Microvascular oxygen delivery-to-utilization mismatch at the onset of heavy-intensity exercise in optimally treated patients with CHF

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[1]Pulmonary Function and Clinical Exercise Physiology Unit (SEFICE), Division of Respiratory Diseases, Department of Medicine, Federal University of Sao Paulo (UNIFESP), São Paulo; [2]Division of Cardiology, Department of Medicine, Federal University of Sao Paulo (UNIFESP), São Paulo; and [3]Cardiopulmonary Laboratory, Nucleus of Research in Physical Exercise, Federal University of São Carlos (UFSCar), São Carlos, SP, Brazil

Sperandio PA, Borghi-Silva A, Barroco A, Nery LE, Almeida DR, Neder JA. Microvascular oxygen delivery-to-utilization mismatch at the onset of heavy-intensity exercise in optimally treated patients with CHF. *Am J Physiol Heart Circ Physiol* 297: H1720–H1728, 2009. First published September 4, 2009; doi:10.1152/ajpheart.00596.2009.— Impaired muscle blood flow at the onset of heavy-intensity exercise may transiently reduce microvascular O_2 pressure and decrease the rate of O_2 transfer from capillary to mitochondria in chronic heart failure (CHF). However, advances in the pharmacological treatment of CHF (e.g., angiotensin-converting enzyme inhibitors and third-generation β-blockers) may have improved microvascular O_2 delivery to an extent that intramyocyte metabolic inertia might become the main locus of limitation of O_2 uptake ($\dot{V}O_2$) kinetics. We assessed the rate of change of pulmonary $\dot{V}O_2$ ($\dot{V}O_{2p}$), (estimated) fractional O_2 extraction in the vastus lateralis (~Δ[deoxy-Hb+Mb] by near-infrared spectroscopy), and cardiac output ($\dot{Q}T$) during high-intensity exercise performed to the limit of tolerance (Tlim) in 10 optimally treated sedentary patients (ejection fraction = 29 ± 8%) and 11 controls. Sluggish $\dot{V}O_{2p}$ and $\dot{Q}T$ kinetics in patients were significantly related to lower Tlim values ($P < 0.05$). The dynamics of Δ[deoxy-Hb+Mb], however, were faster in patients than controls [mean response time (MRT) = 15.9 ± 2.0 s vs. 19.0 ± 2.9 s; $P < 0.05$] with a subsequent response "overshoot" being found only in patients (7/10). Moreover, $\tau\dot{V}O_2$/MRT-[deoxy-Hb+Mb] ratio was greater in patients (4.69 ± 1.42 s vs. 2.25 ± 0.77 s; $P < 0.05$) and related to $\dot{Q}T$ kinetics and Tlim ($R = 0.89$ and -0.78, respectively; $P < 0.01$). We conclude that despite the advances in the pharmacological treatment of CHF, disturbances in "central" and "peripheral" circulatory adjustments still play a prominent role in limiting $\dot{V}O_{2p}$ kinetics and tolerance to heavy-intensity exercise in nontrained patients.

blood flow; chronic heart failure; hemodynamics; near-infrared spectroscopy; oxygen consumption

THE TIME COURSE IN WHICH pulmonary oxygen uptake ($\dot{V}O_{2p}$) adapts to dynamic exercise is characteristically slowed in patients with chronic heart failure (CHF) compared with age-matched controls (7, 58, 61). The slowed $\dot{V}O_{2p}$ kinetics (i.e., larger O_2 deficit) lead to greater reliance on O_2-independent pathways for ATP regeneration and accumulation of by-products related to increased muscle fatigability (e.g., inorganic phosphate and H^+) (2, 56). In fact, faster $\dot{V}O_{2p}$ kinetics after selected therapeutic and rehabilitative strategies have been associated with improved exercise tolerance in CHF patients (12, 48, 63), suggesting that amelioration or resolution of the impaired oxidative metabolism at the onset of exercise has important clinical implications (as reviewed in Ref. 1).

It is widely recognized that disturbances in the diffusive and/or convective transport of O_2 to skeletal muscle mitochondria (31, 41) and/or intramyocyte metabolic machinery (9, 25, 26) could explain the slowness of $\dot{V}O_{2p}$ kinetics in patients with cardiopulmonary and metabolic disorders (7, 51, 61). In this context, it can be anticipated that if the increase in muscle microvascular O_2 delivery ($\dot{Q}O_{2mv}$) slows to a greater extent than the rate of change in muscle $\dot{V}O_2$ (as estimated by the kinetics of the "primary" component of $\dot{V}O_{2p}$) (2, 25, 56), fractional O_2 extraction [~changes (Δ) in the deoxygenated hemoglobin + myoglobin ([deoxy-Hb+Mb]) signal by near-infrared (NIR) spectroscopy (NIRS)] would be accelerated in CHF patients (14, 22, 23, 28). Conversely, if the rate of increase in fractional O_2 extraction is slowed in CHF patients at the onset of exercise, this would argue against a predominant role of insufficient $\dot{Q}O_{2mv}$ in limiting $\dot{V}O_2$ kinetics, thereby suggesting that $\dot{V}O_2$ dynamics are limited by a slow activation of intracellular metabolic pathways (9, 25, 26).

The dynamic relationship between $\dot{Q}O_{2mv}$ and O_2 utilization, however, has been to date explored only in animal models with nontreated CHF induced by myocardial infarction (5, 6, 18, 20, 35, 45). By using phosphorescence quenching to obtain intravital measurements of microvascular PO_2 (PO_{2mv}) (59), previous investigators reported that CHF was indeed associated with $\dot{Q}O_{2mv}$-to-$\dot{V}O_2$ mismatching, a finding that was modulated by disease severity (18, 20), fiber typing (5, 45), and senescence (6, 20). However, it is unknown whether these seminal observations are actually applicable to humans with naturally occurring CHF receiving contemporary pharmacological treatment. In fact, the last decades brought about major changes in the treatment paradigms of CHF [e.g., angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin-receptor blockers (ARBs) and β-adrenergic blockers] (17, 32), which might be effective in improving CHF-related endothelial dysfunction (49, 55) and excessive sympathetic and neurohumoral activation (16, 19) with positive consequences on muscle blood flow (52, 55). In fact, combined therapy with ACEIs and ARBs and carvedilol, a β-adrenergic antagonist with vasodilatory properties (α_1-antagonism), is particularly emphasized in clinical guidelines (17, 32). These recommendations were based on the evidence that these drugs might work synergistically to improve left ventricular (LV) ejection fraction and lessen LV remodeling with positive consequences on hospitalizations and

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survival (17, 32, 53). However, the effects of CHF on the dynamics of (estimated) muscle $\dot{Q}_{O_{2mv}}$-to-$\dot{V}_{O_2}$ matching at the onset of exercise in optimally treated humans with naturally occurring forms of the disease remain unknown.

