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ORIGINAL SCIENTIFIC PAPER

Peripheral oxygenation in heart failure patients with periodic breathing: insights from NIRS

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Aims Periodic breathing (PB) is characterized by cyclic fluctuations in ventilation and expired gases. PB is observed at rest or during exercise and is a marker of poor prognosis. In this study, we investigated whether PB affects oxygen availability in peripheral muscles.

Materials and results This pilot, prospective, single-centre study enrolled severe reduced ejection fraction heart failure (HF) patients exhibiting PB. Oxygenated (O_2Hb) and deoxygenated haemoglobin (HHb) in the quadriceps femoralis were measured using near-infrared spectroscopy (NIRS), along with ventilation and expired gases. NIRS and ventilation data were collected at rest and analysed for cyclic patterns. Clinical evaluations, including the cardiopulmonary exercise test (CPET) and echocardiography, were performed. The Metabolic Exercise Combined with Cardiac Kidney Indexes (MECKI) score was used for prognosis evaluation. Twenty HF patients with PB were evaluated. NIRS revealed two distinct periodic behaviours: in 7 patients, O_2Hb and HHb fluctuated in-phase; in 13, they were out-of-phase. In-phase patients had higher left ventricular ejection fraction, lower LV volumes, and lower BNP and soluble interleukin 1 receptor family member ST2 concentrations. Out-of-phase patients had more severe HF, with longer, less variable cycles and a higher MECKI score. Six of 13 out-of-phase patients died within 6 months, compared with 2 of 7 in-phase patients.

Conclusion PB is associated with distinct peripheral oxygenation patterns, potentially representing disease progression stages. In-phase O_2Hb and HHb suggest blood flow cycling, while out-of-phase behaviour suggests periodicity in ventilation/perfusion mismatching. These findings provide novel insights into the dynamic effects of PB on peripheral oxygenation.

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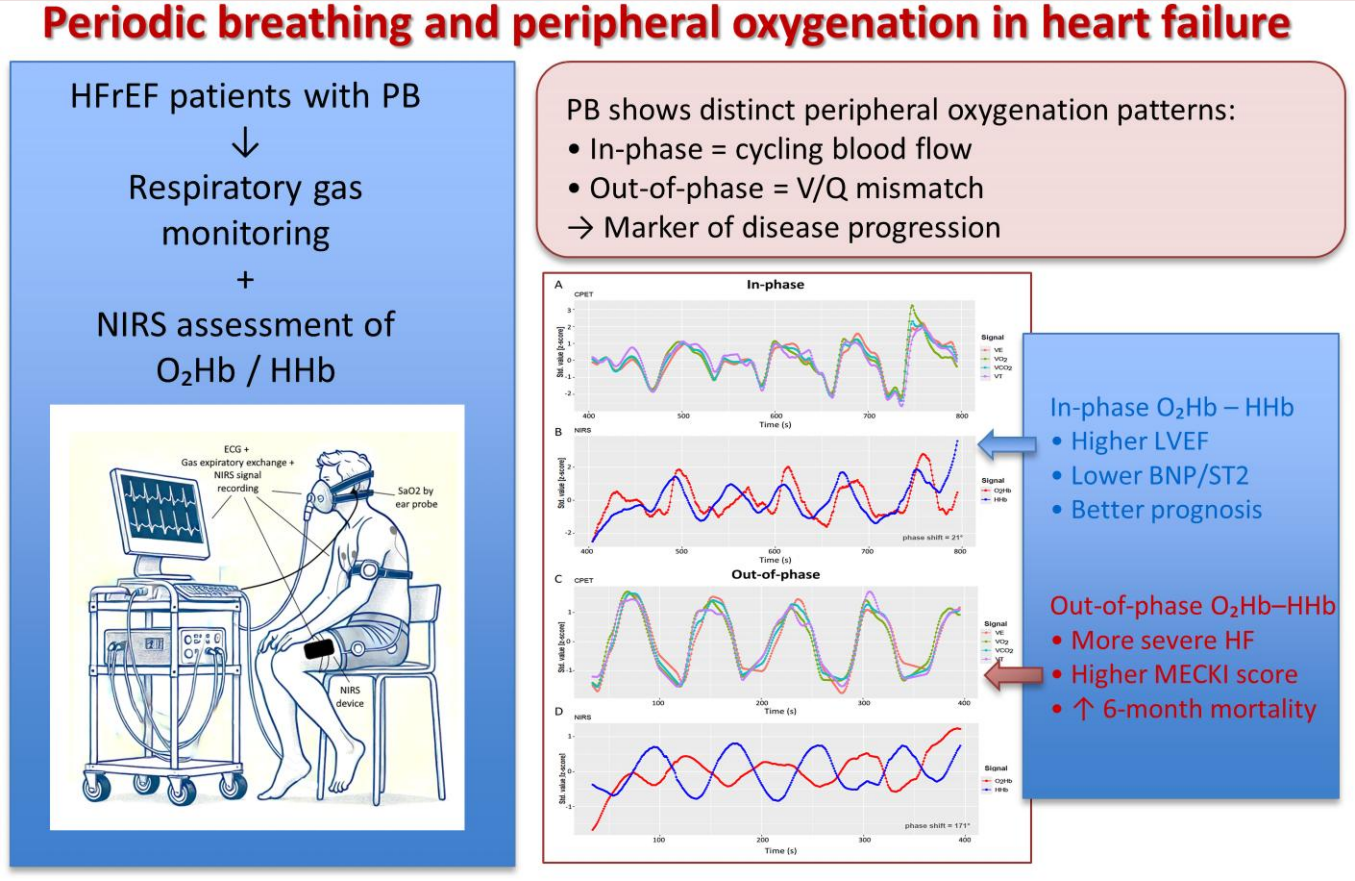
Graphical Abstract



