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HRV strongly depends on breathing. Are we questioning the right suspect?

Teodor Buchner (1) Working Group of Cardiovascular Physics, Faculty of Physics,
Warsaw University of Technology, Koszykowa 75, 00-662 Warszawa, Poland,
Corresponding author: buchner@if.pw.edu.pl

Abstract— **The fact that the heart rate variability (HRV) depends on breathing is well known. The HRV is an important phenomenon which reflects the functional state of the autonomous nervous system (ANS), although there are some doubts concerning the actual interpretation of spectral components of HRV and their postulated balance. The assessment of the functional state of the ANS is the task of paramount importance in risk stratification of cardiological patients. HRV is considered to depend mainly on the properties of the sinus node (SN), which achieves neurohumoral input from the ANS. Interestingly, there is growing evidence that the relation between the heart rate (HR) and breathing rate (BR) is really strong. The variety of breathing-related effects that are present in HRV is very rich, including respiratory sinus arrhythmia (RSA), cardiorespiratory synchronization and vivid heart rate response to breathing disorders. If the mean frequency of any of rhythms is changed, the other rhythm adjusts itself. This provokes the question on the actual source of the dynamics observed in the HRV. Is it possible that we observe mainly the dynamics of the respiratory rhythm which is just transduced by the heart effector? What might be the role of the intrinsic dynamics of this effector? Is the RSA a product of neural regulation or rather a by-product: what is its teleological role? In consequence: if we concentrate on the sinus node and its properties in order to understand the nature of the HRV - are we questioning the right suspect? The reasoning is supplied by suitable choice of literature and by the analysis of the computational model. Various consequences are discussed.**

I. INTRODUCTION

Since Aristotle (384-322 BC), who laid foundation for modern analytic approach, which led the mankind to derive many specific sciences from the stem of philosophia naturalis, there is a tradition in science to treat distinct organs separately, even if they are close neighbors (e.g. sharing one chest). Indeed, the heart and the lungs from the point of view of their control mechanisms are quite different but, as will be discussed, their activity must be strictly synchronized. In the following chapters, we will describe the elements that play key roles in the cardiorespiratory dynamics and then various aspects of their strong but complex interrelation.

II. THE ELEMENTS

A. The heart

The heart has a top-level, self-sustaining physiological pacemaker: the sinus node (SN). Due to the property of automatism, the SN is able to initiate spontaneously the action potential not only when totally denervated, but also in *ex vivo* preparations. In order to enhance the functional independence of the heart effector, there is also a cascade of lower order pacemakers: the atrio-ventricular node (AV) and the His-Purkinje network. All these secondary pacemakers in physiological conditions do not utilize their automatism but introduce the life-saving escape rhythms whenever the higher level pacemaker ceases to function. By teleological argumentation we can see that the main goal in the design of the heart pacemaker system was to build an independent, redundant, reliable effector. This effector has its intrinsic rate and residual intrinsic variability, but apart from that, it is subject to neural, humoral and mechanical factors that give rise to the phenomenon of the heart rate variability. The humoral input includes plasma catecholamines which (apart from other effects) induces a chronotropic effect on the heart. The mechanical input appears even in the hearts denervated after transplant: when the blood pressure in the right atrium is modulated, strech receptors alter the rate of depolarization of the action potential. This effect is rather residual, being much smaller than the physiological variability [2]. The neural input is transmitted by two separate branches of the ANS: through sympathetic and vagal(parasympathetic) innervation. The sympathetic activity is known to provide information from the baroreceptors and chemoreceptors, whereas the vagus nerve (X) provides information on breathing. Despite what is commonly assumed, from the theory of homeostasis, it is not exactly clear what does it mean that the sympathetic and parasympathetic branch of the ANS are balanced in the heart effector and is their action is not necessarily unilateral: this idea will be addressed later on. In parasympathetic control of the HR the so-called vagal paradox [3] was found: the mean frequency and the variability of the HR changes with breathing frequency but this change is non-monotonous and the structure which may be observed resembles the Arnold tongues (see [24] and [1] with references therein). This fact is mentioned to show that in the neural control of a rhythm there is no place for direct reciprocity.