The objective of the present study, therefore, was to investigate the relationship between the dynamics of $\dot{Q}_{O_{2mv}}$ and O_2 utilization at the onset of heavy-intensity exercise in nontrained patients with advanced CHF receiving contemporary pharmacological therapy. We tested the hypothesis that the therapeutic advances in the treatment of CHF (17, 32) might have improved $\dot{Q}_{O_{2mv}}$ to an extent that the slowness of intramyocyte metabolic machinery would become the limiting step of $\dot{V}_{O_{2p}}$ kinetics. For this purpose, we simultaneously assessed the rate of change of $\dot{V}_{O_{2p}}$, Δ[deoxy-Hb+Mb], and cardiac output ($\dot{Q}_T$) during an exercise bout performed above the gas-exchange threshold (GET) to the limit of tolerance (Tlim) in a group of CHF patients and age-matched controls. We reasoned that knowledge of the precise etiological mechanisms leading to the microcirculatory O_2 exchange impairment in CHF is crucial to understanding the mechanisms of exercise intolerance and the planning of effective rehabilitative strategies aimed to decrease its clinical burden in this patient population.

METHODS

Subjects

This was a prospective study involving 10 nonsmoking men recruited from the CHF Outpatients Clinic of our institution and 11 age- and sex-matched controls. Patients had an established diagnosis of CHF for at least 4 yr, three-dimensional echodopplercardiography showing left ventricle ejection fraction (LVEF) < 35%, and New York Heart Association classification scores II–III. The patients have been optimally treated for CHF for at least 3 yr (Table 1) according to the American Heart Association/American College of Cardiology treatment recommendations for stage "C" patients, i.e., reduced LVEF and current or previous symptoms of heart failure (32). No patients had a history of hospitalization or disease exacerbation in this timeframe. Patients were excluded from study if they had clinical and/or functional evidences of obstructive pulmonary disease (forced expiratory volume in 1 s-to-forced vital capacity ratio (< 0.7) anemia ([Hb] < 13 g%), exercise-induced asthma, diabetes mellitus or other metabolic diseases, unstable angina or significant cardiac arrhythmias, and myocardial infarction within the previous 12 mo. To avoid the confounding effects of physical activity on the determinants of $\dot{V}_{O_{2p}}$ kinetics (56), no patient had ever been submitted to cardiovascular rehabilitation. The control group was also carefully selected to recruit subjects who had not take part into any exercise training program in the preceding 5 yr and had no regular physical activity either at work or during leisure time. Subjects were required to be free of chronic pulmonary, cardiovascular, immune, and metabolic diseases. Prior to entering the study all healthy controls were submitted to clinical evaluation and they were screened by pulmonary function tests, analysis of blood biochemistry, electrocardiography, echocardiography, and a stress exercise testing. Study participants gave written, informed consent, and the study protocol was approved by the Institutional Medical Ethics Committee.

Study Protocol

After familiarization, subjects performed a ramp-incremental exercise test (5–10 W/min in patients and 15–20 W/min in controls) to determine parameters of aerobic function during exercise. The difference between $\dot{V}_{O_{2p}}$ at the GET and $\dot{V}_{O_{2p}}$ at peak exercise ($\Delta\dot{V}_{O_{2ppeak\text{-}GET}}$) was determined. On a different day, subjects were submitted to a constant-work-rate exercise test to the Tlim (s) at a $\dot{V}_{O_{2p}}$ equivalent to

Table 1. *Resting and exercise data from healthy subjects and optimally treated patients with CHF*

	Controls, $n = 11$	CHF, $n = 10$
Anthropometrics/demographics		
Age, yr	62.4±5.9	60.9±8.8
Body mass, kg	78.4±15.9	76.9±13.7
Body mass index, kg/m²	23.9±3.8	22.5±4.1
Echocardiography		
Left ventricle ejection fraction, %	59.7±5.0	29.1±8.2*
Drugs		
Diuretics		7
Spironolactone		4
Digitalis		5
Carvedilol		10
ACE inhibitors/AR blockers		10
Incremental exercise		
Power, W	132±19	83±14*
$\dot{V}_{O_{2p}}$, ml/min	1,708±204	1,315±192*
$\dot{V}_{O_{2p}}$, ml·min⁻¹·kg⁻¹	23.1±4.2	15.1±2.8*
$\dot{V}_{O_{2p}}$, % pred	88.9±10.1	53.1±19.4*
$\dot{V}_{O_{2pGET}}$, ml/min	1,080±175	785±128*
HR, bpm	153±12	134±10*
HR, % pred	95.3±4.7	74.1±10.9*
Constant work rate exercise		
Power, W	90±13	58±12*
Time to exercise intolerance, s	495±168*	315±103
$\dot{V}_{O_{2p}}$, ml/min	1,684±181	1,292±200*
HR, bpm	145±10	130±9*
SV, ml	104.3±16.1	80.2±14.3*
$\dot{Q}_T$, l/min	14.8±2.1	9.9±2.4*

Values are means ± SD. CHF, chronic heart failure; ACE, angiotensin-converting enzyme; AR, angiotensin-receptor; $\dot{V}_{O_{2p}}$, pulmonary oxygen uptake; GET, gas-exchange threshold; HR, heart rate; SV, stroke volume; $\dot{Q}_T$, cardiac output. *$P < 0.05$ (nonpaired t-test).

40–50% of the $\Delta\dot{V}_{O_{2ppeak\text{-}GET}}$ [~70–80% peak work rate]. Tlim was defined as the time point at which subjects signaled to stop exercising or could not maintain the required pedaling rate for 10 s despite being encouraged by the investigators. Subjects avoided caffeine, alcohol, or heavy meals before testing.