O_2Hb, oxygenated haemoglobin; HHb, deoxygenated haemoglobin; PB, periodic breathing; LVEF, left ventricular ejection fraction

Keywords Heart failure • Periodic breathing • Cardiac output • Peripheral muscles

Introduction

Periodic breathing (PB) is defined as a cyclic fluctuation of minute ventilation ($\dot{V}_E$), oxygen uptake ($\dot{V}O_2$), and carbon dioxide elimination ($\dot{V}CO_2$). PB may be observed either at rest or during exercise in patients and even in healthy subjects.[1,2] Resting and exercise PB are recognized signs of poor prognosis in heart failure (HF).[3] In addition to respiratory fluctuations,[4] it has been suggested that oscillations are present also in blood flow.[5] As regards the genesis of PB, two opposite theories have been proposed, one postulating either the ventilatory control or the circulation as PB *primum movens*.[4–7] At present, it is unknown what happens during PB at the periphery and whether oxygen availability in the muscle undergoes periodic fluctuations. To provide novel insights into peripheral oxygenation dynamics and, potentially, reveal new aspects in the pathophysiology of PB, we measured the relative changes in haemoglobin (Hb) concentration, in both its oxygenated (O_2Hb) and deoxygenated (HHb) forms in patients with severe HF-related PB by near-infrared spectroscopy (NIRS) at rest.

Methods (see also supplemental methods)

This was a pilot, prospective, single-centre study. The primary endpoint of the study was to assess whether PB at rest is associated with distinct peripheral oxygenation patterns at the muscle level, as measured by NIRS.

Study cohort

We enrolled patients with severe HF with reduced ejection fraction (1 with left ventricular assist device, LVAD) and PB at rest. In patients who were able to perform an exercise, a ramp cardiopulmonary exercise test (CPET) was done.

HF severity was assessed by clinical evaluation, echocardiographic data, and biomarkers [brain natriuretic peptide, BNP, and soluble interleukin 1 receptor-like 1 (sST2)].

Prognosis was evaluated by the Metabolic Exercise Combined with Cardiac Kidney Indexes (MECKI) score.[8–10]

Details on methodology and statistical analysis are provided in the Supplemental material.

