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ORIGINAL ARTICLE

Relation of respiratory muscle strength, cachexia and survival in severe chronic heart failure

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Abstract
Background Respiratory muscle (RM) function predicts prognosis in non-cachectic patients with chronic heart failure (CHF). We hypothesized that weakness of RM (maximum inspiratory mouth occlusion pressure, Pi_{max}) is a function of body mass index, and that outcome is more a function of BMI than of Pi_{max} or ventilatory drive (P0.1).
Subjects and methods We enrolled 249 CHF patients (11.2 % female, median age 54.2 years) at the German Heart Institute Berlin. Patients were in NYHA classes I/II/III/IV by n=16/90/108/35. All patients underwent tests of pulmonary function, RM (Pi_{max}, P0.1), cardiopulmonary exercise testing (peakVO2, VE/VCO2-slope), and right heart catheterization.
Results Mean follow-up time was 18 (1–36) months, 47 patients (18.9 %) died or underwent cardiac assist implantation. Pi_{max} correlated weakly with BMI (r=0.19), peakVO2 (r=0.15), and FEV1 (r=0.34, all p<0.02), and was lower in females compared to males (3.9±1.7 vs. 6.6±2.7 kPa; p<0.001). P0.1 correlated with pulmonary pressure (rho= 0.2; p<0.01) and peakVO2 (rho=−0.14; p<0.02). Neither Pi_{max} [hazard ratio (HR) 0.98; confidence interval (CI) 0.88–1.08] nor P0.1 (HR 0.52; 0.06–4.6) predicted survival. Multivariate regression analysis revealed gender, BMI, and FEV1 as cofactors of Pi_{max}, with only BMI (HR 0.87; CI 0.80–0.95) predicting survival independently. The lowest quintile in BMI had the worst outcome (log-rank χ^2=13.5, p=0.009).
Summary In CHF patients including cachexia and NYHA IV, Pi_{max} does not predict survival. Pi_{max} depends on gender, BMI, FEV1, and peakVO2, with only BMI and peakVO2 predicting survival. The impaired Pi_{max} in CHF might be a result of catabolism and weight loss and is not a predictive factor in itself.

Keywords Cachexia · Chronic heart failure · Respiratory muscle · Prognosis

Abbreviations

ACE	Angiotensin converting enzyme
ARB	Angiotensin receptor blocker
BMI	Body mass index
CHD	Coronary heart disease
CHF	Chronic heart failure
CI	Confidence interval
CO	Cardiac output
COPD	Chronic obstructive pulmonary disease
DCM	Dilative cardiomyopathy
ECCS	European Community of Coal and Steel
eGFR	Estimated glomerular filtration rate (MDRD formula)

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FEV1	Forced expiratory volume in 1 s
FVC	Forced vital capacity
IQR	Interquartile range
LVEDd	Left ventricular enddiastolic diameter
LVEF	Left ventricular ejection fraction
MVV	Maximum voluntary ventilation
NYHA	New York Heart Association functional class
PAPm	Mean pulmonary artery pressure
PCWP	Pulmonary capillary wedge pressure
peakVE	Peak ventilation per minute
$peakVO_2$	Peak oxygen uptake
$p_{ET}O_2$	End-tidal oxygen partial pressure
$p_{ET}CO_2$	End-tidal carbon dioxide partial pressure
Pi_{max}	Maximum inspiratory mouth occlusion pressure
P0.1	Inspiratory pressure at 0.1 s after start of tidal volume inspiration
RAPm	Mean right atrial pressure
SD	Standard deviation
$TLCO_{VA}$	Transfer factor for carbon monoxide per alveolar volume
VC	Vital capacity
VE	Ventilation volume per minute
VE_{max}	Ventilation volume per minute at maximum exercise
VE/VCO_2 slope	Slope of the relationship between ventilation and carbon dioxide output

1 Introduction

Both the clinical picture and the prognosis of patients with congestive heart failure (CHF) are characterized by impaired exercise tolerance and dyspnoea, and the impact of respiratory muscle dysfunction on these symptoms has been evaluated since the early 1990s [1–4]. These studies proved that weakness of respiratory muscles expressed as maximum inspiratory pressure Pi_{max} is not only a predictor of worse outcome in patients with CHF [5] but also an independent risk factor for cardiovascular events in an elderly normal population [6]. Several factors may contribute to this respiratory muscle weakness, among which are at cellular level a metabolic impairment and structural abnormalities of myocytes [7, 8] , and at tissue level an altered blood flow [9] and switch from type I into type II fibers [10]. Recent studies found structural tissue changes in the diaphragm of heart failure rats, with degradation of sarcomer and mitochondria and expansion of intermyofibrillar spaces [11]. At level of the entire organism, these processes result in general loss of skeletal muscle which impairs chemo- and baroreflex control independently from the peripheral chemoreceptors. This dysfunction of feedback may limit exercise and aggravate dyspnoea, as it was outlined in the "muscle hypothesis of CHF" [12]. Recently, a close relation between inspiratory muscle strength and pulmonary hypertension has been described in patients with left [13] and right [14] ventricular dysfunction.

