ON THE ANALYSIS OF BAROREFLEX SENSITIVITY

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1. Introduction

The most important responsibility of the cardiovascular blood pressure adjustment system is to maintain a suitable general blood pressure level in order to prevent disturbances to the functions of the body and its organs. Sufficiently high blood pressure guarantees that different organs receive the blood flow required for maintaining normal operation. If blood pressure is too low or high the control of blood flow cannot be maintained as required and some organs may even suffer damage. In stable conditions the regulation of blood pressure is reasonably simple but in practice the situation is much more complex. When a person stands up the regulative system must respond very quickly in order to guarantee sufficient blood flow e.g. to the brain. Without a quickly responding regulative system a person would faint almost immediately. The body must also adapt itself to very varying states of loading in which the muscles must be guaranteed a sufficient supply of oxygen rich blood. Thus a well-maintained sufficiently stable blood pressure is a fundamental factor of everyday health.

The blood pressure system can be considered as a closed loop regulation system, which consists of sensors which measure the pressure (so called baroreceptors) and of a pumping system responsible for maintaining the pressure. The pumping system in turn consists of the heart and the blood vessels. Baroreceptors are specialized nerve cells, which measure the blood pressure indirectly by sensing the stretching of blood vessels. Baroreceptors can be found especially in the aorta region but also elsewhere in the larger veins. A simplified explanation is that the average pressure in the blood vein system is regulated by adjusting the heart rate according to the input from the pressure sensing baroreceptor sensor system. This closed loop system is able to compensate within certain limits and conditions the changes imposed upon the body from different positional changes and loading caused by different activities. In reality the situation is certainly much more complex because both the sympathetic and parasympathetic parts of the central nervous system adjust the overall system in many different ways. In addition the time scales of the adjustment range from a period between two consecutive heart beats to several hours and even days. This paper will focus on those parts of the adjustment system in which the response may be measured within few tens of seconds.

When measuring the quick response capability of the adjustment system to changing conditions the so-called baroreflexivity (BRS, Baroreflex Sensitivity) is a fundamental factor. BRS measures the capability of the body to change the heart rate in response to a certain change in blood pressure. When the pressure increases the RR-interval must increase accordingly so that the pressure could be lowered back to its initial start value. This effect works similarly in the other direction. BRS is usually given in *ms/mmHg* and has usually a positive prefix. A higher BRS value indicates that the system reacts to pressure changes faster, i.e. the system is more sensitive. The idea behind BRS is to try to describe the quality of operation of the total adjustment system with a single numerical value, which of course is actually impossible. However, in practice BRS is a useful measure, which even has a clear diagnostic purpose. Next we describe different ways of defining BRS when two different parameters, EKG and continuos blood pressure, are measured.

2. Slope method

This is the most traditional method used to define BRS and is also used routinely in clinical work. The basic idea of this method is to disturb the blood pressure regulating system in a major way after which the reaction to the disturbance is measured. The disturbance is formed by adjusting the blood pressure quickly with external methods. One of the most common ways includes the use of certain drugs, which change the function of the system in some controllable way. A drug called phenylephrine is one of the most popular choices and raises the blood pressure. Nitroprusside in turn lowers blood pressure. The chosen drug is given intravenously with EKG and blood pressure monitored simultaneously.

Figure 1 shows the results from a typical phenylephrine based test. From this figure we can see how systolic pressure increases and heart rate correspondingly decreases, i.e. the RR-interval becomes longer. From analytical point of view the problem is how to select the area of interest because the exact moment of pressure rise as well as the point when the heart rate begins to slow down may be difficult to define. Unfortunately limiting the area of interest also effects clearly the acquired numerical BRS-value.

The simplest way of calculating baroreflex sensitivity would be to measure absolute changes from SAP and RRI signals but the difficulty lies in defining the base level. Instead BRS is calculated by describing the SAP corresponding RRI-signal as xy-values and by fitting a regression line to the values.

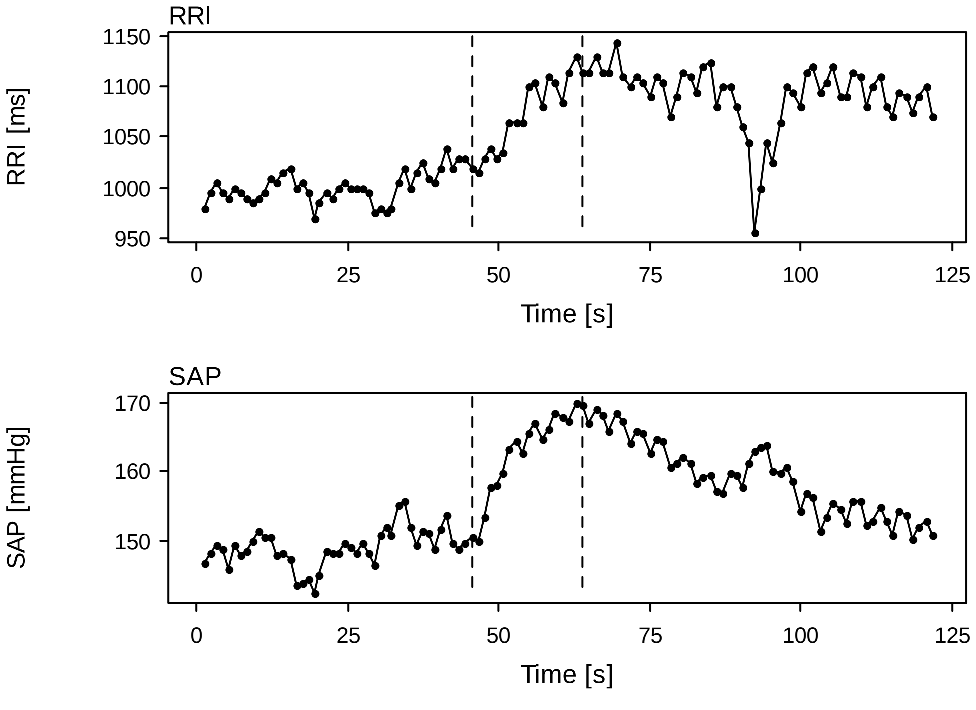

Figure 1. RRI and SAP time series from a phenylephrine based test. The rise of pressure and the lowering of the heart beat appear in the area limited by the cursors.

