The relation between cardiac output kinetics and skeletal muscle oxygenation during moderate exercise in moderately impaired patients with chronic heart failure

Ruud F. Spee,[1,5] **Victor M. Niemeijer,**[1] **Thijs Schoots,**[1] **Pieter F. Wijn,**[2,3] **Pieter A. Doevendans,**[4,5] **and Hareld M. Kemps**[1]

[1]*Department of Cardiology, Máxima Medical Centre Veldhoven, The Netherlands;* [2]*Department of Clinical Physics and Clinical Informatics, Máxima Medical Centre Veldhoven, The Netherlands;* [3]*Department of Applied Physics, Eindhoven University of Technology, Eindhoven, The Netherlands;* [4]*Department of Cardiology, University Medical Centre Utrecht, the Netherlands; and* [5]*ICIN, Netherlands Heart Institute, Utrecht, The Netherlands*

Spee RF, Niemeijer VM, Schoots T, Wijn PF, Doevendans PA, Kemps HM. The relation between cardiac output kinetics and skeletal muscle oxygenation during moderate exercise in moderately impaired patients with chronic heart failure. *J Appl Physiol* 121: 198–204, 2016. First published June 9, 2016; doi:10.1152/japplphysiol.00079.2016.— Oxygen uptake ($\dot{V}O_2$) kinetics are prolonged in patients with chronic heart failure (CHF). This may be caused by impaired oxygen delivery or skeletal muscle derangements. We investigated whether impaired cardiac output ($\dot{Q}$) kinetics limit skeletal muscle oxygen delivery relative to the metabolic demands at submaximal exercise in CHF patients by evaluating the relation between $\dot{Q}$ kinetics and skeletal muscle deoxygenation. Forty-three CHF patients, NYHA II-III, performed a constant-load exercise test at 80% of the ventilatory aerobic threshold (VAT) to assess $\dot{V}O_2$ kinetics ($\tau\dot{V}O_2$). $\dot{Q}$ kinetics ($\tau\dot{Q}$) were assessed by a radial artery pulse contour analysis method. Skeletal muscle deoxygenation was assessed by near infrared spectroscopy at the m. vastus lateralis, using the minimal value of the tissue saturation index during onset of exercise (TSI_{min}). Patients were categorized in slow and normal $\dot{Q}$ responders relative to metabolic demands ($\tau\dot{Q}/\dot{V}O_2 \geq 1$ and $\tau\dot{Q}/\dot{V}O_2 < 1$, respectively), $\tau\dot{Q}$ (62 ± 29 s), and $\tau\dot{V}O_2$ (60 ± 21 s) were significantly related ($r = 0.66$, $P = 0.001$). There was a significant correlation between $\tau\dot{Q}$ and TSI_{min} in the slow $\dot{Q}$ responders [$r_s = -0.57$, $P = 0.005$, $n = 22$ (51%)]. In conclusion, in moderately impaired CHF patients with relatively slow $\dot{Q}$ kinetics, central hemodynamics may limit skeletal muscle oxygenation during moderate-intensity exercise.

chronic heart failure; oxygen uptake kinetics; cardiac output kinetics; skeletal muscle oxygenation

NEW & NOTEWORTHY

This study extends current understanding of limitations of oxygen uptake kinetics during moderate exercise in patients with chronic heart failure (CHF) by using simultaneous measurements of cardiac output, skeletal muscle oxygenation, and pulmonary oxygen uptake. In our study, half of the patients showed slow $\dot{Q}$ kinetics relative to the metabolic demands. In this group, $\dot{Q}$ kinetics were related to the degree of skeletal muscle deoxygenation, suggesting that central hemodynamics may limit submaximal exercise performance in a substantial subset of moderately impaired CHF patients.

PATIENTS WITH CHRONIC HEART failure (CHF) suffer from fatigue and impaired exercise tolerance. These symptoms are particu-

larly experienced during daily life, which mainly consists of repetitive submaximal activities. Previous studies in CHF patients have indeed shown that oxygen uptake kinetics are prolonged, compared with healthy individuals (19, 39). Therefore, assessment of oxygen uptake kinetics as a measure for submaximal exercise is particularly indicative of the functional capacity and prognosis of CHF patients (38).

From a clinical point of view, detailed knowledge on the pathophysiological mechanisms underlying impairments of submaximal oxygen uptake kinetics in individual CHF patients is important for tailoring of treatments and for development of new therapeutic strategies. Currently, however, there is still an on going debate whether oxygen uptake kinetics in CHF are primarily limited by central and/or microvascular oxygen delivery or intrinsic oxidative capacity of the skeletal muscle (34, 35). Whereas some studies showed that the inability to increase oxygen uptake during submaximal exercise was related to an impaired cardiac output ($\dot{Q}$) response (19, 25, 29), other studies found an impaired skeletal muscle function to be related to the reduced submaximal exercise capacity (6, 16). A possible explanation for these seemingly conflicting results may be that central and peripheral measurements were not performed simultaneously in these studies, making it difficult to distinguish the main limiting factor. Another explanation may be that physiological heterogeneity exists between different CHF subgroups. Recent animal studies showed that submaximal exercise capacity is only limited by oxygen delivery when microvascular oxygen pressure (Pmv_{O_2}) during exercise falls below a critical level at which oxygen diffusion into the myocyte becomes impaired (4, 11). Computer modeling studies of oxygen uptake dynamics revealed that such a "critical" Pmv_{O_2} level was reached only when the rate of increase in muscle blood flow is slowed to a greater extent than the rate of increase in muscle metabolic demand (1, 2, 5). Currently, it is not feasible to directly assess Pmv_{O_2} in humans. However, near infrared spectroscopy (NIRS), a technique using near infrared light to assess changes in tissue oxygenation, was shown to be a useful alternative to study exercise-induced changes of muscle oxygenation in humans (13) and may therefore be a valuable tool to study pathophysiological mechanisms of impaired oxygen uptake kinetics (39).

