The Increase of Respiratory Sinus Arrhythmia during Low Dose Atropine Is not due to Changes of the Sinus Node Transfer Function or Baroreflex

A Porta[1], N Montano[1], M Pagani[1], A Malliani[1], P van de Borne[2], VK Somers [3]

[1]DiSP LITA di Vialba, Universita' degli Studi di Milano, Milan, Italy
[2]Hypertension Clinic, Department of Cardiology, Erasme Hospital, Brussels, Belgium
[3]Department of Internal Medicine, Mayo Clinic, Rochester, MN, USA

Abstract

Low dose of atropine increases heart period and respiratory sinus arrhythmia, while at high doses the peripheral parasympathetic blockade becomes appreciable. The mechanisms underlying this phenomenon are investigated in a set of 10 healthy young humans by means of a linear causal open loop model. This model allows us to contemporaneously and non invasively derive an estimate of the sinus node transfer function and of the baroreflex gain. Neither the dynamic properties of the sinus node nor the baroreflex gain appear to be modified by the low dose administration of atropine. These results support the conclusion that the increase of respiratory sinus arrhythmia does not depend on either a modification of the transduction properties at the sinus node level or an increased responsiveness of the baroreflex but may have a central origin.

1. Introduction

While the administration of a high dose of atropine induces tachycardia and the elimination of respiratory sinus arrhythmia as a result of complete vagal blockade at the sinus node level, low dose (LD) atropine provokes opposite effects [1]. The mechanism underlying this phenomenon is not completely understood. Several hypotheses have been proposed: i) a vagal activation independent of the baroreflex only partially compensated by the peripheral blockade of the muscarinic receptors (a central vagotonic activation) [1,2]; ii) a vagal activation mediated by an increase of the baroreflex responsiveness (a baroreflex-mediated vagotonic activation) [3]; iii) an augmentation of the sinus node response to the vagal efferent traffic (an increase of the gain of the sinus node transfer function) [4].

In man these hypotheses have not been tested together yet, thus preventing a general conclusion. This deficiency is mainly the result of the difficulty of assessing sinus node transfer function. This evaluation requires the stimulation of the cardiac efferent neural activity at rates randomly modified around an average one [5,6] and the evaluation of the transfer function between the neural activity and the evoked heart rate variability.

The aim of this study is to utilize a previously validated non invasive model-based procedure for the estimation of the gain of the sinus node transfer function [7] and of the baroreflex [8] in healthy humans before (baseline, B) and after LD to clarify the mechanism underlying the increase of the respiratory sinus arrhythmia.

2. Methods

2.1. Model-based estimation of the sinus node transfer function

The model, designed to extract non invasively the dynamic properties of the sinus node, is defined in the beat-to-beat domain (i is the progressive cardiac beat number) as

$$rr(i) = h_{rr-rr}(l) \cdot rr(i-l) + ex_{rr}(i) + u_{rr}(i)$$

The model decomposes the heart period variability rr (rr is the RR interval value minus the average) in three parts due to the effect of the previous RR interval change rr(i-1), of exogenous influences ex_{rr} and of unmeasurable inputs u_{rr}. The exogenous influences are modelled as

$$ex_{rr}(i) = \sum_{k=0}^{p} h_{rr-sap}(k) \cdot sap(i-k) + \sum_{k=0}^{p} h_{rr-resp}(k) \cdot resp(i-k)$$

thus taking into account the influences of p systolic arterial pressure changes (sap is the SAP value minus the average) and of p respiratory variations (resp is the RESP value minus the average). Unmeasurable inputs u_{rr} takes the form of an autoregressive process of order p

$$u_{rr}(i) = \sum_{k=1}^{p} h_{urr-urr}(k) \cdot u_{rr}(i-k) + w_{rr}(i)$$

where w_{rr} is a white noise with zero mean and variance λ_{rr}^2. The model aims at describing: i) dynamic properties of the sinus node capable to impose dependencies of the current rr interval from at least one past value though the coefficient $h_{rr\text{-}rr}(1)$; ii) the activation/deactivation of the baroreflex through the parameters $h_{rr\text{-}sap}$; iii) direct

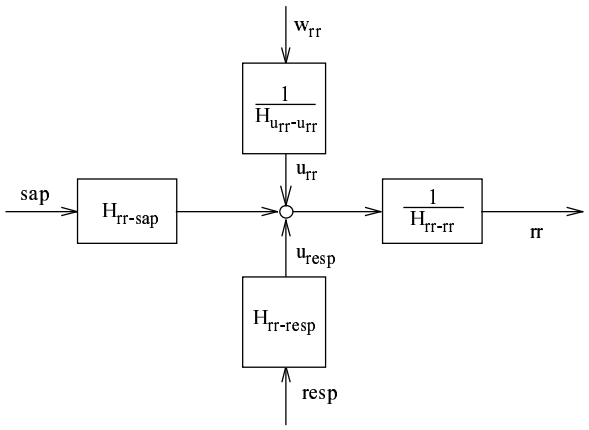

Figure 1. Model describing the interactions between rr, sap and resp signals. The block $1/H_{rr\text{-}rr}$ represents the sinus node transfer function.

influences of respiration capable to drive rr interval independently of sap through the coefficients $h_{rr\text{-}resp}$; iv) central neural actions capable to modify rr interval independently of baroreflex and in frequency bands different from the respiratory one (likely in low frequency (LF) band, from 0.04 to 0.14 Hz) through the parameters $h_{urr\text{-}urr}$.