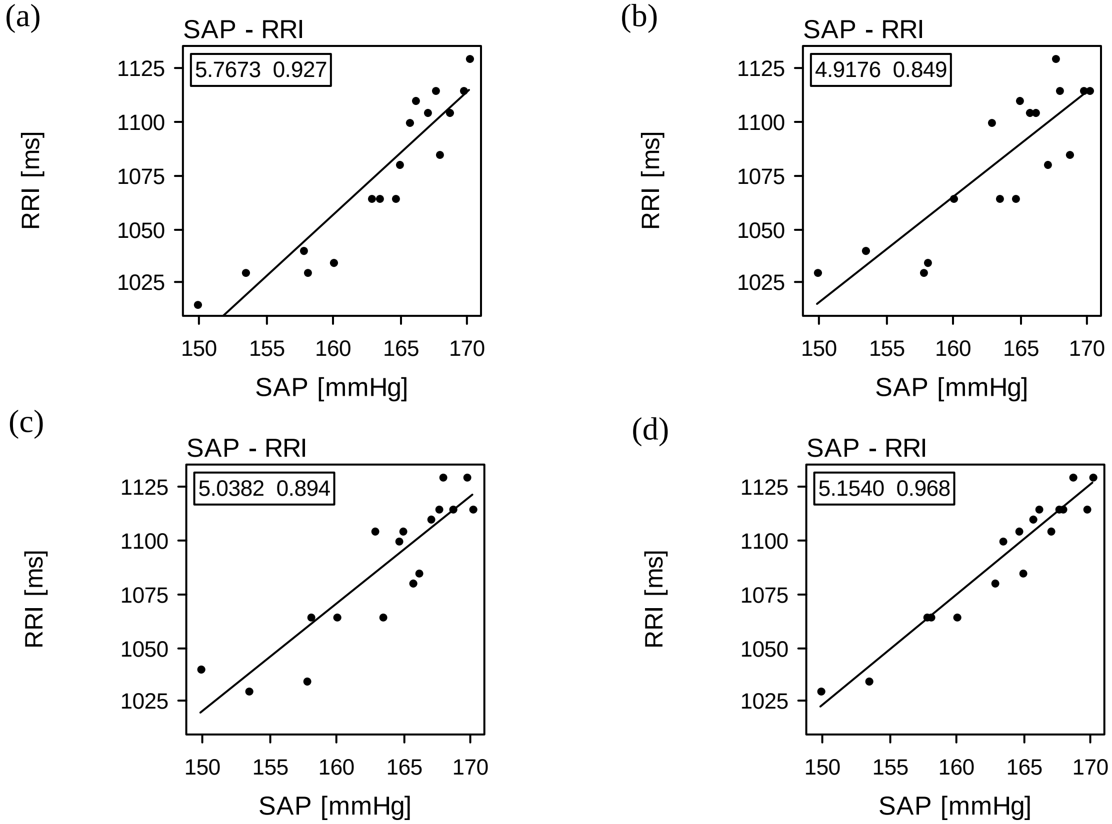

Figure 2. The SAP and RRI values from figure 1 as xy-pairs. In (a) both values are taken at the same moment, in (b) the RRS signal has been moved forward by one beat, in (c) by two and in (d) by three beats. The slope and the corresponding correlation factor of the regression line are indicated in the above left hand corner of each curve.

BRS is then defined as the slope of this regression line. Figure 2(a) shows such a xy-pair set with the corresponding baroreflex sensitivity of 5.8 ms/mmHg and correlation factor of 0.93, which indicates a rather good fit. This method does however contain a certain number of assumptions. When the xy-pair is formed always using the simultaneous SAP and RRI values the assumption is that the system has no delay or that the delay is extremely short, i.e. a change in pressure would be apparent almost immediately in the heart rate. On the other hand many studies have shown that this is supposedly not true.

Figures 2(b), 2(c) and 2(d) show corresponding curves with a delay of one, two and three beats correspondingly, i.e. the RRI time series has now been made using a value after one, two or three beats correspondingly. We can see from the figures that correlation becomes worse with longer delay but surprisingly becomes better with a three beat delay and is then actually better than without a delay. In this particular case a delay of three beats corresponds to a delay of over three seconds and it is unclear whether this can be interpreted as an internal delay of the adjustment system or not. On the other hand different patients may have large differences in response and response times so analysis of delay makes sense. As we can see from figure 2, different delays also produce slightly differing BRS values.

3. Advanced slope method

The method described in chapter 2 may be used to find out with which delay the best fit between the SAP and RRI values can be achieved but the delay cannot be adjusted in finer steps than one beat. An improvement would be achieved by interpolating both time series and by sampling them at a high enough frequency in which case we may study the effects of much smaller delays. It must be said however that this method also has its drawbacks because the effects of interpolation are difficult to estimate since the signals are basically time series without an underlying continuos signal, which would be "by chance" sampled in phase with the beats.

