Muscle fibre satellite cells are located at a greater distance from capillaries in patients with COPD compared with healthy controls

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Abstract

Background COPD is a disease characterised by skeletal muscle dysfunction. A spatial relationship exists between satellite cells and muscle fibre capillaries, which has been suggested to be of major importance for satellite cell function. In the present study we compared the spatial relationship between satellite cells and capillaries in patients with COPD and age-matched healthy older adults.

Methods Muscle biopsies were obtained from the *vastus lateralis* of n=18 patients with COPD (8 female, 10 male; age 66±5 years, mild-to-severe airflow obstruction) and n=18 age-, sex- and body mass index-matched healthy control adults (8 female, 10 male; age 68±5 years). Immunohistochemistry was used to assess type I/II muscle fibre size, distribution, myonuclear content, satellite cell number and fibre capillarisation. In addition, type I/II muscle fibre satellite cell distance to its nearest capillary was assessed.

Results The percentage of type II muscle fibres was significantly greater in patients with COPD (62±10%) compared with controls (50±12%, $p<0.05$). Muscle fibre capillarisation was significantly lower in patients with COPD compared with controls ($p<0.05$). While satellite cell content was not different between groups, type I and type II satellite cell distance to its nearest capillary was significantly greater in patients with COPD (type I: 21.3±4.8 µm; type II: 26.7±9.3 µm) compared with controls (type I: 16.1±3.5 µm; type II: 22.7±5.8 µm; $p<0.05$).

Conclusion Satellite cells are located at a greater distance from their nearest capillary in patients with COPD compared with age-matched controls. This increased distance could play a role in impaired satellite cell function in patients with COPD.

Introduction

Skeletal muscle dysfunction is a well-recognised extrapulmonary manifestation in patients with COPD [1]. Key features include predominant lower-limb muscle weakness [2], muscle atrophy [3, 4], reduced endurance capacity [5] and a shift towards type II muscle fibres [6], all of which are associated with exercise intolerance and poor disease prognosis, independent of the degree of lung function [1].

Ageing *per se* is characterised by type II muscle fibre atrophy, which is accompanied by a decline in number and function of type II muscle fibre stem cells, also known as satellite cells [7–9]. Muscle satellite cells play a

crucial role in supporting muscle fibre homeostasis, repair and reconditioning [10–13]. In response to appropriate cues (*e.g.* exercise or injury), satellite cells become activated after which they proliferate and subsequently differentiate to provide additional myonuclei to support the multi-nucleated muscle fibre or return back to quiescence to maintain the satellite cell pool size [10]. The reduction in satellite cell number and/or function is an important contributing factor in the impaired muscle fibre repair response after injury and/or adaptive response following exercise, and as such, reduced muscle tissue health and function with age [10].

The muscle fibre microvascular network is critical for growth factor and/or cytokine distribution and is essential for the myogenic programme [14]. However, in tandem with the decline in type II muscle fibre size and satellite content/function, muscle fibre capillarisation declines specifically in type II muscle fibres with age [15, 16]. Additionally, satellite cell loss has been shown to be proportionate to capillary loss in humans, with satellite cells being strongly colocalised with the remaining capillaries [17]. So, we have shown that muscle fibre capillarisation is a determining factor in the muscle satellite cell pool expansion following exercise [18]. Moreover, a spatial relationship between the muscle fibre capillary network and satellite cells has been identified, with type II muscle fibre satellite cells located ±27% further away from their nearest capillary in healthy older compared with young adults [15]. This increased spatial distance between satellite cells and capillaries has been suggested to be a key factor in the impaired muscle satellite cell function during post-exercise recovery in older adults [15, 19]. While muscle satellite cell number does not appear to differ between patients with COPD and healthy controls [20, 21], satellite cell function (*i.e.* proliferation capacity) is significantly reduced in patients with COPD [20, 22]. Furthermore, the muscle tissue of patients with COPD is not only characterised by substantial muscle fibre atrophy, but also by an increased loss in muscle fibre capillarisation compared with healthy controls [23, 24]. However, whether the anatomical relationship between muscle satellite cells and capillaries is further distorted in COPD, which may potentially explain the reduced satellite cell function in these patients, remains to be established. Therefore, the present study assessed the distance between muscle fibre capillaries and satellite cells in COPD patients compared with healthy older adults. For exploration we additionally assessed whether the satellite cell distance to its nearest capillary was associated with muscle fibre size, fibre type distribution and various indices of muscle fibre capillarisation in patients with COPD and healthy controls.

