

Low frequency ventilatory oscillations in hypoxia are a major contributor of the low frequency component of heart rate variability Running head: Cardiorespiratory coupling at exercise in hypoxia

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| 4 | Running head: Cardiorespiratory coupling at exercise in hypoxia |
| 5 | |
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| 32 | Abstract |
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| 33 | Purpose |
| 34 | Heart rate variability (HRV) may be influenced by several factors, such as environment (hypoxia, hyperoxia, |
| 35 | hypercapnia) or physiological demand (exercise). In this retrospective study, we tested the hypothesis that inter-beats |
| 36 | (RR) intervals in healthy subjects exercising under various environmental stresses exhibit oscillations at the same |
| 37 | frequency than ventilatory oscillations. |
| 38 | |
| 39 | Methods |
| 40 | Spectra from RR intervals and ventilation (VE) were collected from 37 healthy young male subjects who participated |
| 41 | in five previous studies focused on ventilatory oscillations (or periodic breathing) during exercise in hypoxia, |
| 42 | hyperoxia and hypercapnia. Bland & Altman test and multivariate regressions were then performed to compare |
| 43 | respective frequencies and changes in peak powers of the two signals. |
| 44 | |
| 45 | Results |
| 46 | Fast Fourier analysis of RR and VE signals showed that RR was oscillating at the same frequency than periodic |
| 47 | breathing, i.e. ~0.09 Hz (11 seconds). During exercise, in these various conditions, the difference between minimum |
| 48 | and maximum HRV peak power was positively correlated to the same change in ventilation peak power ($P < 0.05$). |
| 49 | Low Frequency (LF) peak power was correlated to tidal volume ($P < 0.01$) and breathing frequency ($P < 0.001$). |
| 50 | |
| 51 | Conclusions |
| 52 | This study suggests that low frequency ventilatory oscillations in hypoxia are a major contributor of the LF band |
| 53 | power of heart rate variability. |
| 54 | |
| 55 | Key words: |
| 56 | Heart rate variability, Hypoxia, Exercise, Control of ventilation, Periodic breathing |
| 57 | |
| 58 | Clinical Trial Reg. n°: NCT02201875 |
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63 Introduction

64 Submitting a normal subject to physiological or environmental stress, such as exercise and hypoxia, is known to 65 modify cardiorespiratory outputs, such as minute ventilation (VE), but may also alter respiratory pattern. Altitude 66 promotes the genesis of hypopnea / apnea, during sleep and awakeness (Ainslie et al. 2013), which may lead to or 67 worsen, among other altitude-related pathologies, heart failure, pulmonary hypertension, chronic mountain sickness or 68 polycythemia (Richalet et al. 2005; Xu and Jing 2009; Hernandez and Patil 2016). Moreover, concomitant exercise 69 exacerbates ventilatory oscillations (Hermand et al. 2015b): greater VE oscillations are associated with a rise in 70 cardiac output (Qc), which is opposed to observations made in severe chronic heart failure (CHF) patients showing 71 pronounced central or mixed apneas (Corrà et al. 2002; Garde et al. 2009). Likewise, the period of VE oscillations in 72 healthy subjects exercising in hypoxia is about 11 seconds (Hermand et al. 2015b), much shorter than those observed 73 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 (De Burgh Daly 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).
- prognosis of enrolle heart failure (Ouzzetti et al. 2001, Leung and Dradley 2001; Florea and Conn 2014).
- 81 In normal subjects, the effects of environmental stressors and exercise on HRV have been extensively studied. First,
- 82 despite contradictory observations due to variable study conditions, hypoxia generally induces a lower overall HRV
- and a higher heart rate (HR) (Oliveira et al. 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,
- 86 especially LF and HF power (Tulppo et al. 1996).
- 87 However, most studies about environmental and physiological impacts on HRV are focused on the effects on the 88 different bands of HRV spectrum, but temporal relations between periodic breathing (PB) and HRV oscillations did 89 not receive much attention. A deeper knowledge of this specific relationship could help understand the pattern linking
- 90 these two variables, supporting recent observations in healthy subjects exhibiting central sleep apneas during sleep at
- 91 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. 2015b, a, 2017). Hypoxia and hypercapnia at 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 VE oscillations, evidencing a cardiorespiratory coupling at exercise during hypoxia different from respiratory sinus arrythmia (RSA).
- 100
- 101
- 102 Subjects and methods
- 103

