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ORIGINAL ARTICLE

Low-frequency ventilatory oscillations in hypoxia are a major contributor to the low-frequency component of heart rate variability

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Abstract

Purpose Heart rate variability (HRV) may be influenced by several factors, such as environment (hypoxia, hyperoxia, hypercapnia) or physiological demand (exercise). In this retrospective study, we tested the hypothesis that inter-beat (RR) intervals in healthy subjects exercising under various environmental stresses exhibit oscillations at the same frequency than ventilatory oscillations.

Methods Spectra from RR intervals and ventilation ($\dot{V}E$) were collected from 37 healthy young male subjects who participated in 5 previous studies focused on ventilatory oscillations (or periodic breathing) during exercise in hypoxia, hyperoxia and hypercapnia. Bland and Altman test and multivariate regressions were then performed to compare respective frequencies and changes in peak powers of the two signals.

Results Fast Fourier analysis of RR and $\dot{V}E$ signals showed that RR was oscillating at the same frequency than periodic breathing, i.e., ~0.09 Hz (11 s). During exercise, in these various conditions, the difference between minimum and maximum HRV peak power was positively correlated to the same change in ventilation peak power ($P < 0.05$). Low-frequency (LF) peak power was correlated to tidal volume ($P < 0.01$) and breathing frequency ($P < 0.001$).

Conclusions This study suggests that low-frequency ventilatory oscillations in hypoxia are a major contributor to the LF band power of heart rate variability.

Clinical Trial Reg. no. NCT02201875.

Keywords Heart rate variability · Hypoxia · Exercise · Control of ventilation · Periodic breathing

Abbreviations

ACZ	Acetazolamide
ANOVA	Analysis of variance
CHF	Chronic heart failure
FFT	Fast Fourier transform
HF	High frequency
HR	Heart rate
HRV	Heart rate variability
LF	Low frequency
LOA	Limits of agreement
MAP	Maximal aerobic power
PB	Periodic breathing
RR	Interbeat interval
SD	Standard deviation
Ti	Inspiratory time
Ttot	Total respiratory cycle time
$\dot{V}E$	Ventilation
VLF	Very low frequency
VT	Tidal volume

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Introduction

Submitting a normal subject to physiological or environmental stress, such as exercise and hypoxia, is known to modify not only cardiorespiratory outputs, such as minute ventilation ($\dot{V}E$), but may also alter respiratory pattern. Altitude promotes the genesis of hypopnea/apnea, during sleep and awakeness (Ainslie et al. 2013), which may lead to or worsen, among other altitude-related pathologies, heart failure, pulmonary hypertension, chronic mountain sickness or polycythemia (Richalet et al. 2005; Xu and Jing 2009; Hernandez and Patil 2016). Moreover, concomitant exercise exacerbates ventilatory oscillations (Hermand et al. 2015b): greater $\dot{V}E$ oscillations are associated with a rise in cardiac output ($\dot{V}c$), which is opposed to observations made in severe chronic heart failure (CHF) patients showing pronounced central or mixed apneas (Corrà et al. 2002; Garde et al. 2009). Likewise, the period of $\dot{V}E$ oscillations in healthy subjects exercising in hypoxia is about 11 s (Hermand et al. 2015b), much shorter than those observed in CHF patients (Olson and Johnson 2014).

Apart from mechanisms of respiratory system dysregulation, the aforementioned recent studies also point out the role of the autonomic nervous system (ANS) in the complex cardiorespiratory control system in a subject submitted to various physiological (exercise), environmental (hypoxia, hyperoxia, hypercapnia) and pharmacological (acetazolamide, ACZ) stressors. This phenomenon illustrates a tight link between cardiovascular and respiratory systems (Burgh 2011), although the underlying mechanisms are still yet to be fully understood. Heart rate variability (HRV), as an indirect measurement of sympathovagal balance is now widely used in the diagnosis and prognosis of chronic heart failure (Guzzetti et al. 2001; Leung and Bradley 2001; Florea and Cohn 2014).

In normal subjects, the effects of environmental stressors and exercise on HRV have been extensively studied. First, despite contradictory observations due to variable study conditions, hypoxia generally induces a lower overall HRV and a higher heart rate (HR) (Oliveira and Rohan 2017). A lower low-frequency (LF) power is counterbalanced by an even greater withdrawal in the high-frequency (HF) band, which switches the sympathovagal balance to a sympathetic predominance (Zhang et al. 2014). Second, exercise deeply alters HRV components by decreasing overall HRV, especially LF and HF power (Tulppo et al. 1996).

