Bedside assessment of quadriceps muscle using ultrasound following admission for acute exacerbations of chronic respiratory disease

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Author contributions

NG, TH-D, SS and MS conceived the study. NG, TH-D, EC, and EV recruited patients and conducted the study. Data analysis was performed by NG, MM, SS and MS. All authors contributed to the writing of the paper.

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Running Head: Ultrasound measurement of quadriceps following acute exacerbation of chronic respiratory disease

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At a Glance Commentary

Scientific Knowledge on the Subject

Hospitalisation, and subsequent readmission, for exacerbations of chronic respiratory diseases are associated with worse health status and higher risk of death. Systemic effects, such as skeletal muscle dysfunction, are known to be of prognostic importance in the stable state, but its effects during severe exacerbations on long-term outcome are unknown.

What this Study Adds to the Field

Skeletal muscle dysfunction, measured using ultrasound, is an independent risk factor for hospital readmission. Patients with smaller quadriceps are more likely to be readmitted to hospital.

Abstract

Rationale: Hospitalisation represents a major event in patients with chronic respiratory disease with high risk of readmission, which over the longer term may be related more closely to the underlying condition of the patient, such as skeletal muscle dysfunction.

Objectives: We assessed the risk of hospital readmission at one year, including measures of lower limb muscle as part of a larger clinical trial.

Methods: Patients hospitalised with an exacerbation of chronic respiratory disease underwent measures of muscle function including quadriceps ultrasound. Independent factors influencing time to hospital readmission or death were identified. Patients were classified into four quartiles based on quadriceps size and compared.

Results: 191 patients (mean age 71.6 [SD 9.1] years) were recruited. 130 (68%) were either readmitted or died. Factors associated with readmission or death were age (odds ratio 1.05, 95% CI 1.01-1.08; p=0.015), MRC dyspnoea grade (4.57, 2.62-7.95; p<0.001), home oxygen use (12.4 4.53-33.77; p<0.001), quadriceps cross sectional area (Q_{csa}) (0.34, 0.17-0.65, p=0.001) and hospitalisation in the previous year (4.82, 2.42-9.58; p<0.001). In the multivariate analyses, home oxygen use (4.80, 1.68-13.69; p=0.003), MRC dyspnoea grade (2.57, 1.44-4.59, p=0.001), Q_{csa} (0.46, 0.22-0.95; p=0.035) and previous hospitalisation (3.04, 1.47-6.29; p=0.003) were independently associated with readmission or death. Patients with the smallest muscle spent more days in hospital than those with largest muscle (28.1 (SD 33.9) days versus 12.2 (SD 23.5) days; p=0.007).

Conclusions: Quadriceps muscle measured using ultrasound in the acute care setting is an independent risk factor for unscheduled readmission or death, which may have value both in clinical practice and for risk stratification.

Abstract Word Count: 257

MeSH terms:

1) Pulmonary Disease, Chronic Obstructive
2) Muscle, Skeletal
3) Ultrasonography
4) Risk factors
5) Frail Elderly

Introduction

Hospitalisation for exacerbations of Chronic Obstructive Pulmonary Disease (COPD) and other Chronic Respiratory Diseases (CRD) are associated with worse health status and higher risk of death and subsequent readmission[1 2]. Measurements obtained during routine clinical care during hospitalisation can predict short term outcomes (for example in-hospital mortality and length of hospital stay)[3] but identifying those at risk of readmission over the longer term has proved more challenging. In the stable COPD population, previous exacerbations were the single most powerful predictor of subsequent events[4].

The risk of subsequent events following hospitalisation over the longer term may be related more closely to the underlying condition of the patient, including known systemic features of the disease such as skeletal muscle function. Previous studies have indicated that assessments of skeletal muscle function and mass predict mortality and symptom burden in the stable state independently from the severity and character of lung function impairment[5 6]. However, the predictive value of these indices in patients who have been hospitalised for an acute exacerbation (the population most at risk of adverse outcomes) is unknown. This is in part because technologies for assessing muscle function and mass that could be utilised at the bedside in acutely unwell subjects were not available. Simple measurements of muscle strength can be performed at the bedside but may be limited in this setting by their reliance on patient effort. Recent studies have suggested that ultrasound assessment of rectus femoris cross-sectional area (Q_{csa}) is a surrogate for

lower limb muscle mass which can be performed at the bedside and is independent of patient effort[7-9].

