Baroreflex Contribution to Linear and Nonlinear Blood Pressure and Heart Rate Coupling in Daily Life: an Assessment by Cross Mutual Information

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Abstract

A new procedure has been developed to 1) investigate the coupling between arterial blood pressure and heart rate variability in daily life and 2) identify the baroreflex contribution to such a coupling. The algorithm is based on the estimation of the Cross-Mutual Information (CMI) between systolic blood pressure (SBP) and RR-Interval (RRI) beat-to-beat values. CMI has been selected because of its capability to quantify both linear and nonlinear components of the coupling between variables.

This procedure has been used to analyze data recorded in spontaneously behaving cats before and seven days after the surgical opening of the baroreflex loop as obtained by a sino-aortic denervation.

Use of CMI indicates that over a time scale in the order of minutes the arterial baroreflex is the major determinant of the SBI-RRI link, accounting for about 2/3 of the total (linear and nonlinear) coupling measured between these variables.

1. State of the art and aims

The presence of a coupling between blood pressure, BP, and heart rate (or its reciprocal, the RR-interval, RRI) over different time scales can be easily observed just by visual inspection of chart recordings (Fig.1). From the same figure it is also evident that the phase between BP and RRI signals is different at different time scales (180° for time scales of hours and 0° for time scales of minutes and seconds). This observation is consistent with the hypothesis that the overall BP-RRI coupling - the level of which has never been quantified so far- might actually be due to a variety of biological mechanisms, each characterized by a specific time constant and delay, simultaneously impinging on the cardiovascular system. Among these mechanisms, a substantial contribution to the BP-RRI coupling is expected to be provided by the arterial baroreflex. Indeed, it is known that in order to maintain BP homeostasis arterial baroreflex buffers BP perturbations by driving several cardiovascular variables,

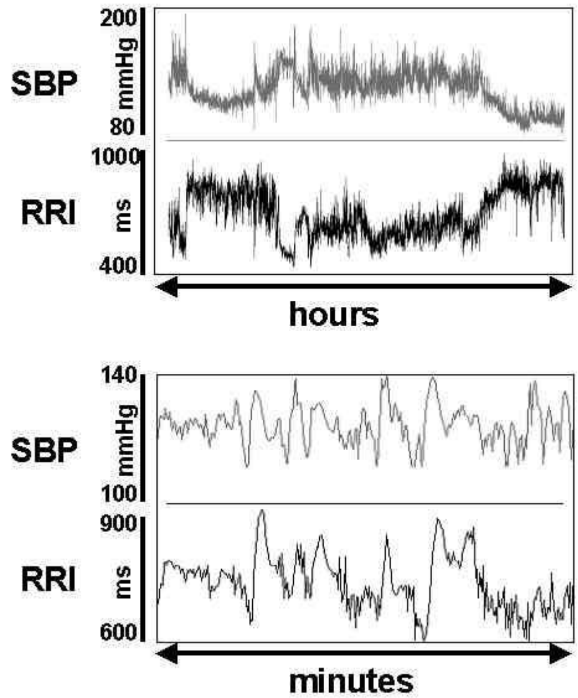

Figure1. Example of SBP and RRI profiles recorded during spontaneous behaviour and plotted over different time scales. It is worth noting that signals are in phase over a time scale of minutes and 180° out of phase over a time scale of hours.

including RRI [1]. This buffering action of the arterial baroreflex unavoidably contributes to the overall coupling between BP and RRI. The degree of this contribution, however, has never been fully explored. This is because till now most of the interest of clinicians and researchers was directed to the assessment of the gain of the baroreflex control of the heart (usually termed baroreflex sensitivity, BRS) rather than to the level of the BP-RRI coupling produced by the baroreflex function. It is a matter of facts that at present the BP-RRI coupling is considered solely for evaluating spontaneous BRS whenever the latter is derived from the analysis of BP and