However, most studies about environmental and physiological impacts on HRV are focused on the effects on the different bands of HRV spectrum, but temporal relations between periodic breathing (PB) and HRV oscillations did not receive much attention. A deeper knowledge of this specific relationship could help understand the pattern linking these two variables, supporting recent observations in healthy subjects exhibiting central sleep apneas during sleep at high altitude, in which amplitudes of HRV parameters were correlated to respiratory amplitude (Insalaco et al. 2016).

We recently pointed out the existence of ventilatory oscillations in normal subjects submitted to various environmental, physiological and pharmacological stressors (Hermand et al. 2015a, b, 2017). Hypoxia and hypercapnia during exercise exacerbate whereas hyperoxia and acetazolamide (ACZ) blunt ventilatory oscillations.

While the physiological significance of the LF band is still being debated (Electrophysiology Task Force of the European Society of Cardiology the North American Society of Pacing 1996; McCraty and Shaffer 2015), we hypothesize that in normal subjects exercising at mild intensity, HRV oscillations located in this band, at around 0.1 Hz, are concomitant to $\dot{V}E$ oscillations, evidencing a cardiorespiratory coupling during exercise during hypoxia different from respiratory sinus arrhythmia (RSA).

Subjects and methods

Subjects

This retrospective study is based upon data retrieved from five previous research protocols including 12–14 male subjects each (27.7 ± 7.0 years old, 175.9 ± 7.2 cm, 73 ± 11.1 kg) (Hermand et al. 2015a, b). All were non-smokers, in good physical condition, with a moderate to high level of regular physical activity (from 2 to 10 h per week). Preliminary medical examinations showed no evidence of cardiovascular or pulmonary disease. The protocols were approved by the Ile-de-France Ethics Committee (CPP-IDF2) and individual written informed consents were collected from all subjects.

Procedure

All subjects were first asked to perform a standard ramp test protocol on a cycloergometer to determine their maximal aerobic power (MAP) and $\dot{V}O_{2\,max}$ (254.5 ± 54.1 W, 52.6 ± 9.3 mL min^{-1} kg^{-1}, respectively): after a 3-min warm-up at 60 W, power output was increased by 30-W steps every 2 min until voluntary exhaustion, validated by a respiratory quotient above 1.1 and a maximal heart rate within a 10 bpm range of its theoretical value (American College of Sports Medicine et al. 2018). The following protocols are described elsewhere (Hermand et al. 2015a, b). Briefly, several tests were randomly conducted, in normoxia, hypoxia (O_2 14.5%), hyperoxia (O_2 100%) and hypercapnic hyperoxia (O_2 93%, CO_2 7%); one additional condition was

added in the hypoxia protocol where subjects were under ACZ treatment in a double-blind experiment (Hermand et al. 2015a). After 1-min rest for material habituation and stabilization of cardiorespiratory parameters, subjects were first asked to keep a resting sitting position on the ergometer for 6 min, and then to pedal for 6 min at around 65 rpm pedaling cadence at an intensity of 30% of MAP.

$\dot{V}E$ (L min^{-1}), tidal volume (VT, L) and heart rate (HR, bpm) were measured breath-by-breath, via a mouthpiece, through an ECG-metabograph (Vmax Encore, SensorMedics, Yorba Linda, CA). Total respiratory cycle time (Ttot, s) and inspiratory time (Ti, s) were derived from the ventilation signal. RR intervals were recorded by a Suunto Memory Belt (Suunto Oy, Vantaa, Finland). Data were transferred to a computer for further variability analysis. The signal stationarities were verified at each interval with a portmanteau test (Ljung–Box test), and were spline-interpolated and resampled to a 1 Hz sample frequency. A fast Fourier transform (FFT) was then applied to the breath-by-breath ventilation, extracted from the raw data, of 128-point windows (one point per s) in rest and exercise phases (Olson and Johnson 2014). This method allowed us to detect the presence of peaks in the frequency domain of the ventilation signal (Fig. 1) (Olson and Johnson 2014; Hermand et al. 2015b). Two main parameters were derived from the FFT: the frequency in hertz (or period in s) of the larger peak and its power estimated as the area under the peak at ± 0.02 Hz around the peak (in L^2 min^{-2}). Thus, a high peak power translates into greater ventilatory oscillations.