In CHF patients, the role of central hemodynamics in relation to oxygen delivery to utilization (mis)matching in skeletal muscles during moderate-intensity exercise (i.e., an exercise intensity that is indicative of regular daily activities) has yet to

be elucidated. Therefore, this study aimed to investigate whether the rate of increase in cardiac output during moderate exercise is related to the degree of skeletal muscle deoxygenation in patients with CHF. Based on the results of previous animal and computer modeling studies we hypothesized that in CHF patients with a relatively slow increase in cardiac output relative to the metabolic demands, i.e., poor matching of Q̇ and V̇O$_2$, central hemodynamics have a more profound influence on skeletal muscle deoxygenation.

METHODS

Subjects

Forty-three patients with CHF were recruited from our outpatient clinic from March 2012 until April 2014. Subject characteristics are listed in Table 1. Criteria for eligibility were stable systolic heart failure attributed to either dilated cardiomyopathy or ischemic heart disease due to myocardial infarction, New York Heart Association (NYHA) functional Class II or III (without change in class or medication ≤3 mo before inclusion), and left ventricular ejection fraction ≤40% (assessed by echocardiography or cardiac MRI maximal 2 mo before inclusion). Exclusion criteria were recent myocardial infarction (≤3 mo prior); angina pectoris at rest; clinical signs of decompensated heart failure; pulmonary, neurological, or orthopedic disease limiting the ability to exercise; and a history and/or clinical signs of peripheral vascular disease.

The study protocol was approved by the local Research Ethics Committee of Máxima Medical Centre, Veldhoven, The Netherlands. The study was conducted according to the Helsinki Declaration and all participants provided written and signed informed consent.

Exercise Testing

Exercise testing was performed in an upright seated position on an electromagnetically braked cycle ergometer (Lode Corrival; Lode, Groningen, The Netherlands). A 12-lead electrocardiogram (ECG) was registered continuously. Patients were instructed to maintain a pedaling frequency of 70 rotations per minute (RPM) during all exercise phases.

Maximal exercise testing was used to determine the workload for the submaximal exercise test. This test was performed at least 1 day before the submaximal test. It consisted of a symptom-limited test using an individualized ramp protocol aiming at total test duration of 8–12 min. The test was preceded by 4 min of unloaded pedaling and was ended when the patient was not able to maintain the required pedaling frequency. Peak workload was defined as the final registered workload.

Submaximal exercise testing commenced with a 2-min resting period, passively maintaining the right leg in a fixed position, followed by a 6-min bout at 80% of the workload corresponding to the ventilatory aerobic threshold (VAT), achieved during the maximal exercise test. Thereafter, there was a 5-min recovery phase with the same fixed leg position as during the resting period.

During the tests ventilatory parameters were measured breath-by-breath (ZAN 680 USB; ZAN Messgeräte, Oberthulba, Germany) and were averaged over 10-s intervals after removal of outliers (values >3 SD from the local mean) (26). Volume and gas analyzers were calibrated before each test. V̇O$_{2 \, peak}$ and peak respiratory exchange ratio (RER) were defined as the final 30-s averaged value of the maximal exercise test. VAT was assessed by the V-slope method (3).

Central Hemodynamics

Assessment of cardiac output (Q̇) was performed by a radial artery pulse contour analysis method (LiDCO, London, UK). This technique determines beat-to-beat changes in central hemodynamics by calculating nominal stroke volume (SV) from a pressure-volume transformation of the radial artery pressure waveform.

Before the exercise test, a 20-gauge arterial catheter was inserted into the radial artery. The radial artery catheter was connected to the LiDCO plus monitor. To convert nominal to absolute Q̇, the system was calibrated at rest in supine position by echocardiography (Philips CX50, handheld). Resting Q̇ was calculated by assessing the product of heart rate and SV. SV was determined by the product of the cross-sectional area and the velocity time integral of the left ventricular outflow tract (27). After the calibration procedure, patients were positioned upright on the cycle ergometer and the exercise protocol was started. Data were sampled beat-by-beat and stored offline for analysis. Outliers were removed using a moving average filter with a window of 11 data points (Python 2.7; Python Software Foundation).

Previous studies showed that radial artery pulse contour analysis is a reproducible and accurate method for assessment of cardiac output (Q̇) under a variety of physiological conditions (17, 20). In particular, we showed, using the Fick method as a reference, that this technique is highly accurate for continuous assessment of Q̇ during maximal and submaximal exercise testing in CHF patients (20).

Skeletal Muscle (De-)Oxygenation

In the present study, NIRS measurements were performed using a portable continuous wave near-infrared spectrophotometer (Portamon; Artinis, Elst, The Netherlands). This technique is based on the modified Lambert-Beer law and is able to distinguish between oxygenated (O$_2$Hb) and deoxygenated hemoglobin (HHb) by measuring the absorption of emitted light at two different wavelengths (760 nm for HHb and 841 nm for O$_2$Hb). With the application of spatially resolved spectroscopy, the tissue saturation index (TSI) was used to estimate absolute values of skeletal muscle deoxygenation during constant load exercise (see also section data analysis). TSI equals the ratio of oxygenated hemoglobin (O$_2$Hb) divided by total Hb (tHb) and is expressed as a percentage. The theoretical principles and clinical utility of the measurement technique have been described elsewhere (13).

