Regulation of the microvasculature during small muscle mass exercise in chronic obstructive pulmonary disease vs. chronic heart failure

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Aim: Skeletal muscle convective and diffusive oxygen (O_2) transport are peripheral determinants of exercise capacity in both patients with chronic obstructive pulmonary disease (COPD) and chronic heart failure (CHF). We hypothesised that differences in these peripheral determinants of performance between COPD and CHF patients are revealed during small muscle mass exercise, where the cardiorespiratory limitations to exercise are diminished.

Methods: Eight patients with moderate to severe COPD, eight patients with CHF (NYHA II), and eight age- and sex-matched controls were studied. We measured leg blood flow (Q_{leg}) by Doppler ultrasound during submaximal one-legged knee-extensor exercise (KEE), while sampling arterio-venous variables across the leg. The capillary oxyhaemoglobin dissociation curve was reconstructed from paired femoral arterial-venous oxygen tensions and saturations, which enabled the estimation of O_2 parameters at the microvascular level within skeletal muscle, so that skeletal muscle oxygen conductance ($D_{SM}O_2$) could be calculated and adjusted for flow ($D_{SM}O_2/Q_{leg}$) to distinguish convective from diffusive oxygen transport.

Results: During KEE, Q_{leg} increased to a similar extent in CHF (2.0 (0.4) L/min) and controls (2.3 (0.3) L/min), but less in COPD patients (1.8 (0.3) L/min) ($p < 0.03$). There was no difference in resting $D_{SM}O_2$ between COPD and CHF and when adjusting for flow, the $D_{SM}O_2$ was higher in both groups

compared to controls (COPD: 0.97 (0.23) vs. controls 0.63 (0.24) mM/kPa, p= 0.02; CHF 0.98 (0.11) mM/kPa vs. controls, p= 0.001). The $\dot{Q}$-adjusted $D_{SM}O_2$ was not different in COPD and CHF during KEE (COPD: 1.19 (0.11) vs. CHF: 1.00 (0.18) mM/kPa; p= 0.24) but higher in COPD vs. controls: 0.87 (0.28) mM/kPa (p= 0.02), and only CHF did not increase $\dot{Q}$-adjusted $D_{SM}O_2$ from rest (p= 0.2).

Conclusion: Disease-specific factors may play a role in peripheral exercise limitation in patients with COPD compared with CHF. Thus, low convective O_2 transport to contracting muscle seemed to predominate in COPD, whereas muscle diffusive O_2 transport was unresponsive in CHF.

Introduction

Exercise intolerance is a cardinal feature of both chronic obstructive pulmonary disease (COPD) and chronic heart failure (CHF) (Vestbo et al., 2013; Buber and Robertson, 2022). The associated decline in peak oxygen uptake (VO₂peak) during whole-body exercise in these disease states has been attributed to 'central' factors, i.e., cardio-pulmonary limitations, but emerging evidence suggests that peripheral factors, such as limb muscle dysfunction, also contributes to the exercise intolerance (Maltais et al., 2014; Keller-Ross et al., 2019). The limb muscle dysfunction, characterised by a low oxidative enzyme capacity, fibre type shift (type I to II) and muscle wasting, is quite similar in COPD and CHF (Zizola and Schulze, 2013; Ausín et al., 2017). Thus, studying how the skeletal muscle maladapts to chronic pulmonary or cardiac disease may enhance our understanding of the peripheral contribution to exercise intolerance in these common disorders.

The diminished VO₂peak in both COPD and CHF during whole-body exercise may be explained by any limiting factor of the integrated O_2 transport system, including ventilation, alveolar-to-capillary diffusion, cardiac output, blood volume, muscle blood supply and muscle diffusion (Wagner, 1996; Houstis et al., 2018). Whole body VO₂peak testing provoke cardio-respiratory symptoms in COPD and CHF due to the large muscle mass activated, thus masking any peripheral skeletal muscle limitations (Mortensen and Saltin, 2014; Poole et al., 2018; Dempsey, 2019). Small muscle mass exercise using one-legged knee-extensor exercise (KEE) is an established method to determine peripheral limitations to VO₂peak in COPD and CHF, because both cardiac output and minute ventilation are affected to a lesser degree compared to whole body exercise (Mortensen et al., 2010). Importantly, a higher skeletal muscle peak oxygen uptake (VO₂SMpeak) may be obtained during KEE compared to whole-body exercise in these patients (Richardson et al., 2004; Barrett-O'Keefe et al., 2014).