Methods

Participants

18 patients with COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [25] (n=10 males and n=8 females) were recruited at the Respiratory Medicine Department outpatient consultation of Jessa Hospital (Hasselt, Belgium). An additional n=18 age-, sex- and body mass index (BMI)-matched healthy older adults (n=10 males and n=8 females) were recruited in the greater area of Hasselt University (Hasselt, Belgium) and Maastricht University (Maastricht, the Netherlands) as controls. Inclusion and exclusion criteria have been reported previously [26] (see supplementary material for more details). The present retrospective study used baseline data from two randomised controlled trials performed in patients with COPD and healthy older adults (ClinicalTrials.gov identifier NCT02770417, Belgian study registration number B243201628086; and International Clinical Trials Registry Platform (https://trialsearch.who.int) identifier NTR7681) [26]. All participants provided written informed consent before inclusion in the study. The study was approved by the local Medical Research Ethics Committees (Maastricht University, the Netherlands, and Jessa Hospital and Hasselt University, Belgium) and complied with the guidelines set out in the most recent version of the Declaration of Helsinki.

Clinical parameters

From all participants, age, sex, body weight and height were obtained and BMI was calculated. Participants completed the modified Medical Research Council scale for dyspnoea (mMRC). Patients scoring mMRC grade 2 or higher were classified as severely dyspnoeic [25]. Next, participants completed the COPD assessment test (CAT); patients scoring ⩾18 points were classified as highly symptomatic [27]. Spirometry was performed in accordance with the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines [28, 29]. Walking exercise capacity was assessed *via* a 6-min walking test in a 30-m long hallway [30]. These clinical outcome parameters were assessed in all (n=18) patients with COPD and a subgroup (n=8) of healthy controls.

Muscle biopsy sampling and analyses

A muscle sample was obtained from the middle region of the *vastus lateralis*, approximately 15 cm above the patella and 3 cm below entry through the fascia, by using the percutaneous needle biopsy technique [31]. The muscle samples were processed and stored as described previously [26, 32]. Immunohistochemistry combined with fluorescent microscopy was used to determine various muscle fibre characteristics in all muscle biopsy samples (figure 1 and figure 2). Please see supplementary material for details.