The probe was connected to the right thigh with adhesive tape and kept in place by an elastic strap. It was located at 20 cm proximally from the lateral patellar edge over the centre of the m. vastus lateralis. A dark cloth impeded ambient light. Data were sampled at 10 Hz and stored for offline analysis. Before the test, the skinfold thickness at the site of NIRS was measured with a skinfold caliper (Harpenden; Baty International, West Sussex, UK). The thickness of the measured

Table 1. *comparison of patient and disease characteristics between slow Q̇ and normal Q̇ responders*

	Slow Q̇ Responder (n = 22)	Normal Q̇ Responder (n = 21)	P
Age, yr	66 ± 11	64 ± 6	NS
Age category (<60/60–70/>70 yr)	6/6/10	4/13/4	NS
Gender (male/female)	18/4	18/3	NS
Etiology (ICM/DCM)	13/9	11/9	NS
Duration of heart failure, mo	44 ± 46	64 ± 64	NS
NYHA class (II/III)	9/13	13/8	NS
Weber class (A/B/C/D)	6/8/7/1	9/8/4/0	NS
LVEF, %	31 ± 10	28 ± 12	NS
β-Blocker (n)	20	19	NS
ACE/ARB (n)	21	21	NS
Peak V̇O$_2$, ml·min^{-1}·kg^{-1}	17.7 ± 6.1	20.5 ± 6	NS
Peak Q̇, l/min	10.9 ± 4.7	11.1 ± 3.9	NS

Values are presented as mean ± SD or number. ICM, ischemic cardiomyopathy; DCM, dilated cardiomyopathy; BMI, body mass index; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction, ACE angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; V̇O$_2$, oxygen uptake; Q̇, cardiac output.

double skinfold was divided by two to obtain an estimate of the adipose tissue thickness.

Data Analysis

Kinetic analysis. The reproducibility and reliability of analysis of kinetics of $\dot{V}O_2$ and $\dot{Q}$ during onset of the constant-load tests were reported previously (19, 21). First, all data were resampled into 10-s intervals. Considering exercise onset, the first 20 s of the $\dot{V}O_2$ data set were omitted, as it is generally accepted that during this period (cardiodynamic phase) the increase in $\dot{V}O_2$ reflects merely an increase in pulmonary blood flow, rather than changes in tissue gas exchange. To calculate time constants of onset of $\dot{V}O_2$ and $\dot{Q}$ a nonlinear least squares regression procedure (Python 2.7; Python Software Foundation) was applied to the onset phase, using the following formula:

$$Y(t) = Y_{baseline} + A \times \left(1 - e - \left(t - T_d\right)/\tau\right)$$

where Y is $\dot{V}O_2$ or $\dot{Q}$, A is the amplitude during exercise onset, T_d is time delay (s), and τ is time constant (s). The "goodness of fit" was determined by the coefficient of determination (R^2).

TSI values. In a previous study, we demonstrated that absolute values of TSI showed better relative reliability compared with kinetic values. As such, absolute TSI values (described below) may be more appropriate for determining physiological differences between patients (32). Absolute baseline values of TSI were defined as the average values during the last minute of the resting period, and end exercise values as the average values during the last minute of exercise ($TSI_{endexercise}$). The minimal value of TSI (TSI_{min}) was defined as the lowest 5-s averaged value during the initial decay. The amplitude of TSI (TSI_{amp}) was defined as TSI baseline minus TSI_{min}. Figure 1 shows an example of calculation and fitting of absolute and kinetic parameters for $\dot{Q}$, $\dot{V}O_2$, and TSI.

Q̇ response relative to metabolic demand. Patients were categorized in two groups: patients with a relatively slow increase in cardiac output relative to the metabolic demands (ratio of $\tau\dot{Q}/\dot{V}O_2 \geq 1$, slow $\dot{Q}$ responders) and normal $\dot{Q}$ responders (ratio of $\tau\dot{Q}/\dot{V}O_2 < 1$). From a physiological point of view, a ratio exceeding 1 reflects poor matching of oxygen delivery and consumption, which necessitates greater fractional oxygen extraction to sustain a given metabolic rate (4, 10).

Statistical analysis. All data were analyzed using SPSS 19.0.0 statistical software (SPSS, Chicago, IL). Results are presented as mean value ± SD or numbers (*n*). Distribution of data was checked for normality by skewness and kurtosis. The independent *t*-test was used for unpaired observations. Differences between categorical data were assessed by the χ^2-test. Relations between variables were assessed by Pearson correlation coefficient for normal distributed data and Spearmans rho (r_s) for not normal distributed data. For all statistical comparisons the level of significance was set at $P < 0.05$.

RESULTS

All 43 patients successfully performed both maximal and submaximal exercise tests without any untoward events. Mean peak $\dot{V}O_2$ was 19.1 ± 6 ml·min^{-1}·kg^{-1}, mean peak $\dot{Q}$ was 11 ± 4.3 l/min, and mean peak workload corresponded to 127 ± 54 W.