B. The respiratory pattern generator

The respiratory pattern generator (RPG) is a multicomplex structure of complex function, located in brain stem [4]. The respiratory system shares the upper airway tract with the digestive system and with higher evolutional function: the speech. Therefore, the respiratory pattern which is generated has to be synchronized with many other actions that appear in the living body: swallowing and speech, to name just two

most important. Respiration can be also ceased voluntarily for a short amount of time. Initiation of a breathing cycle has to appear in a very specific range of time in order not to disturb other rhythmic or non-rhythmic functions of the body. Due to this, the dynamic control of the respiratory rhythm is performed relatively high in the ANS. There is no low-level simple autonomous pacemaker as in the heart: spinal cord injuries in the cervical segment result in loss of diaphragm function and inability to breathe. One of important inputs to the RPG is the so-called respiratory drive, which originates from baroreflex and chemoreflex. This input appears as a common factor which affects both the respiration and the heart rate. The vagal nerve provides to the RPG feedback from the chest wall. From the teleological point of view, the respiratory rhythm is rather cooperative and non-autonomous.

III. The relation between heart rhythm and breathing rhythm

As already mentioned, there is growing evidence that the relation between the heart rhythm and breathing rhythm is strong (c.f [5], [6] and references therein). This relation has many aspects and in the following chapters, the phenomena that engage both rhythms are described one by one. The nature of the cardiorespiratory coupling has been studied using various methods: from nonlinear phase analysis [12] to information theory [25].

A. Mean frequency ratio adjustment

In order to maintain the homeostatic blood gasometry, the mean alveolar ventilation and the pulmonary blood flow have to be adjusted. Their ratio has to be equal to the magic value of 0.85 which is maintained homeostatically [7]. The most obvious and the easiest quantities to regulate in order to achieve this ratio are the heart rate and the breathing rate. In physiological conditions of gas exchange and for the normal hemodynamical state of the heart, the frequency ratio between the heart rate and the respiratory rate is 3:1 (when coupled). This ratio is quite constant, although specific patterns of phase coupling may have slightly different ratio: e.g. 5:2, 2:1 [8]. This phenomenon is called cardiorespiratory synchronization [8]. When both rhythms are decoupled, this ratio grows to 8:1 [5]. Such a change in frequency ratio was also observed in a mathematical model of pulse coupled oscillators, which mimics this physiological model [9].

B. Simultaneous response to baroreflex input

A reflex, considered to be the most important in the regulation of the blood pressure (BP) is the baroreflex which enables the ANS to respond to sudden changes of BP such as hemorrhage or sudden increase of the BP. The response to this reflex is said to be predominantly mediated by the sympathetic nervous system. It is also considered whether the direction of information flow in this reflex is more feedback or more feedforward. What is not considered in this context is, that actually the heart and the respiratory pattern generator share the same neural input: the baroreflex sympathetic activity a.k.a the respiratory drive. The dynamic response to sudden changes of the BP may as well appear in both coupled rhythms simultaneously and baroreflex may also act through the change of coupling. Trzebski has shown that the amplitude of baroreflex response in the HR depends strongly on the phase of breathing in which a transmural stimulus (neck collar with negative pressure) is applied [11]. The consequences of this fact to the analysis of the baroreflex sensitivity (BRS) should be drawn. Such an analysis should probably include both the heart rhythm and the breathing rhythm in order to describe the whole phenomenon as it may manifest itself not only in sympathetic branch of the ANS but in the parasympathetic branch as well.

C. The meaning of respiratory sinus arrhythmia

A well-known phenomenon in HRV which originates from breathing is the presence of the respiratory sinus arrhythmia (RSA). It is a rhythmic change in heart rate, most prominent during sleep and in well-trained athletes, which develops when the newborn infants start to breathe [12]. The question of a possible teleological role of the RSA is still open. A postulated explanation of this phenomenon has been published recently [13]. According to this hypothesis, the role of RSA is to buffer the respiratory-related changes of blood pressure. Interestingly, it seems that the actual neural input transmitted by the vagi is not directly dependent on respiratory BP fluctuations but rather on input from mechanoreceptors in chest wall (this sole fact was used in a modeling context by Clynes [14]). This leads to an interesting effect: as buffering does not directly monitor the blood pressure fluctuations, in the supine body position the buffering effect actually enhances the fluctuations. This effect was observed experimentally [16] and the authors of the mentioned paper claim to give an explanation of this phenomenon.

D. Functional state of the Autonomous Nervous System and its impact on HRV

Interestingly, it seems that the breathing-related sinus node response to humoral sympathetic activation is in some sense opposite to that of the neural sympathetic activation. It was shown that the neural sympathetic input is modulated by breathing. Therefore as far as the neural interactions are concerned, the parasympathetic nervous system seems to dominate over the sympathetic (as it imposes its modulation on the sympathetic signal). But, on the other hand, plasma katecholamines were shown to effectively block any neural parasympathetic input on the level of the effector by imposing the relatively high and nearly constant value of the HR [17]. It is well known fact in the analysis of the HRV that the variability depends strongly on the mean HR, which is the reason for the characteristic shape of RR phase portraits (c.f. [18]).