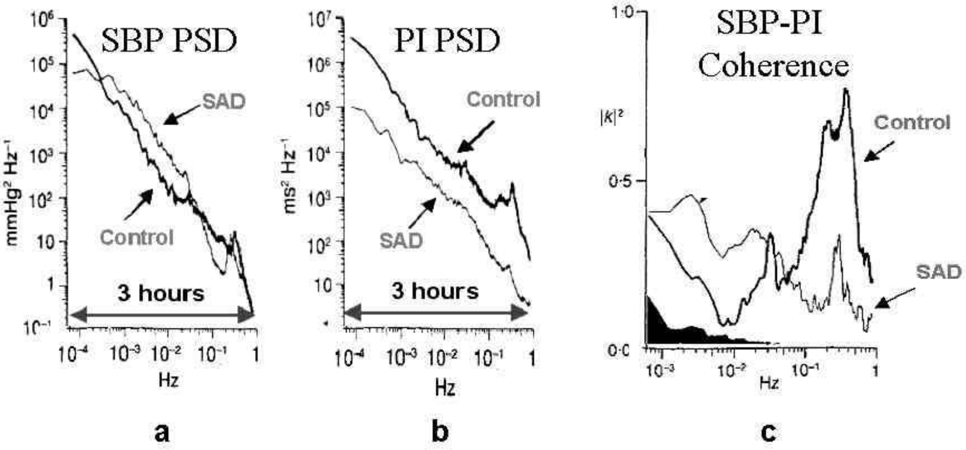

Figure 2. Results of a broadband spectral analysis of SBP and PI data collected in 8 cats before (control) and after sino-aortic denervation (SAD) *Panel a*: SBP spectrum averaged over the whole group of animals. *Panel b*: average PI spectrum. *Panel c*: Broadband coherence between SBP and PI signals in control and SAD conditions. Redrawn from [5], with permission.

RRI spontaneous beat-to-beat variability [2,3]. In this context, however, only selected components of the coupling are considered and only the *linear* dependences in these components are evaluated. Obviously, such an assessment may be adequate for evaluating BRS but is not sufficient to fully explore the BP-RRI coupling from a physiological perspective. On the other hand, neglecting nonlinear components in the estimation of the coupling may leave an important fraction of signal variability virtually unexplored and may mask significant aspects of the cardiovascular control. Indeed, the whole cardiovascular autonomic control system and the arterial baroreflex in particular are characterized by several functional and biological nonlinearities. Concerning the arterial baroreflex, it includes a number of nonlinear elements, starting from the baroreceptors that "quantify" blood pressure through the stretch of the arterial walls, namely, through a nonlinear phenomenon [1]. Because of the baroreflex involvement in the BP-RRI coupling, it is conceivable that the nonlinearities in the baroreflex structure may be at least in part reflected into the BP-RRI dependences. Actually, nonlinearities have been indirectly observed in the baroreflex influences on the spectral components of systolic blood pressure, SBP, and pulse interval, PI, variability (PI is the equivalent of RRI but is estimated from the blood pressure signal instead of ECG and is defined as the time interval between consecutive systolic blood pressure peaks) [4,5]. These observation have been obtained done by comparing the spectral characteristics of SBP and PI signals in a group of 8 freely moving cats before and after the baroreflex deactivation as obtained by a sino-aortic denervation (SAD) namely, by the surgical opening of the baroreflex loop. It was shown that during spontaneous behaviour the baroreflex exerted an important influence on both SBP and PI spectra over a wide frequency region ranging from about 0.2 Hz to 0.001 Hz (Fig.2). This influence was revealed by the significant power changes observed in such a frequency region after denervation. Interestingly, at frequencies lower than 0.02 Hz, namely within the region where the baroreflex was active, coherence was quite depressed in intact animals while it increased significantly after the baroreflex deactivation. This suggests that at least in this frequency region the baroreflex action may introduce nonlinear dependencies between SBP and PI signals.

On the base of the above findings, we further explored the issue of the BP-RRI link in daily life by proposing a novel procedure specifically designed for 1) providing a comprehensive quantification of the coupling existing between SBP and RRI variability during spontaneous behavior and 2) identifying the baroreflex contribution to such a coupling.

Core of the procedure is the estimation of the Cross-Mutual Information (CMI) between SBP and RRI beat-to-beat values. CMI has been selected because of its capability to quantify both linear and nonlinear components of the coupling between variables.

The new procedure has been used for analysing experimental data recorded in two spontaneously behaving cats before and after SAD. This allowed us to determine the baseline level of the SBP-RRI coupling in intact animals and the fraction of coupling due to the baroreflex. The latter issue was estimated as a difference between the level of coupling observed in intact condition and that surviving abolition of the baroreflex control.

2. Methods

2.1 Mutual information

Mutual information I(ξ,η) describes the amount of information on a given random quantity η we can obtain from the observation of another quantity ξ. The concept of mutual information goes back to Shannon [6] and was originally applied to quantify information transmission over noisy channels. It is based on Shannon's entropy

$$H(\xi) = -\sum_m p_m \log_2 p_m$$

for a discrete distribution $\{p_m\}$ of any random variable ξ.

Mutual information is defined by:

$$I(\xi,\eta) \equiv H(\eta) - [H((\xi,\eta)) - H(\xi)]$$

where $H(\eta)$ is the a-priori-uncertainty with regard to η, $H((\xi,\eta)) = -\sum_{m=1;n=1}^{M,N} s_{m,n} \log_2 s_{m,n}$, is a measure of the uncertainity with regard to any pair of values ξ and η may jointly assume ($[s_{m,n}]$ being the joint probability density of (ξ,η)) and $H((\xi,\eta))-H(\xi)$ is the remaining a-posterior-uncertainty with regard to η if ξ is known.