But regardless of these cellular and functional explanations, the relation between respiratory muscle dysfunction and impaired exercise capacity is loose, and joining cofactors have to be assumed. So far, there are data of only one prospective study that proved the prognostic significance of maximum mouth occlusion pressure Pi_{max} and peak oxygen uptake $peakVO_2$ [5], but excluded explicitly patients with weight loss and cachexia. In extension of these findings, we hypothesized that just this presence or absence of wasting would determinate respiratory muscle weakness, and that the patients' prognosis is mainly depending on cachexia and the respiratory muscle is rather subordinated in this catabolic process. To prove this hypothesis, we analysed the data of a large study on CHF patients and pulmonary hypertension that has been published in part before [13]. In contrast to this former study, we included only patients with known BMI and documented weight measures within the last 6 months. Our assumptions were (a) a close relation between body mass index BMI and Pi_{max} and (b) a prognostic significance of this relation with regard to prognostic factors (e.g. LVEF, $peakVO_2$, serum sodium, and cardiac index) in CHF patients [15].

2 Methods

2.1 Study population

We enrolled 249 consecutive patients (11.2 % female) with mild to severe congestive left heart failure at the outpatient transplantation centre of the German Heart Institute Berlin. The original study contained 292 patients, and only the subjects with complete tests on respiratory muscle function and documented course of body weight were included in this analysis. The median age was 54.2 years [interquartile range (IQR) 11.8 years, range 20–66 years], and the aetiology of heart failure (defined as LVEF<40 % at rest) was based on left heart catheterisation: dilative cardiomyopathy in 168 (67.5 %) patients, coronary heart disease in 74 (29.7 %), congestive valvular disease in 7 (2.8 %), and 1 patient (0.3 %) suffered from a congenital but operated vitium. All patients had to be clinically stable, i.e. with no clinical or radiological signs of decompensation and with unchanged cardiac medication for at least 4 weeks. Patients were classified to NYHA I n=16 (6.4 %), NYHA II n=90 (36.1 %), NYHA III n=108 (43.4 %), and NYHA IV n=35 (14.1 %).

There were n=26 (10.4 %) patients suffering from cachexia. These patients were characterized by a BMI< 21 kg/m^2 (n=18 patients, 7.2 %) or by weight loss>6 % in the last year (n=10 patients, 4.0 %), with two of these patients matching both criteria of cachexia.

Since patients were included in the study between 1998 and 2002, medical therapy with beta blockade (64.3 %) and aldosteron inhibition (20.5 %) was not yet ubiquitary in CHF patients, whereas ACE inhibitors/angiotensin receptor blockers (95.6 %), diuretics (92.4 %), and oral anticoagulation (78.7 %) were widely used. Concomitant conditions that could influence respiratory muscles were diabetes mellitus (20.1 %), chronic renal failure (18.5 %), previous sternotomy (17.3 %), implanted cardioverter/defibrillator (19.7 %), and chronic obstructive pulmonary disease (COPD, 8.8 %). The QRS duration was prolonged to >120 ms in 155 patients (62.2 %), thus again representing the state-of-the-art before introduction of cardiac resynchronisation therapy.

The baseline clinical and functional characteristics of the patients are presented in Table 1. In addition to the parameters explained below, we applied the characteristical parameters of right heart catheterization: mean pulmonary artery pressure (PAPm), pulmonary capillary wedge pressure (PCWP), cardiac output (CO), and cardiac index (CI). The data collection and analysis were approved by the local ethics committee and have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Table 1 Clinical and functional characteristics of patients at baseline