Oxygen transport to skeletal muscle determines peripheral exercise capacity, which depends on the convective delivery of blood flow (Q) to the capillary bed and diffusive transport from red blood cells to myocyte mitochondria (Poole et al., 2022). Blood flow to contracting muscle is tightly regulated to match oxygen delivery to metabolic demand in healthy humans (Saltin, 1985; Mortensen and Saltin, 2014). The pulmonary diffusion deficits in COPD or reduced cardiac output in CHF are likely to impact regulation of muscle convective and diffusive O_2 transport in response to exercise, as both diseases share limb muscle maladaptions abnormalities. Notwithstanding, the neural and metabolic interactions, that may also contribute to the peripheral exercise intolerance (Gagnon et al., 2012; Maltais et al., 2014; Smith et al., 2020). Indeed, previous findings suggest that both peripheral muscle O_2 convective delivery (Brønstad et al., 2012) and diffusive O_2 transport are impaired during maximal KEE in COPD (Broxterman et al., 2021), while muscle convective O_2 delivery has been shown to be attenuated in CHF (Barrett-O'Keefe et al., 2014, 2019).

As of now, no studies have directly compared the peripheral limitations of the oxygen transport cascade in these predominantly centrally limited disease states to determine whether disease-specific microvascular (mal)adaptations are present. In the present study, we hypothesised that such disease-specific differences between the COPD and CHF patients are present, with COPD showing both convective as well as diffusive limitation whereas CHF are mainly limited on their convective capacity compared to controls.

Materials and methods

Ethical approval

The studies were approved by the Ethical Committee of the Capital Region of Copenhagen (H-2–2013–150; H-3–2013–048) and performed according to the guidelines of the Declaration of Helsinki. All subjects provided oral and written informed

TABLE 1 Subject characteristics.

Baseline	COPD	CHF	Control
Age (years)	63 (8)	57 (10)	64 (7)
Men/women	6/2	7/1	7/1
BMI	26 (4)	29 (6)	25 (3)
BP systolic (mmHg)	142 (10)	144 (16)	136 (11)
BP diastolic (mmHg)	87 (7)	85 (7)	85 (9)
Watt max one leg (W)	36 (12)	34 (17)	41 (11)
6MWT (m)	605 (64) #	549 (99) #	663 (47)
VO_{2peak} (ml/min)	1819 (358) #	2129 (409)	2575 (549)

Data in means (standard deviation). We performed a one-way ANOVA, and if significant, a Tukey's honest significant difference was used to analyse the differences between groups. # Different from control group ($p <0.05$). n = 8 in all groups. Abbreviations: COPD: chronic obstructive pulmonary disease. CHF: Chronic heart failure. BMI: body mass index. BP: blood pressure. 6MWT: 6 min walking test. VO_{2peak}: Peak oxygen consumption.

consent prior to enrolment. Experiments were performed in the same laboratory as a part of a larger study and some results have previously been published (Iepsen et al., 2017; Munch et al., 2018). The present study involves novel analyses of arterio-venous blood gases in response to KEE from the two studies to address an independent working hypothesis.

Participants

We included eight COPD patients (Global Initiative for Chronic Obstructive Lung Disease (GOLD) II and III), eight patients with heart failure with reduced ejection fraction (HFrEF) (New York Heart Association Classification (NYHA) class II), and eight healthy age- and sex-matched controls (Table 1). In the previous study by Iepsen et al., 10 COPD patients were included, but due to technical issues with placement of the arterial catheters, two could not participate in the invasive part of the study (Iepsen et al., 2017). In the study by Munch et al. (Munch et al., 2018), eight healthy controls were included, but two of them did not want to participate in the training intervention and were only enrolled in the cross-sectional study. Due to the invasive nature of this experiment, the control group was the same for both studies. Thus, we studied 8 COPD patients, 8 CHF patients and 8 healthy controls unexposed to exercise training. In one of the COPD patients, we could only calculate arterial blood gas values at rest, and therefore, we excluded this subject from the exercise analyses.

Inclusion criteria for COPD patients were a forced expiratory volume in 1 s (FEV_1)/forced vital capacity ratio <0.70, $FEV_1 \leq$ 70% of predicted, modified Medical Research Council Dyspnoea Scale ≤2, resting arterial oxygenation >90%, and age 40–80 years. Eligibility criteria for CHF patients were left ventricle ejection fraction <40%, NYHA class < eller lig II and age 40–80 years. All patients were clinically stable and primarily recruited from

outpatient clinics. Exclusion criteria were use of anticoagulant medications, diabetes, hypertension, claudication, heart failure (COPD and controls) COPD (CHF and controls), unstable ischemic heart disease or malignant diseases. Sitting spirometry (Model 2120, Vitalograph Ltd. Buckingham, United Kingdom) in COPD, standard echocardiography (Vivid 9, GE Healthcare, Pittsburgh, PA) in CHF, and a general medical examination including blood testing prior to inclusion.