Measurements

Exercise tests. The tests were performed on an electronically braked cycle ergometer (Corival 400, Lode, The Netherlands) at 60 rpm and they were preceded by an unloaded baseline pedaling at 0 W for 2 min. $\dot{V}_{O_{2p}}$ (ml/min), $\dot{V}_{CO_{2p}}$ (pulmonary carbon dioxide output, ml/min), minute ventilation ($\dot{V}_E$, l/min), and end-tidal partial pressures (PET) for O_2 and CO_2 (mmHg) were measured breath by breath using a computer-based system (CardiO$_2$ System, Medical Graphics). Gas-exchange variables measured during the incremental test were averaged every 15 s. $\dot{V}_{O_{2peak}}$ was defined as the highest value achieved during the test and compared with Brazilian standards (50). Heart rate (HR, bpm) was determined by using the R-R interval from a 12-lead electrocardiogram. Arterial oxyhemoglobin saturation was determined by pulse oximetry (%; POX 010–340, Mediaid) with its analog signal being directed to the system. Subjects were also asked to rate their "shortness of breath" at exercise cessation using the 0–10 Borg's category-ratio scale. The $\dot{V}_{O_{2pGET}}$ was estimated by the gas-exchange method, inspecting visually the inflection point of $\dot{V}_{CO_{2p}}$ with regard to $\dot{V}_{O_{2p}}$ (modified V-slope) and secondarily confirmed by the ventilatory method when $\dot{V}_E/\dot{V}_{O_{2p}}$ and $P_{ET}O_2$ increased while $\dot{V}_E/\dot{V}_{CO_{2p}}$ and $P_{ET}CO_2$ remained stable. The reading was performed independently by two experienced observers without knowledge of other results or subject identities.

Skeletal muscle oxygenation. Skeletal muscle oxygenation profiles of the left vastus lateralis were evaluated with a commercially available NIRS system (Hamamatsu NIRO 200, Hamamatsu Photonics).

The theory of NIRS has been described in detail elsewhere (21). Briefly, one fiber optic bundle carried the NIR light produced by the laser diodes to the tissue of interest while a second fiber optic bundle returned the transmitted light from the tissue to a photon detector in the spectrometer. The intensity of incident and transmitted light were recorded continuously and, along with the relevant specific extinction coefficients, used to measure changes in the oxygenation status of Hb and Mb. A set of optodes was placed on the belly of the vastus lateralis muscle midway between the lateral epicondyle and greater trochanter of the femur. The optodes were housed in an optically dense plastic holder, thus ensuring that the position of the optodes, relative to each other, was fixed and invariant. The optode assembly was secured on the skin surface with tape and then covered with an optically dense, black vinyl sheet, thus minimizing the intrusion of extraneous light and loss of NIR light.

The variables assessed by NIRS are the concentration (denoted by square brackets) of oxygenated, deoxygenated, and total Hb. Among the NIRS variables, several laboratories have adopted the [deoxy-Hb+Mb] signal as the preferred indicator of changes in muscle microvascular oxygenation during exercise (11, 14, 23, 28). The [deoxy-Hb+Mb] response to exercise is then considered a proxy of fractional O_2 extraction in the microcirculation, reflecting the balance between O_2 delivery and utilization. The device used herein did not measure the reduced-scattering of the tissue (36), preventing determination of absolute values of [deoxy-Hb+Mb] (in μM). Therefore, values were recorded as a delta (Δ) from baseline in units of micromolar per centimeter and expressed relative (%) to the amplitude of variation from baseline to the steady state.

Central hemodynamics. $\dot{Q}_T$ (l/min) and stroke volume (SV, liters) were measured noninvasively throughout the constant work rate test by impedance cardiography (PhysioFlow PF-05, Manatec Biomedical). The PhysioFlow device and its methodology have been thoroughly described elsewhere (10). This methodology is different from previously used impedance systems as its algorithm does not require basal thoracic impedance measurement (Z_0). Before each exercise test, the system was autocalibrated taking into consideration age, stature, body mass, and blood pressure values. Signal quality was verified by visualizing the electrocardiography (ECG) tracing and its first derivative (dECG/dt) and the impedance waveform (ΔZ) with its first derivative (dZ/dt). In preliminary experiments the coefficient of variation for changes in $\dot{Q}_T$ and SV during exercise were 3.3 and 4.1%, respectively. In these preliminary trials the changes in $\dot{Q}_T$ measured by impedance cardiography were consistent with those predicted from $\dot{V}O_{2p}$ values using the submaximal $\dot{Q}_T$-$\dot{V}O_{2p}$ relationship described in CHF patients (8).

Kinetics analysis. The breath-by-breath $\dot{V}O_{2p}$, Δ[deoxy-Hb+Mb] and hemodynamic ($\dot{Q}_T$, SV, and HR) data were time aligned to the start of exercise and interpolated second by second. The kinetics of these responses were determined by nonlinear regression using a least square technique (Marquardt-Levenberg, SigmaPlot 10.0, Systat Software). The $\dot{V}O_{2p}$ responses to exercise in the intensity domain used in our investigation are characterized by the presence of a slow component (2, 56). We checked the absence of the onset or emergence of the slow component in the first 180 s after the start of exercise by certifying that the monoexponential fit (*Eq. 1*) did not demonstrate a discernible departure from the measured response profile, i.e., maintenance of the flat profile of the residual plot. If the slow component was not discernible, we opted to fit $\dot{V}O_{2p}$ from 30 s of baseline pedaling to the steady-state value; otherwise, data were fitted from 30 s of baseline pedaling to 180 s after the onset of exercise. For Δ[deoxy-Hb+Mb] kinetics the analyses were conducted on data from 30 s of baseline cycling to the steady-state response to minimize distortion of the curve-fitting seen when longer periods are analyzed. Theoretical (22) and empirical studies (11, 14, 23, 28) suggest that the primary phase of the Δ[deoxy-Hb+Mb] response is complete within this time window.