E. Phase domain and frequency domain

An interesting observation concerning the nature of HRV may be done in frequency domain . If we analyze both

rhythms in frequency domain, we may observe that actually all the activity at specific frequencies present in power spectrum of the HR (e.g. 1/f noise and 0.1 Hz peak) are also present in the breathing rhythm. It occurs that the neural modulating input delivered to the SN is modulated itself. This seems to be an interesting case for the theory of modulation: properties and presence of the secondary modulation. Another interesting phenomenon from modulation theory, which may be observed in HRV is aliasing: faster breathing rates are sampled by the heart rate below the Nyquist frequency of breathing [15]. Note for example that the HRV spectrum of a heart transplant patient, published in [2], does not exhibit 1/f character. Further consequence is interesting: it seems that all the important components of the HRV come from appropriate modulation of breathing. It occurs that the only frequency component in HRV which is not inherited from the power spectrum of breathing is the respiratory modulation itself i.e. the HF peak.

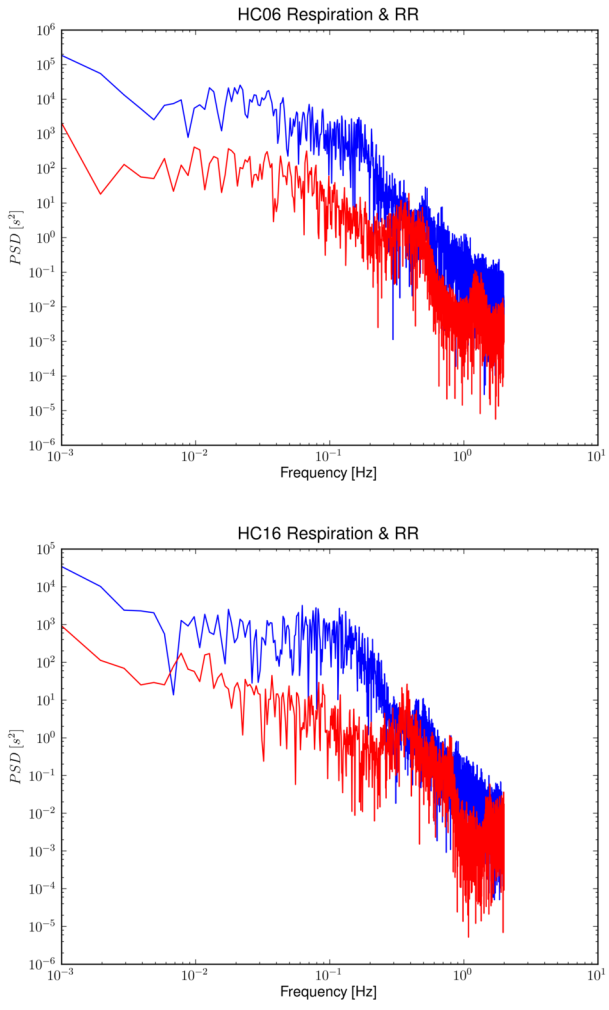

Fig. 1. Simultaneously registered spectra of the interbreath interval and the RR interval from polysomnographic recordings of two healthy individuals studied in [5]. Note the presence of the 0.1 Hz peak and the 1/f character of the spectrum (linear in a log-log plot).

F. Phase domain

The term phase domain describes one or many oscillators represented by their phases. In phase domain synchronization effects may be studied (e.g. [21], [12], [8], [20]). In either breathing or heart period one can define phase as: $\phi_i = t_i/T$, where t_i is time from the beginning of current cycle and T is base period, being e.g. an unperturbed period of oscillation (with no coupling) (e.g. [3]). In phase-domain, synchronization between two rhythms was observed using a technique called synchrogram [8]. Synchrograms were shown to change rapidly at borders of sleep stages which is interpreted as phase transition [20]. In phase domain breathing and heart may be described [9] as two delayed pulse-coupled oscillators [19] with the relation between them described using phase response curve (PRC). This model was inspired by a model of breathing pattern generator, tightly coupled to heart rhythm, formulated and confirmed experimentally in [10]. An extended version of this model, defines the dynamics of two phases as follows:

$$\dot{\phi} = r + m \cdot f(\phi)\delta\left(t - t_j - \tau_1\right) \quad (1)$$

$$\dot{\Phi} = R + M \cdot F(\Phi)\delta\left(t - t_i - \tau_2\right) \quad (2)$$