We hypothesised that measurements of lower limb muscle function (mass and strength) and functional exercise capacity performed during acute exacerbation of chronic respiratory disease would be a risk factor for hospital re-admission in the subsequent 12 months. This was investigated prospectively by recording these assessments in a cohort of patients recruited within 48 hours of acute hospital admission to a clinical trial of early rehabilitation where 12 month readmission rate was the primary outcome. In this study no difference was seen in hospitalisation rate, though a higher mortality rate was seen in those in which those that received early rehabilitation compared to usual care[10].

Methods

Study design and population

Subjects were recruited to a randomised controlled trial of an early rehabilitation intervention initiated during hospitalisation for acute exacerbation of chronic respiratory disease. The outcome of the trial including recruitment, inclusion and exclusion criteria have previously been described[10]. This was an observational analysis of a subgroup of participants recruited at one of the study centres (Glenfield Hospital, Leicester, UK) where ultrasound assessments of muscle mass were made. Eligibility for the current study was defined by the performance of Q_{csa} prior to randomisation. Because the study intervention had no effect on hospital readmission or functional performance (see[10]), the treatment and control

groups were combined for this analysis. Ethical approval for the study was given by the National Research Ethics Service, Nottingham REC 1 committee (09/H0403/76) and the study was registered on the ISRCTN (N05557928).

Outcome measures

Outcome measures were performed at recruitment (within 48 hours of acute admission) apart from spirometry and shuttle walk tests which were performed at hospital discharge because subjects were too unwell to perform them. Demographics, including MRC dyspnoea grade when at stable state (range 1-5), maximal isometric quadriceps strength (QMVC), measured using an isometric dynamometer[11], St George's Respiratory Questionnaire (SGRQ)[12]and rectus femoris cross sectional area were (Q_{csa}) taken at time of recruitment. Spirometry, measured to BTS/ARTP standards[13], functional exercise performance, measured using the incremental shuttle walk test (ISWT)[14] and endurance shuttle walk tests (ESWT)[15], were performed at discharge. Previous hospitalisation over the previous 12 months was identified from hospital and General Practice records and patient recollection.

Rectus femoris cross sectional area (Q_{csa})

Q_{csa} was measured using B mode ultrasonography (Hitachi). Images were captured using a 7.5 MHz 7cm linear probe. Rectus femoris of the right leg was used as a single muscle of the quadriceps as to allow whole muscle on a single image. Images were taken using the mid-distance between the greater trochanter and knee joint. This distance was measured on the anterior aspect of the thigh from the superior patellar border. The transducer was placed

perpendicular to the leg, with minimal pressure to provide an adequate view in order to minimise muscle compression. Oblique images were minimised by placing the transducer perpendicular to the muscle and ensuring minimal cross sectional area on the image. Images were frozen and the outline of the rectus femoris traced to obtain cross sectional area measurement. Q_{csa} was taken as the mean of three consecutive measurements within 10% from separate frozen images. In order to adjust for the size of the individual Q_{csa} was standardised to height squared.

Hospitalisation and admission data

The primary outcome of the study was hospital readmission at 12 months, which was collected from local hospital databases and GP records. Date of admission, and length of hospital stay were recorded at 12 months. Death was identified from hospital databases, GP records, and death certificates at 12 months.