The model used for fitting the kinetic response of $\dot{V}O_{2p}$ and Δ[deoxy-Hb+Mb] was

$$[Y]_{(t)} = [Y]_{(b)} + A \cdot (1 - e^{-(t-\text{TD})/\tau}) \qquad (1)$$

where b refers to baseline unloaded cycling and A, TD, and τ are the amplitude, time delay, and time constant of the exponential response, respectively. For $\dot{V}O_{2p}$ analysis we deleted the data relative to the cardiodynamic phase, which duration was individually determined according to standard procedures (2). Therefore, $\tau\dot{V}O_{2p}$ represents the time course of the primary component − an estimate of the muscle $\dot{V}O_2$ kinetics (25) (see *Methodological Considerations and Interpretative Issues*). The overall kinetics of Δ[deoxy-Hb+Mb] (~time to reach 63% of the response following the onset of exercise) were determined by the mean response time (MRT = τ + TD). To relate the kinetics of O_2 utilization to the dynamics of (estimated) fractional O_2 extraction, we calculated the ratio $\tau\dot{V}O_{2p}$/MRT-Δ[deoxy-Hb+Mb]. Therefore, the higher this ratio, the faster the Δ[deoxy-Hb+Mb] kinetics in relation to $\dot{V}O_{2p}$ dynamics, suggesting slower adaptation of $\dot{Q}O_{2mv}$ (11). For the hemodynamic data, we opted to calculate the individual half-time ($t_{1/2}$, s) as the low signal-to-noise ratio for SV and $\dot{Q}_T$ precluded an adequate monoexponential fitting in some patients. This parameter was defined as the time in which the physiological response reached half of the difference between 180 s and the onset of exercise (SigmaPlot 10.0). An estimate of MRT was then obtained as $t_{1/2} \times 1.44$.

Based on previous findings with other disease populations (3, 11), we systematically looked at the presence or not of an "overshoot" in Δ[deoxy-Hb+Mb] after the initial "fast" response (see RESULTS). A two-component, monoexponential model was applied to these data:

$$[Y]_{(t)} = [Y]_{(b)} + A_1 \cdot (1 - e^{-(t-\text{TD}_1)/\tau_1}) - A_2 \cdot (1 - e^{-(t-\text{TD}_2)/\tau_2}) \quad (2)$$

where the subscripts 1 and 2 correspond to the two sequential components (upward and downward, respectively). This model was applied to adequately define the duration of the upward component, i.e., TD_2. Considering, however, the uncertainties about the actual physiological meaning of the downward component, only the describing parameters of the upward component were considered for statistical analysis. Assuming that a larger area under the Δ[deoxy-Hb+Mb] overshoot would be conceptually similar to a greater "undershoot" in the $P_{O_{2mv}}$ (22, 23, 57), the former variable was used as an additional index of impaired microvascular O_2 delivery. On preliminary trials, the coefficient of variation for the kinetic parameters of the Δ[deoxy-Hb+Mb] response ranged between 5–11% [1st test − 2nd test mean bias and range: τ = 0.3 s (−0.3 s to 0.8 s) and TD = 0.1 s (−0.4 to 0.5 s)].

Statistical Analysis

Results were summarized as means $\pm$ SD. To contrast between-subject resting and exercise responses, nonpaired t or Mann-Whitney tests were used as appropriate. Pearson's product moment correlation was used to assess the level of association between continuous variables. The level of statistical significance was set at $P < 0.05$ for all tests.

RESULTS

Subject Characteristics and Maximal Exercise Capacity

There were no significant differences on anthropometric attributes in CHF patients vs. age-matched controls (Table 1). Etiology of CHF was mostly nonischemic and patients had severe LV dysfunction at rest. In contrast, peak work rate and peak $\dot{V}O_{2p}$ were only moderately reduced with eight patients being classified as Weber's class II and two patients as class III. The GET was identified in all subjects, and patients had lower $\dot{V}O_{2pGET}$ than controls ($P < 0.05$). Patients showed

impaired chronotropic responses and lower tolerance to constant work-rate exercise (Tlim) compared with controls (Table 1; $P < 0.01$).

Pulmonary Gas Exchange and Cardiovascular Dynamics

The kinetics of $\dot{V}O_{2p}$ and hemodynamic responses were slower in patients than controls (Fig. 1 for $\dot{V}O_{2p}$ and $\dot{Q}T$; Table 2). In a subgroup of subjects in whom the tests were repeated (6 patients and 6 controls), the coefficient of variation for $\tau\dot{V}O_{2p}$ and $t_{1/2}$ $\dot{Q}T$ averaged 8.4 and 9.9%, respectively. Estimated MRT-$\dot{Q}T$ was consistently slower than $\tau\dot{V}O_{2p}$ in both groups ($P < 0.05$) (Fig. 1; Table 1). MRT-HR was particularly impaired in patients compared with controls (CHF-controls/controls $\times$ 100 = 84.7 $\pm$ 32.3% and 34.7 $\pm$ 19.5% for HR and SV responses, respectively). There was a significant relationship between $\tau\dot{V}O_{2p}$ and $t_{1/2}$ $\dot{Q}T$ only in patients ($R = 0.79$); in addition, both variables were related to Tlim in CHF patients ($R = -0.81$ and $R = -0.69$, respectively; $P < 0.05$) but not in controls.

Muscle Oxygenation and Estimated $\dot{Q}O_{2mv}$

The $\Delta[deoxy\text{-}Hb+Mb]$ response displayed a region in which the signal remained stable or decreased transiently with similar duration in both groups (time delay). After this phase, $\Delta[deoxy\text{-}Hb+Mb]$ increased rapidly with a response kinetics that were much faster than the $\dot{V}O_{2p}$ and $\dot{Q}T$ responses in both groups (Figs. 1 and 2; Table 2).

There were substantial differences in the $\Delta[deoxy\text{-}Hb+Mb]$ dynamics in patients vs. controls. Therefore, $\tau\Delta[deoxy\text{-}Hb+Mb]$ (Figs. 1 and 2; Table 2) and MRT-$\Delta[deoxy\text{-}Hb+Mb]$ (Fig. 2) were significantly faster in patients compared with controls ($P < 0.05$). In addition, $\tau\dot{V}O_2/MRT\text{-}\Delta[deoxy\text{-}Hb+Mb]$ was greater in patients (4.69 $\pm$ 1.42 s vs. 2.25 $\pm$ 0.77 s; $P < 0.05$) and an overshoot in the $\Delta[deoxy\text{-}Hb+Mb]$

Table 2. *Kinetic parameters for $\dot{V}O_{2p}$, $\Delta[deoxy\text{-}Hb+Mb]$, and $\dot{Q}T$ by transthoracic impedance in healthy subjects and optimally treated patients with CHF*

