Muscle fibre type shifting in the vastus lateralis of patients with COPD is associated with disease severity: a systematic review and meta-analysis

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ABSTRACT

Skeletal muscle dysfunction is a common feature in chronic obstructive pulmonary disease (COPD) which is associated with intrinsic muscular abnormalities. One of the most consistently reported alterations is a I to II fibre type shift in the vastus lateralis of these patients. Surprisingly, the relationship between this shift and COPD severity and phenotype remains unclear. This study was conducted to address the question whether vastus lateralis muscle fibre type proportions are associated with COPD disease severity and to provide reference values for vastus lateralis fibre type proportions in COPD. A systematic review and a meta-analysis were conducted for which muscle fibre type data and markers of disease severity were collected from the literature. The forced expired volume in one second (FEV₁), the FEV₁/forced vital capacity and the body mass index were positively associated with fibre type I proportion in COPD. A proportion of 51% for vastus lateralis fibre type I and 13% for fibre type IIX were calculated from the combined data as normal values for the typical GOLD stage III-IV COPD range of 60-70 years. Based on these reference values a fibre type I proportion below 27% and a fibre type IIX proportion above 29% were defined as pathologically abnormal. This review sheds new light on the relationship between skeletal muscle abnormalities and important hallmarks of the disease in severe COPD and identifies absence of data in GOLD I-II. In addition, for diagnostic purposes this review provides a frame of reference on fibre type composition in COPD.
INTRODUCTION

Peripheral skeletal muscle dysfunction is a well recognized disabling feature of chronic obstructive pulmonary disease (COPD), which manifests itself in reduced muscle strength and reduced endurance.[1] Loss of muscle strength can largely be attributed to the loss of muscle bulk, which in turn is caused by muscle fibre atrophy.[2] However, loss of muscle mass does not account for the attenuated endurance, suggesting that intrinsic muscular alterations are involved as well.[3] A disturbed oxidative phenotype, which is reflected by a fibre type shift from type I to II (or slow-twitch to fast-twitch) accompanied by reduced activities of enzymes involved in oxidative energy metabolism,[1] is one of the most obvious alterations in peripheral skeletal muscles of patients with COPD.

In almost all studies that examined peripheral muscle biopsies of patients with COPD, the target muscle of investigation has been the vastus lateralis (part of the quadriceps femoris). These studies, in which fibre type distribution itself was the main focus, consistently showed reduced fibre type I proportion in COPD patients as compared to healthy age-matched subjects. Subsequently, several biopsy studies were conducted in which muscle fibre type distribution was measured in the vastus lateralis to phenotype COPD patients for various other research questions. Surprisingly, although most of these reports present fibre type data in combination with relevant patient characteristics, very little information is available regarding the relation between fibre type proportions and hallmarks of COPD, such as FEV1, FEV/FVC, DLCO, PaO2, and BMI. This may be related to the fact that group sizes in the majority of these studies were too small and most studies comprised highly selected patient groups. Therefore, the main objective of the current report is to investigate a potential relation between fibre type proportions and markers of disease severity of COPD in a larger study population. For this, we conducted a literature search for relevant reports from which the required data was subsequently collected and combined.

Pulmonary rehabilitation in COPD has proven (evidence level A) to be very successful in terms of improving skeletal muscle dysfunction, exercise capacity and quality of life.[4] Regarding the physiological properties of type I fibres (fatigue resistant but slow contraction speed) and type II fibres (low fatigue resistance but strong and fast contractions), fibre typing could be a valuable diagnostic tool for choice and components of rehabilitation programs, such as strength or endurance training. It is therefore crucial to be able to assess when a certain fibre type proportion can be considered within the normal range or pathologically abnormal. However, limited data on quadriceps fibre type distribution is available in the literature for healthy subjects in the age range 60-70, which is the average age of COPD patients included in most studies. Furthermore, control group sizes of the individual studies published so far are too small to make an accurate prediction. Therefore, a secondary aim of the current study is to define reference values for vastus lateralis fibre type proportions for the COPD patients studied so far, using the combined data collected from the literature.
METHODS

Search strategy
We screened relevant electronic databases to find studies in which muscle fibre type proportions have been determined in the quadriceps femoris of patients with COPD. Reviews and non-human studies were excluded using available filter options and no language limitation was used. First PubMed (1966 to January 2007) was searched using the following search algorithm.

