite variable. Thus, HRV from the pressure pulse cannot be assumed identical to HRV from the ECG R–wave. We, therefore, call it pulse rate variability, PRV.

Given this preamble we decide to combine the time–domain computation of HRV measures on the pulse waves detected in a finger pressure pulsation with the time–domain computation of BRS, since the same input data file is used and the same algorithm to reject beats with an artifact bit. In addition, according to the Task force HRV is presented as a series of statistics and a histogram. Presenting BRS in a similar way might offer advantages. Instantaneous BRS is a number which shows substantial scatter upon subsequent determinations. Statistics techniques could usefully be applied to series of BRS determinations to obtain at a more stable and perhaps a more representative number.

For PRV the program determines the standard deviation of the pulse intervals (SDPP), the pulse rate variability triangular index (PRVti), which is based on a histogram of pulse intervals and equal to the inverse of the percent frequency of the

mode of the distribution, the standard deviation of the period averages of the pulse interval (SDAPP), with the period taken as 5 min, and the root mean squared value of the sequential differences in pulse interval (RMSSD). These measures are the ones recommended by the Task force for time–domain evaluation.

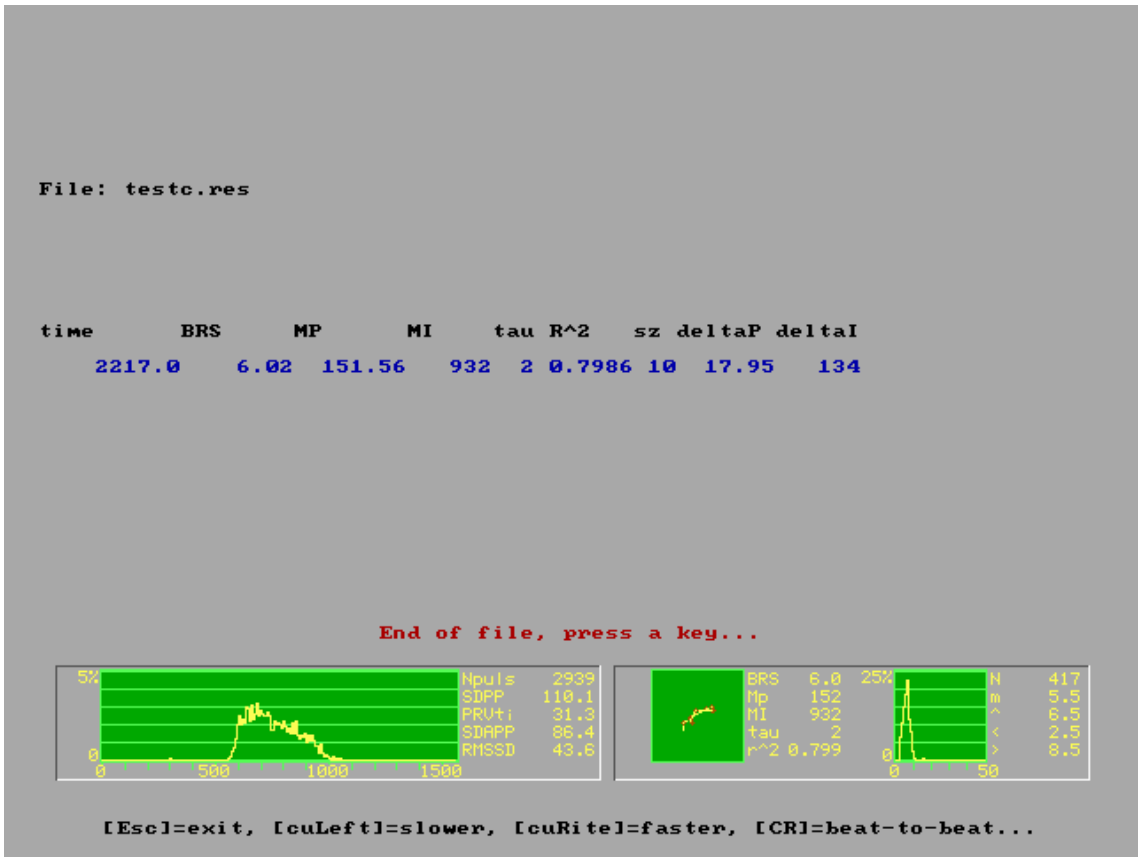


Figure 3 Screen display of program PRVBRS showing from above 1/ the name of the input file, 2/ the line of the current BRS data as also saved in the specified output file, 3/ a message that end–of–file has been reached, 4/ a panel with the PRV histogram and summary table, the p–I plot and its describing data, and a BRS histogram and its statistics, 4/ finally, the keyboard input required to control the velocity of program execution.