	Controls, $n = 11$	CHF, $n = 10$
$\dot{V}O_{2p}$		
Baseline, ml/min	484 $\pm$ 123	409 $\pm$ 108
Amplitude, ml/min	908 $\pm$ 134	584 $\pm$ 149*
τ, s	40.5 $\pm$ 11.3	65.3 $\pm$ 16.7*
TD, s	10.8 $\pm$ 8.7	9.5 $\pm$ 10.1*
$\Delta[deoxy\text{-}Hb+Mb]$		
Baseline, %	0.1 $\pm$ 2.1	−0.4 $\pm$ 1.9
Amplitude, %	96.4 $\pm$ 7.5	114.2 $\pm$ 9.3*
τ, s	9.3 $\pm$ 1.6	5.9 $\pm$ 1.7*
TD, s	10.7 $\pm$ 1.9	10.0 $\pm$ 2.0
$\dot{Q}T$		
Baseline, l/min	6.5 $\pm$ 1.9	4.9 $\pm$ 1.7*
Amplitude, l/min	5.2 $\pm$ 1.5	3.1 $\pm$ 1.3*
$t_{1/2}$, s	40.2 $\pm$ 7.5	70.7 $\pm$ 13.0*

Values are means $\pm$ SD. $\Delta[deoxy\text{-}Hb+Mb]$, changes in deoxy-hemoglobin+myoblobin by near-infrared spectroscopy; TD, time delay; τ, time constant; $t_{1/2}$, half-time. $\Delta[deoxy\text{-}Hb+Mb]$ values expressed relative to steady-state, baseline variation. *$P < 0.05$ (nonpaired t-test).

response was found in 7 of 10 patients but in no control (see Fig. 2 for a representative patient).

There was a significant relationship between $\tau\dot{V}O_2/MRT\text{-}\Delta[deoxy\text{-}Hb+Mb]$ and the area under the overshoot in these patients ($R = 0.74$; $P < 0.05$). Importantly, $\tau\dot{V}O_2/MRT\text{-}\Delta[deoxy\text{-}Hb+Mb]$ was also significantly related to both $t_{1/2}$ $\dot{Q}T$ and Tlim (Fig. 3) in CHF patients.

DISCUSSION

This is the first study, to our knowledge, to investigate whether the dynamic matching of (estimated) $\dot{Q}O_{2mv}$ and $\dot{V}O_2$ at the onset of heavy-intensity exercise is impaired in optimally treated (17, 32) humans with CHF. We found that phase II
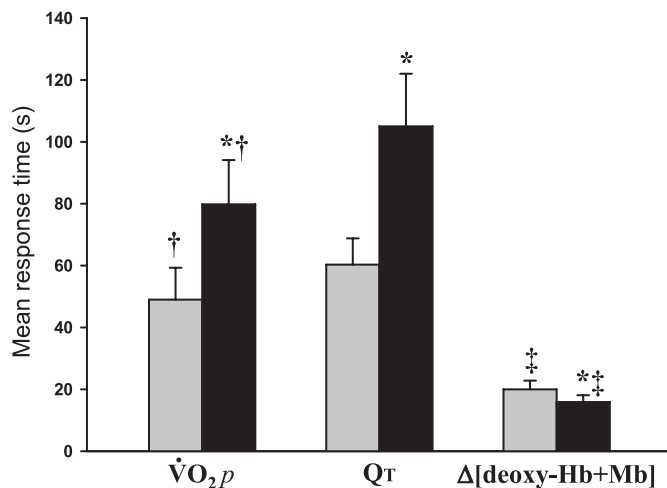

Fig. 1. Mean response time of pulmonary $\dot{V}O_2$ ($\dot{V}O_{2p}$), cardiac output ($\dot{Q}T$), and changes in deoxy-hemoglobin+myoglobin measured by near-infrared spectroscopy ($\Delta[deoxy\text{-}Hb+Mb]$; ~fractional O_2 extraction) at the onset of heavy-intensity exercise in age-matched sedentary controls (shaded bars) and optimally treated patients with chronic heart failure (CHF) (solid bars). Note that the kinetics of $\dot{V}O_{2p}$ and $\dot{Q}T$ were slower in CHF patients; in contrast, patients presented with faster $\Delta[deoxy\text{-}Hb+Mb]$ dynamics compared with healthy controls, suggesting impaired microvascular O_2 delivery. Data are means (SD). *$P < 0.05$ for between-group comparisons; †$P < 0.05$ for within-group comparisons of $\dot{V}O_{2p}$ vs. $\dot{Q}T$; ‡$P < 0.05$ for within-group comparisons of $\Delta[deoxy\text{-}Hb+Mb]$ vs. $\dot{V}O_{2p}$ and $\dot{Q}T$.
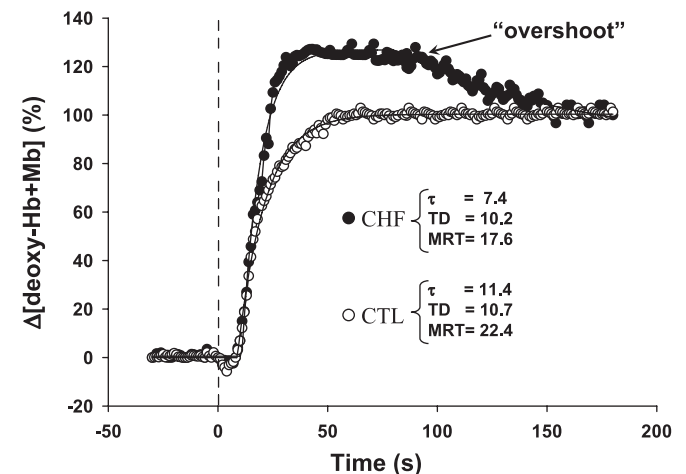