Table 2 shows the results of the submaximal exercise test. The mean workload for slow $\dot{Q}$ responders was 53 ± 24 W and for normal $\dot{Q}$ responders 57 ± 23 W This was at, respectively, 41% (± 8) and 47% (± 11%) of the maximal achieved workload. The mean coefficient of determination (R^2) of $\dot{V}O_2$ onset kinetics was 0.87 (± 0.11) and 0.80 (± 0.20) for $\dot{Q}$ onset kinetics. The time constant of $\dot{V}O_2$ ($\tau\dot{V}O_2$) was significantly correlated with the time constant of $\dot{Q}$ ($\tau\dot{Q}$) ($r = 0.66$, $P < 0.0001$).
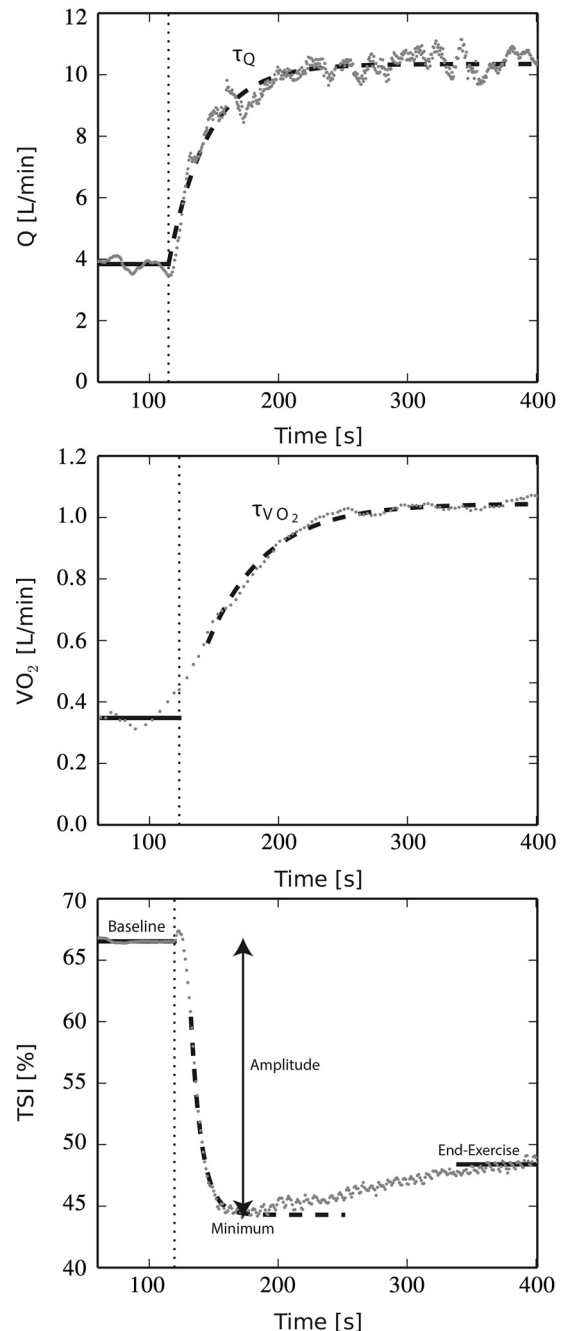

Fig. 1. Example of oxygen uptake ($\dot{V}O_2$), cardiac output ($\dot{Q}$), and skeletal muscle deoxygenation (TSI) response at the onset of submaximal exercise. Measured study parameters are as shown.

Patient and Disease Characteristics Between Slow and Normal Q̇ Responders

Table 1 represents a comparison between slow and normal $\dot{Q}$ responders. No statistical differences in disease characteristics as for instance etiology, duration of heart failure, NYHA, Weber class, presence of ischemia, mitral regurgitation, or dyssynchrony were observed. The median duration of CHF in slow $\dot{Q}$ responders was 37 mo (range 4–192), while in normal $\dot{Q}$ responders the median duration of CHF was 18 mo (range 3–130). This was not statistical significant. The use of β-block-

Table 2. *Comparison of submaximal exercise data of oxygen uptake, cardiac output, and skeletal muscle (de-)oxygenation between slow Q and fast Q responders*

	Slow $\dot{Q}$ Responder ($n = 22$)	Normal $\dot{Q}$ Responder ($n = 21$)	P
$\tau\dot{Q}$, s	76 ± 24	47 ± 27	0.01
$\tau\dot{V}o_2$, s	56 ± 19	63 ± 23	NS
$\dot{V}o_2$ baseline, ml/min	337 ± 85	341 ± 77	NS
$\dot{V}o_2$ steady state, ml/min	$1,080 \pm 334$	$1,228 \pm 309$	NS
$\dot{Q}$ baseline, l/min	4.3 ± 1.3	3.8 ± 1.2	NS
$\dot{Q}$ steady state, l/min	8.0 ± 2.7	7.9 ± 2.8	NS
TSI_{bl}, %	67 ± 5	67 ± 6	NS
TSI_{min}, %	60 ± 7.6	58 ± 10	NS
$TSI_{endexercise}$, %	63 ± 6.0	62 ± 7.7	NS
TSI_{amp}, %	7.2 ± 5.0	8.4 ± 5.9	NS

Values are presented as mean $\pm$ SD. $\dot{Q}$, cardiac output; $\dot{V}o_2$, oxygen uptake; tau, time constant; TSI_{bl}, baseline value of tissue saturation index (TSI); TSI_{min}, minimal value of TSI; $TSI_{endexercise}$, TSI value at end of exercise; TSI_{amp}, amplitude of the TSI response between the baseline and minimal value.

ers and ACE inhibitors/angiotensin II receptor blocker was similar in both groups.

Relationship Between Cardiac Output and Muscle Deoxygenation

There were no statistical significant correlations between TSI parameters and $\tau\dot{V}o_2$ or $\tau\dot{Q}$. Twenty-two (51%) patients were categorized as slow $\dot{Q}$ responders ($\tau\dot{Q}/\tau\dot{V}o_2 > 1$) and 21 patients (49%) as normal $\dot{Q}$ responders ($\tau\dot{Q}/\tau\dot{V}o_2 < 1$).

Figure 2, *A* and *B*, shows the relation between $\tau\dot{Q}$ and the minimal attained value of TSI. In slow $\dot{Q}$ responders, both TSI_{min} and TSI_{amp} were significantly correlated to $\tau\dot{Q}$ (respectively, $r_s = -0.57$, $P < 0.005$ and $r = 0.44$, $P = 0.04$), while no significant correlations were observed in normal $\dot{Q}$ responders ($r_s = 0.15$, $P = 0.52$ and $r_s = 0.09$, $P = 0.7$ respectively). The absolute values of TSI parameters did not differ statistically in both groups (Table 2).