In the same manner, RR data were analyzed with Kubios software (University of Eastern Finland, Kuopio/Finland), which performed a Welch spectral transform (Estévez et al. 2015) to extract the spectral curve (Tarvainen et al. 2014) and its subsequent peaks' power, during the 6-min rest and exercise phases. The limits for frequency bands of HRV recordings in normal subjects are 0–0.04 Hz (VLF), 0.04–0.15 Hz (LF) and 0.15–0.4 Hz (HF). Corresponding HRV measures are computed bands: VLF, LF and HF powers (ms^2), LF/HF power ratio (LF peak power)/(LF power) ratio, and total spectral power. The frequency corresponding to the peak in each band was also assessed. In all conditions, the main HRV peak power matched the LF band and we, therefore, specially studied the LF peak power (ms^2), LF peak frequency (Hz) and LF period (s). Finally, ventilatory responses to hypoxia and hypercapnia were assessed by a rest/exercise test in normoxia and hypoxia (O_2 12.5%), and a rebreathing test, respectively, as described before (Duffin 2011; Hermand et al. 2015b).

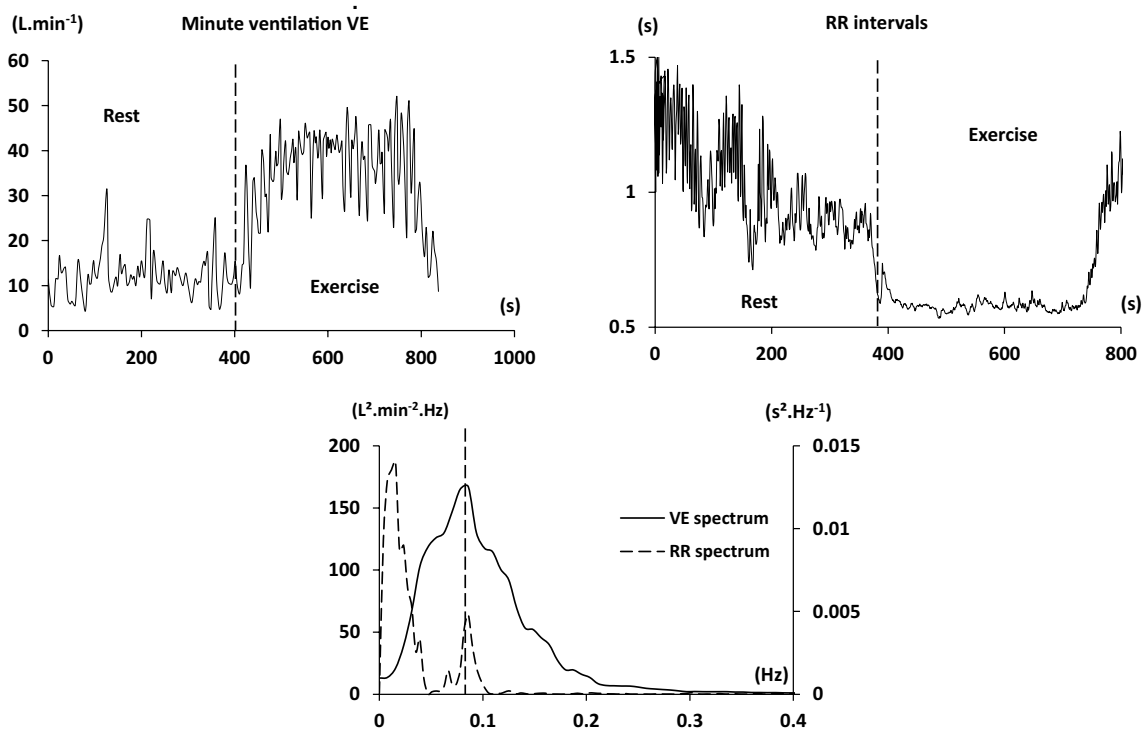

Fig. 1 Example of a breath-by-breath ventilation recording (top left) and RR signal (top right) in hypoxia (Hermand et al. 2015b), and the corresponding spectral analysis (bottom) during exercise. A peak is noticeable in both the spectra at ~0.85 Hz