Here ϕ denotes the phase of the heart rhythm whereas Φ the phase of the breathing rhythm. Both phases are in $1/2\pi$ units so that phase difference 1 is equal to full rotation. Parameters r and R define the angular velocity of each of oscillators; in physiological conditions $r = \omega \cdot R$, where $\omega = 8$ - as approximately such is the ratio of frequencies between breathing rate and heart rate when uncoupled [5]. The definition of firing times t_i and t_j is: $t_i : \phi\left(t_i\right) = i; \quad t_j : \Phi\left(t_j\right) = j$. In short words: when a full cycle is complete, phase in either t_i or t_j has an integer value. Both oscillators are pulse-coupled: at delay $\tau_1(\tau_2)$ after time t_j (t_i), when breathing (the heart) "fires", the heart (breathing) is kicked by a delta pulse of height m (M). The height of kick is modified by the functions f and F describe the PRC (i.e. the sensitivity to external stimulus) of the heart and breathing, respectively. After [22], the PRC used in this context is that of Seidel-Herzel model:

$$f(\phi) = \phi^{1.3} \cdot (\phi - 0.45) \cdot \frac{(1-\phi)^3}{(1-0.8)^3 + (1-\phi)^3} \quad (3)$$

Examples of experimentally determined PRC can be found in [10] and [3]. The above description, must be further developed in order to properly describe the heart dynamics: in present form, the coupling acts on heart phase only during one beat, while other beats have unperturbed period. Anyway, even in present form, the model properly describes the phase transition at the border of sleep stages [20]: it seems to be related with rapid change of breathing rate, which, in turn, is caused by a rapid change in metabolic rate. In current form, the power spectrum of breathing is delta shaped, instead of the postulated 1/f with 0.1 Hz. The 1/f shape may be easily obtained e.g. by introducing a suitable generator: e.g. the one defined in [23] where phase rises linearly until it reaches random threshold, which seems very natural in physiological context.

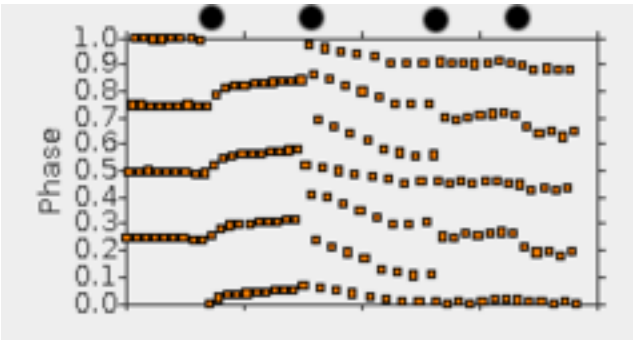

Fig. 2. Synchrogram from a SynchroWIM applet [26] in a phase transition point. Here $M = 0$ (unidirectional coupling), $\tau_1 = \tau_2 = 0$ (no delay) $f(\phi)$ is half of sine of variable amplitude. Black dots show points where subsequent changes were applied: the breathing rate was changed slightly (1), then rapidly (2). The heart rhythm was unable to synchronize as the rates were incommensurate. Two subsequent increases of the amplitude of the PRC (3) and (4) enabled synchronization. Note that the rotation number changed from 4 to 5.

IV. Discussion

This contribution presents in a concise form complex interactions between heart rate and breathing. The depth of these relations suggests that these two phenomena should not be treated separately. It seems that the most important features of the power spectrum, that were so far considered to be the landmarks of the HRV signal (1/f noise, presence of the 0.1 Hz peak), are also present in breathing rhythm. If so, the HRV should not be treated as a sole phenomenon and many questions concerning for example the interpretation of certain frequency bands in the power spectrum of the HRV, phase transitions, assessment of the neural control, baroreflex sensitivity could be better accomplished by the supplementary analysis of the respiratory pattern.

V. Conclusions

The variability of the heart rate depends strongly on the breathing rate variability (BRV) which is controlled by the ANS. The heart appears in two contexts. Firstly, EKG provides an easy method to observe the results of the breathing rate variability. Secondly, the heart effector transduces the BRV signal. The properties of the heart as the transducer also depend on the functional state of the ANS, specifically on the level of the adrenergic drive. It may occur fruitful for future analysis of the HRV to apply the controller-transducer schema. This may provide valuable results for cardiological risk stratification and diagnosis.

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