Experimental procedures

Prior to the experimental day all subjects visited the laboratory to be familiarised to the KEE-model, and performed; (1) an incremental bicycle test on a bicycle ergometer (Monark 839E; Monark, Varberg, Sweden) to determine whole body V_{O2peak} (l/min,) and peak workload ($Watt_{peak}$) while oxygen consumption was measured breath-by-breath using a Quark gas analyser (Cosmed, Italy) (2) an incremental KEE test, to determine peak workload, (3) 6 minutes walking distance (6MWD) and (4) whole-body dual-energy X-ray absorptiometry scanning (Lunar Prodigy Advance; GE Healthcare, Madison, WI).

On the experimental day participants refrained from caffeine, alcohol, and exercise for 24 h. The COPD patients paused their medications for 24–48 h depending on the drug profile to avoid potential vasoconstrictor effects of inhaled β_2-agonists and muscarinic antagonists. The CHF patients paused their ACE-inhibitors 48 h prior to the experimental day, whereas beta-blockers, anti-platelet and diuretic drugs were withdrawn 24 h prior to the experimental day. After local anaesthesia (lidocaine 2%), catheters were placed in the femoral artery and vein of the experimental leg and one in the brachial artery.

KEE at 10 W was performed by all subjects using the same protocol. Prior to the acute exercise bout, the experimental leg was moved passively by an investigator at 60 kicks/min and subjects were instructed to keep that pace during exercise. Leg haemodynamics were evaluated, and arterio-venous blood samples were collected at baseline and during active knee-extensions at steady state (3.5 min of active contractions). Common femoral arterial blood flow was measured by the same sonographer using Doppler ultrasound (Logic E9, GE Healthcare, Milwaukee, WI, United States) equipped with a linear probe (9 MHz), as previously described (Iepsen et al., 2017; Munch et al., 2018). In brief, the site of the blood flow measurements was below the inguinal ligament but well above the bifurcation of the artery and recordings were obtained at the lowest possible insonation angle and always below 60°. The sample volume was maximised according to the width of the vessel and kept clear of the walls. Arterial diameter was measured during systole from resting arterial B-mode images with the transducer parallel to the vessel. Doppler tracings were averaged

over eight heart cycles at the same time as the blood sampling. Blood samples were drawn simultaneous from the femoral venous and arterial catheters and blood gases were immediately analysed (ABL 725, Radiometer, Glostrup, DK).

Calculations

Oxygen content (C_xO_2) was calculated as:

$$CxO_2 = Hb \cdot SxO_2 + \alpha O_2 \cdot PxO_2 \tag{1}$$

Where S is the oxygen saturation of haemoglobin (fraction) and P is the partial pressure of oxygen (kPa). x denotes either arterial (a), femoral-venous (v), or capillary (cap) blood, Hb (mmol L^{-1}) is the haemoglobin concentration and α is the solubility coefficient of oxygen in blood (0.01 mmol L^{-1} kPa^{-1}). Oxygen delivery ($DelO_2$) to and the fractional oxygen extraction (EO_2) by skeletal muscle were calculated as:

$$DelO_2 = CaO_2 \cdot \dot{Q}_{leg} \tag{2}$$

$$EO_2 = \frac{a - vDO_2}{CaO_2} \tag{3}$$

where avDO$_2$ is the arterial-to-femoral venous oxygen content difference.

Skeletal muscle oxygen uptake ($\dot{V}O_{2SM}$) was calculated as:

$$\dot{V}O_{2SM} = avDO_2 \cdot \dot{Q}_{leg} \tag{4}$$

Leg vascular conductance (LVC) was calculated as:

$$LVC = \frac{\dot{Q}_{leg}}{MAP} \tag{5}$$

Where MAP is mean arterial blood pressure (=1/3 systolic blood pressure +2/3 diastolic blood pressure) or area under the curve (AUC) over 8 heart cycles for invasive experiments with pulse contour analysis.