After the signals have been interpolated and sampled one could use xy-pairs as before with different delay values but the search for the optimal delay, i.e. the best correlation factor of the regression line, would be tedious using manual methods. Instead the analysis can be automated by calculating the regression line slope directly and by calculating the correlation factor as a function of the delay. Figure 3 represents an example using such an approach. Both signals have been sampled at 20 Hz in which case the delay may be adjusted in 50 ms steps. The result shows that the slope i.e. BRS value changes clearly as a function of the delay, but that is has a plateau between 1000 ms and 2000 ms.

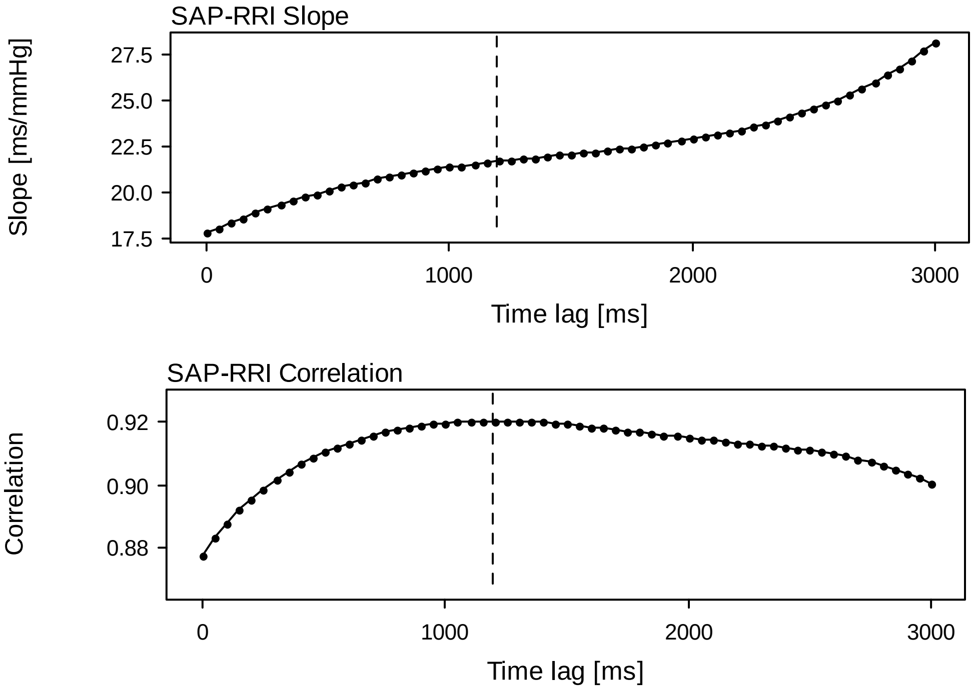

Figure 3. The slope of the regression curve and correlation factor as a function of the delay between SAP and RRI calculated for a phenylephrine-based test and for the area of pressure rise. Maximum of correlation is marked by a dashed line.

In practice the functional shape of the slope may vary greatly but often has a plateau similar to the one shown in figure 3 or a clear maximum.

The correlation factor has a rather even top but nevertheless has a maximum value at 1200 ms, which corresponds to a BRS value of 21.8 ms/mmHg. In this case the BRS value does not change much even if we were to change the delay slightly but this not always the case and the maximum may lay in the part where the slope changes drastically in which case the result is strongly dependent upon the chosen delay. Even though the optimal delay defined in the described way cannot be directly linked to a possible physiological delay this method does present a possibility of defining the delay and via the delay the corresponding BRS value in a unique way. One must still remember that the selection of the area of interest affects the final result also using this calculation method.
One could still improve the method by optimising the start and end locations but it is far from clear whether the maximum correlation would then correspond to the physiologically most meaningful situation.

4. Sequence method

In the sequence method BRS is evaluated exactly in the same way as in the slope method, but instead of concentrating on a singular pressure rise or fall period the calculation is performed several times along the SAP and RRI signals. In this case the pressure rise and fall is not activated using external means. Instead, naturally occurring fluctuations of these signals are utilized.

There are certain conditions which much be fulfilled before we can accept a sequence for BRS calculations. Firstly, in the sequence to be used both SAP and RRI signals must be rising or falling monotonically in the same direction for at least three beats. Normally one is using RRI signal values, which have been moved forward by one beat in order to compensate for the assumed adjustment delay. Secondly each consecutive change of SAP and RRI values much exceed a certain limit. This condition acts as a kind of filter, which removes random noise related changes. The value of the limits critically effects how many acceptable sequences can be found and they must be selected case by case. The minimum change of SAP, 0.5 mmHg and the minimum change of RRI, 1 ms may be used as starting values. These values correspond to the typical measurement resolutions for the said signals. In sequence method one should analyse rising and falling sequences separately since the underlying physiological mechanisms are most likely slightly different.