In our case, where two different signals ξ(t) and η(*t*+τ) are involved, I([ξ(t),η(*t*+τ)]) estimated for different values of τ is called *cross mutual information function, CMIF(τ).* For any given time lag τ, CMIF may assume values determined by the following relation:

$$0 \le \mathrm{CMIF}(\tau) \le -\log_2 \varepsilon$$

where ε is the relative measuring precision of the signals and it is related to the partitioning of the amplitude range of each signal in bins. CMIF(τ) was then normalized so that it could vary between 0 and 1 (0= no coupling and 1= maximal coupling between signals). It should be emphasized that, in contrast to many other techniques so far used for investigating cardiovascular variables, CMIF quantifies both linear and non-linear dependencies between signals. Moreover, being a pure statistical approach, it does not require any a-priori assumption on the nature of the signals, apart from the general assumption of ergodicity. In the present paper CMIF was used to quantify the linear and nonlinear cross-dependencies between SBP and PI as a function of the lag τ between signals, where τ is the number of heart beats. Further details on the CMIF estimation can be found elsewhere [7,8,9].

2.2 Data collection and processing

In two cats (#A and #B) arterial blood pressure was intra-arterially recorded twice, before and seven days after the surgical opening of the baroreflex loop as obtained by a sino-aortic denervation (SAD). During the recordings, each lasting three hours, the cats were free to move within a large plexiglass box (see details in [4]). BP tracings were sampled at 200 Hz and edited from artifacts by an interactive procedure. From each pressure waveform SBP and PI were identified, the resulting series were detrended, purified from outliers and split into 11 contiguous data segments each including 2048 beats. CMIF was then estimated for each data segment with τ ranging from –10 to +10 beats.

3. Results

The cumulative CMIF plots estimated for the 11 consecutive data windows in animal #A and #B before and after denervation are shown in Fig.3.

If we consider the CMIF-max (i.e. the maximum value of each CMIF curve) we can observe that in intact condition the average coupling level is about 50% of the possible maximal value for cat #A and about 35% for cat #B.

After denervation a dramatic fall in the CMIF curves was observed. On average, the CMIF-max dropped from 0.5 to 0.12 (-76%) for cat #A and from 0.35 to 0.1(-67%) for cat #B. Such an important reduction in CMIF after SAD reveals the major role played by the baroreflex in the genesis of the coupling existing between SBP and RRI in intact condition. It should be additionally noted that in each cat CMIF values were not fixed over time but rather fluctuated possibly as a consequence of the animals' spontaneous activity.

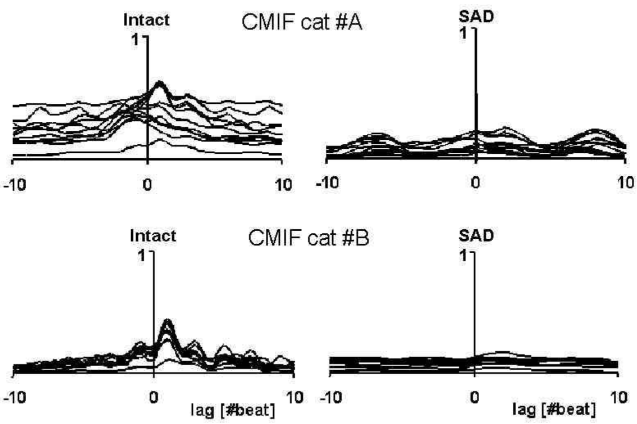

Figure 3. Superimposition of Cross Mutual Information Functions estimated over the 11 data segments for cats #A and cat #B in intact condition and after SAD.

4. Conclusion

Use of mutual information provided us with a comprehensive quantification of the physiological coupling existing between blood pressure and cardiac rhythm during spontaneous behaviour. Obviously, the presence of interactions between SBP and RRI has been known since a long time and partial quantifications of specific aspects of this interaction have already being obtained through linear techniques [2].

A specific advantage of the proposed procedure is the wider perspective from which this phenomenon can be evaluated, which allows for the first time obtaining the overall quantification of the SBP-RRI coupling, including non-linear dependencies between signals.

This first application of the procedure on experimental data has shown that in daily life the physiological coupling between SBP and RRI is quite remarkable (30-50% of the maximal theoretical coupling). Moreover this analysis has also shown that the arterial baroreflex is the major determinant of the above coupling, accounting for more than 2/3 of coupling existing between SBP and RRI.

Finally a methodological note. The positive results obtained in this study also indicate that use of CMIF may represent an additional tool for the analysis of baroreflex characteristics and can provide us with new information on the baroreflex function which complements the traditional BRS estimate.

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