Lastly, skeletal muscle oxygen conductance ($D_{SM}O_2$) was calculated as:

$$D_{SM}O_2 = \frac{\dot{V}O_{2SM}}{\bar{P}capO_2} \tag{6}$$

where $\bar{P}capO_2$ is the mean capillary oxygen tension (see below). Given that $D_{SM}O_2$ has both a convective and a diffusive component, it was adjusted for $\dot{Q}_{leg}$ by division to provide a surrogate measure of the non-convective, i.e. the diffusive, component:

$$\dot{Q} - \text{adjusted } D_{SM}O_2 = \frac{avDO_2}{\bar{P}capO_2} \tag{7}$$

Given that i) the oxygen dissociation curve (ODC) is gradually modulated during the red blood cells' passage though the microcirculation, e.g., due to changes in pH, PaCO$_2$ and temperature, and ii) that the OCD may differ

between individual capillaries throughout the skeletal muscle tissue, an ideal 'averaged' capillary ODC was modelled using paired arterial and femoral-venous blood gas values. For simplicity, and in accordance with our previous study (Dahl et al., 2020), 'capillary' here refers to the part of the microvasculature where gas exchange between blood and tissue takes place. However, it should be kept in mind, that this is not a well-defined anatomical entity, since gas exchange also takes place in other parts of the microvasculature, notably upstream and less so downstream of the anatomically defined capillary bed (Pittman, 2000; Shibata et al., 2006). Thus, it was assumed that measured blood gas values equal the oxygen tension and saturation in the arterial inlet and venous outlet of the gas exchanging microvasculature.

This averaged OCD was defined by the capillary P_{50} (P_{50cap}), which reflects the dissociation constant of haemoglobin, and the capillary Hill coefficient, h_{cap}, which is the cooperativity. A pair of P_{50cap}- and h_{cap}-values was calculated that fulfils the Hill equation in both arterial and femoral-venous blood (Dahl et al., 2020):

$$h_{cap} = \frac{\ln\left(\frac{SaO_2}{1 - SaO_2}\right) - \ln\left(\frac{SvO_2}{1 - SvO_2}\right)}{\ln\left(PaO_2\right) - \ln\left(PvO_2\right)} \tag{8}$$

P_{50cap} was then calculated by insertion of the Hill coefficient into the Hill equation using arterial or femoral-venous blood gas values.

$$P_{50cap} = PaO_2 \cdot \left(\frac{SaO_2}{1 - SaO_2}\right)^{-\frac{1}{h_{cap}}} = PvO_2 \cdot \left(\frac{SvO_2}{1 - SvO_2}\right)^{-\frac{1}{h_{cap}}} \tag{9}$$

The mean capillary oxygen tension ($(\bar{P}capO_2)$ and saturation in the skeletal muscle microvasculature was determined based on similar principles to those previously outlined for the cerebral microcirculation (Dahl et al., 2020). Notably, the total capillary oxygen content ($CcapO_2$) is assumed to decrease proportionally with the distance travelled as blood flows through the capillary from the arterial inlet to the venous outlet. Formulas for calculation of these parameter are given below:

$$\bar{P}capO_2 = PvO_2 + (PaO_2 - PvO_2) \cdot \frac{CaO_2 - C'}{CaO_2 - CvO_2} \tag{10}$$

$$\bar{S}capO_2 = SvO_2 + (SaO_2 - SvO_2) \cdot \frac{CaO_2 - C''}{CaO_2 - CvO_2} \tag{11}$$

where C' and C'' are defined:

$$C' = \alpha O_2 \cdot \frac{PaO_2 + PvO_2}{2} + Hb \cdot \bar{S}_{ODC} \tag{12}$$

$$C'' = \alpha O_2 \cdot \bar{P}_{ODC} + Hb \cdot \frac{SaO_2 + SvO_2}{2} \tag{13}$$

Here $\bar{S}_{ODC}$ and $\bar{P}_{ODC}$ are the mean oxygen saturation and tension measured on the ODC, which are calculated by integration of the Hills equations from the arterial inlet to venous outlet.

$$\bar{S}_{ODC} = \frac{1}{PaO_2 - PvO_2} \cdot \int_{PvO_2}^{PaO_2} \left(1 + \left(\frac{P_{50cap}}{PcapO_2} \right)^h \right)^{-1} dPcapO_2$$

$$(14)$$

$$\bar{P}_{ODC} = \frac{1}{SaO_2 - SvO_2} \int_{SvO_2}^{SaO_2} P_{50cap} \cdot \left(\frac{ScapO_2}{1 - ScapO_2} \right)^{\frac{1}{h_{cap}}} dScapO_2$$

$$(15)$$

Statistics

All statistical analyses were performed using R statistical software version 4.1.1 (R Project for Statistical Computing) within RStudio statistical software version 1.4.1717 (RStudio). Normality of data was confirmed by normality plots and homogeneity of variance was tested using the Bartlett test and data was collected in an independent manner. Changes from rest to KEE were analysed using a paired T-test. A one-way analysis of variance (ANOVA) was used to detect differences between groups and if the F test was significant ($p < 0.05$), we used a Tukey's *post-hoc* test for all group comparison combinations. Data are presented as mean (standard deviation), and differences are presented as mean. Significance was established at $p < 0.05$. Effect sizes were calculated by Cohen's D method.