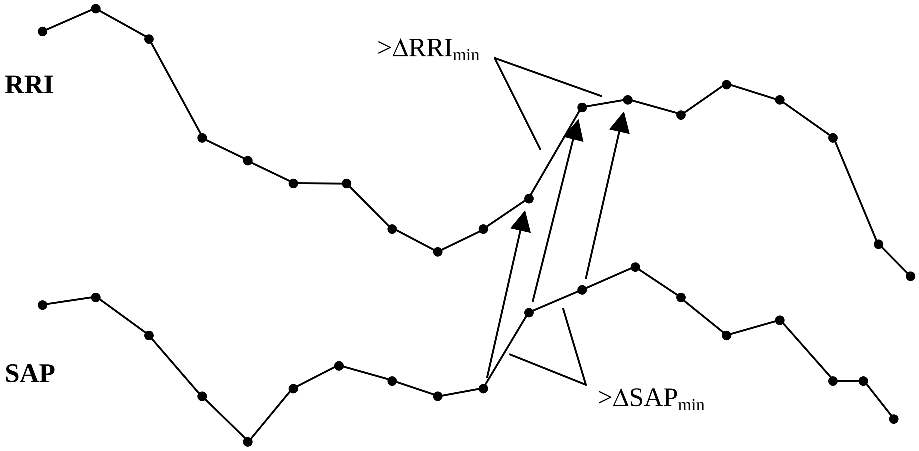

Figure 4. In the sequence method SAP and RRI signals are analysed for sequences with a minimum of three consecutive rising (or falling) values. Consecutive values must exceed the set limit values ΔSAP_{min} or ΔRRI_{min}. RRI values are moved forward by one beat. Results are shown as xy-pair curves into which a regression curve is fitted in which case the slope of the curve will give the local BRS value.

Figure 4 contains short SAP and RRI time series with one rising sequence which fulfils the requirements. The SAP and RRI values belonging to the sequence are formed into xy-pairs and a regression curve is fitted. The slope of the curve gives the BRS value related to the curve. When the whole time series is analysed in similar fashion the result is the BRS as a function of time but not as a continuos function since acceptable sequences are found only intermittently, as shown in the example in figure 5. The BRS values calculated using the sequence method typically show a very large deviation. In addition to baroreflexivity also the relation of acceptable sequences to all data points, typically 15 – 20%, may give useful information.

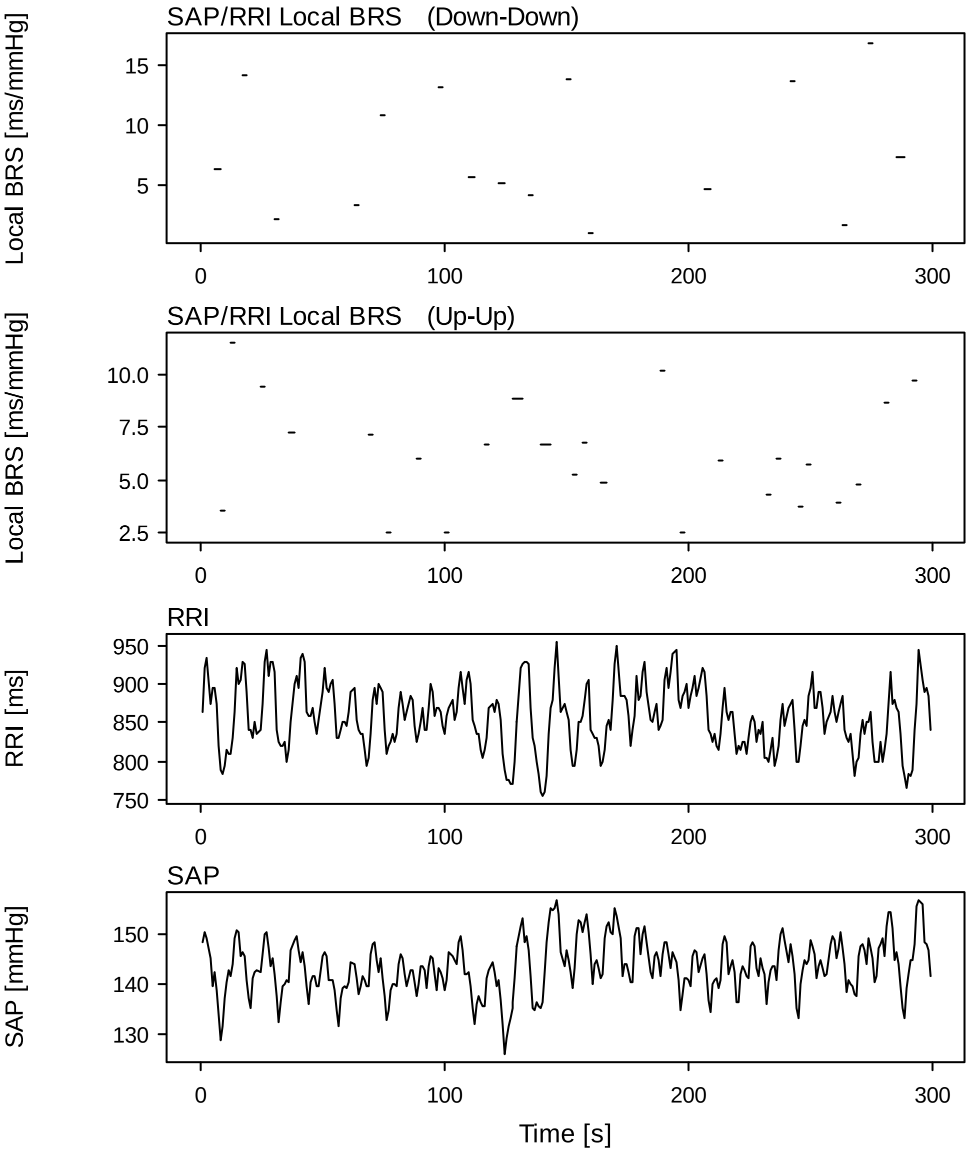

Figure 5. SAP and RRI signals and the periods acquired using the sequence method. Analysis is performed separately for ascending (up-up) and descending (down-down) sequences. Average up-up BRS = 6.26 (23.5 % of all points) and down-down BRS = 7.57 (15.5% of all points).

