The Effects of Time-varying Breathing on Human Neurophysiological and Cardiovascular Mechanisms

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Abstract— **We varied the timing of respiration as a means to modulate and better understand otherwise hidden human central neural and cardiovascular mechanisms. Time-frequency methods (wavelet transform, wavelet phase coherence, and directional coupling) were applied to analyze these time-varying signals. We found that respiration causally modulates both sympathetic (weakly) and vagal motoneuron (strongly) oscillations over a wide frequency range – one that extends well below the frequency of actual breaths. Breathing frequency does not affect phase coherence between diastolic pressure and muscle sympathetic oscillations, but it augments phase coherence between systolic pressure and R-R interval oscillations over a limited portion of the usual breathing frequency range.**

I. INTRODUCTION

Respiration exerts major influences on autonomic function: respiratory periodicities can be discerned in both skin and muscle sympathetic neural outflows [1], [2], and in R-R intervals and hemodynamic parameters. The influence of the respiration on the cardiorespiratory interactions has been identified as a direct coupling component linked to the respiration sinus arrythmia [3], [4]. Respiration phasically alters the responsiveness of sympathetic [5] and vagal motoneurons [6] to stimulatory inputs, and mechanically alters arterial pressure [7] and associated baroreceptor nerve activity.

The great significance of respiration for physiological research is that humans can alter their central oscillatory milieu simply and precisely by controlling their breathing [8]. We exploit this convenience to perturb respiration and explore the human neurophysiological and cardiovascular mechanisms [2].

II. METHODS

The *protocol* comprised of uncontrolled spontaneous breathing followed by periods of steadily increasing or decreasing ramp breathing frequencies in the range 0.05 to 0.25 Hz. We studied 13 healthy subjects, and the spontaneous and ramp breathing segments were 6 and 9 minutes long, respectively. We recorded muscle sympathetic nerve activity (MSNA) and the usual hemodynamic parameters electrocardiogram (ECG) and blood pressure from which we derived the R-R interval, systolic and diastolic pressure signals. Tidal CO_2 was measured [2] from air withdrawn from a port in the face mask.

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The *analysis* included three methods: wavelet transform, wavelet phase coherence and directional coupling. Arguably the most appropriate method for treating time-varying multimode oscillating signals is by wavelet transform [9]. Wavelet phase coherence is a powerful technique for observing the phase coordination of two oscillatory processes [10]. Of especial interest to the ramp study is the windowed wavelet phase coherence method [10], which allows one to trace the time-variability of the coherence. In order to explore the causal relationships between the oscillatory processes we estimated the coupling strengths and directionality with a method based on conditional mutual information [11]. We analyzed fixed-frequency ranges of 0.021-0.052, 0.052-0.145, and 0.145-0.5 Hz [9].

III. RESULTS

A. Wavelet transform power

In order to explore if the ramp breathing protocol induced significant changes we compared the wavelet power of the different physiological parameters during *spontaneous* and *ramp* breathing segments. We found that the wavelet power of MSNA ramp segments was significantly lower than the spontaneous segments on the usual breathing interval, while it was significantly higher on the low-frequency interval. This effect can be explained on the bases of respiratory gating of stimulatory inputs to muscle sympathetic motoneurons [5].

At low frequencies, diastolic and systolic pressure and R-R interval wavelet powers were significantly greater during ramped-frequency than spontaneous breathing. At very low frequencies, one that extend well bellow the actual ramp protocol breathing, diastolic and systolic pressure and R-R interval wavelet powers were significantly greater during spontaneous in comparison to ramped-frequency breathing. The latter effect might be on account of coupling from other oscillatory processes in the cardiovascular system [9], which are directly affected by the ramp breathing.

B. Wavelet phase coherence

The results in Fig. 1 A, B and C, indicate that during both spontaneous and ramped-frequency breathing, wavelet phase coherence between CO_2 and R-R interval oscillations was high. However, significance was limited almost exclusively to the usual breathing frequency interval. The ramp time-variability is very clearly detected (Fig. 1 B), which goes in line with the recent findings about the time-variability of cardiorespiratory coupling function [12]. This strong coherence is a consequence of the direct coupling component linked to the respiration sinus arrythmia [3], [4].