Results

Baseline characteristics are presented in Table 1. The VO_2peak in the COPD group was similar to that of the CHF group, but COPD showed lower VO_2peak compared to controls and there was no difference between CHF and controls The COPD and CHF group had similar 6MWD that were lower than in controls. The 10W workload during KEE comprised a similar percentage of maximal workload in the three groups (COPD: 33 (4) vs. CHF: 38 (23) vs. controls: 26 (7) %.

Haemodynamics

At rest, there were no differences in MAP (COPD: 110 (14) vs. CHF: 103 (8) vs. controls: 113 (11) mmHg; $p=0.23$), LVC (COPD: 2.3 (1.1) vs. CHF: 1.8 (0.5) vs. controls: 1.9 (0.2) ml/(min*mmHg); $p=0.25$) or Q_{leg} (COPD: 222 (112) vs. CHF: 166 (43) vs. controls: 178 (22) ml/min; $p=0.27$) between the three groups.

During exercise, the Q_{leg}, MAP and LVC all increased within both COPD, CHF, and controls (P<0.05). The change (Δ) from rest to exercise Q_{leg} responses were similar in COPD vs. CHF, lower in COPD vs. controls, but similar in CHF vs. controls (Figure 1). There were no differences in ΔMAP between groups. Therefore, ΔLVC responses during KEE in COPD vs. CHF were not different, lower in COPD vs. controls, and similar in CHF vs. controls.

Skeletal muscle oxygen consumption and microvascular oxygenation

Resting SaO_2 and PaO_2 were lower in the COPD group compared to the control group (Table 2). We found no differences in $DelO_2$ between the three groups at rest (COPD: 2.1 (1.1) vs. CHF: 1.4 (0.4) vs. controls: 1.5 (0.1) mmol O_2/min; $p=0.2$). Likewise, there was no difference in VO_{2SM} between COPD and CHF at rest (COPD: 1.1 (0.2) vs. CHF: 0.9 (0.3) mmol O_2/min, ($p=0.57$). Resting VO_{2SM} was higher in COPD compared to controls (COPD: 1.1 (0.2) vs. controls: 0.7 (0.2) mmol O_2/min; $p=0.03$), with no difference between CHF and controls groups. $\bar{P}capO_2$ and $\bar{S}capO_2$ were lower in both COPD and CHF compared to controls at rest (Figure 2).

Exercising SaO_2 and PaO_2 were also lower in COPD vs. controls. We found no differences in $DelO_2$ during KEE (COPD: 16.5 (3.3) vs. CHF: 17.0 (3.7) vs. controls: 20.6 (3.1) mmol O_2/min; $p=0.2$). The $\Delta DelO_2$ was higher in controls compared to COPD in response to exercise (Figure 3), but similar to CHF, with no difference between COPD and CHF. The $\bar{S}capO_2$ was lower in COPD than in controls during exercise, but not between the other groups (CHF vs. COPD or control vs. CHF). Despite these differences, the VO_{2SM} increased to almost similar absolute levels in all three groups during KEE (COPD: 11.2 (1.6) vs. CHF: 11.0 (1.8) vs. controls: 12.1 (2.8) mmol O_2/min; $p=0.57$).

Skeletal muscle oxygen conductance

At rest, there were no difference in $D_{SM}O_2$ between COPD and CHF (COPD: 0.21 (0.08) vs. CHF 0.16 (0.04) mmol/min/kPa; $p=0.2$), but $D_{SM}O_2$ was higher in both COPD and CHF than controls (0.11 (0.04) mmol/min/kPa, $p=0.005$). After Q-adjustment, there was still no difference in resting $D_{SM}O_2$ between COPD and CHF, and likewise, both groups showed higher Q-adjusted $D_{SM}O_2$ than controls (COPD: 0.97 (0.23) vs. controls 0.63 (0.24) mM/kPa, $p=0.02$; CHF 0.98 (0.11) mM/kPa vs. controls, $p=0.001$)