DISCUSSION

This study showed that in moderately impaired CHF patients with a slow cardiac output increase relative to the increase in whole body oxygen uptake (i.e., poor matching of $\dot{Q}$ and $\dot{V}o_2$), slower cardiac output kinetics were related to a higher degree of skeletal muscle deoxygenation during moderate-intensity exercise. In contrast, cardiac output kinetics were not related to the degree of skeletal muscle deoxygenation in patients with relative fast cardiac output kinetics. These findings suggest heterogeneity in the pathophysiological determinants of delayed oxygen uptake kinetics of CHF patients. This different response could not be predicted by patient or disease characteristics such as age, etiology, NYHA class, or medication use.

The lack of correlation between the amount of skeletal muscle deoxygenation and cardiac output kinetics in relative fast $\dot{Q}$ responders suggests that the ability to increase cardiac output is not necessarily the main determinant of the amount of deoxygenation in exercising skeletal muscles. These results seem to be in contrast with the findings of Sperandio et al. (39), who observed a high correlation between the kinetics of cardiac output and microvascular blood flow. This discrepancy

could be explained by several factors. First, substantially higher exercise intensity was used, which may have compromised blood flow to exercising muscles to a greater extent, resulting in a more pronounced discrepancy between microvascular oxygen delivery and the metabolic demands. These findings are in line with an earlier study by Sullivan et al. (41), showing that, compared with healthy individuals, exercising leg blood flow in CHF patients was reduced, relatively more at maximal compared with submaximal exercise. Second, our study population has a considerable higher maximal exercise capacity at baseline ($\dot{V}o_{2\,peak}$ 19.1 ± 6 vs. 15.1 ± 2.8 ml·min^{-1}·kg^{-1}). It is known from animal studies that severe heart failure is associated with an impaired skeletal muscle oxygenation (10, 11). Therefore, this baseline difference in exercise capacity may limit comparison of both studies. Third, methodological differences may have played a role. For instance, HHb was measured, compared with TSI in our study, to assess skeletal muscle deoxygenation. Although the optimal assessment parameter is still under debate (18, 36), a major concern of using HHb to assess changes in skeletal muscle oxygenation is that it is less sensitive to exercise-induced
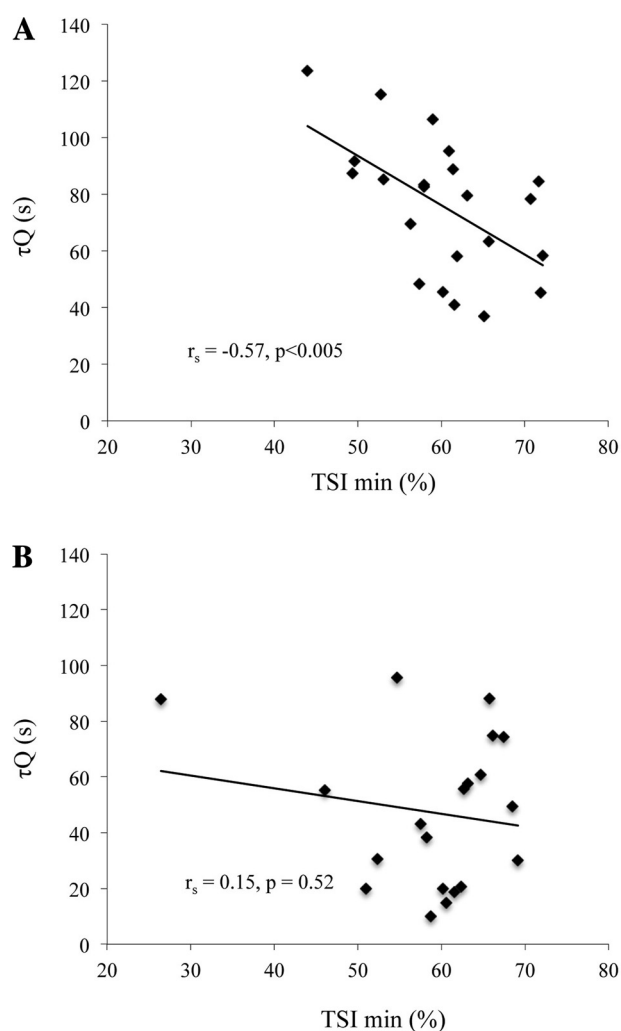

Fig. 2. *A* and *B*: relationship between the rate of increase in cardiac output ($\tau\dot{Q}$) and the minimal value of skeletal muscle deoxygenation (TSI_{min}) in slow $\dot{Q}$ responders ($\tau\dot{Q}/\tau\dot{V}o_2 > 1$) (*A*) and normal $\dot{Q}$ responders ($\tau\dot{Q}/\tau\dot{V}o_2 < 1$) (*B*). r_s = Spearmans correlation coefficient; P = level of significance.

hyperemia than TSI (22). Also, the NIRS technique used by Sperandio et al. (7) did not permit assessment of absolute values. Yet, it was shown recently that the use of relative concentrations of HHb resulted in exaggerated deoxygenation responses compared with using absolute values. In addition, kinetic analysis may be less suitable to assess exercising skeletal deoxygenation in CHF patients than evaluation of absolute values (32). Finally, Barbosa et al. (1) showed that monoexponential fitting may be inadequate to characterize deoxygenation onset kinetics in the presence of an overshoot, which is frequently present in CHF patients.