Body mass index BMI (kg/m^2)	26.3±3.9
Cachectic by BMI<21 kg/m^2 (n, %)	18 (7.2 %)
Cachectic by BMI or weight loss (n, %)[a]	26 (10.4 %)
Systolic blood pressure (mmHg)	119±21
Diastolic blood pressure (mmHg)	72.5±11.5
Heart rate (min^{-1})	79±17
Sodium (mmol/L)	139.1±3.5
eGFR (mL/min/1.73 m^2)	74.2±2.2
Haemoglobin (mg/dL)	14.4±1.6
LVEF (%)	23.5±9.3
Cardiac index (mL/min/m^2)	2.2 [0.91]
NYHA	2.6±0.8
peakVO_2 (mL/kg/min)	14.3±4.8
VE/VCO_2 slope	34.0 [14.0]
FVC (% of predicted)	76.4±14.5
FEV1 (% of predicted)	74.7±17.4
FEV1%FVC	74.6±9.9
$TLCO_{VA}$ (% of predicted)	71.1±20.2
Pi_{max} (kPa)	6.3±2.7
P0.1 (kPa)	0.18 [0.17]
$P0.1/P0.1_{max}$ (%)	13.2 [12.4]

If not stated as number and percent, values indicate mean±standard deviation. Nonparametric variables are given as median with interquartile range in square brackets

eGFR estimated glomerular filtration rate (MDRD formula), *LVEF* left ventricular ejection fraction, *NYHA* New York Heart Association functional class, *FVC* forced vital capacity, *FEV1* forced expiratory volume in 1 s, $TLCO_{VA}$ transfer factor for carbon monoxide per alveolar volume, Pi_{max} maximum inspiratory pressure, *P0.1* inspiratory pressure at 0.1 s after inspiration start, $P0.1/P0.1_{max}$ relation of inspiratory pressure 0.1 after inspiration to pressure at maximum inspiration

[a] Weight loss was defined as unintended loss >6 % of body weight within 6 months

2.2 Pulmonary and respiratory muscle function tests

Vital capacity (VC), forced vital capacity (FVC), and forced expiratory volume in 1 s (FEV1) were measured in sitting position using a pneumotachograph (Erich Jaeger, MasterLabPro 4.2, Wuerzburg, Germany), and the ECCS predicted values for age, sex, and height were used [16]. Pi_{max} was determined at least three times through a flanged mouthpiece in deep inspiration from functional residual capacity against a shutter with a minor air leak preventing undesired glottis closure (Erich Jaeger, as above). Of three measurements with <5 % variability, the highest pressure was used for analysis. Mouth occlusion pressure P0.1 was assessed 0.1 s after the onset of inspiration during spontaneous breathing. Both Pi_{max} and P0.1 are expressed as positive values, although they are negative with respect to atmosphere. The ratio $P0.1/Pi_{max}$ was calculated to determine the inspiratory capacity per breath.

2.3 Exercise testing

A symptom-limited cardiopulmonary exercise test was performed on a treadmill according to the modified Naughton protocol [17]. Expired gas was sampled through a Rudolph mask, conveyed to a spirometer and to oxygen and carbon dioxide detectors (MedGraphics, Minnesota, USA). VO_2 and VCO_2, end-tidal expiratory gas concentrations $p_{ET}O_2$ and $p_{ET}CO_2$, and ventilation per minute VE were measured breath-by-breath. All patients were monitored with a continuous 12-lead electrocardiogram (CardioPerfect, Welch Allyn New York, USA) and non-invasive blood pressure measurement at rest, at every stage of exercise and during recovery. Exercise time was recorded, and symptoms at peak exercise were documented. All patients exercised until limited by symptoms. For peakVO_2, peakVCO_2, and peakVE, the highest readings of each parameter in the final 30 s of exercise were used. The maximum voluntary ventilation MVV was calculated by multiplying the forced expiratory volume FEV1 with the factor 41, and the ratio peakVE/MVV served as a measure of the utilisation of the breathing

reserve. Ventilatory efficiency during exercise was measured by plotting VE against VCO_2, values due to hyperventilation (acidosis) in the last minutes of exercise were excluded, and the slope of the revealed linear relationship (VE/VCO_2 slope) was calculated by linear regression and accepted if correlation coefficient was $r>0.95$.

2.4 Blood samples

Peripheral venous blood samples were taken at the beginning of the outpatients' visit after 30 min resting without eating or drinking before and analysed immediately.

2.5 Clinical course

All patients were followed by regular outpatient visits, and in case of missed visit by telephone calls to the patient or the home physician, so that a complete follow-up was available respectively the exact date of death was known for the deceased patients. The end-point was death from any course. Patients who underwent heart transplantation were followed until date of surgery and classified as survivors regardless of the postoperative outcome. Nine patients (3.6 %) showed a rapid deterioration and needed urgent implantation of a cardiac assist device. Because they were supposed to have died immediately without assist surgery, these patients were classified as non-survivors and represented 19 % of the overall mortality.