Statistical analysis

Results are presented as mean ± standard deviation. Normality of log-transformed HRV data was verified for each condition (rest/exercise, normoxia/hypoxia/hyperoxia/hypercapnia, placebo/ACZ) by a Shapiro–Wilk test. Thus, according to the studied condition, a two- or three-way analysis of variance (ANOVA) with repeated measures was done, including interactions between factors. A post hoc paired Student's test was used when applicable. As $\dot{V}E$ and RR signals were acquired independently, in different timescales (breath-by-breath for $\dot{V}E$ and interbeat intervals for RR), a direct cross-spectral analysis between breath-by-breath signal of $\dot{V}E$ and RR intervals was not feasible; however, agreement between $\dot{V}E$ and LF periods was analyzed with Bland–Altman plots (1986) where mean difference, standard deviation (SD), and upper and lower limits of agreement (LOA, 1.96 × SD) were calculated. As our RR analyses are focused on the LF band, from 0.04 to 0.15 Hz, these limits will define the validity of LOA. Finally, linear and multivariate regressions were carried out to establish potential correlations between LF peak power and period on the one hand, and cardiorespiratory parameters on the other hand: $\dot{V}E$ peak power and period, $\dot{V}E$, Ttot, Ti, VT and HR. For this specific analysis, as variability of HRV components might be high between subjects, it is more relevant to investigate variations of cardiorespiratory parameters in one subject successively submitted to various conditions: rest/exercise, normoxia/hypoxia/hyperoxia/hypercapnia or placebo/ACZ. Two conditions are then selected, at maximal and minimal values of $\dot{V}E$ peak power, i.e., when amplitudes of periodic breathing are the strongest and lowest. The absolute difference between the two values ($\Delta\dot{V}E$ peak power) is then calculated. For each of these two values, the corresponding other parameters are extracted (LF peak power, VT and T_{tot}) and their differences computed (ΔLFpeak power, ΔVT, ΔT_{tot}). Regression analysis will point out a correlation between the changes in $\dot{V}$E peak power and the variation of LF peak power, VT or T_{tot}, to assess potential parallel patterns.

Results

Examples of $\dot{V}E$ and RR signals, and their corresponding spectra are presented in Fig. 1.

Effect of exercise vs. rest (Fig. 2a)

Pooling values of all environmental and pharmacological conditions, exercise depressed all HRV parameters: VLF, LF and HF powers (Fig. 2a, $P < 0.001$) and total power (not shown, $P < 0.001$). The LF/HF and LF/(LF + HF) ratios were increased by exercise (not shown, $P < 0.05$ and $P < 0.01$, respectively).

Exercise decreased LF period (Fig. 2b left, $P < 0.05$) and peak power (Fig. 2b right, $P < 0.001$).

Effect of hypoxia vs. normoxia (Fig. 2c, d)

Hypoxia had no effect on LF period and power, but decreased LF and total powers (Fig. 2c, $P < 0.05$), with a similar trend for HF power ($P = 0.085$). However, during exercise, all power components (VLF, LF, HF) were reduced by hypoxia (Fig. 2d, $P < 0.05$, $P < 0.01$, $P < 0.001$, respectively), as well as LF peak power and (LF peak power)/(LF power) ratio (not shown, $P < 0.01$ and $P < 0.05$, respectively).

Effect of ACZ vs. placebo (Fig. 2c, d)

ACZ did not impact any of the studied HRV parameters, although there was a tendency for ACZ to blunt all spectral components (Fig. 2c).

Effect of hyperoxia and hypercapnia vs. normoxia (Fig. 2c, d)

None of the studied HRV parameters were affected by hyperoxia or hypercapnia.

LF and $\dot{V}E$ periods (Fig. 3)

Mean difference between LF and $\dot{V}E$ periods followed a normal distribution and the Bland and Altman plots showed a very low bias (0.0005 ± 0.017 Hz). Upper and lower LOA were 0.035 and − 0.034 Hz, respectively, and less than 2.4% of data were out of the 95% limits of agreement.

Linear and multivariate regression analyses: LF and $\dot{V}E$ peak powers (Fig. 4)

There was a positive correlation between $\Delta\dot{V}E$ peak power and ΔLF peak power during exercise (Fig. 4 top, $P < 0.05$), indicating that larger $\dot{V}E$ oscillations are associated with larger RR oscillations in the LF band. This relation was even tighter in hypoxia ($P < 0.01$, coefficient 0.0006, not pictured). ΔLF power was also positively correlated to ΔVT and ΔT_{tot} (Fig. 4 bottom left and right, $P < 0.01$ and $P < 0.001$, respectively).

Multivariate regression evidenced a strong positive correlation between LF peak power and Ttot ($P < 0.001$).