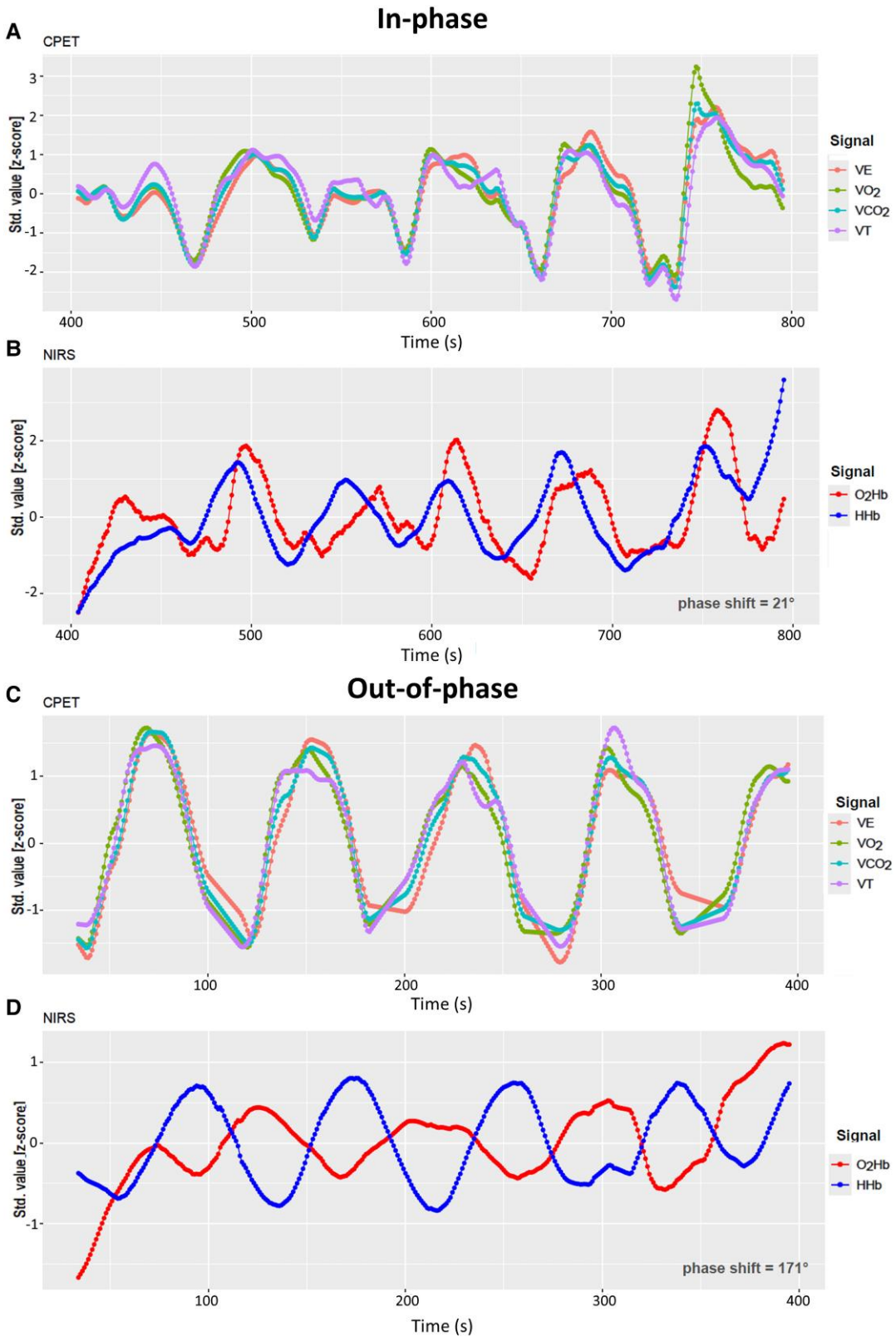


Figure 1 Comparison of cardiopulmonary exercise testing (CPET) and near-infrared spectroscopy (NIRS) signals over time. Panels A and C show the standardized values (z-scores) of two CPET signals over time, including ventilation ($\dot{V}_E$), oxygen uptake ($\dot{V}O_2$), carbon dioxide output ($\dot{V}CO_2$), and tidal volume (TV). The panel B and D present NIRS signals, highlighting changes in oxygenated haemoglobin (O_2Hb) and deoxygenated haemoglobin (HHb). The time axis is presented in seconds, indicating the dynamics of physiological responses during the exercise period between 400 and 800 s. Panels A and B represent a patient with PB and O_2Hb and HHb signals in-phase, whereas panels C and D represent another patient with PB but O_2Hb and HHb signals out-of-phase. Intensity values of signals have been standardized to allow for clear comparisons.