104 Subjects

This retrospective study is based upon data retrieved from five previous research protocols including 12 to 14 male subjects each $(27.7 \pm 7.0 \text{ years old}, 175.9 \pm 7.2 \text{ cm}, 73 \pm 11.1 \text{ kg})$ (Hermand et al. 2015b, a). 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.

111

112 **Procedure**

113 All subjects were first asked to perform a standard ramp test protocol on a cycloergometer to determine their maximal 114 aerobic power (MAP) and $\dot{V}O_2max$ (254.5 ± 54.1 W, 52.6 ± 9.3 mL.min⁻¹.kg⁻¹, respectively): after a 3-minute warm-115 up at 60 watts, power output was increased by 30-watt steps every two minutes until voluntary exhaustion, validated 116 by a respiratory quotient above 1.1 and a maximal heart rate within a 10 bpm range of its theoretical value (American 117 College of Sports Medicine et al. 2018). The following protocols are described elsewhere (Hermand et al. 2015b, a). 118 Briefly, several tests were randomly conducted, in normoxia, hypoxia (O₂ 14.5%), hyperoxia (O₂ 100%) and 119 hypercapnic hyperoxia (O₂ 93%, CO₂ 7%); one additional condition was added in the hypoxia protocol where subjects 120 were under ACZ treatment in a double-blind experiment (Hermand et al. 2015a). After 1 min rest for material 121 habituation and stabilization of cardiorespiratory parameters, subjects were first asked to keep a resting sitting position 122 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

123 MAP.

124 VE (L.min⁻¹), tidal volume (VT, L) and heart rate (HR, bpm) were measured breath-by-breath, via a mouthpiece, 125 through an ECG-metabograph (Vmax Encore, SensorMedics, Yorba Linda, CA). Total respiratory cycle time (Ttot, s) 126 and inspiratory time (Ti, s) were derived from the ventilation signal. RR intervals were recorded by a Suunto Memory 127 Belt (Suunto Oy, Vantaa, Finland). Data were transferred to a computer for further variability analysis. The signals 128 stationarities were verified on each interval with a portmanteau test (Ljung-Box test), and were spline-interpolated and 129 resampled to a 1 Hz sample frequency. A Fast Fourier Transform (FFT) was then applied to the breath-by-breath 130 ventilation, extracted from the raw data, of 128-point windows (one point per second) in rest and exercise phases 131 (Olson and Johnson 2014). This method allowed us to detect the presence of peaks in the frequency domain of the 132 ventilation signal (Fig. 1) (Olson and Johnson 2014; Hermand et al. 2015b). Two main parameters were derived from 133 the FFT: the frequency in hertz (or period in seconds) of the larger peak and its power estimated as the area under the 134 peak at \pm 0.02 Hz around the peak (in L².min⁻²). Thus, a high peak power translates into greater ventilatory 135 oscillations.

136 In the same manner, RR data were analyzed with Kubios software (University of Eastern Finland, Kuopio/Finland), 137 which performed a Welch spectral transform (Estévez et al. 2015) to extract the spectral curve (Tarvainen et al. 2014)

138 and its subsequent peaks power, during the 6-min rest and exercise phases. The limits for frequency bands of HRV

139 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

140 measures are computed bands: VLF, LF and HF powers (ms²), LF/HF power ratio, (LF peak power)/(LF power) ratio,

141 and total spectral power. The frequency corresponding to the peak in each band was also assessed. In all conditions,

- 142 the main HRV peak power matched the LF band and we therefore specially studied the LF peak power (ms²), LF peak
- 143 frequency (Hz) and LF period (s). Finally, ventilatory responses to hypoxia and hypercapnia were assessed by a

144 rest/exercise test in normoxia and hypoxia (O₂ 12.5%), and a rebreathing test, respectively, as described before 145 (Duffin 2011; Hermand et al. 2015b).