2.6 Statistical analysis

All data are given as mean±standard deviation for normally distributed variables, and as median with IQR in square brackets for non-normally distributed variables (i.e. age, time of follow-up, cardiac index, VE/VCO_2 slope, LVEF, P0.1, and $P0.1/Pi_{max}$). The normality of the data was verified with the Kolmogorov–Smirnov test. Differences between groups of patients (survivors/non-survivors) were identified by Student's unpaired t test if parametric, and by Wilcoxon signed-rank test if non-normally distributed. Univariate linear regression was utilised to evaluate the relationship between quantitative parameters, and the regression coefficient noted as "r". Spearman's correlations were necessary for the non-normally distributed parameters, and the resulting coefficient was discriminated as "ρ". Survival curves were calculated using the Kaplan–Meier method. Cox proportional hazard linear regression analysis was conducted to determine the association between a continuous variable (BMI, $peakVO_2$, PAPm) and time to adverse outcome. All analyses were performed using PASW 18.0 (2010, IBM Corp., Somers, New York).

3 Results

3.1 Respiratory muscle strength Pi_{max}

Higher anthropometric measures (height, weight, and BMI) were formally correlated with respiratory muscle strength Pi_{max} (cf. to BMI $r=0.19$, cf. to weight $r=0.29$, cf. to height 0.25, all $p\leq0.003$, see Fig. 1). A division of patients in quintiles proved an increase in Pi_{max} from low BMI (1st quintile BMI<23.2 kg/m^2 and $Pi_{max}=5.6\pm2.5$ kPa) to high BMI (5th quintile BMI>29.4 kg/m^2 and $Pi_{max}=7.4\pm2.9$ kPa, ANOVA $p=0.03$, Fig. 2). Pi_{max} of cachectic patients, i.e. with BMI<21 kg/m^2 or more than 6 % weight loss was lower than of the remaining patients (5.8±2.3 kPa vs. 6.4±2.8 kPa), but this trend did not reach significance ($p=0.23$).

Pi_{max} correlated with most parameters of pulmonary function, such as VC ($r=0.36$), FEV1 ($r=0.34$), $TLCO_{VA}$ ($r=0.2$; all $p\leq0.002$). There was no correlation of Pi_{max} with any of cardiac parameters (blood pressure, heart rate, PAPm, PCWP, cardiac index, LVEF, LVEDd, all r resp. $\rho<0.06$; $p>0.1$).

Pi_{max} was significantly lower in females (3.9±1.7 kPa) than in males (6.6±2.7 kPa; $p<0.001$). However, there were no differences between males and females in haemodynamic parameters (cardiac index, PAPm, RAPm, LVEDP), and in percentage of predicted values of pulmonary function (VC, FEV1, $TLCO_{VA}$), and of exercise parameters ($peakVO_2$, VE/VCO_2 slope). Concomitant diseases as COPD, diabetes mellitus, chronic renal failure, or previous sternotomy revealed no differences in Pi_{max}, P0.1, or $P0.1/Pi_{max}$. Similarly, a different medication (ACE-inhibitors, ARB, beta-blocker, diuretics, and aldosteron antagonist) or NYHA classification did not separate patients in relation to parameters of ventilatory muscle.

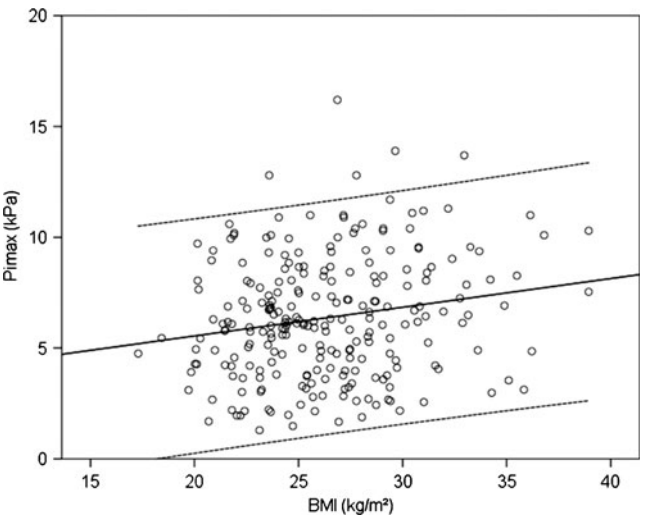

Fig. 1 Pi_{max} as a function of BMI. Pi_{max}=BMI 0.13+2.8; $r=0.19$; $p=0.003$. *Continuous line*, mean regression. *Dotted line*, 95 % confidence intervals