Statistical analysis

A composite endpoint of either hospitalisation or death in the follow up year was used as the primary outcome measure in this study. Statistical analysis was conducted using STATA SE version 13 (Statacorp, USA)). Factors associated with hospitalisation were identified by univariate model by logistic regression. Factors tested were any baseline characteristic or outcome measure tested during the index admission. Multivariate analyses with the selected factors identified from the univariate analysis were conducted with binary logistic regression using a backward stepwise approach, offset by

exposure time. All analyses used the treatment allocation as a co-variate. Quadriceps mass, corrected by height squared, was divided into quartiles and the groups compared. Time to hospitalisation or death were compared using Cox regression. Total number of hospital days were compared using Kruskal-Wallis. Finally the clinical characteristics of the different groups identified were compared using independent ANOVA and Kruskal-Wallis for parametric and non-parametric continuous data as appropriate. Categorical measures were compared using chi-squared.

Results

Baseline characteristics and readmission

A total of 191 subjects underwent ultrasound of the Q_{csa} at baseline and were included in the analysis. This represented 96% of those enrolled at the Glenfield site in the original clinical trial (n=200). Baseline characteristics and measures are shown in table 1. 130 (68%) of the subjects were either readmitted or died in the year following their index admission, of which 121 were admitted and 9 died without readmission. Mean time to readmission or death was 120 (95% CI 101-139) days. Test-retest correlation between left and right Q_{csa} was 0.92 and ICC Cronbach's alpha = 0.95, which is similar to previous data[7 16].

Factors associated with time to hospitalisation or death

In the univariate logistic regression analysis of all available in-hospital assessments, the risk of either hospitalisation or death was calculated. Factors significantly associated with readmission were MRC grade, home

oxygen use, quadriceps cross sectional area and previous hospitalisation and age (table 2).

Significant factors from the univariate analysis were entered into a multivariate model using a backward stepwise approach. Factors associated independently with further hospitalisation were MRC grade, quadriceps cross-sectional area, previous hospitalisation and home oxygen. Age was not significantly associated (p=0.272). Odds ratios are shown in table 3.

Clinical characteristics of Patients of Different Quadriceps Mass

Participants were grouped into quartiles based on their quadriceps mass (quartile 1 range 0.816-1.407 cm^2/m^2, quartile 2 range 1.408-1.722 cm^2/m^2, quartile 3 range1.731-2.053 cm^2/m^2, quartile 4 range 2.059-3.500 cm^2/m^2) Baseline characteristics and demographics were compared between the groups (table 4). Subjects with a smaller Q_{csa} were more likely have a lower BMI and weight, and be weaker. There was a trend to worse FEV_1 in the smaller muscle groups and a longer index length of hospital stay.

Risk of Hospitalisation

In the year following the index admission the mean number of admissions were; quartile one (smallest muscle) 2.5 (95% CI 1.4-3.2), quartile two 1.3 (95% CI 0.8- 1.7), quartile three 1.5 (95% CI 1.0-2.0) and quartile four (largest muscle) 1.7 (95% CI 1.0-2.4) (p=0.025). Risk of hospitalisation using Cox regression was significantly higher in the smallest muscle group compared to largest (HR 1.99, 95% CI 1.21-3.27, p=0.007) (figure 1).

Number of Hospital Days

The number of hospital days in the year following the original admission was significantly higher in the smallest muscle group (p=0.007) with 28.1 (SD 33.9) days per subject in quartile one, 11.9 (SD19.0) in quartile two, 12.9 (SD 23.1) in quartile three and 12.2 (SD 23.5) in the largest muscle group (quartile four) (figure 2).

Mortality

13 (28%) of the smallest muscle group (quartile one) died compared with 10 (21%) of quartile two, 7 (15%) of quartile three and 5 (10%) of the largest muscle group (quartile four) with no difference between groups at 12 months (p=0.145). No difference in mortality was seen when correcting for MRC dyspnoea grade, previous hospitalisation, home oxygen and treatment allocation using cox regression (Smallest [reference variable] versus largest muscle groups, HR 0.43, 95% CI 0.15-1.21, p=0.110).

Mortality in the different quartiles were compared between the intervention and usual care groups to test if the excess mortality observed in the intervention group in the original trial was in a specific quadriceps size. The difference in mortality between intervention and usual care groups was similar in all quadriceps sub groups (see Table S1 in supplement, p=0.404).