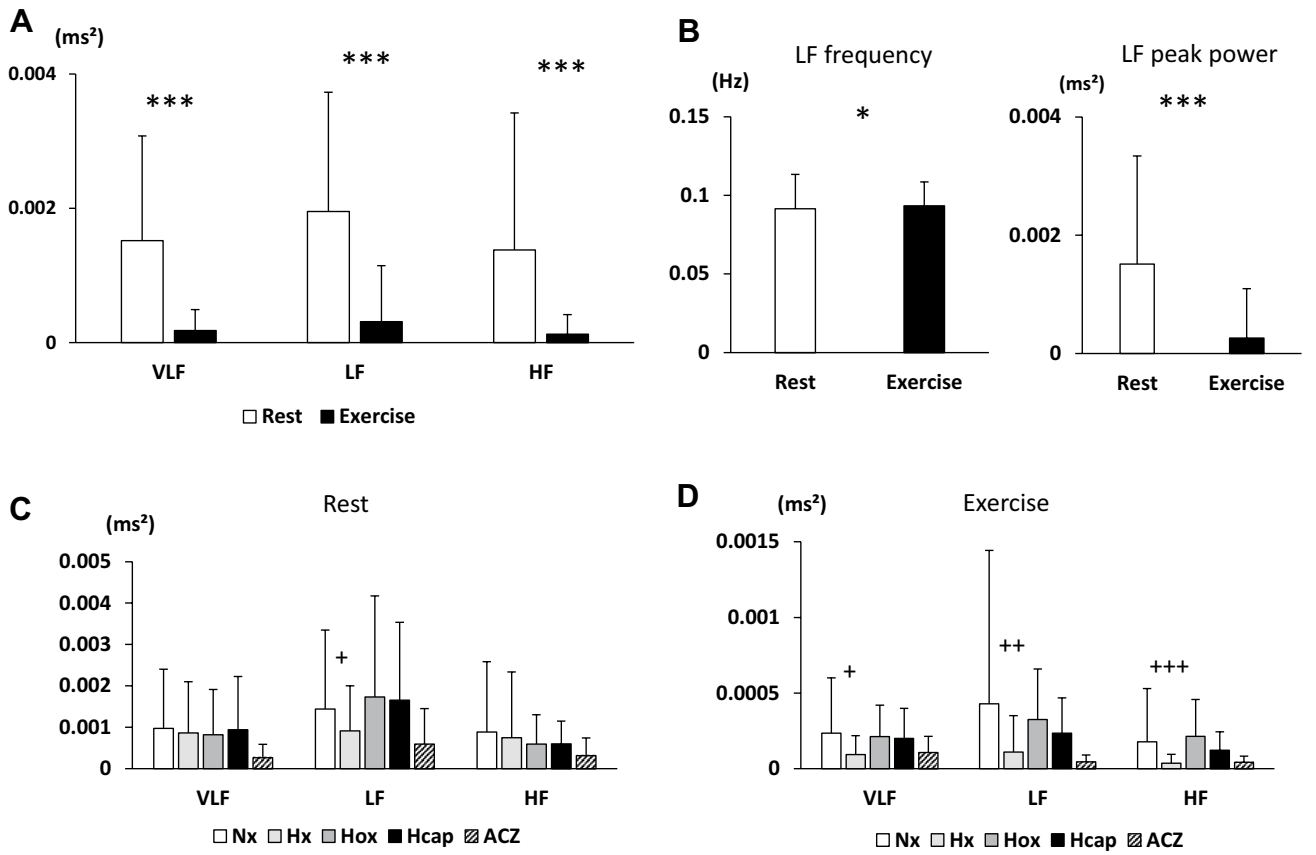

Fig. 2 Top left (**a**): means (±SD) of HRV power spectral densities in VLF, LF and HF bands, at rest and during mild exercise. Exercise vs rest: ***, $P<0.001$. Top right (**b**). Left: means (±SD) of LF period at rest and during mild exercise. Right: means (±SD) of LF peak power at rest and during mild exercise. Exercise vs rest: *, $P<0.05$; ***, $P<0.001$. Bottom left (**c**): means (±SD) of HRV power spectral densities in VLF, LF and HF bands, at rest, for several conditions: normoxia (Nx), hypoxia (Hx), hyperoxia (Hox), hypercapnia (Hcap) and acetazolamide (ACZ). Hx vs Nx: +, $P<0.05$. Bottom right (**d**): means (±SD) of HRV power spectral densities in VLF, LF and HF bands *during exercise*, for several conditions: normoxia (Nx), hypoxia (Hx), hyperoxia (Hox), hypercapnia (Hcap) and acetazolamide (ACZ). Hx vs Nx:+, $P<0.05$; ++, $P<0.01$; +++, $P<0.001$

Discussion

This retrospective study completes with previous papers on periodic breathing during exercise in hypoxia (Garde et al. 2012; Latshang et al. 2013; Hermand et al. 2015a, b). Our main findings evidenced concomitant oscillations in the LF band of RR signal with $\dot{V}E$ oscillations (Fig. 1) suggesting a strong interplay between ventilatory and cardiovascular adjustments during exercise. This cardiorespiratory coupling was observed despite the well-known blunting effect of exercise on overall HRV (Tulppo et al. 1996; Sarmiento et al. 2013).