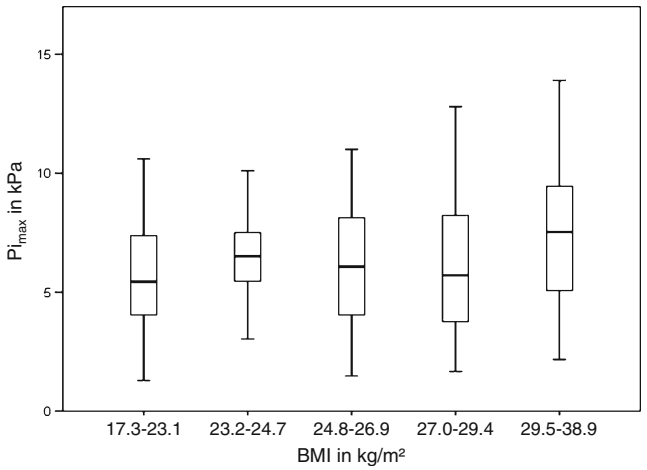

Fig. 2 Pi_{max} vs. quintiles of BMI. ANOVA p=0.03. *Boxes* indicate mean and 75th percentile, *error bars* indicate 90th percentile. Absolute values see below time axis

3.2 Ventilatory drive P0.1 and inspiratory effort per breath P0.1/Pi_{max}

Neither body mass index nor its constituents height and weight correlated with P=0.1 or P0.1/Pi_{max} (ρ=−0.1 to 0.006; p>0.1). Similarly, there was no difference between cachectic and non-cachectic patients regarding P0.1 [0.22 (0.08) vs. 0.18 (0.07)kPa] and P0.1/Pi_{max} [4 % (1.4 %) vs. 3 % (1.1 %); all p>0.3].

The ventilatory drive P0.1 depended on pulmonary pressure (PAPm ρ=0.2; p=0.002). A higher ratio P0.1/Pi_{max} correlated with lower respiratory efficiency (VE/VCO_2 slope, ρ=0.16, p=0.015) and a higher exhaustion of the breathing reserve peakVE/MVV (ρ=0.26; p<0.001), and P0.1/Pi_{max} was inversely correlated with peakVO_2 (ρ=−0.16, p=0.011). As to Pi_{max}, there was no relation to P0.1 with renal function, sodium or haemoglobin concentration (all p>0.12). Ventilatory drive was higher in females [P0.1=0.24 (0.29) vs. 0.18 (0.15)kPa; p=0.21], and the respiratory pump was more utilized [P0.1/Pi_{max} 6 % (1.6 %) vs. 2.8 % (1.1 %); p<0.001 Mann–Whitney test].

3.3 Baseline parameters and survival

The median time of follow-up was 18.8 months with a range from 1 to 36 months. During this time, 38 (15.3 %) patients died, 9 (3.6 %) underwent urgent implantation of a cardiac assist device, and 22 patients (8.8 %) were heart transplanted. Patients with heart transplantation were statistically treated as survivors up to the date of transplantation and censored. Fatal events and assist implantations (in the following: "death/assist") sum up to 47 patients (18.9 %), according to a 1-year event rate of 16.7 %. Compared to survivors, patients in the death/assist group had a lower weight, BMI, diastolic blood pressure, FEV1, $TLCO_{VA}$, peakVO_2, eGFR, and higher uric acid and VE/VCO_2 slope. Both groups did not differ in age, haemodynamic parameters except LVEF, peakVE/MVV, sodium, haemoglobin, and all parameters of respiratory muscle function and ventilatory drive (see Table 2). The aetiology of heart failure (dilative cardiomyopathy, coronary or valvular heart disease) did not influence outcome (χ^2=0.04; p=0.8), as well as the concomitant diseases diabetes mellitus (χ^2=3.4; p=0.06), renal failure (χ^2=1.7; p=0.2), and previous sternotomy (χ^2=3.7; p=0.053), whereas only COPD (χ^2=4.5; p=0.03) was linked to a higher event rate.

Kaplan–Meier survival curves allowed the best prognostic stratification according to body mass index. The lowest quintile (BMI<22.3 kg/m^2, n=49) had a significantly worse outcome compared to all other quintiles (Log rank χ^2=13.5; p=0.009; Fig. 3). The division of patients in cachectic (n=26) and non-cachectic was also of prognostic evidence, and stratification was of a similar significance (Log rank χ^2=9.4; p=0.002; Fig. 4). Additionally, peakVO_2 was able to predict survival if patients were grouped by peakVO_2 ≤14 and >14 ml/min/kg (Log rank χ^2=3.8; p=0.05).