The BRS value acquired using the sequence method clearly differs from values acquired using phenylephrine-based tests because the definitions differ greatly. In phenylephrine based method blood pressure is manipulated strongly in which case the system may be considered to shift temporarily to a completely different operation point in contradiction to the sequence method in which the system is allowed to oscillate freely around a stable operation point. Another point to consider is the source of these naturally occurring fluctuations. More detailed research has indicated clearly that a major part of these oscillations are caused by breathing, which modulates blood pressure and heartbeat. For this reason the results acquired using the sequence method may depend on the depth of breathing and on breathing frequency. If the heartbeat is very slow, i.e. RRI is clearly > 1 second, and breathing is done in phase with a metronome set to a 4 second beat, one sequence practically never contains three consecutive rising data values in which case the evaluation of BRS may prove impossible.

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5. Spectral methods

The natural oscillation of RRI and SAP signals and through these also the baroreflex mechanism may be studied more closely using the spectra of the signals. Figure 6 shows the spectrum (spectral densities) of both signals acquired with FFT method. Both spectra consist of two main components. One is the modulation caused by breathing, which in this example was regulated with the help of a metronome set at 0.25 Hz (corresponding to a 4 second time period). The other is an oscillation related to the pressure regulation mechanism of the sympathetic nervous system with a frequency of 0.1 Hz (corresponding to a 10 second time period). This oscillation is often referred to as Mayer waves. In addition to these it is also possible to observe oscillations with a period of 1 - 2 minutes, which may be connected to the heat regulation system or other mechanisms of the body.

Spectra are often divided into different bands according to their effect mechanism. Fast mainly breathing related components belong to the HF band (0.15 - 0.4 Hz), adjustment related to the sympathetic nervous system occurs on the LF band (0.04 – 0.15 Hz) while the rest are slow changes occurring on the VLF band (0.003 – 0.04 Hz). If the recording time is long (>30 minutes) it is also possible to define very slow frequency components, belonging to the ULF band (<0.003 Hz). Whether the breathing component actually lies on the HF band depends naturally on the test setup since without a metronome-assisted timing the natural frequency of breathing may sometimes be quite low, even clearly belonging to the LF band.

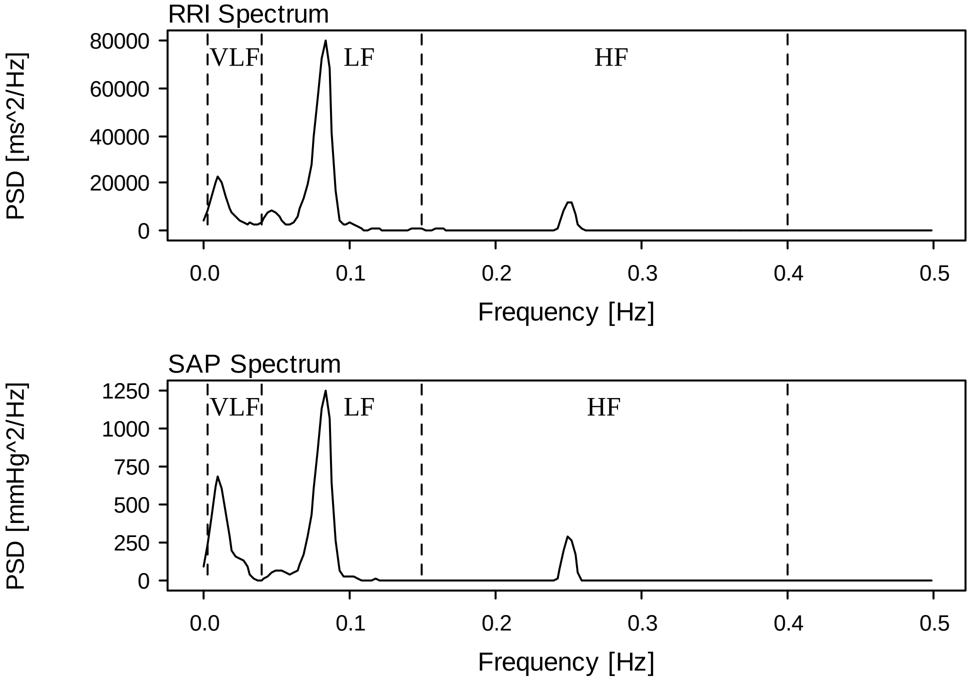

Figure 6. The spectra of RRI and SAP signals as derived with FFT method. Recording time of signals was 5 minutes. The spectral peaks related to breething (0.25 Hz) and the so called Mayer waves (10 second oscillation) are clearly visible.

Because the spectrum reflects the strength of different frequency components in the signal, the height of a specific peak in spectra might be used as such to measure the said amplitude but in practice this is not recommendable. The absolute height of the peak may vary for many reasons such as the used spectrum calculation method and its parameters. It is also possible that the desired band contains more than one peak. A better way of assessing the relative effect of a certain frequency component in a signal is to calculate the integral of the spectrum over a certain frequency band. This is a natural approach since the integral over the whole spectrum gives the variance, i.e., the square of the deviation. The square root of the spectral power calculated in the described way corresponds to the variability of the signal in similar fashion compared to deviation.

Spectral baroreflexivity may be defined in many ways depending on what or which frequency bands are included in the integral. The simplest choice is to use the LF band:

$$BRS_{LF} = \sqrt{\frac{\text{RRI power in LF band}}{\text{SAP power in LF band}}}\,.$$

If we assume that the adjustment of blood pressure is managed mainly by LF band oscillations this definition makes sense. Because spectral power for RRI is ms^2 and for SAP mmHg^2 BRS_{LF} is given in the familiar form ms/mmHg.