The Bland and Altman analysis (Fig. 3) reported a noticeable low bias, inferior to 0.001, which shows that LF and $\dot{V}E$ periods were deeply intricate and hereby corroborates the hypothesis of tight cardiorespiratory coupling through the ANS function. Similarly, LF period was much shorter than the one observed in CHF patients (Pinna et al. 1996), following the ~ 1-min apnea–hyperpnea cycles, but remains similar to $\dot{V}E$ period (Fig. 3), at around 11 s (Hermand et al. 2015b). It is equally remarkable to note, despite the overall depressing effect of exercise on HRV power and on RSA, that LF peak power was positively correlated to $\dot{V}E$ peak power: as in CHF patients during sleep (Leung et al. 2003), the amplitude of RR rises with ventilatory oscillations at mild exercise, in a more pronounced manner in hypoxia. However, this tight relationship was not found in hyperoxic hypercapnia, where large $\dot{V}E$ oscillations were still observed (Hermand et al. 2015a). Further studies are needed to explain this discrepancy, but the potential blunting role of O_2 on HRV, here noticed, overpassing CO_2 activation could be further explored.

The (LF peak power)/(LF power) ratio, illustrating the contribution of peak power on the LF band, indicates that more than a third of LF power is concentrated in the LF peak and remains constant for almost all conditions. This novel and fundamental discovery might explain the origin

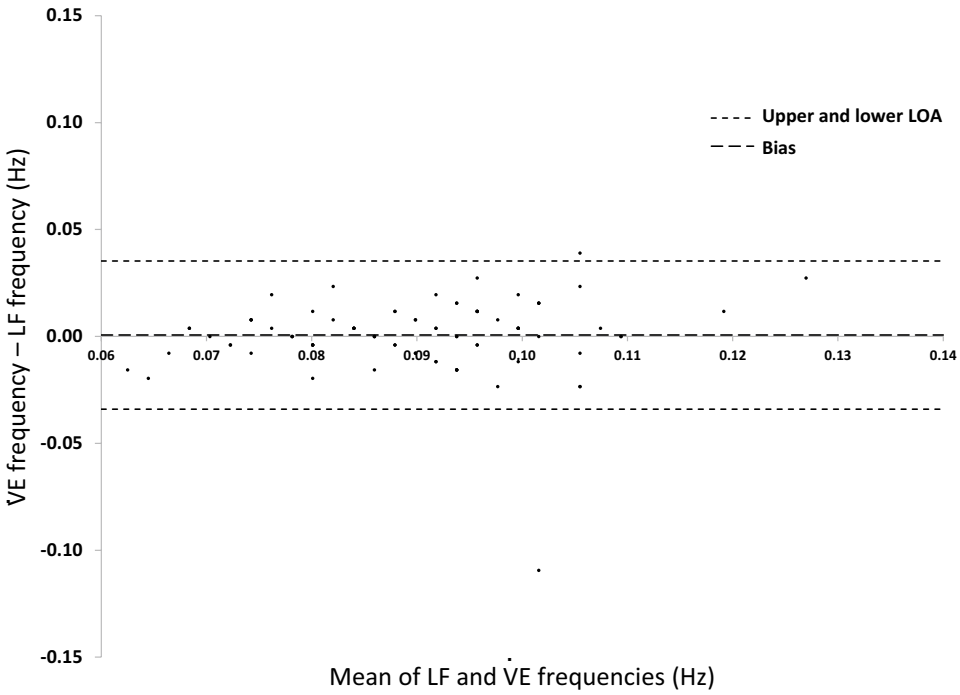

Fig. 3 Bland and Altman plot showing the agreement between LF and $\dot{V}E$ periods during exercise. Bias = 0.00065 Hz, LOA = − 0.034/+ 0.035 Hz. Percentage of data out of LOA: 2.4%

of the power of LF band, between 0.04 and 0.15 Hz, where ventilatory and RR oscillations occur. Only exposure to hypoxia slightly decreased this ratio by 6%, potentially illustrating its sympathetic action on ANS (Liu et al. 2001; Povea et al. 2005), as average LF power might be increased around LF peak.

The physiological origin of HRV oscillations, such as RSA, has been debated for decades. It involves a complex interplay between numerous components: cardiorespiratory rhythm generators, baroreceptor and chemoreceptor activities, cardiac and pulmonary reflexes, mechanical and metabolic factors (Berntson et al. 1993). More precisely, these oscillations reflect the level of harmonization between pulmonary and cardiac rhythms to optimize gas exchange in the lung through the successive intrathoracic inspiration–expiration cycles. As a consequence, in gradual-building Cheyne–Stokes breathing in CHF patients, the succession of apneas–hyperpneas at a 30–60-s period will cause a peak in the VLF spectrum band. The same mechanism may explain our present observations, in much shorter cycles, with a frequency spectrum mainly located in the LF band, around 0.09 Hz.