Fig. 2. $\Delta[deoxy\text{-}Hb+Mb]$ at the onset of heavy-intensity exercise in a representative age-matched control (CTL) and an optimally treated patient with CHF. Values are expressed relative to the amplitude of variation from baseline to the steady state. Note the signal "overshoot" after a more rapid rate of change in $\Delta[deoxy\text{-}Hb+Mb]$ [i.e., lower mean response time (MRT = τ + TD)] in the CHF patient, suggesting a faster kinetics of fractional O_2 extraction and impaired microvascular O_2 delivery. TD, time delay; τ, time constant.
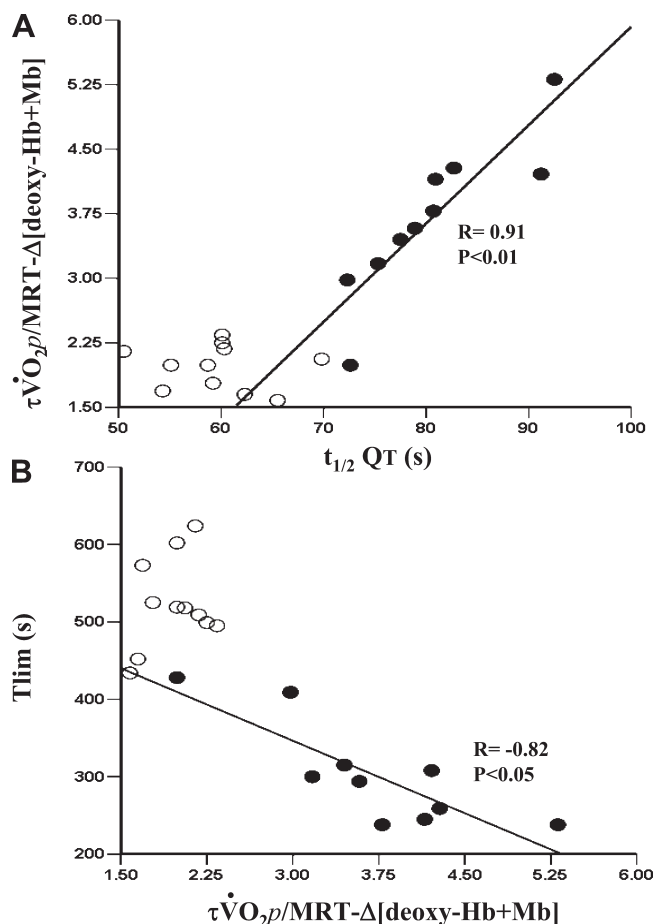
Fig. 3. Relationship between time constant of the "primary" component of the on-transient $\dot{V}O_{2p}$/MRT of Δ[deoxy-Hb+Mb] with the dynamics of $\dot{Q}T$ (A) and time to exercise intolerance (Tlim) (B) in optimally treated patients with CHF (●) and healthy controls (○). These data suggest that the sluggish kinetics of microvascular O_2 delivery have been mechanistically linked to slower "central" cardiovascular adjustments (A) and contributed to decreased exercise tolerance in CHF patients (B).

$\dot{V}O_{2p}$ kinetics were slower in patients than controls and significantly related to decreased exercise tolerance (Tlim). Patients also displayed sluggish kinetics of $\dot{Q}T$ and faster dynamics of fractional O_2 extraction (~Δ[deoxy-Hb+Mb] by NIRS) (11, 14, 23, 28), suggesting impaired adaptation of $\dot{Q}O_{2mv}$. This contention was further supported by the findings of higher values of the $\tau\dot{V}O_{2p}$/MRT-Δ[deoxy-Hb+Mb] ratio in patients, i.e., for a given rate of change in $\dot{V}O_{2p}$, Δ[deoxy-Hb+Mb] adapted more rapidly in patients than controls. Moreover, an overshoot in Δ[deoxy-Hb+Mb] signal was found in 7 of 10 patients but in none of the controls. Importantly, higher $\tau\dot{V}O_{2p}$/MRT-Δ[deoxy-Hb+Mb] values were associated with slower dynamics of $\dot{Q}T$ and shorter Tlim (Fig. 3), suggesting that the slowness of $\dot{Q}O_{2mv}$ kinetics have been mechanistically linked to the sluggish "central" cardiovascular adjustments and contributed to decreased exercise tolerance. These data, therefore, provided evidence that contemporary pharmacological therapy (17, 32) does not preclude that central and "peripheral" circulatory disturbances still play a prominent role in limiting the initial rate of change in the muscle oxidative metabolism and tolerance to high-intensity exercise in humans with CHF.

Mechanisms for Slower $\dot{V}O_{2p}$ Kinetics in Humans With CHF

It has long been demonstrated that the dynamics of $\dot{V}O_{2p}$ are slowed in patients with CHF (7, 61) and related to a number of clinical and functional outcomes (1, 12, 48, 63). In this context, derangements of convective and diffusive O_2 delivery to mitochondria (i.e., O_2 transport) and/or impaired muscle utilization (i.e., intramyocyte metabolic inertia) may account for the prolonged $\dot{V}O_{2p}$ kinetics (56). Potential mechanisms leading to impaired O_2 delivery include the central hemodynamic effects of CHF (46, 62), heightened neurohumoral activation (16, 49), impaired nitric oxide- (24) and endothelium-dependent (4) vasodilation, and/or impaired blood flow redistribution from the nonexercising tissues to the exercising muscles (47).

Conversely, CHF is also associated with profound bioenergetic disturbances in the skeletal muscles that could also limit the rate of increase in $\dot{V}O_{2p}$ (15). For instance, $\dot{V}O_{2p}$ kinetics are not always accelerated in heart transplant recipients (39) and remain abnormal during small muscle mass exercise in which the central cardiovascular constraints are no longer operative (33). In addition, increased $\dot{Q}T$ after cardiac reinnervation has not been consistently associated with faster $\dot{V}O_{2p}$ kinetics (43). Further evidence for a relevant role of intramuscular factors was provided by Zelis et al. (66), who found slower rates of NIRS-measured muscle deoxygenation during arterial occlusion in patients with severe CHF and by the findings of Diederich et al. (18) and Behnke et al. (6), who described slower, rather than faster, rates of decrease in PO_{2mv} in rat with severe vs. moderate CHF.

In the clinical context, this issue is further complicated by the potential effects of contemporary pharmacological treatment of CHF on the main determinants of O_2 delivery in patients with CHF. More specifically, ACEIs and ARBs plus β-blockers have been found to be effective in improving CHF-related endothelial dysfunction (49, 55) and reduce excessive sympathetic outflow to the limbs (16, 19) with positive effects on muscle blood flow (52, 55). Collectively, these data might indicate that such improvements in CHF treatment may have enhanced the dynamics of muscle O_2 delivery to an extent that intramuscular metabolic inertia would become the main factor limiting $\dot{V}O_{2p}$ kinetics. Several variables measured and estimated in our study suggest that this may not be the case during exercise of heavy intensity in nontrained men with stable CHF.