(fiber-type OR fiber-types OR fibre-type OR fibre-types OR fibre OR fibres OR fiber OR fibers OR "myosin heavy chain" OR "myosin heavy chains") AND (vastus OR quadriceps OR knee-extensor OR knee-extensors OR "skeletal muscle" OR "skeletal muscles") AND (copd OR "chronic obstructive pulmonary disease" OR emphysema OR bronchitis OR "chronic obstructive lung disease")

A similar search algorithm was also used to screen EMBASE (1989 to January 2007) and The Cochrane Library. The electronic searches were supplemented by scanning the reference lists from retrieved articles and relevant reviews to identify additional studies that may have been missed during the initial search. Online abstracts of relevant conferences were also screened (American Thoracic Society 2001-2006 and European Respiratory Society 2001-2005). From the selected reports, fibre type composition, predicted values of the FEV1, FVC, and DLCO, as well as the FEV1/FVC, BMI, and PaO2 were collected (units were converted to those presented in table 1 when required). The primary authors of articles/abstracts published in 2000 or later were contacted for missing data whenever required and/or possible († in table 1). For control values of quadriceps femoris fibre type proportions we used age-matched healthy control groups of the COPD related papers described above.

Statistics
Data are represented as the mean ± SD. In some papers the COPD groups were divided into subgroups; these were pooled to form a single group († in table 1) and the SD for these combined subgroups were calculated according to equation 1.

Inter-study analysis
Associations (for COPD populations only) between the study average fibre type proportions and study average FEV1, FEV1/FVC, DLCO, BMI, PaO2, and age were estimated using linear regression analyses with group size (N) as weight factor. For COPD and healthy controls weighed averages (with corresponding SD according to equation 1) were calculated for fibre type proportions I, IIA and IIX and the unpaired Student’s t test was used to test whether there were differences in these fibre type proportions. A two-tailed probability value of less than 0.05 was considered statistically significant.

Intra-study analysis
Heterogeneity was tested using the Q-test of homogeneity and subsequently heterogeneity was quantified using the I² index as described by Higgens et al.[5] Study specific mean differences (MD) of fibre type proportions between control and patient groups were calculated from those papers that contained these data. The corresponding SEs were calculated as $\sqrt{(SE^2_{controls} + SE^2_{patients})}$. A pooled MD was calculated by means of random effects meta-analysis using the STATA statistical software package.
RESULTS

The PubMed search for fibre types in the quadriceps femoris of patients with COPD yielded 38 citations. One additional publication, that we were aware of, did incorrectly not appear in the search results because fibre typing was not mentioned in the abstract.[6] Of these 39 papers, 20 were excluded for the following reasons; 15 were false positive hits (e.g. fibre type proportions were not studied or they were studied in skeletal muscles other than the quadriceps femoris), 2 studies had overlapping data ([7] with [8] and [9] with [10]), and 3 because of co-morbidity.[6, 11, 12] The remaining 19 articles were included in the current study (table 1), all biopsies being obtained from the vastus lateralis. Data from relevant conference abstracts was most often already published in the full articles that were found. However, 3 abstracts contained data not (yet) published elsewhere and these were therefore also included (table 1). The search in EMBASE and The Cochrane Library did not yield any citations in addition to those found in PubMed or the online conference abstracts. The inclusion process is shown in figure 1. The collected data is presented in table 1.

Inter-study analysis

In COPD, there was a strong positive association between the FEV$_1$ %predicted and fibre type I proportion (r=0.56; p<0.001; figure 2A) and between the FEV$_1$/FVC and fibre type I proportion (r=0.57; p<0.001; figure 2B) as well. BMI was moderately associated to fibre type I proportion (r=0.34; p<0.001; figure 2F). DL$_{CO}$ was weakly but significantly associated to fibre type I proportion (r=-0.15; p=0.013; figure 2C). There were no significant relations between PaO$_2$ or age and fibre type I proportion (figures 2D,E). Because fibre types are always expressed proportionally to each other, opposite relations are per definition true for total fibre type II proportion. However, most of the 22 studies also distinguished between type IIA and IIX fibres and some weak to moderate relations were found: Fibre type IIA proportion was negatively associated with FEV$_1$ %predicted (r=-0.21; p<0.001), FEV$_1$/FVC (r=-0.32; p<0.001), and BMI (r=-0.14; p=0.010) and was positively associated with DL$_{CO}$ (r=0.37; p<0.001), and PaO$_2$ (r=0.18; p=0.002). Fibre type IIX proportion was positively associated with FEV$_1$/FVC (r=0.25; p<0.001) and DL$_{CO}$ (r=0.31; p<0.001).