2.2. Sinus node transfer function

The sinus node transfer function takes the following form

$$G_{rr-rr}(z)=\frac{1}{H_{rr-rr}(z)}=\frac{1}{1-h_{rr-rr}(1)\cdot z^{-1}}$$

where $z=h_{rr\text{-}rr}(1)$ is a real pole with $-1<h_{rr\text{-}rr}(1)<+1$ as the $G_{rr\text{-}rr}(z)$ is stable and z^{-1} is the one delay operator in the Z-domain. When $h_{rr\text{-}rr}(1)=0$, the transfer function behaves as an all-pass filter with a unitary gain and null phase (no dynamic effect is described). While increasing $h_{rr\text{-}rr}(1)$ above 0 the transfer function operates as a low pass filter with a role off becoming steeper and steeper and a phase more and more negative. While increasing $h_{rr\text{-}rr}(1)$ below 0, the transfer function works as a high-pass filter with a more and more increasing derivative effect and a phase more and more positive.

2.3. Testing the ability of $G_{rr\text{-}rr}$ to describe the sinus node gain

We tested the ability of $G_{rr\text{-}rr}$ to describe the sinus node transfer function on a set of heart transplant patients less than 14 months after transplantation. In this population our model correctly detected a sinus node transfer function with a flat gain (all-pass filter). Indeed, as a result of the complete cardiac denervation, the dynamic properties of the block $G_{rr\text{-}rr}$ describing the relationship between the cardiac efferent activity (both parasympathetic and sympathetic) and heart rate were abolished [7]. In addition, we found that, after the administration of a high dose of atropine, the role off of $G_{rr\text{-}rr}$ is faster [7]. Indeed, accordingly with the exclusion of the parasympathetic system, the sinus node transfer function was more similar to the relationship between the sympathetic activity and heart rate and, therefore, with a steeper gain [5].

3. Experimental protocol and data analysis

Ten healthy young men (age from 20 to 32) were studied in the supine position before (baseline, B) and after low dose administration of atropine (LD, 2 μg/kg). We recorded ECG (lead II), invasive arterial pressure (via a catheter inserted into the radial artery) and respiration (with a thoracic belt).

The heart period was approximated with the distance between two consecutive R peaks detected on the ECG (RR interval). SAP was calculated as the maximum of the arterial pressure signal inside the RR interval. As the i-th SAP value could affect the i-th RR interval, fast (within a beat) baroreflex influences were allowed. The respiratory signal was sampled once per cardiac beat at the beginning of the RR interval (RESP(i)) to extract the respiratory frequency (referred to as high frequency, HF). According to previous studies [1-3], after LD we observed that the mean RR interval and respiratory sinus arrhythmia (the power of the RR interval series at the respiratory frequency) increased, while the mean SAP and respiratory rate were unchanged.

The identification of the model (Fig.1) and the selection of the model order p were performed on about 300 consecutive and corresponding samples of RR, SAP and RESP via generalized least squares and Akaike criterion respectively [7], thus allowing the direct evaluation of $h_{rr\text{-}rr}(1)$. The baroreflex gain α was obtained

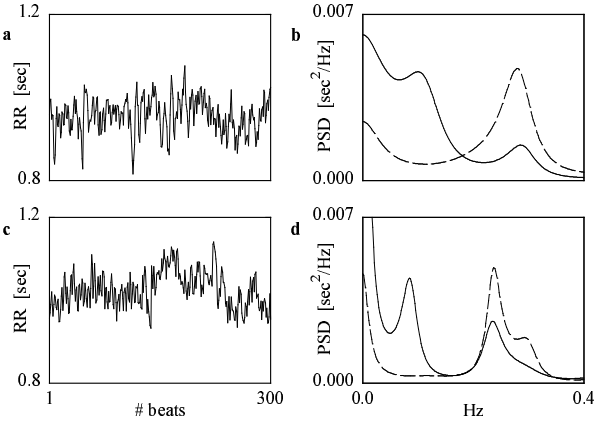

Figure 2. RR interval series before (a) and after LD (c) are shown with their power spectral densities (b and d, solid line). The dashed line represents the power spectral density of the respiratory signal (b and d).