Microvascular O_2 Delivery During Exercise in CHF

Our data demonstrated that CHF patients showed faster kinetics of muscle microvascular fractional O_2 extraction (as estimated by Δ[deoxy-Hb+Mb]) and slower kinetics of phase II than controls, suggesting that $\dot{Q}O_{2mv}$ adapted at a slower rate in patients (14, 22, 23, 28). Moreover, the ratio $\tau\dot{V}O_{2p}$/MRT-Δ[deoxy-Hb+Mb] was closely related to the overall kinetics of central cardiovascular adjustments and exercise tolerance (Fig. 3). These results are of particular clinical relevance because the patients have been therapeutically optimized for at least 3 yr (17, 32) and the confounding effects of training status and comorbidities (such as anemia and diabetes) have been carefully avoided. It is appropriate, however, to point out that the order of speed of responses was similar in patients and controls, i.e., Δ[deoxy-Hb+Mb], $\dot{V}O_{2p}$, and $\dot{Q}T$ (Fig. 1). Consequently, it is conceivable that insufficient rates of muscle O_2

delivery also limited the rate of increase in $\dot{V}O_2$, albeit in a lesser extent, in our middle-aged to aged controls (6, 20).

NIRS is a noninvasive technique that allows continuous measurement of key determinants of peripheral muscle oxygenation during exercise (21). The time course of Δ[deoxy-Hb+Mb] in particular reflects the local balance between O_2 delivery and uptake in the area under investigation (14, 22, 23, 28). Several studies have shown that Δ[deoxy-Hb+Mb] provides a surrogate of fractional O_2 extraction (see *Methodological Considerations and Interpretative Issues*), and its measurement in parallel with (muscle) phase II $\dot{V}O_{2p}$ kinetics can give useful inferences regarding $\dot{Q}O_{2mv}$ via the Fick principle (14, 22, 23, 28). In this context, it is widely recognized that the muscle hemodynamic response at the onset of exercise is characterized by a fast "phase I" response related to the mechanical effect of muscle contraction (i.e., muscle pump) and, probably, rapid vasodilation and a slower "phase II" matched with metabolic demand, resulting from metabolic feedback control (60). In contrast, muscle $\dot{V}O_2$ response appears to be well characterized by a single monoexponential function from the start of exercise (2). Therefore, the resulting response of fractional O_2 extraction ($\sim\Delta$[deoxy-Hb+Mb]) encompass an early delay where O_2 delivery meets (or exceeds) demand (TD) and a rapidly increasing response when the dynamics of capillary flow blood is slower than the rate of change in O_2 utilization (57). In this construct, the overall Δ[deoxy-Hb+Mb] kinetics are expected to be inversely related to the dynamics of $\dot{Q}O_{2mv}$ (14, 22, 23, 28).

In the present study, CHF patients showed faster overall Δ[deoxy-Hb+Mb] kinetics (i.e., lower MRT values) due to a more rapid rates of change (τ) despite unaltered TD values. Consequently, it seems that the phase II of microvascular blood flow has been particularly impaired in our patients (22, 23). In line with this notion, we observed a transient overshoot in the Δ[deoxy-Hb+Mb] response after the initial "fast" response in most CHF patients (Fig. 2), suggesting that estimated fractional O_2 extraction increased above the steady-state level because of impaired muscle blood flow relative to $\dot{V}O_2$ (3, 22, 23, 57). Interestingly, this pattern of response is qualitatively similar to the undershoot in the capillary PO_2 responses previously observed in the exercising muscle of diabetic (54) and CHF animals (5, 6, 18, 35) and identical to the Δ[deoxy-Hb+Mb] profiles described in patients with Type 2 diabetes (3) and chronic obstructive pulmonary disease (11). This specific pattern of response is thought to be related to a transient lowering of capillary PO_2 that seems to be large enough to reduce the diffusion gradient from capillary to mitochondria thereby impairing O_2 flux and constraining the rate of increase in muscle $\dot{V}O_2$ (22, 23, 57).

Our results add novel information to previous studies that used NIRS-based measurements during incremental (65) or small muscle mass exercise (44) in patients with CHF. In fact, the single study that has looked at the kinetics of Δ[deoxy-Hb+Mb] at the onset of moderate-intensity exercise (40) evaluated CHF patients after heart transplantation. Interestingly, these authors did not find significant differences in Δ[deoxy-Hb+Mb] kinetics in recipients vs. normal controls, despite slower $\dot{V}O_{2p}$ kinetics in patients (40). These findings suggest that the metabolic abnormalities in the skeletal muscles were the main mechanism leading to slower $\dot{V}O_{2p}$ kinetics in their subjects which is at marked variance with the present

findings in less severe patients. Conversely, our data are consistent with previous animal studies that suggest that the behavior of PO_{2mv} (and, conceivably, Δ[deoxy-Hb+Mb] on the inverse direction) is critically influenced by disease severity in rats with CHF, i.e., faster PO_{2mv} kinetics associated with a signal undershoot in moderate CHF and slower PO_{2mv} dynamics without undershoots in more advanced CHF (6, 18). These findings were interpreted as evidence that severe CHF has been associated with proportional impairments in $\dot{Q}O_{2mv}$ and muscle oxidative metabolism with the net effect being slower rather than faster rates of change in PO_{2mv} (6, 18).

There are several putative explanations by the persistently abnormal $\dot{Q}O_{2mv}$ kinetics at the onset of exercise despite optimal medical therapy. Firstly, $\dot{Q}_T$ kinetics were significantly slower in CHF patients than controls (Fig. 1, Table 2). In this context, the strong cardiac β_2-blocking effect of carvedilol was likely to be instrumental (19) because MRT-HR was $\sim$80% lower in patients than controls. A study with "old," nonselective β-blockers did find a slowing effect on-exercise $\dot{V}O_{2p}$ kinetics (30), and Guazzi and Agostoni (29) reported that carvedilol failed to accelerate $\dot{V}O_{2p}$ kinetics in moderately impaired patients with CHF. In fact, despite positive effects on mortality (53), most of the large randomized controlled trials actually failed to demonstrate a significant effect of newer β-blockers upon submaximal exercise tolerance (19). The positive effects of carvedilol-related α-adrenergic blockade on vascular tone might have also vanished over time (37). Noteworthy, patients' therapy had been optimized according to current clinical guidelines (17, 32) that do not include a formal assessment of pulmonary gas-exchange kinetics to titrate the prescribed doses of medication. Consequently, we cannot rule out that would be necessary higher doses of ACEIs and ARBs to counterbalance the potentially deleterious effects of β-blockade in the $\dot{Q}O_{2mv}$ dynamics at the on-exercise transient. Secondly, despite potential improvements in central cardiovascular performance, pharmacological treatment may have failed to ameliorate the impairment in muscle microvascular function in CHF (49, 55). In fact, a recent study combining NIRS and ^{31}P magnetic resonance spectroscopy found that the recovery kinetics of [deoxy-Hb+Mb] were slower than that of phosphocreatine after single-leg extension exercise in well-treated New York Heart Association class II–III patients (34). These findings suggest that impaired microvascular function might have contributed to limit muscle O_2 availability because the exercise paradigm was not associated with substantial increases in the central cardiovascular demands. Finally, patients were submitted to supra-GET exercise, thereby predisposing $\dot{V}O_{2p}$ kinetics to be delivery limited (56). However, this exercise intensity domain was deemed the most adequate to test the main study hypothesis since it would pose a higher-than-usual burden to the cardiovascular system under treatment. In fact, despite the exercise test has been performed at submaximal intensities, $\dot{V}O_{2p}$ at Tlim was quite similar to peak $\dot{V}O_{2p}$ (Table 1), suggesting the development of a marker of heavy-intensity exercise, i.e., the $\dot{V}O_{2p}$ "slow" component (56).