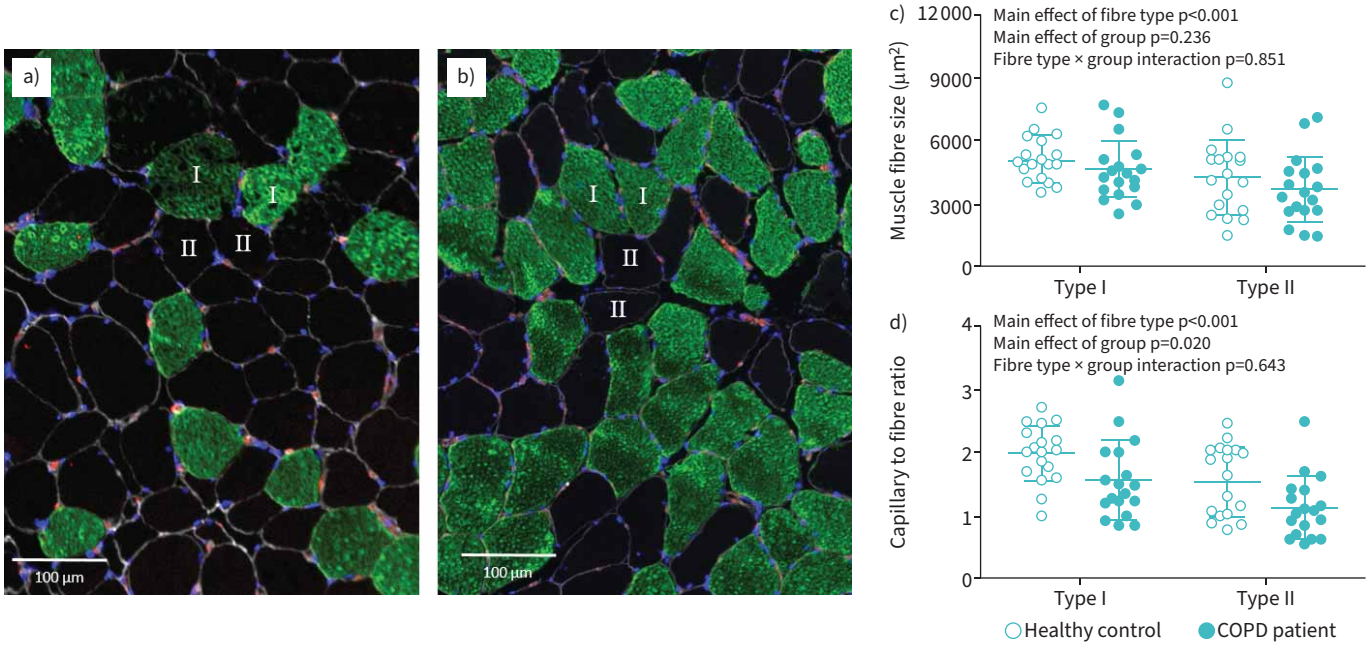

FIGURE 1 Representative images for assessment of type I and type II skeletal muscle fibre distribution, fibre size, myonuclear content and capillarisation in a) patients with COPD and b) healthy older adults. Myosin heavy chain (MHC)-I (green) plus laminin (white) plus 4′,6-diamidino-2-phenylindole (DAPI) (blue) plus CD31 (red) staining. Type I and type II c) muscle fibre size and d) capillary-to-fibre ratio. Data are presented as mean±SD, as well as individual data points.

Statistical analyses

Descriptive data were expressed as mean±SD or median (quartile 1–quartile 3), as appropriate. Differences in clinical and muscle fibre characteristics between patients with COPD and healthy controls were assessed by an independent-samples t-test or Mann–Whitney U-test. Differences in muscle fibre characteristics was evaluated by repeated measures ANOVA with fibre type (I *versus* II) as a within-subject factor and group (patients with COPD *versus* healthy controls) as a between-subject factor. Explorative correlation analyses were performed to investigate the relationship between various muscle fibre characteristics within both patients with COPD and healthy controls, using Pearson (r) correlation or Spearman rank (ρ) correlation analyses. A significance value of r or ρ of 0–9 was regarded as "very weak", 0.2–0.39 as "weak", 0.40–0.59 as "moderate", 0.6–0.79 as "strong" and 0.8–1 as "very strong" correlation. Statistical significance was accepted as $p<0.05$. All calculations were performed using SPSS (SPSS version 27.0, IBM Corp., Armonk, NY, USA).

Results

Clinical characteristics

Age, height, weight and BMI were no different between patients and controls. Patients with COPD had a mild-to-severe degree of airflow limitation, resulting in a lower forced expiratory volume in 1 s (FEV_1) compared with healthy controls ($p<0.05$; table 1). Patients with COPD scored higher on the CAT compared with healthy controls ($p<0.05$; table 1), with four patients (22%) being highly symptomatic. The 6-min walk distance was lower in patients with COPD compared with controls ($p<0.05$; table 1).

Muscle fibre type distribution, size and myonuclear content

The percentage of type I muscle fibres was lower in patients compared with controls (table 2; $p<0.05$). No significant fibre type × group interaction was observed for muscle fibre size and myonuclear content. For muscle fibre size, a main effect of fibre type ($p<0.001$) was observed, with type II (COPD 3666±1605 μm^2 and controls 4264±1811 μm^2) being smaller than type I muscle fibres (COPD 4611±1428 μm^2 and controls 5141±1075 μm^2). No significant difference was observed in type I and type II muscle fibre size between patients with COPD and healthy controls (figure 1c). A main effect of fibre type ($p<0.001$) was observed for myonuclear content, with type II showing lower myonuclear number per fibre than type I muscle fibres, with no difference between groups (table 2).