Table 1 Comparison between out-of-phase and in-phase patients

	Out-of-phase (n = 13)				In-phase (n = 7)				P
	n				N				
Age (years)	13	68.8	±	11.8	7	64.0	±	10.4	0.374
Weight (kg)	13	74.4	±	10.7	7	78.9	±	14.0	0.433
Height (cm)	13	175	±	11	7	177	±	7	0.679
BMI (kg/m^2)	13	24.4	±	2.5	7	25.0	±	4.5	0.673
Idiopathic aetiology (n, %)	13	5 (39%)			7	5 (71%)			0.337
Ischaemic aetiology (n, %)	13	7 (53%)			7	2 (29%)			
NYHA II (n, %)	13	1 (8%)			7	2 (29%)			0.386
NYHA III (n, %)	13	9 (69%)			7	3 (43%)			
NYHA IV (n, %)	13	3 (23%)			7	2 (40%)			
LVEF (%)	13	21.5	±	4.4	6	36.2	±	13.7	**0.002**
TDV (ml)	13	291	±	69	6	225	±	66	0.065
TSV (ml)	13	230	±	61	6	150	±	64	**0.018**
PAPS (mmHg)	13	45.9	±	13.3	5	41.6	±	21.8	0.618
SBP (mmhg)	10	95	±	6	6	92	±	13	0.564
DPB (mmhg)	10	60	±	5	6	84	±	41	0.077
HR at rest (bpm)	13	70	±	13	7	69	±	18	0.892
Peak $\dot{V}O_2$ (mL/min)	9	881	±	223	7	1046	±	478	0.372
Peak $\dot{V}O_2$ (mL/min/kg)	9	11.74	±	2.80	7	12.77	±	4.68	0.592
Peak $\dot{V}O_2$ (% pred)	9	41.20	±	10.20	7	45.30	±	16.70	0.547
Peak HR (bpm)	9	101	±	12	7	98	±	9	0.595
Peak load (Watt)	9	72	±	21	7	80	±	41	0.638
Peak pulse (bpm/mL)	9	8.82	±	2.11	7	10.44	±	4.14	0.324
$V_E/\dot{V}CO_2$ slope	9	50.7	±	14.0	7	52.4	±	15.3	0.824
$V_E/\dot{V}CO_2$ slope (%)	8	179	±	39	7	199	±	53	0.432
$\dot{V}O_2$/work slope	8	7.60	±	1.43	7	7.97	±	1.36	0.618
Peak tidal volume (L)	9	1.70	±	0.42	7	1.47	±	0.52	0.329
Respiratory rate (breath/min)	9	33	±	9	7	35	±	7	0.530
VE (l/min)	9	56.1	±	20.5	7	54.6	±	24.7	0.897
RER	9	1.09	±	0.09	7	1.03	±	0.10	0.211
Creatinine (mg/dL)	13	1.27		[1.11–2.22]	7	1.07		[0.98–1.90]	0.832
Sodium (mM)	13	139.4	±	3.5	7	141.0	±	3.0	0.316
Potassium (mM)	13	4.33	±	0.47	7	4.33	±	0.63	0.978
Haemoglobin (mg/dL)	13	13.15	±	2.75	7	14.39	±	1.88	0.304
BNP (pg/mL)	11	1436		[738–33342]	7	231		[189–497]	**0.008**
Nt-BNP (pg/L)	6	7006		[1313–14317]	1	57980			0.286
Ferritin (ng/mL)	13	112	±	78	5	93	±	60	0.316
Transferrin (mg/L)	12	260	±	70	5	237	±	83	0.558
Serum iron (ug/dL)	12	51.4	±	26.5	5	72.0	±	18.6	0.138
Interleukine ST2 (ng/mL)	7	50.3	±	18.7	6	32.7	±	11.2	0.07
MECKI score	9	0.33		[0.19–0.39]	6	0.08		[0.05–0.34]	**0.050**

Values <0.05 are in bold to indicate statistical significance.

NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; VTD, tele-diastolic volume; TDS, tele-systolic volume; PAPs, pulmonary artery pressure; SPB, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; $\dot{V}O_2$, oxygen intake; $\dot{V}CO_2$, carbon dioxide production; VE, minute ventilation; RR, respiratory rate; RER, respiratory exchange ration; BNP, brain natriuretic peptide type B; Nt-BNP, *N*-terminal prohormone of brain natriuretic peptide; MECKI, metabolic exercise test data combined with cardiac and kidney indexes; Interleukine ST2, interleukin-1 receptor family member ST2.