From a physiological point of view, the lack of correlation between the rate of cardiac output increase and skeletal muscle deoxygenation in the moderate-intensity domain in normal Q̇ responders may have different explanations. First, the impaired oxygen uptake kinetics may be primarily determined by a reduced ability to utilize oxygen. This view is supported by a study in isolated canine gastrocnemius muscle preparations showing that improvement in oxygen delivery did not result in faster oxygen uptake kinetics (14). Although human studies in CHF patients using this approach are not available, numerous studies demonstrated intrinsical skeletal muscle abnormalities (e.g., decreased oxidative enzymes and mitochondria), suggesting that skeletal muscle myopathy plays a major role in the reduced exercise capacity (9, 12, 28, 40). A second explanation may be that changes in microvascular blood flow and cardiac output during moderate exercise are not directly related. Although previous studies in CHF patients demonstrated a clear relation between exercise-induced changes in cardiac output and leg blood flow (41, 43), studies investigating the relation between leg blood flow and microvascular blood flow in exercising muscles in CHF patients are scarce. Theoretically, several factors may constrain microvascular muscle blood flow in CHF patients, including mechanical (e.g., vascular stiffness, decreased perfusion pressure), neurohumoral (e.g., increased levels of endothelin, angiotensin and catecholamines), and inflammatory factors (e.g., TNF-α, reactive oxygen species). In a study, in healthy humans it was shown that the onset kinetics of femoral leg blood flow were faster than microvascular blood flow, suggesting that leg blood flow in conduit arteries may not be a representative of microvascular blood flow (15). In addition, both animal and human studies demonstrated heterogeneity in blood flow responses within and between skeletal muscles (31, 37). Yet, the fact that we did observe a significant correlation between the amount of deoxygenation and the prolonged cardiac output response in slow Q̇ responders would argue against a complete uncoupling between central and microvascular blood flow.

The most important finding of this study is that, in contrast to patients with a normal increase in cardiac output relative to the metabolic demands, we did observe a significant correlation between the rate of increase in cardiac output and the amount of skeletal muscle deoxygenation (TSI$_{min}$) in patients with poor matching of Q̇ and V̇o$_2$ kinetics. This finding confirms our hypothesis and suggests that in these patients the delayed increase in cardiac output induces a compensatory increase in skeletal muscular oxygen extraction. This concept was demonstrated before in an animal study (4). Whether our findings reflect an actual central hemodynamic limitation of oxygen uptake kinetics is difficult to establish from our data since the critical level of TSI below which the blood-myocyte O$_2$ flux

compromises mitochondrial control is currently not known (24). Moreover, TSI is a surrogate for Pmv$_{O_2}$ and it is not clear if it represents absolute values of Pmv$_{O_2}$. Nevertheless, our results indicate that in a subset of relatively young, well-treated patients with moderately impaired exercise capacity, the cardiac output response may be a limiting factor, even during moderate-intensity exercise. Although this does not detract the fact that treatment strategies aiming at improvement of daily exercise performance should be directed at improving the skeletal muscle metabolic capacity (e.g., the intra-\myocyte milieu, mitochondrial mass, etc.), these findings suggest that improving the "central pump" in CHF patients should also be an important treatment goal. Clinical predictors of pathophysiological limitations to exercise capacity might be useful for customizing care and thereby improving the response to treatment (8, 42). In the present study, however, we did not find an association between disease and demographic characteristics and the rate of increase in cardiac output. Yet, in a previous animal study, it was shown that more severe heart failure was associated with a more pronounced skeletal muscle deoxygenation (11). Since we evaluated moderately impaired CHF patients (V̇o$_{2\ peak}$ 19.1 $\pm$ 6 ml·min^{-1}·kg^{-1}), future studies evaluating clinical predictors of pathophysiological limitations to exercise should also include CHF patients with lower exercise capacities.

Limitations

Before drawing definite conclusions from this study, some limitations should be acknowledged. First, the sample size was too low to draw definite conclusions on clinical and disease predictors for the heterogeneity in submaximal exercise capacity.

Our patients resembled a "typical" CHF study population of predominantly moderately impaired, middle aged men. Whether our results can be extrapolated to an older population, women, or more severely impaired patients remains to be determined. A second limitation concerns the performance of one submaximal exercise bout. More repeats are definitely needed in case of a low number of study participants (e.g., $n < 10$) and when individual patients are evaluated. However, in this rather larger group of CHF patients the influence of bout-to-bout variability will likely not influence between group analysis to a large degree. In addition, in clinical practice, multiple bouts would be time consuming and costly, which hampers implementation of submaximal exercise testing.

The third limitation would be the application of NIRS. Although we standardized the location of the NIRS sensors at the m. vastus lateralis, TSI responses may have been influenced by different muscle fiber type distribution under the area of investigation between subjects as type II fiber differ in their deoxygenation response from type I (30). Also, capillary recruitment patterns in the skeletal muscle at the onset of exercise may have varied between subjects (23, 24). These factors may have contributed to the differences seen in the relationship between τQ̇ and TSI amplitude.

Finally, the pulse contour wave analysis method, used in our study to assess cardiac output kinetics, should be used with caution in patients with an important aortic regurgitation. This may overestimate absolute values. However, this did not apply to our study, as there were no patients with severe aortic

regurgitation (determined with echocardiography or MRI). In addition, the morphology of the arterial waveform may be altered by damping or other technical errors. Although studies do not report measurement error as a result of this phenomenon, this may be a source of error in any form of pulse contour analysis. Because cardiac output is estimated every cardiac cycle, atrial fibrillation may result in irregular data output; however, as data were filtered with a moving average filter, this did not result in exclusion of data (33). Moreover, we showed in a previous study that this method is an accurate measurement for stroke volume with low variability compared with the direct Fick method in CHF patients in the moderate-intensity domain (20).