For BRS the program determines the best cross–correlation value at the optimum delay of pulse interval with respect to blood pressure over running 12 s intervals.

A diagram shows the pressure–interval plot, allowing to judge linearity, scatter and range of the data, together with the mean pressure and interval, the optimal τ, and the coefficient of determination for each determination. A further diagram presents a histogram of the BRS values obtained. Since histograms typically have a log–normal appearance the geometric mean value, the mode, and the 5 and 95% range are listed. A screen layout is shown in Fig. 3 on page 9. The program is Dos software that runs under Dos and most Windows versions. The input and output filenames are given on a command line with optionally the pressure level to use (you may select systolic, diastolic, mean or mid–pressure as input to the analysis with systolic pressure as the default selection). The input file can be played in real–time, 10 times as fast as real–time, as fast as possible given the hardware, or in so–called "batch mode" (specified with `/b`) without onscreen graphics. Below are a number of commands that are typically given, or are placed in a `.bat` file for execution:

```
prvbrs.exe input1.res output1.sys /sys
prvbrs.exe input2.res output2.mid /mid
prvbrs.exe /b input3.res output3.brs
```

Input files must be of the binary type results file available from Beatscope or a Finometer packet file. The software autodetects the type. The first line uses the, default, systolic pressure for input. The second uses mid–pressure for input, computed as (sys + dia) / 2. The third runs in batch mode without user interaction, using systolic pressure as input. Two output files are generated per program execution. The output file as mentioned on the command line contains lines of text as follows:

```
 time    BRS     mn-p    mn-I  tau r^2   xx delta-p delta-I
    88.0    9.70  139.49   766  2 0.7370 10  34.68   409
    89.0   11.15  144.07   807  2 0.9070 10  44.18   489
    90.0    9.50  148.99   842  2 0.8829 10  53.02   489
    91.0    8.68  155.24   859  1 0.8636 11  53.02   489
```

```
      92.0    8.89  157.59   898  2 0.8553 10  51.77   489
      93.0    8.92  159.61   922  2 0.8188 10  51.77   489
      94.0    7.65  160.00   948  2 0.7132 10  51.77   489
      95.0    6.00  159.99   971  2 0.6195 10  51.77   471
      97.0    4.32  156.89   989  2 0.7516 10  61.62   356
...
...
```

in which xx is $12 - \tau$. The time mentioned is the time since the start for the middle position of the thirteen value array of blood pressures. When a time delay is used the number of available data for the regression is reduced and linear regression is computed over a smaller number of values. An extra output file contains the summary statistics and its name is automatically generated by appending the extension `.smm` to the body of the output file name. Thus execution of the first command produces not only `output1.sys` but also `output1.smm`. Its data as follows:

```
Pulse rate variability histogram:
    3.90625      0
   11.71875      0
...
  683.59375      3
  691.40625      2
  699.21875      0
  707.03125      5
  714.84375      2
  722.65625      6
  730.46875      6
  738.28125      7
  746.09375      9
  753.90625      8
```

```
...
 1792.96875      0
 1800.78125      0
Pulse rate variability indices:
Npuls=    263
SDPP =   82.9
PRVti=   14.6
SDAPP=    0.0
RMSSD=   47.7
Baroreflex sensitivity histogram:
  0.5      0
  1.5      0
  2.5      2
  3.5     14
  4.5     15
  5.5      6
  6.5      7
  7.5     12
  8.5     14
  9.5      7
 10.5      5
...
 49.5      0
 50.5      0
Baroreflex sensitivity histogram parameters:
Nbrs=     90
mean=    6.6
geom=    5.9
mode=    4.5
```

```
left=    3.5
rite=   12.5
```

The data are listed as they appear on screen. Note that a histogram should ordinarily not contain more bins than about equal to the square root of the number of observations, $\sqrt{N}$. For PRV the width of each bin is 1000/128, leading to the nonobvious mid–marks as shown, according the recommendation of the Task force. Clearly, only long files will generate the required amount of data. The Task force recommends that RR–intervals are obtained over a 24–hour period. For BRS both the arithmetic and the geometric means are given. For a subject in one state, for example sitting, a unimodal log–normal distribution is often the result. In case two or more states are combined several log–normal distributions may be seen superimposed. Split the input file in its corresponding sections and evaluate separately to obtain distributions and distinct numbers for each state.