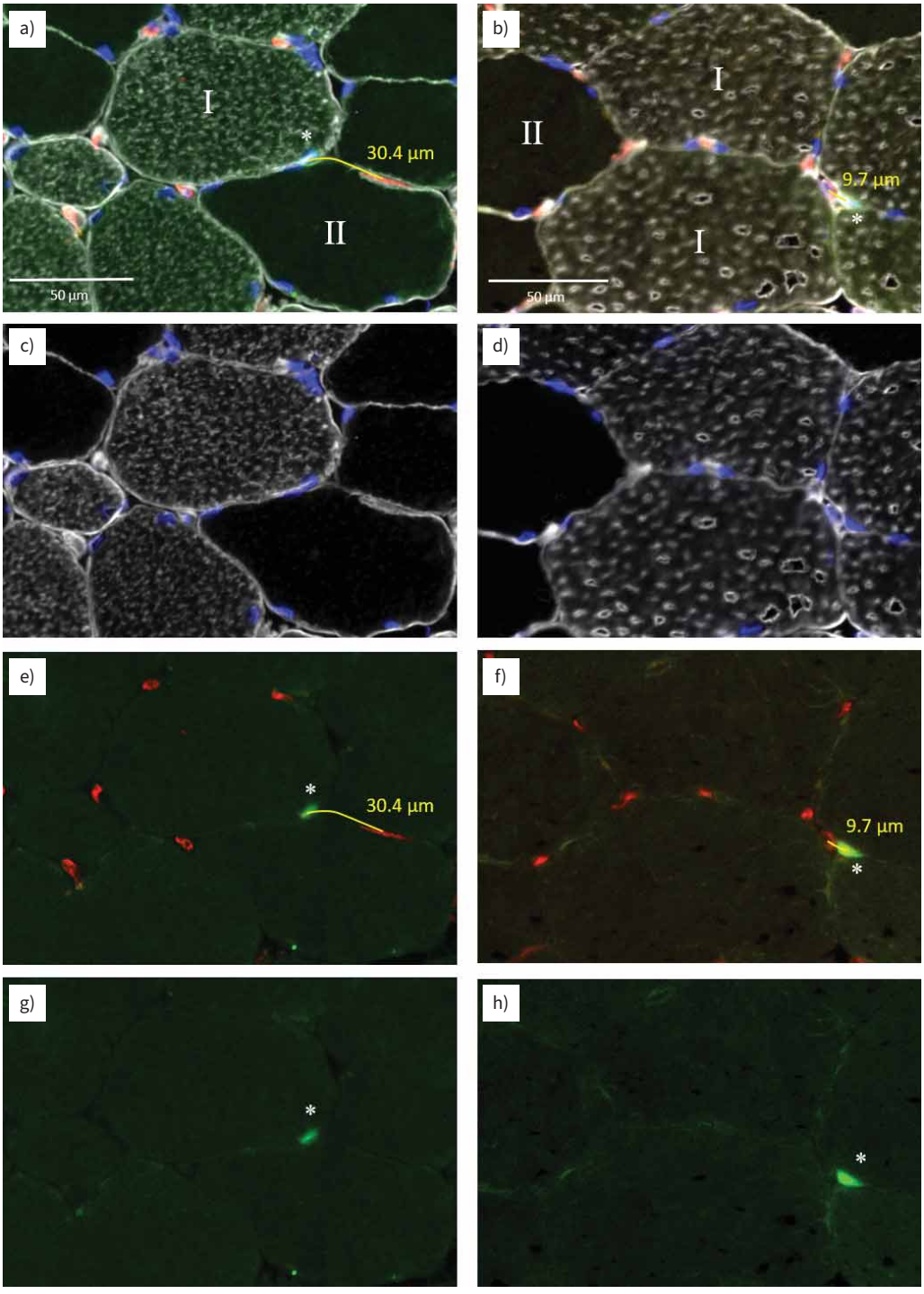

FIGURE 2 Representative images for assessment of type I and type II skeletal muscle satellite cell content and satellite cell distance to its nearest capillary in a,c,e,g) patients with COPD and b,d,f,h) age-matched controls. a,b) Myosin heavy chain (MHC)-I (white) plus laminin (white) plus 4′,6-diamidino-2-phenylindole (DAPI) (blue) plus Pax7 (green) plus CD31 (red) staining. c,d) MHC-I, laminin and DAPI. e,f) CD31 and Pax7. g,h) Pax7 only. Yellow line indicates the measurement of satellite cell distance to its nearest capillary. *: satellite cell.