Compared to the healthy age-matched controls (table 2) the overall fibre type I proportion was reduced in COPD (51% ± 12% vs 33% ± 14%; p=0.004) and fibre type IIX proportion was increased in COPD (13% ± 8% vs 26% ± 14%; p=0.006). The fibre type IIA proportion tended to be higher (7%) in COPD, but this did not reach statistical significance.
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N: study group size; BMI: body mass index; FEV₁: forced vital capacity in 1 second; FVC: forced vital capacity; DLₖₒ: diffusion capacity for carbon monoxide; HC: histochemistry; IHC: immunohistochemistry; SDS PAGE: gel electrophoresis analysis of myosin heavy chain isoforms; † calculated from combined subgroups; † additional data obtained from authors through personal communication, used with permission; † VC instead of FVC; ‡ calculated from group data presented in the paper; ‡ not all subjects had a muscle biopsy; †† data obtained from a related publication; †† determined in a figure; ‡‡ sum of fibre type proportions is not 100% because (small) proportions of hybrid fibres were excluded from analysis; ? indicates that the SD was not given and could not be calculated.

### Table 2. Vastus lateralis fibre typing in healthy age-matched controls.

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N: study group size; HC: histochemistry; IHC: immunohistochemistry; SDS PAGE: gel electrophoresis analysis of myosin heavy chain isoforms; * not all subjects had a muscle biopsy; † determined in a figure; ‡ sum of fibre type proportions is not 100% because (small) proportions of hybrid fibres were excluded from analysis.
**Intra-study analysis**

From the 22 selected studies, 11 included fibre type data of a healthy control group. In 3 of these studies the control group was not age-matched [16,19,20] and these studies were therefore excluded from this analysis (see flow diagram in figure 1). The Q-test of homogeneity indicated that there was no heterogeneity (fibre type I: Q=10.261, p=0.17; fibre type IIA: Q=8.467, p=0.21; fibre type IIX: Q=9.98, p=0.19). However, an \( I^2 \) index of about 30% (32%, 29% and 30% for fibre type I, IIA and IIX respectively) was found. Because this indicates that 30% of the variance can still be explained by heterogeneity it was decided to use a random effects model. The results of the meta-analysis based on the 8 remaining studies (table 2) for fibre type proportions are shown in figure 3. The pooled mean differences between patients and control groups in type I, IIA and IIX fibre proportions were 22% ± 5%, -7% ± 4% and -13% ± 4% respectively.

**DISCUSSION**

To date it is unclear whether changes in lower limb muscle fibre type distribution in COPD are related to disease severity. The most prominent marker of disease severity is the FEV\(_1\)[35] but surprisingly most of the currently reviewed papers did not mention a relation between FEV\(_1\) and fibre type proportion. In the current review all the group data of these individual studies were pooled and when the FEV\(_1\) was plotted against fibre type I proportion it became clear that the fibre type I proportion in the vastus lateralis of patients with COPD decreases with increasing disease severity. This relation also exists for the FEV\(_1\) corrected for the FVC. The currently observed positive relation between BMI and fibre type I proportion further underlines that fibre type I proportion declines with increasing disease severity, considering low BMI as an important marker of systemic disease severity.[36] For fibre type II these relations are the inverse, by the definition of fibre type proportions. Inverse associations between fibre type IIA proportion and markers of disease severity were indeed found, but not for the IIX proportion.

There are however some unexplored areas. From this review it became clear that most studies focused on GOLD stages III and IV, being the patients with more severe COPD. To study the natural course of muscle impairment in COPD it would be interesting to investigate muscle fibre type distribution in patients with mild to moderate COPD (stages I and II). The current review also suggests that there is no relationship between fibre type proportion and the PaO\(_2\). However, hardly any patients with severe hypoxemia (PaO\(_2\)<7.3 kPa) were studied. It is thus possible that severe hypoxemia contributes to altered fibre type proportion in the limb musculature of patients with COPD and therefore fibre type data from this specific subgroup of patients is required. Moreover, patients with moderate hypoxemia may suffer from frequent desaturations during exercise or sleep and the effect of intermittent hypoxemia on muscle abnormalities in COPD has never been studied as well. With respect to cachexia, the only indicator frequently reported in the included studies was the BMI. As mentioned earlier, the currently observed relation between BMI and fibre type I proportion underscores a fibre type I proportion association with disease severity. However, muscle tissue is located in the fat-free mass compartment. Fat-free mass has recently been identified as better predictor of mortality and thus marker of systemic disease than BMI in COPD.[37] Although BMI was weakly associated with fibre types, it remains unclear to what extent muscle wasting per se contributes to fibre type redistribution in COPD. Another aspect that is unclear to date is whether fibre type redistribution is comparable between the COPD subtypes emphysema and chronic bronchitis. The DL\(_{CO}\) generally is lower in the emphysema subtype. Although a weak
though statistically significant associations between the DL\(_{CO}\) and fibre type proportions were observed in the current review, the association between muscle fibre type composition and emphysema requires further investigation using more sensitive markers such as high resolution computed tomography.