Conclusion

The present study demonstrated a slow cardiac output increase relative to the increase in whole body oxygen uptake during moderate-intensity exercise in a substantial subset of moderately impaired CHF patients. In this group, cardiac output kinetics were related to the amount of skeletal muscle deoxygenation, suggesting that central hemodynamics may limit muscle oxygenation during moderate-intensity exercise in these patients.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

R.F.S., V.M.N., P.F.W., P.A.D., and H.M.K. conception and design of research; R.F.S., V.M.N., T.S., and H.M.K. performed experiments; R.F.S., V.M.N., T.S., and H.M.K. analyzed data; R.F.S., V.M.N., T.S., and H.M.K. interpreted results of experiments; R.F.S. prepared figures; R.F.S. and H.M.K. drafted manuscript; R.F.S., V.M.N., T.S., P.F.W., P.A.D., and H.M.K. edited and revised manuscript; R.F.S., V.M.N., T.S., P.F.W., P.A.D., and H.M.K. approved final version of manuscript.

REFERENCES

1. **Barbosa PB, Bravo DM, Neder JA, Ferreira LF.** Kinetics analysis of muscle arterial-venous O(2) difference profile during exercise. *Respir Physiol Neurobiol* 173: 51–57, 2010.
2. **Barstow TJ, Lamarra N, Whipp BJ.** Modulation of muscle and pulmonary O₂ uptakes by circulatory dynamics during exercise. *J Appl Physiol* 68: 979–989, 1990.
3. **Beaver WL, Wasserman K, Whipp BJ.** A new method for detecting anaerobic threshold by gas exchange. *J Appl Physiol* 60: 2020–2027, 1986.
4. **Behnke BJ, Barstow TJ, Kindig CA, McDonough P, Musch TI, Poole DC.** Dynamics of oxygen uptake following exercise onset in rat skeletal muscle. *Respir Physiol Neurobiol* 133: 229–239, 2002.
5. **Benson AP, Grassi B, Rossiter HB.** A validated model of oxygen uptake and circulatory dynamic interactions at exercise onset in humans. *J Appl Physiol* 115: 743–755, 2013.
6. **Bowen TS, Cannon DT, Murgatroyd SR, Birch KM, Witte KK, Rossiter HB.** The intramuscular contribution to the slow oxygen uptake kinetics during exercise in chronic heart failure is related to the severity of the condition. *J Appl Physiol* 112: 378–387, 2012.
7. **Bowen TS, Rossiter HB, Benson AP, Amano T, Kondo N, Kowalchuk JM, Koga S.** Slowed oxygen uptake kinetics in hypoxia correlate with the transient peak and reduced spatial distribution of absolute skeletal muscle deoxygenation. *Exp Physiol* 98: 1585–1596, 2013.
8. **Chomsky DB, Lang CC, Rayos GH, Shyr Y, Yeoh TK, Pierson RN, Davis SF, Wilson JR.** Hemodynamic exercise testing. A valuable tool in the selection of cardiac transplantation candidates. *Circulation* 94: 3176–3183, 1996.
9. **Clark AL, Poole-Wilson AP, Coats AJ.** Exercise limitation in chronic heart failure: central role of the periphery. *J Am Coll Cardiol* 28: 1092–1102, 1996.
10. **Copp SW, Hirai DM, Ferreira LF, Poole DC, Musch TI.** Progressive chronic heart failure slows the recovery of microvascular O₂ pressures after contractions in the rat spinotrapezius muscle. *Am J Physiol Heart Circ Physiol* 299: H1755–H1761, 2010.
11. **Diederich ER, Behnke BJ, McDonough P, Kindig CA, Barstow TJ, Poole DC, Musch TI.** Dynamics of microvascular oxygen partial pressure in contracting skeletal muscle of rats with chronic heart failure. *Cardiovasc Res* 56: 479–486, 2002.
12. **Drexler H, Riede U, Münzel T, König H, Funke E, Just H.** Alterations of skeletal muscle in chronic heart failure. *Circulation* 85: 1751–1759, 1992.
13. **Ferrari M, Muthalib M, Quaresima V.** The use of near-infrared spectroscopy in understanding skeletal muscle physiology: recent developments. *Philos Trans A Math Phys Eng Sci* 369: 4577–4590, 2011.
14. **Grassi B, Gladden LB, Samaja M, Stary CM, Hogan MC.** Faster adjustment of O₂ delivery does not affect V̇o₂ on-kinetics in isolated in situ canine muscle. *J Appl Physiol* 85: 1394–1403, 1998.
15. **Harper a J, Ferreira LF, Lutjemeier BJ, Townsend DK, Barstow TJ.** Human femoral artery and estimated muscle capillary blood flow kinetics following the onset of exercise. *Exp Physiol* 91: 661–671, 2006.
16. **Hepple RT, Liu PP, Plyley MJ, Goodman JM.** Oxygen uptake kinetics during exercise in chronic heart failure: influence of peripheral vascular reserve. *Clin Sci (Lond)* 97: 569–577, 1999.
17. **Jonas MM, Tanser SJ.** Lithium dilution measurement of cardiac output and arterial pulse waveform analysis: an indicator dilution calibrated beat-by-beat system for continuous estimation of cardiac output. *Curr Opin Crit Care* 8: 257–261, 2002.
18. **Jones AM, Davies RC, Ferreira LF, Barstow TJ, Koga S, Poole DC.** Reply to quaresima and ferrari. *J Appl Physiol* 107: 372–373, 2009.
19. **Kemps HM, Schep G, Zonderland ML, Thijssen EJ, De Vries WR, Wessels B, Doevendans PA, Wijn PF.** Are oxygen uptake kinetics in chronic heart failure limited by oxygen delivery or oxygen utilization? *Int J Cardiol* 142: 138–144, 2010.
20. **Kemps HM, Thijssen EJ, Schep G, Sleutjes BT, De Vries WR, Hoogeveen AR, Wijn PF, Doevendans PA.** Evaluation of two methods for continuous cardiac output assessment during exercise in chronic heart failure patients. *J Appl Physiol* 105: 1822–1829, 2008.
21. **Kemps HM, De Vries WR, Hoogeveen AR, Zonderland ML, Thijssen EJ, Schep G.** Reproducibility of onset and recovery oxygen uptake kinetics in moderately impaired patients with chronic heart failure. *Eur J Appl Physiol* 100: 45–52, 2007.
22. **Kime R, Fujioka M, Osawa T, Takagi S, Niwayama M, Kaneko Y, Osada T, Murase N, Katsumura T.** Which is the best indicator of muscle oxygen extraction during exercise using NIRS?: evidence that HHb is not the candidate. *Adv Exp Med Biol* 789: 163–9, 2013.
23. **Koga S, Poole DC, Ferreira LF, Whipp BJ, Kondo N, Saitoh T, Ohmae E, Barstow TJ.** Spatial heterogeneity of quadriceps muscle deoxygenation kinetics during cycle exercise. *J Appl Physiol* 103: 2049–56, 2007.
24. **Koga S, Rossiter HB, Heinonen I, Musch TI, Poole DC.** Dynamic heterogeneity of exercising muscle blood flow and O₂ utilization. In: *Med Sci Sports Exerc* 46: 860–876, 2014.
25. **Koike A, Hiroe M, Adachi H, Yajima T, Yamauchi Y, Nogami A, Ito H, Miyahara Y, Korenaga M, Marumo F.** Oxygen uptake kinetics are determined by cardiac function at onset of exercise rather than peak exercise in patients with prior myocardial infarction. *Circulation* 90: 2324–2332, 1994.
26. **Lamarra N, Whipp B, Ward S, Wasserman K.** Effect of interbreath fluctuations on characterizing exercise gas exchange kinetics. *J Appl Physiol* 62: 2003–2012, 1987.
27. **Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise J, Solo-**