Muscle fibre capillarisation

No significant fibre type × group interaction was observed for muscle fibre capillary contacts (CC), capillary-to-fibre ratio (C/F*i*), capillary-to-fibre perimeter exchange (CFPE) index or capillary density (CD). For muscle fibre CC, C/F*i* and CFPE index, a main effect of fibre type (all $p<0.001$) and group (all $p<0.05$) was observed. Type II muscle fibre CC, C/F*i* and CFPE index were significantly lower compared with type

TABLE 1 Participants' characteristics of healthy controls and patients with COPD

	Healthy controls (n=18)	Patients with COPD (n=18)
Sex, female/male	8/10	8/10
Age, years	68 ± 5	66 ± 5
Height, m	1.71 ± 0.09	1.67 ± 0.07
Weight, kg	75.0 ± 13.7	71.8 ± 14.6
BMI, kg·m^{-2}	25.6 ± 3.0	26.0 ± 5.5
FEV_1, L[#]	3.0 ± 0.6	1.6 ± 0.6*
FEV_1, % of predicted[#]	104 ± 13	57 ± 17*
FEV1/FVC, %[#]	74 ± 8	58 ± 10*
GOLD stage I, II, III and IV, n (%)[#]		3 (17), 10 (56), 4 (22), 1 (5)
mMRC dyspnoea score, points[#]	0 (0–0)	1 (1–2)*
COPD assessment test, points[#]	3 ± 2	14 ± 6*
COPD assessment test ⩾18 points, n (%)[#]	0 (0)	4 (22)*
6-min walking distance, m[#]	661 ± 67	512 ± 75*
6-min walking distance, % of predicted	102 ± 8	83 ± 12*

Data are presented as n, mean±SD, median (quartile 1–quartile 3) or n (%), as appropriate. BMI: body mass index; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; mMRC: modified Medical Research Council scale for dyspnoea. #: assessed in n=18 patients with COPD and n=8 healthy controls. *: significantly different compared with healthy controls, p<0.05.

I muscle fibres in both groups. Type I and type II muscle fibre CC, C/*Fi* and CFPE index were significantly lower in patients compared with controls (figure 1d and table 3). No significant difference in CD was observed between type I and type II muscle fibres or between groups (table 3).

Satellite cell number and distance to nearest capillary

No significant fibre type × group interaction was observed for muscle fibre satellite cell number and distance to nearest capillary. Type II muscle fibre satellite cell number was significantly lower compared with type I muscle fibres, in both patients with COPD (type I 0.061±0.032 *versus* type II 0.039±0.016 satellite cells per fibre) and controls (type I 0.078±0.024 *versus* type II 0.043±0.016 satellite cells per fibre) (main effect of fibre type p<0.001; figure 3a). No difference was observed in type I and type II muscle fibre satellite cell number between groups. For satellite cell distance to nearest capillary a main effect of fibre type (p<0.001) was observed, indicating that the distance was significantly greater in type II compared with type I muscle fibres in both groups (figure 3b). In addition, type I (COPD 21.3±4.8 *versus* healthy control 16.1±3.5 µm) and type II (COPD 26.7±9.3 *versus* healthy control 22.7±5.8 µm) muscle fibre satellite cell distance to the nearest capillary was significantly greater in patients with COPD compared with healthy controls (main effect of group, p<0.05; figure 3b).

Correlation analyses

Muscle fibre type distribution

No correlation was observed between the percentage of type I muscle fibres and type I/II muscle fibre size in both groups (data not shown). The percentage of type I muscle fibres was not significantly correlated with any of the type I/II muscle fibre capillarisation indices (data not shown).