In response to exercise, $D_{SM}O_2$ increased in all groups ($p < 0.05$) to reach similar values (COPD: 2.15 (0.3) vs. CHF: 2.1 (0.4) vs. controls: 2.0 (0.7) mmol/min/kPa. In contrast to the unadjusted $D_{SM}O_2$ response to exercise, the Q-adjusted $D_{SM}O_2$ was significantly increased in COPD ($p=0.01$) and controls ($p=0.03$), but not in the CHF group ($p=0.2$). However, we found no difference between COPD and CHF in Q-adjusted $D_{SM}O_2$ during exercise (COPD: 1.19 (0.11) vs. CHF: 1.00 (0.18) mM/kPa; $p=0.24$), although Q-adjusted $D_{SM}O_2$ was higher in COPD compared to controls (COPD vs. controls: 0.87 (0.28) mM/kPa, $p=0.02$), and similar in CHF and controls.

FIGURE 1
Haemodynamic responses. Panel **(A)** shows the change (Δ) in leg blood flow (Q$_{leg}$) from rest to one leg knee-extensor exercise at 10 W, panel
(B) change in mean arterial pressure (MAP) and panel **(C)** change in leg vascular conductance (LVC). One-way ANOVA, with Tukey's honest test was
used to detect differences between groups marked with a *= (p <0.05) or **= (p <0.01). Dot plots with boxes showing mean and standard deviation
with exact values for each participant. Chronic heart failure (CHF) participants n=8, Chronic obstructive pulmonary disease (COPD) participants
n = 7, healthy control n = 8.

TABLE 2 Blood gas values.

	COPD		CHF		Control	
	Rest	**KEE**	**Rest**	**KEE**	**Rest**	**KEE**
PaO$_2$ (kPa)	10.3 (1.1) #	11.1 (1.1) #	11.1 (1.7)	12.0 (1.6)	12.0 (1.2)	14.5 (2.9) *
SaO$_2$	96 (0.02) #	96 (0.01) #	97 (0.01)	97 (0.01)	97 (0.01)	97 (0.01)
CaO$_2$ (mM)	8.8 (0.7)	9.0 (0.6)	8.4 (0.7)	8.5 (0.7)	8.6 (0.6)	8.7 (0.6) *
CvO$_2$ (mM)	3.8 (1.1)	2.8 (0.7) *	2.9 (0.8) #	2.6 (0.8)	4.8 (1.1)	3.5 (0.8) *
PaCO$_2$ (kPa)	4.4 (0.5)	4.75 (0.4)	4.68 (0.4)	4.7 (0.6)	4.6 (0.4)	4.6 (0.6)
pH (units)	7.43 (0.03)	7.41 (0.02)	7.41 (0.02)	7.40 (0.03) *	7.42 (0.02)	7.41 (0.01)
Lactate (mM)	0.7 (0.3)	1.5 (0.2) *	0.9 (0.4)	3.1 (2) *	0.6 (0.2)	2.1 (1) *

Data in means (standard deviation). Blood gas variables at rest and during one leg knee-extensor exercise (KEE) at 10 W. We performed a one-way ANOVA, and if significant, a Tukey's
honest significant difference was used to analyse the differences between groups. Comparison between rest and exercise was performed using a paired t-test. * = Different from baseline
(p <0.05). # = Different from control group (p <0.05). n=8 for resting COPD, values, n=7 for KEE, values. N=8 for both rest and KEE, values for CHF, and controls. *Abbreviations:* PaO$_2$:
arterial oxygen partial pressure SaO$_2$: arterial oxygen saturation. Hgb: Haemoglobin. CaO$_2$: arterial oxygen content. CvO$_2$: venous oxygen content. Pa$_{CO2}$: arterial carbon dioxide partial
pressure.

Discussion

We studied leg muscle convective and diffusive O$_2$ transport during small muscle mass exercise in COPD, CHF and healthy controls. There were no significant differences between COPD and CHF but we did observe disease-specific macro- and microvascular responses to exercise compared to the healthy condition. We found that while the skeletal muscle O$_2$ delivery during exercise was lower in COPD, the microvasculature responded with an enhanced Q-adjusted D$_{SM}$O$_2$ or perhaps *vice versa*, the O$_2$ delivery adapted to the increased muscle diffusion capacity seen at rest. This response was not observed in CHF, where Q-adjusted D$_{SM}$O$_2$ was unresponsive to exercise, despite high resting D$_{SM}$O$_2$ (Q-adjusted and unadjusted) values compared to controls. Likewise, CHF patients were not able to decrease C$_v$O$_2$ in response to exercise, as observed in COPD and controls, suggesting impaired O$_2$ extraction during exercise. The

LVC responses to exercise in CHF was similar to controls, indicating that the macrovascular response was preserved, while impaired in COPD. Nonetheless, both groups reached normal VO$_{2SM}$ values as expected during submaximal small muscle mass exercise at similar work loads. These data suggest that enhanced diffusive O$_2$ transport capacity of the working muscles in COPD compensates for the attenuated convective O$_2$ transport, while the convective response to exercise in CHF may downregulate muscle diffusive O$_2$ transport capacity.