The approach described above does not guarantee that the oscillations in RRI and SAP signals would in any way be synchronized or even correlated with each other. If a "real" oscillation appears in the beginning of the measurement period of RRI but not in SAP and the same happens vice versa at the end of the measurement period, one cannot easily detect this from the spectra. The main effect is that the spectral lines are strongly widened in which case the above described method of BRS calculation will give a false image of the real situation. In order to make sure that both signals have the same frequency components and that also their phase relations are correct, i.e. the change occurs in SAP first and then in RRI, we must also calculate the coherence and the phase difference as a function of frequency between the two signals.

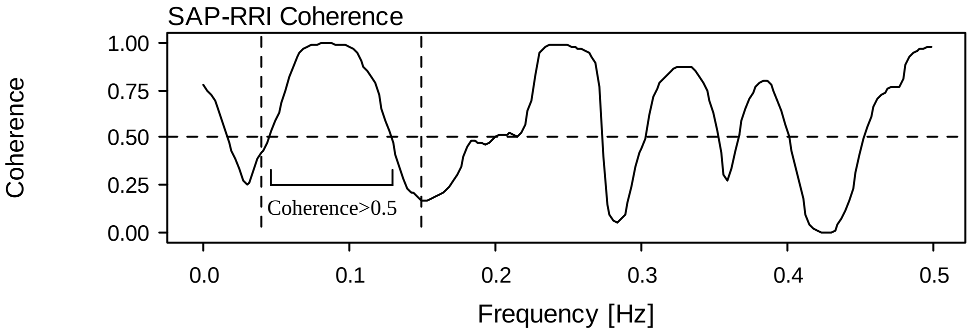

Figure 7. Coherence of SAP and RRI signals as a function of frequency.

Figure 7 shows the coherence between the SAP and RRI signals. Coherence is by its nature a correlation value, which indicates how similarly two signals behave on a certain frequency. Coherence value range is from 0 – 1 just as with correlation and value 1 indicates that the signals are completely identical. Coherence is high near the 10 second oscillation and also at the breathing frequency. From the results we may conclude that at these frequencies both SAP and RRI signals oscillate in the same way. It must be noted that coherence does not indicate in any way how strong the oscillations are but measures only their similarity. High values of coherence at 0.3 - 0.4 Hz is a fact in itself but when we study the spectra of the signals (figure 6) we can see that at this frequency there are no remarkable components.

We can now define baroreflexivity slightly better as:

$$BRS_C = \sqrt{\frac{\text{RRI power in LF band over those frequency bands where coherence} > 0.5}{\text{SAP power in LF band over those frequency bands where coherence} > 0.5}}$$

The basic idea of this definition is to make the integration of spectral density only over those frequency bands in which coherence exceeds a certain limit. An often-used value for this limit is 0.5. This guarantees that the integral will not contain bands in which the oscillations are unsynchronised.

The use of coherence does not guarantee that changes in SAP would occur before changes in RRI, as we should expect based on the general principles of the regulation system. If we calculate the phase difference of the signals as a function of frequency as has been done in figure 8, we can study this point in more detail. From the figure we can clearly see that the phase difference is negative, i.e., changes in SAP predict changes in RRI as expected. On the other hand the phase difference at breathing frequency is nearly zero, from which we can conclude that oscillations occur in both signals in phase. Furthermore we can conclude from the above that the original reason of the oscillation cannot be transferred from SAP signal into the RRI-signal and that more apparently

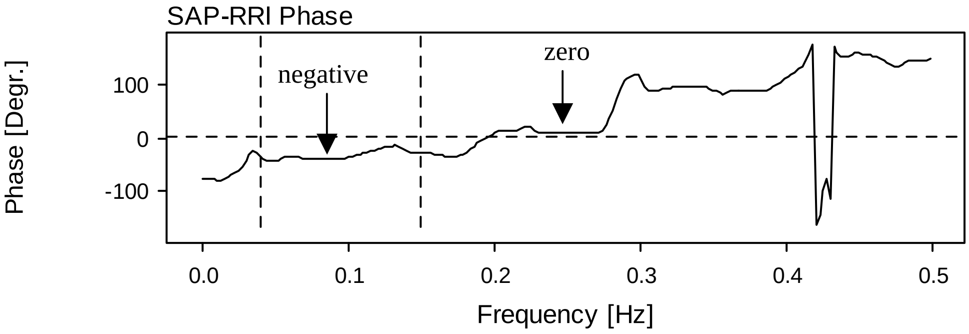

Figure 8. Phase difference of SAP and RRI signals as a function of frequency. If phase difference is negative, a change in SAP occurs before a change in RRI.

breathing modulation seems to effect both signals. This observation already gives some clear indications as to the nature of the basic characters of the regulation system. Sudden changes in the phase are due to its definition (modulo 360 degrees), such a phase jump is visible in figure 8.

Now we can define a new baroreflex sensitivity parameter:

$$BRS_{CP} = \sqrt{\frac{\text{RRI power in LF band where coherence} > 0.5 \text{ and phase} < 0}{\text{SAP power in LF band where coherence} > 0.5 \text{ and phase} < 0}}$$

Even these improved spectral methods for the calculation of baroreflex sensitivity do not guarantee that there is any causality between SAP and RRI signals because phase difference only defines the phase relation of the signals and not in which signal the change occurs first and in which later. In practice this is not a major drawback since because of other factors we may generally assume that the SAP signal is the primary factor when speaking about pressure regulation.