TABLE 2 Muscle fibre characteristics in healthy controls and patients with COPD

	Fibre type	Healthy controls (n=18)	Patients with COPD (n=18)
Muscle fibre type distribution, %	I	50 ± 12	38 ± 10*
	II	50 ± 12	62 ± 10*
Muscle fibre type distribution, % CSA	I	56 ± 16	44 ± 14*
	II	44 ± 16	56 ± 14*
Myonuclei, number per fibre	I	3.24 ± 0.84	3.16 ± 0.80
	II	2.93 ± 1.06[#]	2.77 ± 0.68[#]
Myonuclear domain size, µm^2	I	1643 ± 298	1465 ± 269
	II	1465 ± 342[#]	1286 ± 324[#]

Data are presented as mean±SD. CSA: cross-sectional area. #: significantly different compared with type I muscle fibres within the same group, p<0.05. *: significantly different compared with the healthy control group for the same fibre type, p<0.05.

TABLE 3 Muscle fibre capillarisation in healthy controls and patients with COPD

	Fibre type	Healthy controls (n=18)	Patients with COPD (n=18)
Capillary contacts	I	4.40 ± 1.04	3.39 ± 1.31*
	II	3.77 ± 1.29#	2.87 ± 1.21#,*
	Mixed	4.12 ± 1.07	3.06 ± 1.23*
CFPE index, capillaries per 1000 µm	I	6.32 ± 1.32	5.32 ± 1.68
	II	5.05 ± 1.11#	4.15 ± 1.41#,*
	Mixed	5.69 ± 1.15	4.60 ± 1.47*
Capillary density, capillaries per mm^2	I	414 ± 103	360 ± 197
	II	373 ± 89	353 ± 157
	Mixed	391 ± 90	355 ± 129

Data are presented as mean±SD. CFPE: capillary-to-fibre perimeter exchange. #: significantly different compared with type I muscle fibres within the same group, p<0.05. *: significantly different compared with the healthy control group for the same fibre type, p<0.05.

Satellite cell distance to nearest capillary

No significant correlation was observed between type I or type II satellite cell distance to its nearest capillary and fibre type distribution or size in patients with COPD and controls (supplementary table S2). Type I and type II muscle fibre satellite cell distance to nearest capillary was (or tended to be) significantly correlated with type II muscle fibre size in controls (type I: r=−0.528, p=0.036; type II: r=−0.465, p=0.070). In contrast, no correlation was observed between type I or type II muscle fibre satellite cell distance to nearest capillary and (type I, type II or mixed) muscle fibre size in patients with COPD (supplementary table S2). Interestingly, while no significant correlations were observed for type I fibres, type II muscle fibre satellite cell distances to the nearest capillary showed moderate to strong negative correlations with various indices (CC, C/F*i* and CFPE index) of type II (and/or mixed) muscle fibre capillarisation in controls (supplementary table S2). In contrast, significant moderate to strong correlations were only observed between type I muscle fibre satellite cell distance to nearest capillary and various indices (CC, C/F*i*, CFPE index and CD) of type I (and/or mixed) muscle fibre capillarisation in patients with COPD (supplementary table S2).

Discussion

This study shows that type I and II muscle fibre satellite cell distance to its nearest capillary is greater in patients with COPD compared with healthy controls. Type I and II muscle fibre capillarisation were significantly lower in patients with COPD compared with healthy controls, with no difference in satellite cell number.

One of the hallmarks of skeletal muscle ageing is type II muscle fibre atrophy, which is accompanied by a decline in type II muscle fibre myonuclear content [9]. In the present study, average type II muscle fibre