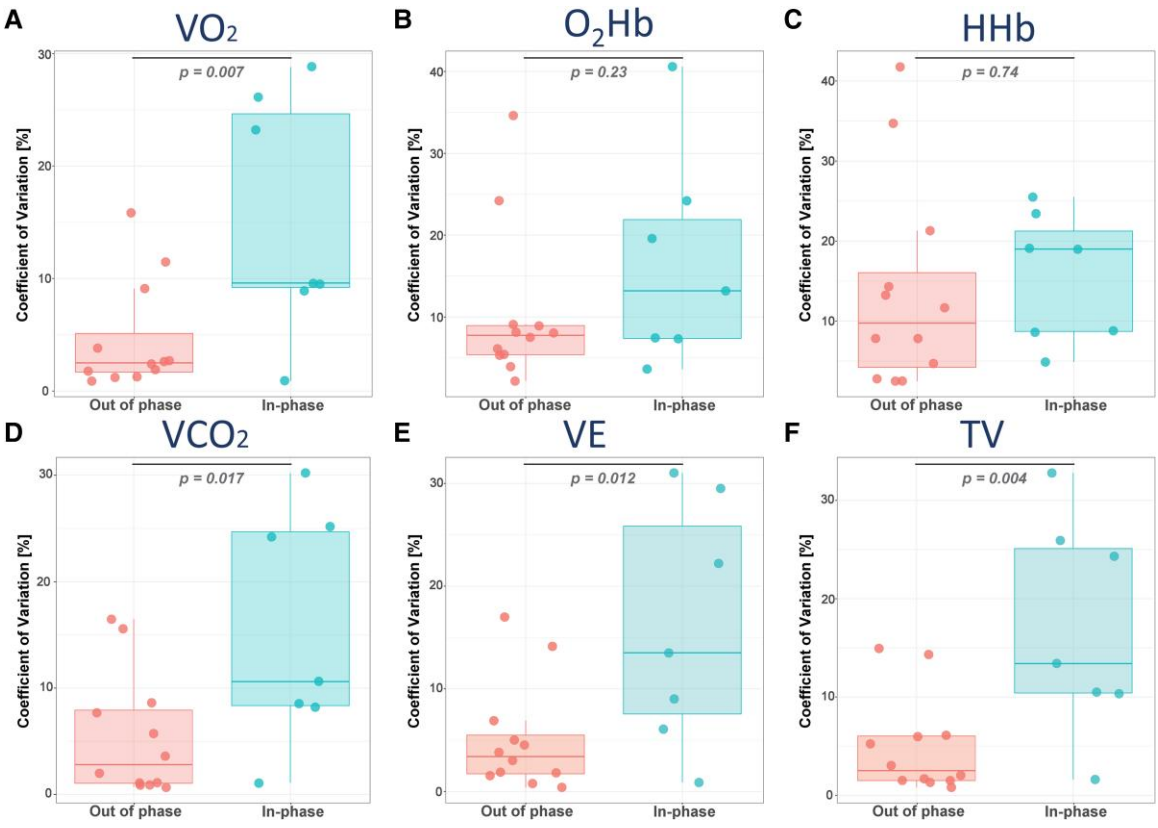


Figure 2 Boxplots representing the coefficient of variation (CV) of cycle duration for VO_2, $\dot{v}CO_2$, $\dot{v}_E$, TV, O_2Hb, and HHb in the out-of-phase and in-phase NIRS categories. Panel A shows a significant increase in cycle duration variability of $\dot{V}O_2$ in the in-phase group compared with the out-of-phase group. On the other hand, in panels B and C, two none significant trends are represented considering cycle duration variability of O_2Hb and HHb, respectively. Similarly, panels D, E, and F show significant differences in cycle variability of $\dot{V}CO_2$, $\dot{V}_E$, and TV. Each point represents a patient, and box plots display the median and interquartile range for each condition, highlighting the distribution and variability of the data. $\dot{V}O_2$, oxygen intake; $\dot{V}CO_2$, carbon dioxide production; O_2Hb, oxygenated haemoglobin; HHb, deoxygenated haemoglobin; $\dot{V}_E$, ventilation; TV, tidal volume.

Results

We considered 28 hospitalized severe HF patients with PB at rest (data in Supplementary material online, *Table S1*). Eight patients were excluded due to poor NIRS signals ($n = 4$) and because PB was no longer detected ($n = 4$). CPET was considered unsafe in four cases.