Baroreflex sensitivity may also be defined as a function of frequency without spectrum using a transfer function. The basic assumption in transfer function based analysis is that the system under investigation may be modelled as a linear system in which the SAP signal is the input and RRI signal the output. Then the transfer function indicates the gain of the system at each frequency, i.e. indicates the strength of the output signal (RRI) when a specific change occurs in the input signal (SAP). This actually is the same parameter as baroreflex sensitivity and even the unit of the transfer function is the same (ms/mmHg). Figure 9 is an example of a typical transfer function. The transfer function contains a lot of information about the system but to have any clinical use one must somehow acquire an essential BRS value. The best method is probably to calculate the mean value of the transfer function over those frequencies (within the LF band) in which the coherence value exceeds 0.5.

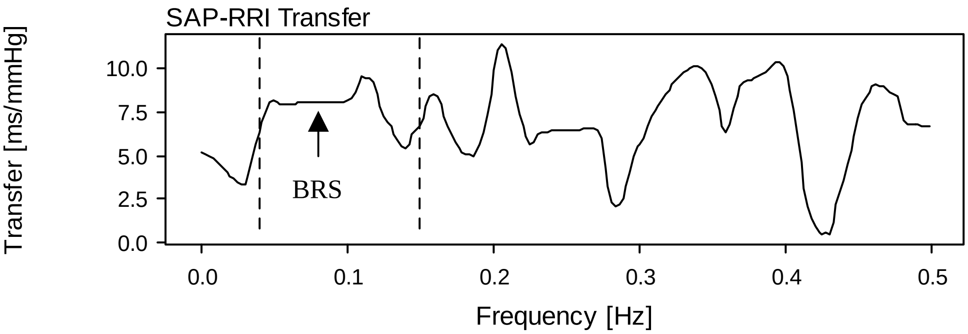

Figure 9. The transfer function between SAP and RRI as a function of frequency.

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6. Complex demodulation method

Complex demodulation (CDM) method is a common nonlinear method used to define the amplitude of a time series as a function of frequency or frequency band. In other words, if the signal to be studied is

$$x(t) = A(t)\cos(\omega t + \phi(t)) + z(t)\,,$$

we must find out the time dependent amplitude A and phase ϕ. The term $z(t)$ contains all other oscillating components (having a frequency different from ω) and possible noise. In the CDM method the original real value signal $x(t)$ is rewritten into complex format

$$x(t) = 0.5A(t)\left\{\exp\left[\,i(\omega t + \phi(t))\right] + \exp\left[-i(\omega t + \phi(t))\right]\right\} + z(t)\,.$$

In the next step all frequency components are shifted by -ω. This operation is made by multiplying the signal with the term

$$y(t) = 2\exp(-i\omega t)\,,$$

by which we get

$$x'(t) = A(t)\exp(i\phi(t)) + A(t)\exp\left[-i(2\omega t + \phi(t))\right] + 2z(t)\exp(-i\omega t)\,.$$

From the result we can see that frequency of the first term is zero and that the frequency of the second term is twice that compared to the frequency of the component under study. The last term does not contain frequencies around zero, because the component $z(t)$ did not contain originally the frequency ω . If the signal $x'(t)$ is fed into a low pass filter with a cut-off frequency at zero, we get a signal

$$x''(t) = A(t)\exp(i\phi(t))\,,$$

from which we can easily calculate the slowly and time dependently changing amplitude

$$A(t) = \left|x''(t)\right|\,.$$

By varying the parameter ω we may then pick from the signal to be analysed the amplitude of any component as a function of time. If the cut-off frequency is $\Delta\omega$ and not exactly zero, the CDM method picks from the signal only the amplitude of those components with a frequency between ω -$\Delta\omega$ ... ω +$\Delta\omega$. In this way it is possible to pick the part of the signal, which belongs for example to the LF band.

In principle the CDM method gives the amplitude at every moment but in reality the time resolution is dependent upon the characteristics of the low pass filter. If the desired frequency band needs to be limited as steeply as possibly one needs to use a high-order filter but in that case one needs more data points to calculate filtering and time resolution will be worse. In practice the time resolution of RRI and SAP signals is approximately 15 seconds meaning that faster changes in the amplitude of the oscillations cannot be clearly distinguished.

When CDM method is applied to RRI and SAP signals with a center frequency ω = 0.09 Hz and when the cut-off frequency of the low pass filter is $\Delta\omega$ = 0.05 Hz, CDM method picks the LF band components. When the amplitude of the RRI signal acquired in this way is divided by the amplitude of the SAP signal, we get a new way of calculating BRS. Figure 10 shows an example of the results based on such an analysis. BRS is quite stable but occasionally has very high values. This is typical of this method, because if the amplitude of the SAP signal drops in the LF band, this usually causes a peak in the BRS since SAP amplitude is the denominator in the BRS formula. It should be remembered that in this method there is no control over whether the signals are coherent with respect to each other or whether a change in SAP signal precedes a change in the RRI signal. The essential idea is that the low frequency component amplitudes of both signals are compared at each specific moment in time.

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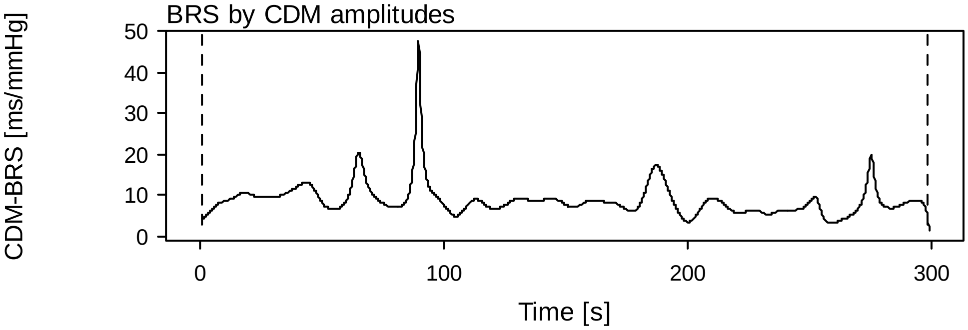

Figure 10. Baroreflex sensitivity as a function of time as calculated using the CDM method for the RRI and SAP time series shown in figure 5.