Discussion

In this study we demonstrate that indices of muscle function measured early during hospitalisation influence the risk of re-admission over the subsequent 12 months. Q_{csa} but not muscle strength was independently associated with hospital re-admission or death and in a multivariate model this association remained significant alongside MRC dyspnoea grade, home oxygen use, and hospitalisation in the previous 12 months. Other measures of functional exercise performance (field walking performance) were also not significantly associated with readmission or death when measured at time of discharge from hospital. Muscle strength can also be performed during the acute illness but did not significantly influence readmission rate possibly because the volitional component of the assessment of strength was affected by the acute illness.

Q_{csa} measurement was used as a marker of muscle mass in the current study. This technique has been previously validated against CT measurements of quadriceps CSA [7] and DEXA[9] in COPD populations and has practical utility in the acute setting because it is independent of patient effort and can be performed at the bedside. Q_{csa} has previously been shown to be related to quadriceps strength and physical activity in stable COPD[17 18], and more recently been used to demonstrate progressive wasting in the intensive care environment[8]. It is likely to offer a more sensitive and reliable measure of muscle mass than other potential bedside measures such as bio-electrical impendence analysis which may not be able to detect regional loss of muscle

mass and is subject to variation due to shifts in hydration status which will be more important during the acute illness.

The impact of an exacerbation of respiratory disease on an individual will be determined by a combination of the severity of the acute event and the pre-morbid condition of the patient. As expected, our data confirm that measures of the physical condition of the patient can predict longer term re-admission risk but importantly indicate that non-volitional measures such as US remain discriminatory for this long term outcome even when performed during the acute event. This contrasts with volitional measurements such as muscle strength or walking performance which were not predictive when performed in this setting presumably because they were influenced by the acuity of the event.

Subjects in the smallest muscle group were more likely to be re-admitted or die (as expected) but also had more days in hospital over the subsequent 12 months. The small muscle group was characterised by muscle strength, with a trend to worse lung function and increased mobility limiting co-morbidities, which might explain the differences in re-admission rate although these factors were not significant in the multivariate regression analysis. It is possible that reduced Q_{csa} is a surrogate for general “frailty” in this population. Objective measurements of frailty (for example 4m gait speed) may also be of discriminatory value in predicting re-hospitalisation.[19].

We observed a higher proportion in the mean number of hospital days between the smallest and largest muscle groups, compared to number of hospital admissions. This suggests that skeletal muscle dysfunction is not only important for admission to hospital but also the severity and duration of

the admission. Better physical condition, represented by larger muscle mass, may allow patients who have been admitted to hospital to be better able to cope with the insult of a severe illness and hospitalisation[20 21], resulting in a shorter length of stay. Interventions to support this concept include Griffiths et al, who observed a decrease in hospital days, but no reduction in hospital admissions following pulmonary rehabilitation[22].

There was no statistical difference in mortality between the smallest muscle and largest muscle groups, though the absolute difference was 18% in favour of the largest muscle group. It is likely that this study was underpowered for this measure and further research would be of benefit, as other studies have suggested that reduced muscle function (mass and strength) is an independent predictor of mortality in COPD[5].

This is the first study to report the predictive value of measurements of muscle function taken during hospitalisation for exacerbations of chronic respiratory disease. Our data is in line with other studies suggesting that self-reported physical activity after discharge[23] and its recovery at one month predict the risk of re-admission[24].

Our study suggests that measures of muscle function can be recorded during hospital admission and may provide an opportunity for future risk stratification. The identification of such risk strata is of considerable interest because of the burden and cost of unscheduled hospitalisation to patients and health care systems and may inform treatment decisions (for example prioritisation of palliative or end of life care) or identify populations suitable for targeted interventions.

The original clinical trial for this study showed no difference in hospitalisation rate between an early rehabilitation intervention and usual care, though an increase in mortality was seen in the intervention group. These data demonstrate, based on quadriceps size, no difference in mortality or efficacy of the intervention in any particular subgroup. It is unknown whether other interventions, such as post exacerbation pulmonary rehabilitation or other targeted therapies would be more effective or more acceptable in patients with a better prognosis (i.e. those with larger muscle)[25-27].