All 20 patients with PB at rest (two cases in *Figure 1* panel A, C) had a periodic fluctuation of O_2Hb and HHb. Specifically, two distinct behaviours were observed: in seven (35%) patients, the O_2Hb and HHb oscillations were almost synchronized, so that the phase shift was <90° (*Figure 1B*). Conversely, in 13 (65%) cases, O_2Hb and HHb were out-of-phase (*Figure 1D*). NIRS data showed a different zenith or nadir delay between HbO_2 and HHb ($P < 0.0001$) in out-of-phase vs. in-phase cases (see Supplementary material online, *Table S2*). The LVAD patient belongs to the out-of-phase group. In-phase patients had a higher left ventricular ejection fraction (LVEF) and lower LV volumes (*Table 1*) and lower BNP and sST2 values. CPET showed a very poor exercise performance in all the cohort (*Table 1*). PB was observed during CPET in all cases ($n = 16$) and lasted for the entire exercise duration in 5 out of 9 out-of-phase cases and in 4 out of 7 in-phase cases. The MECKI score ($n = 15$) at 2 years was 33% [IQR = (19–39), $n = 9$] and 8% [IQR = (5–34), $n = 6$] in out-of-phase vs. in-phase patients ($P = 0.05$). Forty-six percent of patients in the out-of-phase population died due to worsening HF within 6 months, while 29% of patients in the in-phase population died.

Oscillation length for $\dot{V}_E$, TV, $\dot{V}O_2$, and $\dot{V}CO_2$ is reported in Supplementary material online, *Table S2*. In patients with an in-phase behaviour, cycles were shorter with a significant higher variability compared with out-of-phase patients for $\dot{V}O_2$ and respiratory parameters, while only a trend was observed for O_2Hb and HHb (*Figure 2*, Supplementary material online, *Table S2*). Average amplitude of $\dot{V}_E$ and TV swings were 16.3 ± 6.2 L/min and 761 ± 355 mL/min, with no significant difference between groups. Heart rate periodicity was observed in seven cases (2 in-phase and 5 out-of-phase). Considering the entire study population, strong correlations ($R \geq 0.82$) were observed comparing the cycle length of all the measured variables, particularly for $\dot{V}O_2$ and O_2Hb and $\dot{V}O_2$ and HHb, as well as between O_2Hb and HHb (see Supplementary material online, *Figure S1*).

Discussion

This study shows for the first time that, in patients with HF with PB at rest, a periodicity of O_2Hb and HHb can be observed at the muscle level with two patterns: an in-phase and an out-of-phase pattern, the latter associated with more severe HF.

The two distinct behaviours observed at the muscle level suggest different impacts of HF in PB-related muscle oxygenation. Indeed, the in-phase pattern implies a cycling of total Hb and therefore, likely, of blood flow. This suggests that, at the muscle level, blood flow oscillations are present and must be considered as the main mechanism responsible of O_2Hb and HHb oscillation. In contrast, in the out-of-phase pattern, the zenith and nadir of O_2Hb and HHb cycle differently, so that total Hb did not or only slightly changed during time (see Supplementary material online, *Figure S2*), suggesting a constant blood flow delivered to the muscle but with a time-varying amount of O_2Hb and HHb. Of note, the LVAD patient, in whom oscillations of the blood flow at rest are minor if any, belongs to the out-of-phase group. The most likely explanation of this phenomenon is a $\dot{V}_E$/perfusion mismatch oscillation at the lungs. These data suggest that the in-phase pattern could be mainly related to ventricular interdependence, while the respiratory oscillations are likely responsible for the out-of-phase pattern.

The amplitude of oscillation remains similar, being related to differences in thoracic movement capacity, as suggested by previous studies with added dead volume or with acetazolamide treatment, and not to the mechanisms responsible of PB genesis.[11,12]

Patients with the out-of-phase behaviour had more severe HF as documented by lower LVEF, higher LV volumes, higher BNP and sST2, and CPET in out-of-phase cases. Indeed, the presence of relevant congestion and high filling pressure may be the condition sine qua non of the out-of-phase behaviour, so that low tidal volumes are associated with impaired alveolar gas exchange and high tidal volumes with normoxia. In line with the concept of a higher HF severity in the out-of-phase patients are the MECKI score findings, a recognized tool for assessing prognosis. Altogether these data suggest more severe HF status in patients who showed an out-of-phase behaviour with NIRS; however, it is acknowledged that due to the small sample size, these observations should be taken with caution and require confirmation in larger, multicentre studies.