Breathing rate is known to modify HRV components at the same frequency (Pöyhönen et al. 2004; Aysin and Aysin 2006) but did not play a role in the LF band in our study due to its higher frequency. However, we also found a correlation between ΔLF peak power and ΔVT, according to the previous work (Insalaco et al. 2016), highlighting the key role of tidal volume and, therefore, the role of pulmonary stretch mechanoreceptors, in LF oscillations (Insalaco et al. 2016). Nevertheless, other strong correlations between, on the one hand, ΔLF peak power and ΔT_{tot} and on the other hand, between absolute LF peak power and Ttot cannot rule out a major contribution of breathing frequency, regulated by the cyclic firing of excitatory neurons located in the pre-Bötzinger complex, the central pattern generator (Gauda and Martin 2012). Altogether, these results suggest that the LF band of HRV is greatly influenced by ventilatory oscillations through cardiorespiratory coupling and its effect on the autonomic balance (Akselrod et al. 1981; Pomeranz et al. 1985). Our data corroborate a recent paced-breathing study where a VT-controlled ~ 0.08-Hz periodic breathing in resting subjects induced a greater power in the LF band (Beda et al. 2014). In our work, this phenomenon is not only confirmed at rest but also during exercise in response to various environmental stresses, suggesting that this fundamental respiratory-based mechanism is not affected by physiological demands, at least during mild exercise. This mechanism could be then considered similar to the commonly observed peak in the VLF band in CHF patients (Brack et al. 2012), at the same frequency as periodic breathing, at around 0.03 Hz, complementary to the existing respiratory sinus arrhythmia (Saul et al. 1988; Pinna et al. 1995, 1996), and whose origin was later attributed to periodic breathing (Leung et al. 2003).

In a previous work, $\dot{V}E$ peak power was correlated to ventilatory responses to hypoxia (HVR) and hypercapnia (HcVR) (Hermand et al. 2015b, 2016). We did not find any correlation between LF period or peak power (and other HRV components), and HVR and HcVR, reflecting, respectively, O_2 and CO_2 sensitivities. Hence, the role of central