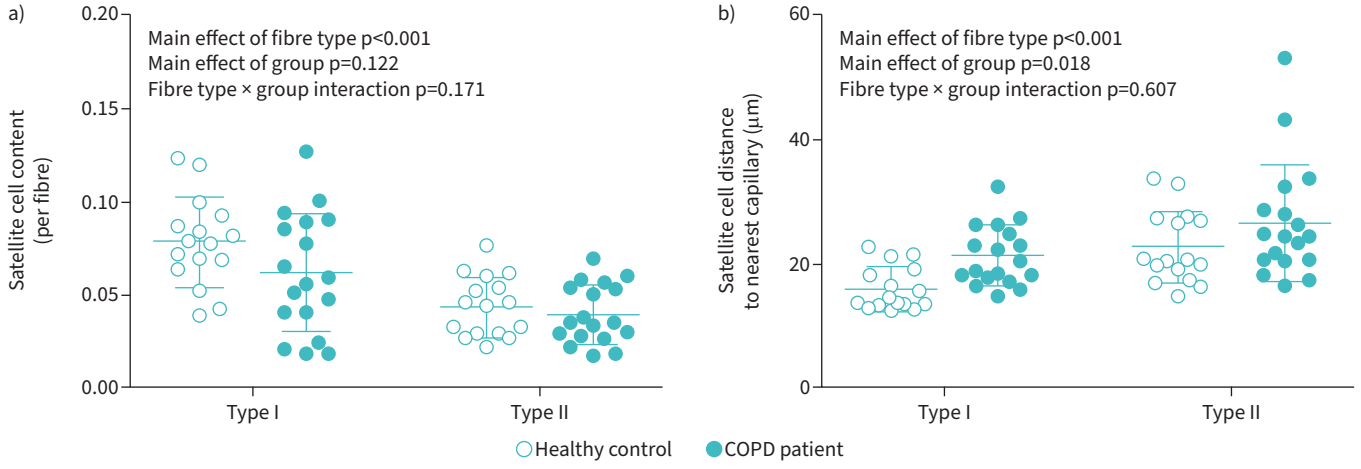

FIGURE 3 Type I and type II muscle fibre satellite cell a) content and b) distance to nearest capillary in patients with COPD and age-matched healthy controls. Data are presented as mean±SD, as well as individual data points.

size was ~15% smaller in patients with COPD compared with healthy controls; however, this difference was not statistically significant. In addition, no difference in type I or type II muscle fibre myonuclear content was observed between patients with COPD and age-matched controls. In the present study, the majority of patients (13 out of 18) were classified as having mild-to-moderate disease (GOLD stage 1–2). Included patients with COPD only had a moderate disease burden (78% of patients scored <18 points on CAT) and a preserved physical fitness (none of the patients walked <350 m in 6 min), which is considered to provide prognostic information to identify high-risk patients with COPD [27, 33]. Disease severity and physical fitness are associated with various skeletal muscle fibre characteristics [1, 6, 26, 34, 35]. This may explain the lack of statistical difference in muscle fibre size and/or myonuclear content between groups. Nonetheless, in line with previous studies [3, 6, 24, 26, 34], we show that the proportion of type II muscle fibres is substantially higher in patients with COPD compared with healthy, age-matched controls. This suggests that patients with COPD experience a major shift towards a more glycolytic muscle phenotype. In the current study, the inter-individual variation in the percentage of type II muscle fibres was considerable, ranging from 44% to 83%, in patients with COPD. Interestingly, however, fibre type distribution was not related to type I or type II muscle fibre size in these patients. This disconnect suggests that different mechanisms may be responsible for the changes in muscle fibre size and type shift typically observed in COPD, which warrants further investigation.

The diffusion and transport of oxygen, nutrients and other growth factors to support muscle fibre homeostasis and remodelling is ultimately limited by the surface area of the microvascular bed (*i.e.* capillaries). Here we show that both type I and type II muscle fibre capillarisation are lower in patients with COPD compared with controls, which is in line with others [35]. Whereas "normal" ageing is typically characterised by a loss of primarily type II muscle fibre capillaries [15, 16], the current study suggests that capillary rarefaction is not only exacerbated in patients with COPD but is also present in both muscle fibre types. Due to the higher oxidative capacity of the type I muscle fibres, muscle fibre capillarisation is generally much greater around type I compared to type II muscle fibres [15, 16, 32]. While "normal" ageing is characterised by a shift towards more type I muscle fibres [36, 37], the opposite is true in limb muscles of patients with COPD [3, 6, 24, 26, 34]. As most capillaries are generally shared between type I and type II muscle fibres, an elevated percentage of type I muscle fibres can (in part) compensate for the typically observed loss of type II muscle fibre capillaries in healthy older adults. The observation that patients with COPD exhibit a high percentage of type II muscle fibres, with already a low number of capillaries, further weakens the overall muscle fibre vascular network and most likely its ability to effectively supply (the already limited) oxygen and further impairs the distribution of circulating growth factors and/or cytokines important for muscle tissue homeostasis and reconditioning. Interestingly, however, the relative high percentage of type II muscle fibres was not correlated with any muscle fibre capillarisation outcome in patients with COPD. This suggests that the shift towards more type II fibres in patients with COPD may occur independently from the loss of muscle fibre capillaries *per se*.