mon S, Spencer KT, St. John Sutton M, Stewart W. Recommendations for chamber quantification. *Eur J Echocardiogr* 7: 79–108, 2006.

28. **Lipkin DP, Jones AD, Round JM, Poole-Wilson AP.** Abnormalities of skeletal muscle in patients with chronic heart failure. *Int J Cardiol* 18: 187–195, 1988.

29. **Matsumoto A, Itoh H, Yokoyama I, Aoyagi T, Sugiura S, Hirata Y, Kato M, Momomura SI.** Kinetics of oxygen uptake at onset of exercise related to cardiac output, but not to arteriovenous oxygen difference in patients with chronic heart failure. *Am J Cardiol* 83: 1573–1576, 1999.

30. **McDonough P, Behnke BJ, Musch TI, Poole DC.** Recovery of microvascular P_{O_2} during the exercise off-transient in muscles of different fiber type. *J Appl Physiol* 96: 1039–1044, 2004.

31. **Musch T, Eklund K.** Altered regional blood flow responses to submaximal exercise in older rats. *J Appl Physiol* 96: 81–88, 2004.

32. **Niemeijer VM, Spee RF, Jansen JP, Buskermolen AB, van Dijk T, Wijn PF, Kemps HM.** Test-retest reliability of skeletal muscle oxygenation measurements during submaximal cycling exercise in patients with chronic heart failure. *Clin Physiol Funct Imaging* 2015 Jul 3. [Epub ahead of print].

33. **Pearse RM, Ikram K, Barry J.** Equipment review: an appraisal of the LiDCO plus method of measuring cardiac output. *Crit Care* 8: 190–195, 2004.

34. **Piepoli MF, Guazzi M, Boriani G, Cicoira M, Corrà U, Libera LD, Emdin M, Mele D, Passino C, Vescovo G, Vigorito C, Villani GQ, Agostoni P.** Exercise intolerance in chronic heart failure. *Eur J Cardiovasc Prev Rehabil* 17: 637–642, 2010.

35. **Poole DC, Hirai DM, Copp SW, Musch TI.** Muscle oxygen transport and utilization in heart failure: implications for exercise (in)tolerance. *Am J Physiol Heart Circ Physiol* 302: H1050–H1063, 2012.

36. **Quaresima V, Ferrari M.** Muscle oxygenation by near-infrared-based tissue oximeters. *J Appl Physiol* 107: 371; author reply 372–373, 2009.

37. **Rudroff T, Weissman a J, Bucci M, Seppänen M, Kaskinoro K, Heinonen I, Kalliokoski KK.** Positron emission tomography detects greater blood flow and less blood flow heterogeneity in the exercising skeletal muscles of old compared with young men during fatiguing contractions. *J Physiol* 592: 337–349, 2014.

38. **Schalcher C, Rickli H, Brehm M, Weilenmann D, Oechslin E, Kiowski W, Brunner-La Rocca HP.** Prolonged oxygen uptake kinetics during low-intensity exercise are related to poor prognosis in patients with mild-to-moderate congestive heart failure. *Chest* 124: 580–586, 2003.

39. **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.

40. **Sullivan MJ, Green HJ, Cobb FR.** Skeletal muscle biochemistry and histology in ambulatory patients with long-term heart failure. *Circulation* 81: 518–527, 1990.

41. **Sullivan MJ, Knight JD, Higginbotham MB, Cobb FR.** Relation between central and peripheral hemodynamics during exercise in patients with chronic heart failure. Muscle blood flow is reduced with maintenance of arterial perfusion pressure. *Circulation* 80: 769–781, 1989.

42. **Wilson JR, Groves J, Rayos G.** Circulatory status and response to cardiac rehabilitation in patients with heart failure. *Circulation* 94: 1567–1572, 1996.

43. **Yamabe H, Itoh K, Yasaka Y, Takata T, Yokoyama M.** The role of cardiac output response in blood flow distribution during exercise in patients with chronic heart failure. *Eur Heart J* 16: 951–960, 1995.