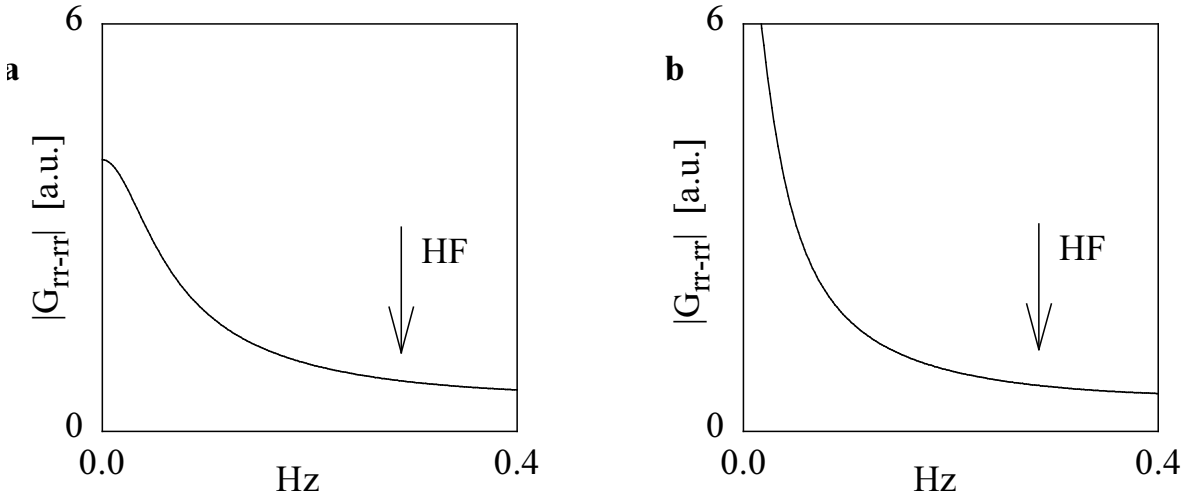

Figure 3. Courses of the gain of the sinus node transfer function $G_{rr\text{-}rr}$ estimated in a healthy young man before (a) and after LD (b). The parameter $h_{rr\text{-}rr}(1)$ is 0.75 and 0.87 in a and b respectively. The RR interval series are depicted in Fig.2. The arrows indicate the respiratory frequency. The gain is expressed in adimensional units (a.u.).

by feeding the block $H_{rr\text{-}sap}$ with an unitary ramp simulating the pressure rise and by measuring the slope of the subsequent heart period increase [8]. The slope was derived as the least squares fitting on the first 15 samples of the response to the SAP rise and expressed in ms/mmHg. One way ANOVA (Bonferroni's test) was utilized to test the significance of the difference in $h_{rr\text{-}rr}(1)$ and α after LD.

4. Results

Fig.2 shows an example of RR interval series before and after LD. The mean RR interval increased after LD (1020 vs 956 ms, Fig.2a,c). The power spectrum densities of the RR interval series showed evident peaks at the respiratory rate both before and after LD (Fig.2b,d). The respiratory sinus arrhythmia (the RR power associated to the respiratory rate) increased after LD (420 vs 259 ms^2). This trend was present in all the subjects.

Fig.3 depicts the gain of the sinus node transfer function $G_{rr\text{-}rr}$ derived from the RR interval series showed in Fig.2 (and from the relevant SAP and respiratory signals). The block $G_{rr\text{-}rr}$ behaved as a low pass filter both before and after LD ($h_{rr\text{-}rr}(1)$ was positive, 0.75 and 0.87 in a and b respectively). This result was confirmed in all the subjects. At B, $h_{rr\text{-}rr}(1)$ was 0.76±0.12 and remained unchanged after LD (0.81±0.15), thus rendering the sinus node gain similar at any frequency.

Fig.4 shows the response of the block $H_{rr\text{-}sap}$ to a unitary SAP ramp (squares) before (a) and after LD (b) in the same human subject whose RR interval series are