Systolic pressure and R-R interval phase coherences (Fig. 1 D, E and F) were high during both breathing modes

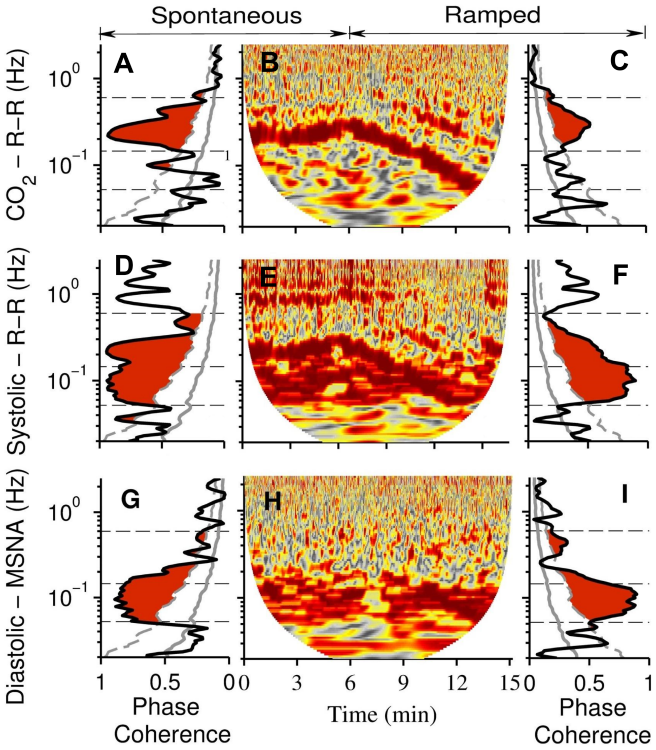

Fig. 1. Wavelet phase coherence for spontaneous and ramp breathing segments from one subject. The left and right panels are time-averaged coherence and only the significant coherence above the surrogate level is shaded in red. The middle panels show windowed wavelet phase coherence which demonstrates the time-evolution of the coherence.

in the low frequency range, while they were different in the respiratory-frequency range where the coherence was confined around the ramp-frequencies. Fig. 1 G-I, indicate that diastolic pressure and muscle sympathetic nerve wavelet phase coherences were significant over a wide frequency range, were concentrated in the low frequency range, and were similar during spontaneous and ramped-frequency breathing. This respiration-independent high coherence could be on account of baroreflex [6] or myogenic [9] mechanisms.

C. Directional coupling

We found that respiration has a relatively high and significant influence on R-R interval, systolic and diastolic pressure for both spontaneous and ramp breathing. The breathing to MSNA coupling was weak and more significant for the ramp segments. Similarly the diastolic pressure causally influences the MSNA oscillations. This coupling was higher when estimated for windows of lengths which can mediate very-low frequency oscillations. The endothelial oscillations could be a possible mechanism behind this effect [9].

IV. DISCUSSION

In conclusion, our study of young men who gradually increased or decreased their breathing frequencies sheds a new light on human cardiovascular system and autonomic neurophysiology [2]. The oscillating processes and their relationships were very persistent and stable under the time-varying ramp breathing protocol. This implies that some of this physiological oscillators might have chronotaxic nature [13], [14].

Respiration causally modulates both sympathetic (weakly) and vagal motoneuron (strongly) oscillations over a wide frequency range – one that extends below the frequency of actual breaths. Breathing frequency does not influence median levels of sympathetic or vagal activity over time.

Phase relations between arterial pressure and sympathetic and vagal motoneuron oscillations are unaffected by breathing, and therefore likely reflect intrinsic responsiveness of these motoneurons to other synaptic inputs. Finally, breathing frequency does not affect phase coherence between diastolic pressure and muscle sympathetic oscillations, but augments phase coherence between systolic pressure and R-R interval oscillations over a limited portion of the breathing frequency range. These results refine the understanding of autonomic and hemodynamic oscillatory processes and physiological mechanisms known as the human respiratory gate [15].

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