146

147

148 Statistical analysis

149 Results are presented as mean ± standard deviation. Normality of log-transformed HRV data was verified on each 150 condition (rest/exercise, normoxia / hypoxia / hyperoxia / hypercapnia, placebo/ACZ) by a Shapiro-Wilk test. Thus, 151 according to the studied condition, a two or three-way analysis of variance (ANOVA) with repeated measures was 152 done, including interactions between factors. A post-hoc paired Student's test was used when applicable. As VE and 153 RR signals were acquired independently, in different time scales (breath-by-breath for VE and interbeat intervals for 154 RR), a direct cross-spectral analysis between breath-by-breath signal of VE and RR intervals was not feasible; 155 however, agreement between VE and LF periods was analyzed with Bland-Altman plots (Bland and Altman 1986) 156 where mean difference, standard deviation (SD), and upper and lower limits of agreement (LOA, 1.96×SD) were 157 calculated. As our RR analyses are focused on the LF band, from 0.04 to 0.15 Hz, these limits will define the validity 158 of LOA. Finally, linear and multivariate regressions were carried out to establish potential correlations between LF 159 peak power and period on one hand, and cardiorespiratory parameters on the other hand: VE peak power and period, 160 VE, Ttot, Ti, VT and HR. For this specific analysis, as variability of HRV components might be high between 161 subjects, it is more relevant to investigate variations of cardiorespiratory parameters in one subject successively 162 submitted to various conditions: rest/exercise, normoxia/hyperoxia/hypercapnia or placebo/ACZ. Two 163 conditions are then selected, at maximal and minimal values of VE peak power, i.e. when amplitudes of periodic 164 breathing are the strongest and lowest. The absolute difference between the two values ($\triangle VE$ peak power) is then 165 calculated. For each of these two values, the corresponding other parameters are extracted (LF peak power, VT and 166 Ttot) and their differences computed (\triangle LF peak power, \triangle VT, \triangle Ttot). Regression analysis will point out a 167 correlation between the changes in VE peak power and the variation of LF peak power, VT or Ttot, to assess potential 168 parallel patterns.

- 169
- 170

171 Results

172 Examples of VE and RR signals, and their corresponding spectra are presented in figure 1.

173

174 Effect of exercise vs. rest (fig. 2A)

175 Pooling values of all environmental and pharmacological conditions, exercise depressed all HRV parameters: VLF,

176 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

177 were increased by exercise (not shown, P < 0.05 and P < 0.01, respectively).

178 Exercise decreased LF period (fig. 2B left, P < 0.05) and peak power (fig. 2B right, P < 0.001).

179

180 Effect of hypoxia vs. normoxia (fig. 2C and 2D)

- 181 Hypoxia had no effect on LF period and power, but decreased LF and total powers (fig. 2C, P < 0.05), with a similar
- 182 trend for HF power (P = 0.085). However, at exercise, all power components (VLF, LF, HF) were reduced by hypoxia

- 183 (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
- 184 (not shown, P < 0.01 and P < 0.05, respectively).
- 185

186 Effect of ACZ vs. placebo (fig. 2C and 2D)

- ACZ did not impact any of the studied HRV parameters, although there was a tendency for ACZ to blunt all spectracomponents (fig. 2C).
- 189

190 Effect of hyperoxia and hypercapnia vs. normoxia (fig. 2C an 2D)

- 191 None of the studied HRV parameters were affected by hyperoxia or hypercapnia.
- 192

193 LF and VE periods (fig. 3)

- Mean difference between LF and $\dot{V}E$ periods followed a normal distribution and the Bland & 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
- 196 % of data were out of the 95 % limits of agreement.
- 197