Limitations to the analysis described in this study are acknowledged. Although the data was collected prospectively, it is a secondary, subgroup analysis of a clinical trial and risk stratification was not the purpose of the investigation. In any multivariate analysis, limitations are posed by the range of measures that are available. Q_{csa} using ultrasound is not a routinely measure. However, it is a simple measure to perform and bedside ultrasound equipment is already routinely available in the acute care setting for other indications, such as the investigation of pleural disease. We used the ISWT and ESWT as measures of maximal and sub-maximal exercise capacity. It is possible that other measures such as the 6 minute walk test (6MWT) may have been of prognostic use. However, both the ISWT and ESWT are well validated[28] and the ESWT and 6MWT have similar exercise response profiles[29], though there has been limited data for any of these tests in the acute hospital setting.

In conclusion, bedside assessment of lower limb muscle mass in the acute care setting is a risk factor for subsequent unscheduled admission to hospital for exacerbations of chronic respiratory disease. Such measurements may

have value in both in clinical practice and as a risk stratification tool in these populations.

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***Table 1**: Clinical characteristics of the subjects at time of recruitment (unscheduled hospitalisation, n=191)*

Variable	Mean	SD
Age (years)	71.6	9.1
BMI (kg/m^2)	26.0	6.0
Gender (% Male)	45.6%	
MRC grade when stable (median)	4	IQR 1
Smoking (% current)	22.1%	
Pack years (years)	46.0	35.9
Home oxygen use (%)	28.3%	
Number of co-morbidities (median)	2	IQR 2
Hospitalised in previous year (% yes)	52.4%	
Co-habitation (% living alone)	38.6%	
Principal Diagnosis		
COPD	80.6%	
Chronic asthma	6.8%	
Interstitial lung disease	5.8%	
Bronchiectasis	6.8%	
SGRQ Symptoms	76.59	18.14
SGRQ Activity	87.16	11.77
SGRQ Impact	57.95	18.51
SGRQ Total	70.06	14.01
Quadriceps strength (kg)	15.5	7.1
Quadriceps Cross sectional area (cm^2)	4.76	1.41
Heart rate (bpm)	85.9	17.8
Incremental shuttle walk test (m)	109	86
Endurance shuttle walk test (s)	112	IQR 144
FEV_1 on discharge (L)	0.97	0.44
FEV_1 % predicted (%)	44	19
FEV_1/FVC (%)	53	15
Medication		
Long acting muscarinic antagonist	52%	
Long acting beta agonist	56%	
Inhaled corticosteroid	77%	
Long term oral steroids	14%	

SGRQ: St George's Respiratory Questionnaire, FEV_1: Forced expiratory volume in one second

Table 2: *Factors associated with re-hospitalisation or death at one year in the univariate analysis. Odds ratios (OR) are shown for each separate variable. Significant variables are shown in bold. Odds ratios are per unit increase for continuous variables. For categorical variables the group for which the OR is shown is provided in the bracket.*

Variable	OR	95% CI	95% CI	p
Age	**1.05**	**1.01**	**1.08**	**0.015**
Gender (female)	0.67	0.35	1.28	0.226
BMI	0.96	0.91	1.02	0.164
Lives with (spouse)	0.56	0.27	1.16	0.118
MRC dyspnoea score	**4.57**	**2.62**	**7.95**	**<0.001**
Main diagnosis (ILD)	1.47	0.36	6.03	0.589
Smoking (yes)	0.46	0.11	1.87	0.280
Pack years	1.00	0.99	1.01	0.608
Long term oxygen therapy (yes)	**12.4**	**4.53**	**33.77**	**<0.001**
Quadriceps strength	0.96	0.92	1.01	0.124
Q_{csa}	**0.34**	**0.17**	**0.65**	**0.001**
ISWT	1.00	0.99	1.00	0.077
ESWT	1.00	1.00	1.00	0.210
FEV_1 on discharge	0.49	0.23	1.05	0.066
Total number of co-morbidities	0.87	0.69	1.12	0.282
Mobility limiting comorbidity* (yes)	0.69	0.36	1.32	0.263
Initial length of hospital stay	1.06	0.99	1.14	0.092
Previous hospitalisation (yes)	**4.82**	**2.42**	**9.58**	**<0.001**
Treatment allocation (intervention)	1.31	0.69	2.49	0.416