3.4 Univariate analysis of survival

Neither Pi_{max} [hazard ratio (HR) 0.98; confidence interval (CI) 0.88–1.08] nor P0.1 [HR 0.52 (CI 0.06–4.6)] predicted survival in the univariate Cox regression analysis. In order to evaluate possible confounding effects, we extended this analysis to all factors associated to Pi_{max}. The parameters correlating to respiratory muscle strength Pi_{max} and predicting survival were, in order of declining hazard ratio, BMI [HR 0.87 (CI 0.8–0.95)], peakVO_2 [HR 0.93 (0.87–0.99)], body mass [HR 0.97 (0.95–0.99)], FEV1 [HR 0.98 (0.96–0.99)], eGFR [HR 0.98 (0.97–0.99)], and $TLCO_{VA}$ [HR 0.98 (0.96–0.99)]. In a multivariate analysis including four factors, only BMI remained an independent prognostic parameter (HR 0.9; CI 0.82–0.98; p=0.017), whereas peakVO_2 (HR 0.95), FEV1 (HR 0.99), and $TLCO_{VA}$ (HR 0.98) lost significance (all p>0.1). Similarly, a reduction to three factors revealed always BMI as the only independent factor, and weight was eliminated in every analysis that included BMI.

4 Discussion

Our data show that neither the respiratory muscle strength (Pi_{max}) nor the ventilatory drive (P0.1) is an independent predictor of survival in the presented CHF patients. Worse outcome is mainly associated with a low BMI, respectively with the development of cachexia, and with low peakVO_2. Formally, the BMI correlates weakly with Pi_{max} and is apart from gender and lung volume the only determinate of Pi_{max},

Table 2 Comparison between survivors and nonsurvivors

Parameter, unit	Survivors	Nonsurvivors (death/assist)	*p*
Age (years)	53.9 [11.9]	54.2 [12.3]	NS[a]
Weight (kg)	82.0±13.7	76.1±14.4	0.009
Height (cm)	175.1±8.0	175.0±9.4	NS
BMI (kg/m^2)	26.7±4.0	24.7±3.3	0.001
Systolic blood pressure (mmHg)	121±21	114±20	NS
Diastolic blood pressure (mmHg)	74±11	68±12	0.005
Heart rate (1/min)	79±16	78±18	NS
PAPm (mmHg)	29.2±11.9	32.5±11.9	NS
PCWP (mmHg)	19.6±9.4	22.2±9.4	NS
LVEF (%)	23.7±7.7	21.5±8.0	0.05
CO (L/min)	4.8±1.5	4.5±1.3	NS
CI (L/min/m^2)	2.2 [0.97]	2.3 [0.52]	NS
FVC (% predicted)	77.1±14.6	73.5±14.0	NS
FEV1 (% predicted)	76.1±17.1	68.7±17.1	0.007
FEV1% FVC			
$TLCO_{VA}$ (% predicted)	73.1±19.7	63.0±20.7	0.002
PeakVO_2 (mL/min/kg)	14.6±4.8	13.1±4.9	0.04
VE/VCO_2 slope	33.0 [13.0]	38.0 [16.5]	0.02[a]
PeakVE/MVV (%)	43.0±16.1	44.6±16.0	NS
Pi_{max} (kPa)	6.4±2.8	6.1±2.6	NS
P0.1 (kPa)	0.18 [0.18]	0.18 [0.13]	NS[a]
P0.1/Pi_{max} (%)	3 [3.0]	2.8 [4.0]	NS[a]
eGFR (mL/min/1.73 m^2)	77.6±21.7	66.7±21.6	0.04
Sodium (mmol/L)	139.1±3.3	139.2±4.2	NS
Uric acid (mg/dL)	7.6±2.5	8.7±3.2	0.02
Haemoglobin (mg/dL)	14.4±1.6	14.2±1.8	NS

The group of nonsurvivors consisted of deceased patients (n=38) and patients with cardiac assist implantation (n=9). Abbreviations as in Table 1. Values indicate mean±standard deviation. Nonparametric variables are given as median with interquartile range in square brackets

NS not significant

[a]Mann–Whitney test , all other *p* unpaired t test

but this relation between body mass and Pi_{max} is too weak to confirm our hypothesis that respiratory muscle weakness could depend on the presence or absence of wasting.