An added value of the current research is that solid references values for fibre type proportions in healthy subjects in the typical age range (60-70y) for COPD GOLD stage III-IV can now be provided. Individual studies did consistently show reduced fibre type I proportion in vastus lateralis biopsies of COPD patients, which was clearly confirmed in the current study. The inter-study analysis revealed a mean difference of 22% and the intra-study analysis resulted in a similar difference of 18%. Likewise, fibre type IIX proportion was 13% higher in COPD in both analyses. However, taking into account the large variation in human muscle fibre type composition[38] we questioned what fibre type proportions can really be considered as pathologically abnormal? Based on the pooled mean of the included control groups, a p-value of 0.05 and an assumed normal distribution, a fibre type I proportion lower than 27% (51% - 1.96 × 12%) can be considered as abnormally low. Likewise, a fibre type IIX proportion higher than 29% (13% + 1.96 × 8%) can be regarded as abnormally high. These results were confirmed when the 8 control groups were extended with age-matched control groups from 9 additional non-COPD related papers (data not shown). These findings may have diagnostic value to identify muscle pathology as therapeutic target.

In the included studies several techniques for the determination of fibre type proportions have been used, but they all have in common that the distinction is based on the content of MyHC isoforms I, IIA, and IIX. The most classical method is based on histochemical staining of the MyHC ATPase activity after selective inhibition of the ATPase domains. Alternatively, immunohistochemistry can be applied using antibodies raised against the different MyHC isoforms. Another approach is to homogenize muscle tissue and separate the MyHC isoforms by gel-electrophoresis followed by quantification of the band-intensities after for example silver staining or western blotting. It is worth mentioning that when only studies in which fibre types were assessed using histochemistry were included in the analyses, the overall outcomes did not change (data not shown).

It must be acknowledged that in the present report interpretations of statistical data were made, whereby inferences about the nature of individuals were based upon aggregate between-study statistics collected for the group to which those individuals belong. In theory, these interpretations could therefore be incorrect, also referred to as the ecological fallacy. The best solution to these issue would be to collect the data of all the individuals of the included studies. However, the associations between fibre type proportions and the FEV\(_1\) or FEV\(_1\)/FVC are quite convincing. Moreover, the fact that the pooled mean differences in fibre type proportions calculated from the meta-analysis (the intra-study analysis) are similar to the differences calculated from the pooled control values and pooled COPD values (inter-study analysis) suggests that ecological fallacy does not play a significant role.

This systematic review shows that the reduction fibre type I proportion that occurs in the lower limb muscle of patients with COPD is strongly associated with disease severity. In addition, we provide a reliable indication of what can be considered as a reference (physiological) fibre type composition in the typical COPD age range of 60-70 years and beyond which limits this can be considered as muscle pathology.
LEGENDS

Equation 1. SDp is pooled standard deviation, N is the total sample size, ni is the sample size of the ith group, k is the number of groups.

Figure 1: Flow diagram of study inclusion for the inter-study and intra-study analyses.

Figure 2. Relationships between vastus lateralis fibre type I proportion and A) FEV1: forced expiratory volume in one second; B) FEV1/FVC (with FVC: forced vital capacity); C) DLco: diffusion capacity for carbon monoxide; D) PaO2: arterial oxygen tension; E) Age and F) BMI: body mass index. Circle sizes represent group sizes. Solid lines represent the weighted linear regression lines (if statistically significant only). Bold circles appear in cases of two overlaying identical data sets.

Figure 3. Forest plot showing the results of the random effects meta-analysis for the mean differences in A) muscle fibre type I proportion, B) muscle fibre type IIA proportion and C) muscle fibre type IIX proportion between control and patient groups. Box sizes represent quality of the study as 1/\sqrt{SE}. Note that IIA data was not provided in one of the eight studies.[22]

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$$SD_p = \sqrt{\frac{\sum_{i=1}^{k} (n_i - 1) s_i^2}{(N - k)}}$$
Potentially relevant studies retrieved from databases (n=42)

false positive hits excluded (n=15)

studies with overlapping data excluded (n=2)

Studies with adequate data on fiber type I proportion and disease severity (n=25)

studies excluded because of comorbidity (n=3)

Studies included for inter-study analysis (n=22)

studies without healthy controls excluded (n=11)

studies without age-matched controls excluded (n=3)

Studies included for intra-study analysis (n=8)
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