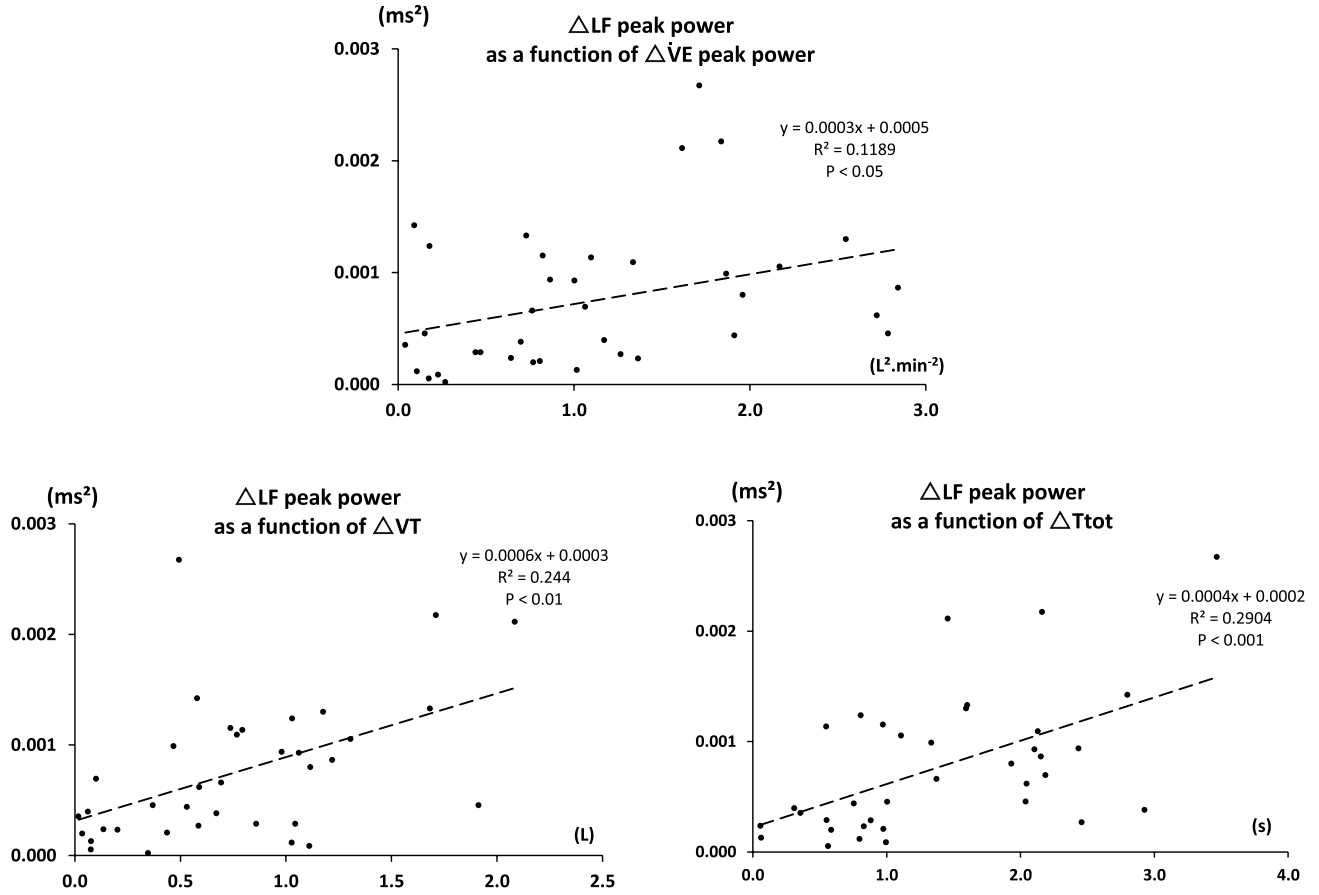

Fig. 4 ΔLF peak power as a function of $\Delta\dot{V}E$ peak power (top), of ΔVT (bottom left) and of ΔT_{tot} (bottom right). $\Delta\dot{V}E$ peak power is the difference between the maximum and the minimum values of $\dot{V}E$ peak power among measured data in various condition (rest/exercise, Nx/Hx/Hox/Hcap, Placebo/ACZ); for each of these two values of $\dot{V}E$ peak power, the corresponding values of LF peak power, VT and T_{tot} were extracted and their respective differences calculated, i.e., ΔLF peak power, ΔVT and ΔT_{tot}

and peripheral chemoreceptors in RR oscillations remains to be confirmed, whereas Siebenmann et al. recently evidenced a tight relationship between vagal activation and arterial chemoreflex (Siebenmann et al. 2018), the latter being involved in the genesis and amplitude of periodic breathing (Hermand et al. 2015b, 2016). Observations in CHF patients also pointed out this link between chemosensitivity and LF power (Ponikowski et al. 1998).

In the light of these data and of our current knowledge, we assume that autonomous cardiac and respiratory systems are linked by RSA in normal conditions, but cyclic patterns unveiled by physiological or pathological stressors tend to synchronize when submitted to conditions such as mild exercise in hypoxia. The ventilatory system is then destabilized, and ANS might modulate cardiac activity to adapt its functioning to breathing, minimizing the feedback of O_2 and CO_2 status. Altogether, any condition leading to breathing instability (hypoxia, exercise, hypercapnia) would promote a "periodic heart beating" synchronized at the same frequency. Observed in both normal subjects and CHF patients, periods of respective cardiac and respiratory oscillations are fundamentally different, much shorter in healthy men exercising in hypoxia. They are not only tightly correlated to the cardiac pump strength but may also rely, in a lesser extent, on a complex interplay between CO_2–O_2 chemoreflexes and respiratory control system.

We did not observe any influence of hypercapnia on HRV, contrary to other studies in normal subjects (Brown and Howden 2008; Brown et al. 2014), and in CHF patients in whom breathing disorders and overall HRV power were blunted by CO_2 inhalation (Leung et al. 2003).

On a side note, studies about the effects of ACZ on HRV spectrum in human are very scarce. An increased vagal tone at high altitude (over 3000 m) was recently observed in ACZ-treated subjects suffering from acute mountain sickness, while apnea–hypopnea index was unexpectedly augmented compared to sea level (Hung et al. 2019), unlike other studies (Richalet et al. 2005). Our data did not

highlight any effect of ACZ on total HRV spectrum, nor in distinct LF/HF band and LF peak power, in healthy subjects.

The main limitation of this work is the independent acquisitions of respective RR and respiratory variables, and the subsequent separate methods of analysis. A synchronized acquisition using a common timescale would have allowed a coherence or cross-spectral analysis for a more accurate assessment of common frequencies between HRV and $\dot{V}E$ peaks (Daoud et al. 2018). Therefore, the causality between periodic breathing and HRV oscillations in the LF band might be considered as speculative.

Further investigations are needed to search complementary parameters to clarify the difference observed between effects of hypoxia and hypercapnia on HRV. Nevertheless, this novel approach highlights a plausible origin for the augmented power in LF band observed in hypoxia, and confirms the tight relationship between autonomous cardiac and respiratory control systems.

Author contributions EH, AP and JPR conceived and designed research. EH, JPR and FL conducted experiments. EH analyzed data. EH wrote the manuscript. All authors read and approved the manuscript.

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