A decline in muscle satellite cell function has been hypothesised to impair the muscle fibre reconditioning response to exercise and, as such, may be also of key importance in muscle tissue maintenance during ageing and/or disease [10]. In line with other studies [20, 21, 34], we report no difference in type I or type II muscle fibre satellite cell content between patients with COPD and controls. Previously, we [15, 19, 32, 38] and others [17] have shown that an anatomical relationship exists between muscle fibre capillaries and satellite cells. In line with our previous publications [15, 19, 32] we show that on average type II muscle fibre satellite cells are located significantly further away from their nearest capillary (~29%) compared with type I muscle fibres in healthy control adults. In the present study, we show, for the first time, that the distance of type I and type II muscle fibre satellite cells to their nearest capillary is significantly larger (~25%) in patients with COPD compared with healthy controls. An increased satellite cell distance to its nearest capillary has been hypothesised to impair optimal satellite cell function by hampering the delivery of growth factors and cytokines that regulate the myogenic programme [14]. We explored whether specific muscle fibre characteristics were differently associated with the satellite cell distance to its nearest capillary in patients with COPD and healthy controls. In healthy controls, we show that distance of type II, but not type I, muscle fibre satellite cells to their nearest capillary mainly relates to type II muscle fibre capillarisation (supplementary table S2). In contrast, in patients with COPD we observed significant correlations between the distance of type I, but not type II, muscle fibre satellite cells to their nearest capillary and type I/II and/or mixed muscle fibre capillarisation (supplementary table S2). We speculate that the increased distance of particularly type I muscle fibre satellite cells to their nearest capillary may be due to a greater loss of both type I and type II muscle fibre capillaries in patients with COPD and, as such, may further impair overall muscle satellite cell function in this patient population. However, due to the cross-sectional nature of the study design, no conclusion can be drawn on causality of the observed relationships. In the present study we were not able to control for habitual physical activity level and the

influence that polypharmacy may have on muscle fibre characteristics and the anatomical relationship between satellite cells and capillaries.

A dense muscle fibre capillary network is thought to be a prerequisite for optimal muscle satellite cell function and subsequent exercise training induced muscle fibre hypertrophy response [19, 32, 39, 40]. Exercise training is widely regarded as the cornerstone of pulmonary rehabilitation in patients with COPD [25]. The present study suggests that patients with COPD may experience a greater loss in muscle fibre capillarisation compared with healthy controls, which increases the anatomical distance with surrounding satellite cells, impairing muscle satellite cell function. Hence, interventions targeting angiogenesis, like aerobic exercise or high-intensity interval training, to increase muscle fibre capillarisation may prove valuable to further maximise the muscle growth response during subsequent resistance-exercise-orientated training programmes in patients with COPD. However, this remains to be established in more long-term experimental studies.

In conclusion, we show that patients with COPD have a greater percentage of type II muscle fibres and lower muscle fibre capillarisation compared with healthy controls. In addition, while satellite cell content is not different, satellite cell distance to its nearest capillary is substantially greater in patients with COPD compared with healthy controls. This increased distance could play a role in impaired satellite cell function in patients with COPD and, as such, may result in a compromised muscle fibre reconditioning response in this patient population.

Provenance: Submitted article, peer reviewed.

The present retrospective study used baseline data from two randomised controlled trials performed in patients with COPD and healthy older adults (ClinicalTrials.gov identifier NCT02770417, Belgian study registration number B243201628086; and International Clinical Trials Registry Platform (https://trialsearch.who.int) identifier NTR7681).

Ethics statement: All participants provided written informed consent before inclusion in the study. The study was approved by the local Medical Research Ethics Committees (Maastricht University, the Netherlands, and Jessa Hospital and Hasselt University, Belgium) and complied with the guidelines set out in the most recent version of the Declaration of Helsinki.

Conflict of interest: All authors report no conflict of interest.

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