ILD: interstitial lung disease, Q_{csa}: Quadriceps cross sectional area over height squared, ISWT: Incremental shuttle walk test, ESWT: endurance shuttle walk test, FEV_1: Forced expiratory volume in one second, Hospitalisation in previous 12 months, *defined as significant cardiac disease, musculo-skeletal disease or vascular disease

Table 3: *Multivariate analysis of variables significantly predictive of hospitalisation or death in the 12 months following measurement. Odds ratios are per unit increase for continuous variables. For categorical variables the group for which the OR is shown is provided in the bracket.*

Variable	OR	95% CI		p
Long term oxygen therapy (yes)	4.80	1.68	13.69	0.003
MRC Dyspnoea Grade	2.57	1.44	4.59	0.001
Admitted in previous year (yes)	3.04	1.47	6.29	0.003
Quadriceps cross sectional area	0.46	0.22	0.95	0.035

Table 4: *Comparison of clinical characteristics of the smaller muscle (Q_{csa}<4.79cm^2) and larger muscle groups (Q_{csa} ≥4.79cm^2). Significant differences are shown in bold.*

Variable	Quartile 1 (Smallest) n=47		Quartile 2 N=48		Quartile 3 N=48		Quartile 4 (Largest) n=48		p
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Age (years)	73	9	72	10	71	9	70	8	0.287
Weight (kg)	**63.6**	**16.8**	**65.1**	**16.6**	**74.2**	**15.3**	**77.3**	**17.9**	**<0.001**
BMI (kg/m^2)	**22.7**	**4.6**	**24.8**	**5.4**	**27.6**	**5.5**	**28.8**	**6.4**	**<0.001**
QMVC (kg)	**12.6**	**7.1**	**13.9**	**5.7**	**18.1**	**7.7**	**17.1**	**6.6**	**<0.001**
ISWT (m)	109	86	100	91	119	85	110	83	0.815
ESWT (s)	103	82	133	202	127	97	131	99	0.725
Oxygen Saturations (%)	93	4	93	3	92	4	93	3	0.908
Heart Rate (bpm)	87	16	89	14	89	11	92	14	0.261
FEV_1(L)	0.90	0.39	0.86	0.39	1.03	0.40	1.09	0.54	0.060
FEV_1(% predicted)	41	19	44	19	46	17	47	21	0.441
MRC dyspnoea grade	4	0	4	1	4	1	4	1	0.281
Number of co-morbidities	3	2	2	2	2	1.5	2	2	0.148
Index length of hospital stay	7	7	5	6.5	6	5	5	5	0.070
Gender (% male)	49%		40%		44%		50%		0.717
Lives with (% alone)	46%		40%		47%		23%		0.158
Principal diagnosis (% COPD)	74%		85%		88%		75%		0.541
Admitted in previous year	66%		50%		48%		46%		0.188
Admitted ≥2 in previous year	32%		29%		19%		17%		0.217
Mobility limiting co-morbidity (%yes)	51%		35%		50%		29%		0.074

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Figure 1*: Cox regression curve of risk of hospitalisation or death for quartiles of different quadriceps muscle size. Covariates in the model are hospitalisation in the previous year, MRC dyspnoea grade and home oxygen use. Significant difference is present between smallest and largest muscle groups at 12 months (p=0.007).*

Figure 2: *Mean number of days spent in hospital in the year following the index admission. Groups shown are quartiles of quadriceps size, measured using ultrasound and corrected for patients' height. Error bars are 95% poisson confidence intervals.*