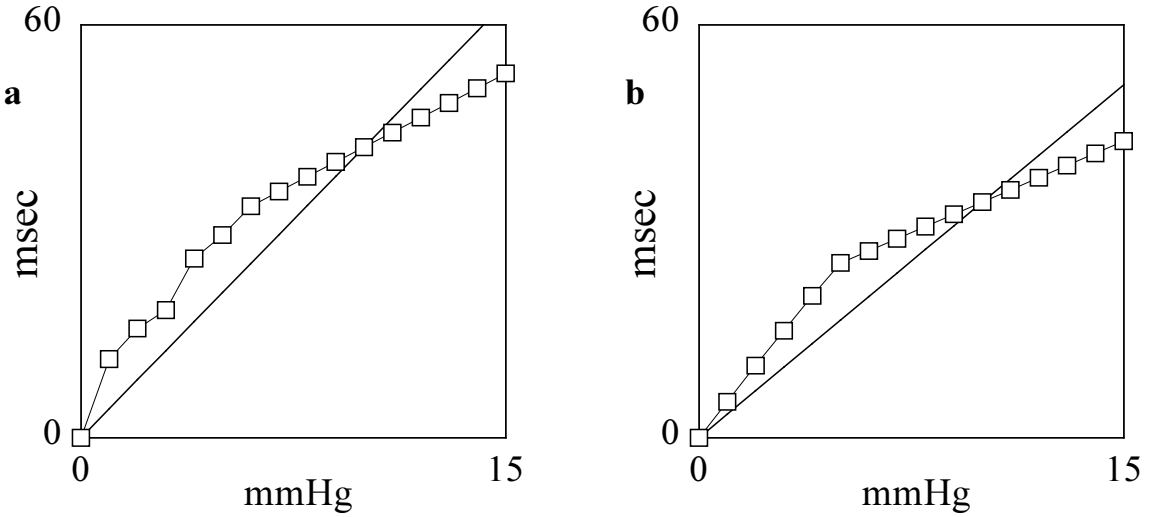

Figure 4. Courses of the first fifteen samples (squares) of the responses of the $H_{rr\text{-}sap}$ block to the unitary pressure rise of SAP and of the linear fitting (solid line) in a healthy young man before (a) and after LD (b). The baroreflex gain α is 4.22 and 3.42 ms/mmHg in a and b respectively. The RR interval series are depicted in Fig.2.

depicted in Fig.2. The slope of the linear fitting (solid line) was taken as a measure of the baroreflex gain α. The slopes were similar (4.22 and 3.42 ms/mmHg in a and b respectively). In the whole set of data, we found that α was 3.86±3.22 ms/mmHg at B and was unmodified after LD (1.84±1.36 ms/mmHg).

5. Discussion

It is well known that low dose administration of atropine increases heart period and respiratory sinus arrhythmia [1-3]. In anesthetized dogs direct recordings of cardiac vagal efferent activity and heart rate have proved that, in the presence of an unchanged baroreflex gain, the respiratory modulation of vagal activity increases, thus allowing to hypothesize a vagal activation not completely blocked by a partial peripheral cholinergic blockade [1]. In man the mechanism underlying the increase of the respiratory sinus arrhythmia after low dose of atropine is not clarified yet, mainly due to the difficulty of directly accessing to the cardiac vagal activity. Raczkowska et al [3] have attributed it to an augmentation of the baroreflex responsiveness (i.e. the baroreflex response to the respiratory modulation of the arterial pressure). Montano et al [2] have attributed it to a larger respiratory modulation of the neural efferent activity (as shown by an increase of the respiratory modulation of the muscle sympathetic activity) mediated by an activation of respiratory centers independently of the action of the baroreflex. Also an increase of the gain of the sinus node transfer function may be responsible for an increase of the respiratory sinus arrhythmia [4]. The results of the present study are in favor of a central activation: indeed, in the presence of an increase of the respiratory sinus arrhythmia, the baroreflex gain and the gain of the sinus node transfer function seem to be unmodified. This study does not confirm the increase of the baroreflex gain reported by Raczkowska et al [3]. This difference can be explained in terms of the methods utilized to estimate the baroreflex gain. In Raczkowska et al [3] the baroreflex gain is calculated as the amplitude of the respiratory sinus arrhythmia normalized by the pressure changes imposed by a neck chamber device. On the contrary, in this study the baroreflex gain is calculated based on a model imposing causality between heart period and systolic arterial pressure and taking into account respiratory influences not mediated by the baroreflex. This model produces a baroreflex gain smaller (if it is the case) than that obtained by traditional methods based on spontaneous variability (e.g. time domain techniques) [9] as a result of its ability in accounting for the effects of mechanisms others than baroreflex (e.g. the activation of low pressure receptors) producing a respiratory sinus arrhythmia independently of the activation of baroreflex and, therefore, an overestimation of the baroreflex gain.

6. Conclusions

The contemporaneous non invasive estimation of the sinus node transfer function and baroreflex gain allows us to go deeper in the mechanisms producing the increase of the respiratory sinus arrhythmia in presence of a partial peripheral cholinergic blockade induced by low dose atropine. It appears that the increase of the respiratory sinus arrhythmia is not due to an augmentation of the gain of the sinus node transfer function or to an increased responsiveness of the baroreflex, thus supporting the hypothesis of a central origin.

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Address for correspondence.

Alberto Porta, PhD
Universita' degli Studi di Milano
Dipartimento di Scienze Precliniche (DiSP)
LITA di Vialba
Via G.B. Grassi 74
20157, Milan
Italy

E-mail: alberto.porta@unimi.it