Methodological Considerations and Interpretative Issues

Because of the cross-sectional and noninvasive nature of the present investigation, several methodological and interpreta-

tive aspects merit further clarification. We, like others (14, 22, 23, 28), assumed that the kinetics of Δ[deoxy-Hb+Mb] measured at a single site reflects the time course of muscle fractional O_2 extraction following the onset of exercise. However, there exists substantial heterogeneity on the distribution of muscle blood flow and $\dot{V}o_2$ (36) that might be more relevant in the poorly perfused muscles of CHF patients. Consequently, it is unlikely that a single-site evaluation provides a full depiction of the complete range of individual intramuscular $\dot{Q}o_{2mv}$-to-$\dot{V}o_2$ relationships. It should also be acknowledged that the lowering effect of CHF on capillary O_2 driving pressure is less prominent in fast- rather than slow-twitch fibers (5). Considering the higher proportion of fast-twitch fibers in the quadriceps of the elderly (6) and patients with CHF (5), we may have underestimated the speeding effect of CHF on the rate of increase in muscle fractional O_2 extraction.

A key argument in favor of the Δ[deoxy-Hb+Mb] response as a noninvasive surrogate of fractional O_2 extraction dynamics is the similar characteristics of Δ[deoxy-Hb+Mb] changes compared with fractional O_2 extraction dynamics calculated in computer simulations (23) and measured in skeletal muscles (27). However, no previous study has confirmed these assumptions in patients with CHF. Another point of concern is the potential interpopulation differences in the relative contribution of Mb to the Δ[deoxy-Hb+Mb] signal (42, 64), which might have also impacted on the magnitude and rate of change in muscle deoxygenation. In this context, Lai et al. (38), using a systems biology approach, reported that the Mb contribution to the whole NIRS signal is particularly relevant during hypoxia compared with normoxia. Assuming that the skeletal muscles contract under more hypoxic conditions in CHF patients than healthy controls, we cannot rule out that the Mb contribution to Δ[deoxy-Hb+Mb] was higher in patients. However, Mb has lower P_{50} values than Hb, an effect that would tend to slow, not accelerate (Table 2, Fig. 2), the rate of muscle deoxygenation in the CHF patients.

We used the kinetics of the primary component of $\dot{V}o_{2p}$ response as an indicator of the muscle $\dot{V}o_2$ response (2, 25). However, it should be acknowledged that the fitting of a single exponential, though statistically justifiable, is not evidence of similar metabolic mechanisms in the two populations, especially during heavy-intensity exercise. More specifically, it is unlikely that the relative contribution of anaerobic glycolysis to ATP regeneration was equivalent in patients and controls (56). We also recognize that slowing of muscle blood flow may create a temporal dissociation between muscle and pulmonary $\dot{V}o_2$ kinetics, with the $\dot{V}o_{2p}$ response becoming faster than the muscle $\dot{V}o_2$ dynamics because of changes in the leg-to-lung transit delay (2). Accordingly, we may have underestimated the slowness of muscle $\dot{V}o_2$ kinetics in CHF patients performing heavy-intensity exercise. Our investigative approach, therefore, used noninvasive methods and was based on several assumptions; consequently, we could only infer the rate of muscle O_2 delivery.

There are some clinical considerations that should be stressed to avoid a widespread extrapolation of our results. Several investigators reported that the likelihood of severe intramyocyte disturbances is increased in patients with end-stage disease (33, 40) and rats with severe CHF (6, 18). Considering that our patients were only moderately impaired (despite severe LV dysfunction by echodopplercardiography)

(Table 1), it remains to be tested whether the present results hold true for humans with more advanced disease. However, our sedentary patients had never been submitted to cardiac rehabilitation, predisposing them to severe impairment in muscle oxidative metabolism. We also admit that the response overshoot in Δ[deoxy-Hb+Mb] (or P_{O2mv} undershoot) is more likely to be found in older subjects (6, 20) than those evaluated in the present study (Table 1). Therefore, our results should be viewed under the perspective that the aging process underlies the behavior of Δ[deoxy-Hb+Mb] and $\dot{V}o_{2p}$ in both groups and further studies are warranted to confirm the present findings in younger CHF patients. In relation to the fitting approach to Δ[deoxy-Hb+Mb] overshoot, it needs to be stressed that a single monoexponential model was used merely for convenience of comparisons and a higher-order model might have better described the observed response profile (Fig. 2).

According to current guidelines, no patient in the present study had clinical indication for resynchronization therapy or LV assist device; nevertheless, it remains to be tested whether the add-on therapy with these nonpharmacological strategies would positively impact on (estimated) $\dot{Q}o_{2mv}$ kinetics. Finally, care should be taken to extrapolate our results for patients with CHF secondary to ischemic heart disease since CHF etiology may impact on the determinants of exercise tolerance in this patient population (13).

Conclusions

The dynamic matching between O_2 delivery to, and O_2 uptake by, the peripheral muscles is significantly impaired at the transition to heavy-intensity exercise in patients with CHF who had been adequately treated with the best-available pharmacological therapy. These abnormalities are closely related to the derangements on the central cardiovascular adjustments to exertion. Our data, therefore, indicate that despite the remarkable advances in clinical management of CHF, disturbances in the cardiocirculatory responses still play a prominent role in limiting $\dot{V}o_{2p}$ kinetics and tolerance to heavy-intensity exercise in humans with naturally occurring forms of the disease.

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