198 Linear and multivariate regression analyses: LF and VE peak powers (fig. 4)

- 199 There was a positive correlation between $\triangle \dot{V}E$ peak power and $\triangle LF$ peak power during exercise (fig. 4 top, P < 200 0.05), indicating that larger $\dot{V}E$ oscillations are associated with larger RR oscillations in the LF band. This relation
- 200 0.05), indicating that harger VI oscillations are associated with harger NK oscillations in the Er band. This relation
- 201 was even tighter in hypoxia (P < 0.01, coefficient 0.0006, not pictured). \triangle LF power was also positively correlated to
- 202 $\triangle VT$ and $\triangle Ttot$ (fig. 4 bottom left and right, P < 0.01 and P < 0.001, respectively)
- 203 Multivariate regression evidenced a strong positive correlation between LF peak power and Ttot (P < 0.001).
- 204

205 Discussion

- This retrospective study completes previous papers on periodic breathing at exercise in hypoxia (Garde et al. 2012; Latshang et al. 2013; Hermand et al. 2015b, a). Our main findings evidenced concomitant oscillations in the LF band of RR signal with VE oscillations (fig. 1) suggesting a strong interplay between ventilatory and cardiovascular adjustments at 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).
- 211 The Bland & Altman analysis (fig. 3) reported a noticeable low bias, inferior to 0.001, which shows that LF and $\dot{V}E$
- 212 periods were deeply intricated and hereby corroborates the hypothesis of tight cardiorespiratory coupling through the
- 213 ANS function. Similarly, LF period was much shorter than the one observed in CHF patients (Pinna et al. 1996),
- following the ~ 1-minute apnea-hyperpnea cycles, but remains similar to VE period (fig. 3), at around 11 seconds (Hermand et al. 2015b). It is equally remarkable to note, despite the overall depressing effect of exercise on HRV
- 216 power and on RSA, that LF peak power was positively correlated to VE peak power: as in CHF patients during sleep
- 217 (Leung et al. 2003), the amplitude of RR rises with ventilatory oscillations at mild exercise, in a more pronounced
- 218 manner in hypoxia. However, this tight relationship was not found in hyperoxic hypercapnia, where large VE
- 219 oscillations were still observed (Hermand et al. 2015a). Further studies are needed to explain this discrepancy, but the
- 220 potential blunting role of O_2 on HRV, here noticed, overpassing CO_2 activation could be further explored.
- 221 The (LF peak power) / (LF power) ratio, illustrating the contribution of peak power on the LF band, indicates that
- 222 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 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.

227 The physiological origin of HRV oscillations, such as RSA, has been debated for decades. It involves a complex 228 interplay between numerous components: cardiorespiratory rhythm generators, baroreceptors and chemoreceptors 229 activities, cardiac and pulmonary reflexes, mechanical and metabolic factors (Berntson et al. 1993). More precisely, 230 these oscillations reflect the level of harmonization between pulmonary and cardiac rhythms in order to optimize gas 231 exchange in the lung through the successive intrathoracic inspiration-expiration cycles. As a consequence, in gradual-232 building Cheyne-Stokes breathing in CHF patients, the succession of apneas-hyperpneas at a 30 to 60 second period 233 will cause a peak in the VLF spectrum band. The same mechanism may explain our present observations, in much 234 shorter cycles, with a frequency spectrum mainly located in the LF band, around 0.09 Hz.