As expected, there is a linear relation between BMI and Pi_{max} over the whole range of body size from underweight to adiposity. However, this relation is quite frail, and one would expect a more pronounced drop in Pi_{max} if BMI falls below a critical value, e.g. <21 kg/m^2, and for this reason, the difference in Pi_{max} of cachectic and non-cachectic patients did not reach significance. Nevertheless, we think that former studies on Pi_{max} and prognosis have to be corrected insofar that Pi_{max} does not predict survival in patients with pre-terminal heart failure or cachexia. As a clinical implication, one could prioritise treatment of catabolism compared to treatment of respiratory muscles, but this is beyond the scopes of our study.

The idea of a connection of BMI and respiratory muscle fatigue was developed from former clinical and experimental findings. Basically, CHF can induce general wasting [7], affecting both skeletal and respiratory muscles. A key mediator in this process could be TNF-alpha, which is increased in chronic heart failure and correlates with BMI and the clinical severity of heart failure [18] but can induce contractile dysfunction without overt catabolism [19]. TNF-alpha compromises the function of diaphragm and limb muscles similarly [20], probably by blunting the response to calcium activation. Conversely, the diaphragm function in congestive heart failure can be improved by inhibition of proteasomes, as shown in rats by van Hees et al. [21]. Moreover, during exercise the diaphragm must compete with locomotor muscles for its share of the impaired cardiac output [22], and the less blood flow is available, the less diaphragmatic work causes fatigue [23]. This is supported by electromyographic studies showing different exhaustion kinetics in inspiratory muscles compared with the calf muscles [24]. Thus, under catabolic conditions and especially in a cachectic state the respiratory muscle can lose function more extensively than skeletal muscles. Moreover, there might be a difference between the diaphragm and accessory respiratory muscles because the diaphragm fatigue does not increase neural respiratory drive [25], whereas recruitment of accessory respiratory muscles does [26]. This may explain why the pulmonary pressure PAPm and the ventilatory efficiency (VE/VCO_2 slope) in our study correlated with P0.1 (representing more the neural drive) but not with Pi_{max}.

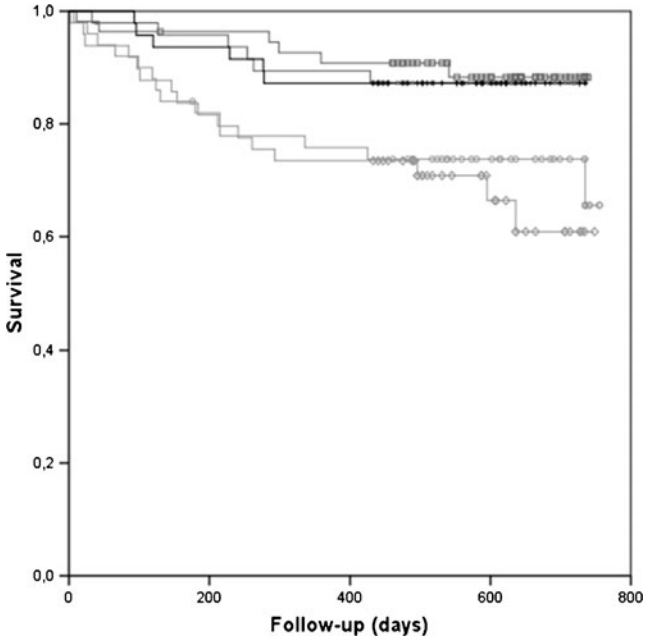

Fig. 3 Kaplan–Meier survival curves of the total study population according to BMI, divided into lowest quintile (BMI<23.2 kg/m^2, *n* =49) and quintiles 2–5. The symbols indicate: *diamond* quintile 1; *circle* quintile 2; *multiplication sign* quintile 3; *square* quintile 4; *plus sign* quintile 5. The difference in survival was significant (log-rank χ^2 =13.5 , df=4, p=0.009). There were 249, 222, 205, and 112 patients at risk at days 0, 200, 400, and 600

The impaired respiratory muscle may feedback on fatigue because vascular conductance in the limb muscles decreases as a consequence of stimulated metaboreceptors in the diaphragm [27]. Thus, a catabolic respiratory muscle is not only weaker (as measured by Pi_{max}) but might additionally lose exercise capacity by inducing a "steal" blood flow towards skeletal muscles.