The duration of cycles was longer and with a lower variability in patients who showed an out-of-phase behaviour, confirming the tight link between respiration and muscle oxygenation cycling. Of note, the lower variability of cycles in out-of-phase cases is suggestive of a more definite cycling. Interestingly, reduced variability in the out-of-phase group may indicate a more rigid and maladaptive feedback loop, consistent with advanced disease. It is unknown how and whether the variation in muscle oxygenation present in the out-of-phase cases could affect *per se* muscle function.

The two PB groups we identified by NIRS behaviour are clearly different with two possible different causes of cycling: circulatory vs. respiratory. However, it is possible to suggest, albeit on a more speculative basis, that the two groups represent different phases, with the out-of-phase cases representing a more advanced stage of HF. Notably, at present it is not possible to define a causality relation between oscillation and HF severity. It is not possible to exclude, however, that in some cases a combination of the two reported mechanisms is present or that other mechanisms are in part responsible of the reported observations.[13,14] As a matter of facts in few out-of-phase cases, a minor oscillation of the total Hb has been observed.

Limitations

- PB is present in different clinical conditions, but we assessed only patients with HFrEF. We do not know how neurological cases or critically ill patients with PB behave as regards muscle oxygenation.
- NIRS data are obtained on a relatively small muscle mass assumed indicative of the entire muscle behaviour.
- We do not know whether similar findings are present in patients with different HF phenotypes, such as HF with preserved ejection fraction, or other conditions, such as obesity.
- LVOT VTI data were not systematically collected; these data should be collected in the future to provide additional haemodynamic insight.
- This study does not allow to evaluate if and how muscle contraction and overall performance is influenced by cycling of peripheral oxygenation.

In conclusion, we showed that PB at rest has two distinct patterns as regards quadriceps muscle oxygenation, an out-of-phase pattern for O_2Hb and HHb, and an in-phase pattern. The former is likely associated with blood flow oscillations and the latter with ventilation/perfusion and respiratory control oscillation during respiration. The out-of-phase path is associated with more severe HF.

Supplementary material

Supplementary material is available at *European Heart Journal: Acute Cardiovascular Care* online.

Author contribution

Elisabetta Salvioni (Data curation, Formal analysis, Validation, Investigation, Visualization, Methodology, Writing—original draft), Mattia Chiesa (Data curation, Formal analysis, Validation, Investigation, Visualization, Methodology, Writing—original draft), Massimo Mapelli (Investigation, Visualization, Methodology, Writing—original draft), Fabiana De Martino (Data curation, Investigation, Validation, Visualization, Writing—review and editing), Gonçalo Cunha (Data curation, Investigation, Validation, Visualization, Writing—review and editing), Irene Mattavelli (Investigation, Validation, Visualization, Writing—review and editing), Jeness Campodonico (Investigation, Validation, Visualization, Writing—review and editing), Anna Apostolo (Investigation, Validation, Visualization, Writing—review and editing), Beatrice Pezzuto (Investigation, Validation, Visualization, Writing—review and editing), Carlo Vignati (Investigation, Validation, Visualization, Writing—review and editing), Pietro Palermo (Investigation, Validation, Visualization, Writing—review and editing), Mauro Contini (Investigation, Validation, Visualization, Writing—review and editing), Paola Gugliandolo (Investigation, Validation, Visualization, Writing—review and editing), Robin Willixhofer (Investigation, Validation, Visualization, Writing—review and editing), Arianna Piotti (Investigation, Validation, Visualization, Writing—review and editing), Rebecca Caputo (Investigation, Validation, Visualization, Writing—review and editing), Erik R. Swenson (Validation, Visualization, Writing—review and editing), and Piergiuseppe Agostoni (Conceptualization, Supervision, Investigation, Validation, Visualization, Writing—original draft, Project administration). All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethical statement

The study was approved by the Ethical Committee of Centro Cardiologico Monzino (Milano, Italy) and registered as CCM 1457-RE 4266. The protocol adheres to the Declaration of Helsinki. All patients signed the informed consent before the study procedures.

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Conflict of interest: none declared.

Data availability

Raw data will be accessible upon reasonable request to Direzione.scientifica@cardiologicomonzino.it at: www.zenodo.org.

Scripts and custom implemented functions are available at https://github.com/BioinfoMonzino/Salvioni_et_al_paper_NIRS_CPET.

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