235 Breathing rate is known to modify HRV components at the same frequency (Pöyhönen et al. 2004; Aysin and Aysin 236 2006) but did not play a role in the LF band in our study due to its higher frequency. However, we also found a 237 correlation between \triangle LF peak power and \triangle VT, according to previous work (Insalaco et al. 2016), highlighting the 238 key role of tidal volume, and therefore the role of pulmonary stretch mechanoreceptors, in LF oscillations (Insalaco et 239 al. 2016). Nevertheless, other strong correlations between, on one hand, $\triangle LF$ peak power and $\triangle T$ tot, and on the 240 other hand, between absolute LF peak power and Ttot, cannot rule out a major contribution of breathing frequency, 241 regulated by the cyclic firing of excitatory neurons located in the pre-Bötzinger complex, the central pattern generator 242 (Gauda and Martin 2012). Altogether, these results suggest that the LF band of HRV is greatly influenced by 243 ventilatory oscillations through cardiorespiratory coupling and to its effect on the-autonomic balance (Akselrod et al. 244 1981; Pomeranz et al. 1985). Our data corroborate a recent paced-breathing study where a VT-controlled ~ 0.08 Hz 245 periodic breathing in resting subjects induced a greater power in the LF band (Beda et al. 2014). In our work, this 246 phenomenon is not only confirmed at rest but also during exercise in response to various environmental stresses, 247 suggesting that this fundamental respiratory-based mechanism is not affected by physiological demands, at least 248 during mild exercise. This mechanism could be then considered similar to the commonly observed peak in the VLF 249 band in CHF patients (Brack et al. 2012), at the same frequency as periodic breathing, at around 0.03 Hz, 250 complementary to the existing respiratory sinus arrythmia (Saul et al. 1988; Pinna et al. 1995, 1996), and whose origin 251 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 O₂ and CO₂ sensitivity. Hence, the role of central 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
- 265 CHF patients, periods of respective cardiac and respiratory oscillations are fundamentally different, much shorter in
- healthy men exercising in hypoxia. They are 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.
- 268 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).
- 271 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 3000m) 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
- 275 LF/HF band and LF peak power, in healthy subjects.
- 276 The main limitation of this work is the independent acquisitions of respective RR and respiratory variables, and the
- 277 subsequent separate methods of analysis. A synchronized acquisition using a common time scale would have allowed
- a coherence or cross-spectral analysis for a more accurate assessment of common frequencies between HRV and VE
- 279 peaks (Daoud et al. 2018). Therefore, the causality between periodic breathing and HRV oscillations in the LF band
- 280 might be considered as speculative.
- 281 Further investigations are needed to search complementary parameters to clarify the difference observed between
- 282 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.
- 285

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| 394 CAPT | IONS |
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395

Figure 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 spectrum analysis (bottom) at exercise. A peak is noticeable in both
 spectra at ~0.85 Hz.

399

400 **Figure 2**. Top left (A): means (\pm SD) of HRV power spectral densities in VLF, LF and HF bands, at rest and during 401 mild exercise. Exercise vs Rest: ***, p < 0.001.

- 402 Top right (B). Left: means (\pm SD) of LF period at rest and during mild exercise. Right: means (\pm SD) of LF peak power 403 at rest and during mild exercise. Exercise vs Rest: *, *p* < 0.05; ***, *p* < 0.001
- 404 Bottom left (C): means (\pm SD) of HRV power spectral densities in VLF, LF and HF bands, *at rest*, for several 405 conditions: normoxia (Nx), hypoxia (Hx), hyperoxia (Hox), hypercapnia (Hcap) and acetazolamide (ACZ). Hx vs Nx: 406 +, *p* < 0.05.
- 407 Bottom right (D): means (\pm SD) of HRV power spectral densities in VLF, LF and HF bands *at exercise*, for several 408 conditions: normoxia (Nx), hypoxia (Hx), hyperoxia (Hox), hypercapnia (Hcap) and acetazolamide (ACZ). Hx vs Nx: 409 +, p < 0.05; ++, p < 0.01; +++, p < 0.001;
- 410

411 Figure 3. Bland & Altman plot, showing the agreement between LF and VE periods during exercise. Bias = 0.00065
412 Hz, LOA = -0.034 / + 0.035 Hz. Percentage of data out of LOA: 2.4%

413

414 **Figure 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).

415 $\Delta \dot{V} E$ peak power is the difference between the maximum and the minimum values of $\dot{V} E$ peak power among measured

- 416 data in various condition (rest/exercise, Nx/Hx/Hox/Hcap, Placebo/ACZ); for each of these two values of VE peak
- 417 power, the corresponding values of LF peak power, VT and Ttot were extracted and their respective differences
- 418 calculated, ie ΔLF peak power, ΔVT and ΔT tot.
- 419

420 Abreviations

| 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 |
| РВ | Periodic breathing |
| RR | Interbeat interval |
| SD | Standard deviation |
| Ti | Inspiratory time |
| Ttot | Total respiratory cycle time |
| ΫE | Ventilation |
| VLF | Very low frequency |
| VT | Tidal volume |







430 Fig. 3





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