Microvascular (mal)adaptation in chronic obstructive pulmonary disease

D$_{SM}$O$_2$ is an estimate of oxygen transport capacity from the capillary to the mitochondria (Østergaard, 2020). It comprises a

FIGURE 2
Capillary oxygen tension and saturation Panel **(A)** shows the capillary oxygen tension (PcapO$_2$) at rest, panel **(B)** the capillary oxygen tension during one leg knee-extensor exercise, panel **(C)** the oxygen saturation (Scap) at rest and panel **(D)** the oxygen saturation during one leg knee-extensor exercise. We performed a one-way ANOVA and if significant, a Tukey's honest significant difference test was used to analyse the differences between groups. Difference between groups marked with a *= ($p < 0.05$), **= ($p < 0.01$), ***= ($p < 0.001$). Dot plots with boxes showing mean and standard deviation with exact values for each participant, marked with a black dot. Chronic heart failure (CHF) participants n=8, Chronic obstructive pulmonary disease (COPD) participants n = 7, healthy control n = 8.

FIGURE 3
Skeletal muscle oxygen delivery and conductance Panel **(A)** shows the change (Δ) in O$_2$ delivery (ΔDelO$_2$) from rest to one leg knee-extensor exercise at 10 W, panel **(B)** change in skeletal muscle oxygen conductance (D$_{SM}$O$_2$) and panel **(C)** change in flow adjusted skeletal muscle oxygen conductance (Q'-adjusted D$_{SM}$O$_2$). We performed a one-way ANOVA and if significant, a Tukey's honest significant difference test was used to analyse the differences between groups. Difference between groups marked with a *= ($p < 0.05$) and **= ($p < 0.01$). Dot plots with boxes showing mean and standard deviation with exact values for each participant, marked with a black dot. Chronic heart failure (CHF) participants n = 8, Chronic obstructive pulmonary disease (COPD) participants n = 7, healthy control n = 8.

convective component and a diffusive component, of which the latter depends on the total capillary wall area available for diffusion during red blood cell passage, reflecting the total number of perfused capillaries and their length, the capillary flow distribution, spatial distribution of capillaries and potential structural changes in the diffusion membrane (Wagner, 2000;

Poole, 2019; Nyberg and Jones, 2022). The relative interdependence of convection and diffusion is difficult to establish during human muscle contractions. If, one is impaired, the other might compensate to some degree. Likewise, low convective response to small muscle mass exercise in COPD is not a universal observation in previous studies. Indeed, although some studies like us have found lower convective responses to exercise in severe COPD compared to controls (Brønstad et al., 2012; Broxterman et al., 2021), others reported either similar (Rossman et al., 2015) or even higher Q_{leg} during exercise (Richardson et al., 2004) in moderate and severe COPD, respectively. These somewhat divergent findings are most likely due to the large difference between the control groups of the abovementioned studies. In our patients with moderate-to-severe COPD (FEV$_1$ ~50% of predicted), diffusive oxygen transport was augmented to enhance skeletal muscle O$_2$ uptake despite an impaired blood flow response. In more severe COPD (FEV$_1$ ~30% of predicted), the diffusive response during KEE has previously been reported to be impaired, appeared to be specifically enhanced by 8 weeks of KEE training (Broxterman et al., 2021). Together with our findings, this indicates that enhanced diffusive oxygen transport has the potential to counter the impact of an insufficient blood flow response on VO$_2$peak and that its gradual decline with disease severity is potentially reversible, i.e., by exercise training.