7. ARMA analysis

If one wants to analyse the baroreflex mechanism in more detail than the previously described methods allow, the only option is to try to model the blood pressure regulating system. Because a genuine physiological model is inevitably very complex one must make certain simplifications. The most natural starting point in such a case is a linear model and especially the so-called ARMA (Autoregressive Moving Average) approach. The next describes such a model consisting of two input signals, SAP and RSP (respiratory) time series and one output signal which is the RRI time series. Then we can generalize

$$RRI_k = \sum_{i=1}^{L} a_i RRI_{k-i} + \sum_{i=M_0}^{M} b_i SAP_{k-i} + \sum_{i=N_0}^{N} c_i RSP_{k-i} + e(k)\,.$$

The first term on the right side of the equal sign is the AR (autoregressive) part of the model and the two next terms form the MA (moving average) parts. The basic idea of the model is that the new RR interval depends linearly on the previous RR intervals and earlier SAP and RSP values. The last term contains the noise, which is uncorrelated with the signal. The fundamental purpose of the ARMA analysis is to fit the above-described model with the data under investigation. If the parameters L, M and N and delays M_0 and N_0 are fixed the calculations can be easily done using e.g. the method of least squares in which case one gets the best values for the factors a_i, b_i and c_i but usually those parameters and delays are not known in advance. Several different strategies have been proposed for determining optimal parameters but the details of these methods are beyond the scope of this paper. It suffices to say that in general the problem is very complex. One option is simply to fix the delays and factors and use the same basic model for all analysis. In such a case there exists, however, the danger that the model is too simple to explain the signal under investigation in which case essential parts of the signal will remain unexplained. On the other, if the model is of a too high degree it will erroneously try to explain noise contained within the signal. The basic idea is to try to determine a model which is as simple as possible yet will explain the signal under investigation as fully as possible in which case the term $e(k)$ will contain only white noise. It should be noted that if the real system in fact is e.g. nonlinear, even the best ARMA model couldn’t describe the signal properly.

After the parameters, delays and factors have been found, the model may also be used to evaluate baroreflex sensitivity. In principle factor b_1 corresponds to the connection between the RRI and the previous SAP value thus representing a simple BRS estimate. In reality, however, the factors in the model may vary greatly although the signals themselves might not. Because of this a better approach to calculate BRS from this model is to investigate its impulse response which is a much more conservative factor, i.e., its shape is not changed too easily with small changes in the details of the signal. When calculating the impulse response, the SAP signal is set with a pressure pulse with a length of one beat after which the response in RRI signal is calculated using the ARMA model.

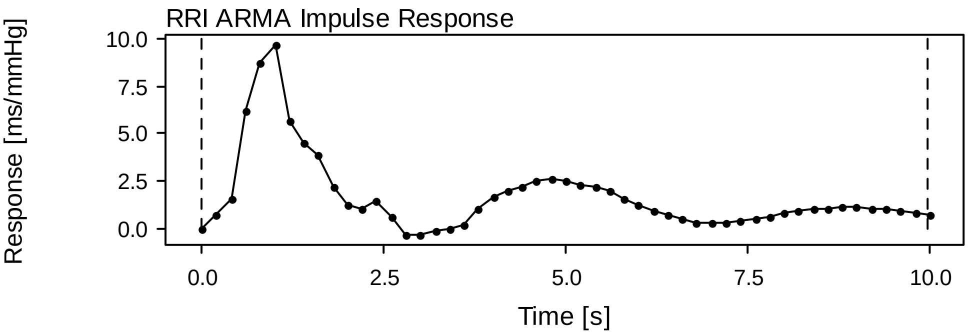

Figure 11. Impulse response calculated using ARMA analysis with RRI as output signal and SAP and breathing volume as input signals. The maximum value which the impulse response reaches after the impulse is used as an approximation of baroreflex sensitivity, which in this case would be approximately 9.5 ms/mmHg.

This type of impulse response investigation actually corresponds with a simulated phenylephrine test. Figure 11 is an example of an impulse response. The diagram clearly shows how RRI signal starts to increase immediately after the pressure signal, reaches the maximum value after a delay of approximately one second and the decays rather rapidly. Baroreflex sensitivity is defined as the maximum value reached after an impulse. Another way of calculating baroreflex sensitivity using ARMA model is to calculate the response to a step pulse, which in fact is the time integral of the impulse response, i.e., the surface area of the area below the curve and above the zero level. Because impulse response remains positive for a rather long time after the impulse as we can also see from figure 11, this integral increases monotonically as a function of time, in which case it will be difficult to estimate which level of step response is to be set as a measure of baroreflex sensitivity.

The ARMA method is in principle perhaps the best way to define baroreflex sensitivity because the model takes into account time related delays and causality but on the other hand it may well be very sensitive to the selection of the factors and delays used. In addition the useability of the model requires that the system wanders in its phase space as much as possible in order for the fitted linear model to describe the real characteristics of the system instead of a small part of it. This requirement may be fulfilled better by using e.g. such a controlled breathing method in which the breathing frequency spectrum is as wide as possible, i.e. breathing rhythm follows white noise type distribution. In practise breathing using greatly varying frequency in a controlled way is difficult, which in itself may fundamentally change the system under investigation. It is also possible to use the spontaneous variation of the patients breathing but then the problem could be the large variation between different test subjects.

References

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