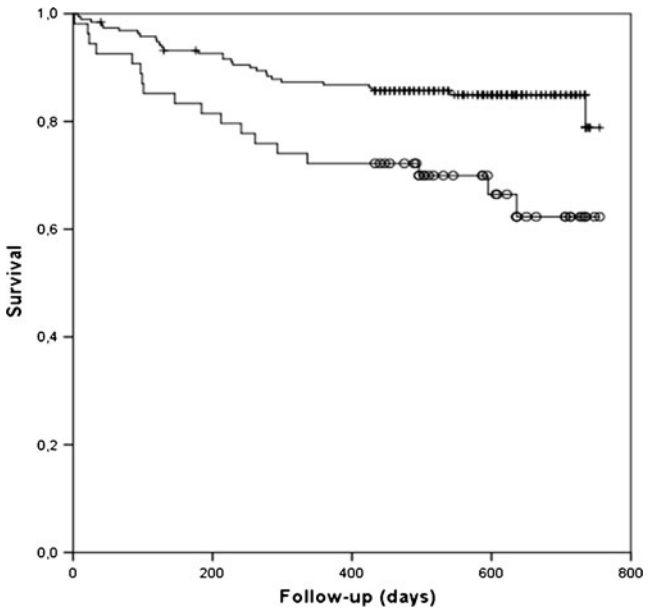

Fig. 4 Kaplan–Meier survival curves of the total study population subdivided by cachectic and non-cachectic patients. The symbols indicate *circle* cachectic *plus sign* non-cachectic. The difference in survival was significant (log-rank χ^2=9.4, *df*=1, *p*=0.002). There were 249, 222, 205, and 112 patients at risk at days 0, 200, 400, and 600

Another link between respiratory muscle weakness and cachexia concerns the peripheral chemosensitivity. CHF patients with cachexia demonstrated a nearly doubled ventilatory response to transient hypoxemia compared to non-cachectic patients with the same severity of heart failure [28]. However, it needs further investigation whether lowered Pi_{max} is a cause or a result of impaired cardiorespiratory reflex control.

These findings are only apparently in contrast to former studies which found a prognostic significance of Pi_{max} in CHF patients (Meyer and co-workers [5, 29]) or confirmed Pi_{max} as risk factor for cardiovascular events in a normal population (van der Palen and co-workers [6]). In our study, gender and BMI determinate Pi_{max}, and since Pi_{max} predicted survival in the mentioned studies, this could have been an unnoticed effect of BMI. The key difference of our study is the inclusion of both NYHA IV and cachectic respectively wasting patients. It is just the NYHA IV patients who are at risk to develop cachexia, and this will be the population with the most impaired muscle function. Possible confounders like the proportion of females and the median age were comparable to Meyer et al. [5], whereas the Cardiovascular Health Study (van der Palen [6]) recruited older patients and about 60 % females. However, the striking lower Pi_{max} in females compared to males in our study corresponds just to the lowered normal values in large population-based studies [30]. The pulmonary function showed a similar dependence on BMI: The non-surviving patients had lower pulmonary parameters like FEV1 and TLC_{VA}, but in the multivariate analysis, only BMI remained an independent prognostic parameter. Pi_{max} was proven to be significantly impaired in COPD patients, but this subgroup was too small in our study to influence the prognosis, and the weak relation between BMI and Pi_{max} persisted if COPD patients were omitted. Similarly, the typical medication in CHF with ACE inhibitors and beta-blockers did not change Pi_{max} or P0.1, in this respect confirming the study of Frankenstein et al. [31].

In summary, CHF is a systemic disease, and single parameters will be of minor and different accuracy in the prediction of survival. With regard to our study, these parameters concern BMI and Pi_{max}, with BMI being closer related to survival in the entire range of CHF severity. The predictive value of Pi_{max} in still non-cachectic, non-wasting and still compensated CHF patients [5] emphasises the finally crucial role of catabolism at end-stage disease.

5 Summary

In patients with chronic heart failure, the respiratory muscle strength Pi_{max} correlates weakly with body mass index, peakVO_2, and parameters of lung volume. Of these parameters, only BMI was an independent predictor of survival. If patients with NYHA IV functional class or patients with cachexia are included, the impaired Pi_{max} cannot be regarded as a predictive factor in itself because muscle function becomes more determinated by catabolism and weight loss.

Conflicts of interest Dirk Habedank, F. Joachim Meyer, Roland Hetzer, Stefan D. Anker, and Ralf Ewert declare that they have no conflict of interest.

Ethical guidelines The authors certify that they comply with the ethical guidelines for authorship and publishing of the *Journal of Cachexia, Sarcopenia and Muscle*, 2010;1:7–8 (von Haehling S, Morley JE, Coats AJ and Anker SD).

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