Microvascular (mal)adaptation in chronic heart failure

In our CHF patients, we found that the diffusive response to KEE seemed to be limited, which is in line with findings in some previous studies (Esposito et al., 2011). Thus, reductions in skeletal muscle diffusive oxygen transport have been reported in patients with CHF NYHA II-III, and of note, Esposito et al (2011) observed that exercise training by KEE over an eight-week period improved the diffusive component in the CHF patients to the same level as the healthy control group at baseline. Furthermore, they observed an augmented capillarization of the quadriceps muscle in parallel with improved peripheral exercise capacity after isolated leg muscle training for 8 weeks, but the cardiac output remained unchanged, suggesting that increases in VO$_{2SM}$ can be obtained without "central" improvements (Esposito et al., 2011). The same group performed another study where the control group was better matched on physical fitness and found no significant differences in haemodynamics and muscle metabolism, comparing CHF (NYHA II-III) and sedentary controls (Esposito et al., 2015). The convective response to small muscle exercise has been reported to be impaired in patients with CHF (Barrett-O'Keefe et al., 2014, 2019), while others have found that if less than 4 kg of muscle is activated the convective capacity was similar to healthy

individuals (Magnusson et al., 1997). Although the numerical values in the present study showed a tendency towards lower convective responses in CHF during KEE, this was not significant when all groups were analysed in parallel and after statistical adjustment (Figure 1). A possible explanation for the divergent results across previous studies and in relation to our COPD group could be the pharmacological management of CHF patients. For example, ACE-inhibitors commonly prescribed to CHF patients affects cardiovascular regulation by relaxation of the vascular smooth muscle of resistance arterioles (Anderson et al., 2000; Radenković et al., 2019). Over the past 30 years, during which the abovementioned studies have been conducted, there has been a decrease in the use of positive inotropes such as digoxin. The interaction between these drugs and exercise must be considered because they affect the autonomic control of cardiovascular function (Watanabe, 1985; Gheorghiade et al., 1989; Heidenreich et al., 1997; van der Harst and de Boer, 2010) and vasodilatory capacity in skeletal muscle (Karsh and Bullock, 1964) which are pivotal to the peripheral adaptations to exercise.

While a reduced blood flow response to exercise in COPD was observed, and potentially also play a role in CHF, the main difference between the two disease categories was that diffusive oxygen transport was either near-maximal already at rest, or simply unresponsive to exercise in CHF, whilst augmented in skeletal muscle in COPD.

Study limitations

This study was performed on data from earlier studies with a new methodology. The mechanisms underlying exercise intolerance are complex and often multifactorial in both COPD and CHF patients. The pathophysiological factors that contribute are ventilatory limitations, gas exchange deficits, reduced cardiac function, and limb muscle dysfunction, and any combination might dominate the phenotype. There were no differences in ΔMAP between groups to suggest a heightened exercise pressor reflex activation, but CHF and COPD patients have been associated with sensitization of the exercise pressor reflex (Smith et al., 2005), which may contribute to their exercise intolerance (Gagnon et al.; Amann et al., 2014; Smith et al., 2020). We cannot exclude that a difference in exercise pressor reflex activation may have influenced our results, as inhibition of lower limb muscle mechano- and metabo-sensitive afferents has shown to increase exercise tolerance in CHF and COPD, perhaps through increased O$_2$ delivery to the working muscle (Amann et al., 2014; Smith et al., 2020). Another challenge for this kind of study is sample size which is relatively small because of the invasive nature of these experiments, and results may not be extrapolated to all patients with COPD or CHF. The present findings were based on the KEE model, but it remains uncertain

whether the findings also apply during more intense exercise involving a larger muscle mass or other muscle groups. It is difficult to find "matched" individuals that are healthy, but still has a very low level of physical activity, making it problematic to compare groups if there are fundamental differences in physical fitness. The effect sizes of these variables ranged from small to large, due to the small number of included patients and the large standard deviations.

Clinical implications

Exercise training, often being conducted on a two-legged bike ergometer, is known to be one of the most effective treatments for improving quality of life and to increase exercise capacity in both CHF and COPD patients, mostly thought to be caused by "central" improvement (Hunt et al., 2005; Stav et al., 2009; Mccarthy et al., 2015; Spruit et al., 2016; Paneroni et al., 2017; Gao et al., 2021). Based on our data and the current literature it seems plausible that there is a potential for improvements of the peripheral oxygen conductance in skeletal muscle in COPD and CHF patients even if cardio-pulmonary function stays unaltered.

Conclusion

Disease-specific factors may play a role in peripheral exercise capacity in patients with COPD and CHF. Thus, low convective O_2 transport to contracting muscle seemed to predominate the peripheral exercise limitation in COPD during small muscle mass exercise, whereas muscle diffusive O_2 transport was unresponsive to exercise in CHF.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethical Committee of the Capital Region of Copenhagen (H-2–2013–150; H-3–2013–048). The patients/participants provided their written informed consent to participate in this study.

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Author contributions

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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