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\textsubscript{max}) is a function of body mass index, and that outcome is more a function of BMI than of Pi\textsubscript{max} or ventilatory drive (P\textsubscript{0.1}).

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\textsubscript{max}, P\textsubscript{0.1}), cardiopulmonary exercise testing (peakVO\textsubscript{2}, VE/VCO\textsubscript{2}-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\textsubscript{max} correlated weakly with BMI (r=0.19), peakVO\textsubscript{2} (r=0.15), and FEV\textsubscript{1} (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). P\textsubscript{0.1} correlated with pulmonary pressure (rho=0.2; p<0.01) and peakVO\textsubscript{2} (rho=−0.14; p<0.02). Neither Pi\textsubscript{max} [hazard ratio (HR) 0.98; confidence interval (CI) 0.88–1.08] nor P\textsubscript{0.1} (HR 0.52; 0.06–4.6) predicted survival. Multivariate regression analysis revealed gender, BMI, and FEV\textsubscript{1} as cofactors of Pi\textsubscript{max}, with only BMI (HR 0.87; CI 0.80–0.95) predicting survival independent of other variables. The lowest quintile in BMI had the worst outcome (log-rank \(\chi^2=13.5, p=0.009\)).

Summary In CHF patients including cachexia and NYHA IV, Pi\textsubscript{max} does not predict survival. Pi\textsubscript{max} depends on gender, BMI, FEV\textsubscript{1}, and peakVO\textsubscript{2}, with only BMI and peakVO\textsubscript{2} predicting survival. The impaired Pi\textsubscript{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)
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
peakVO2 Peak oxygen uptake
pETOC2 End-tidal carbon dioxide partial pressure
Pimax 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
TLCOVA Transfer factor for carbon monoxide per alveolar volume
VC Vital capacity
VE Ventilation volume per minute
VEmax Ventilation volume per minute at maximum exercise
VE/VCO2 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 \( P_{\text{imax}} \) 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 co-factors have to be assumed. So far, there are data of only one prospective study that proved the prognostic significance of maximum mouth occlusion pressure \( P_{\text{max}} \) and peak oxygen uptake \( \text{peakVO}_2 \) [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 \( P_{\text{max}} \) and (b) a prognostic significance of this relation with regard to prognostic factors (e.g. LVEF, \( \text{peakVO}_2 \), 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 aldosterone inhibition (20.5 \%) was not yet ubiquitous in CHF patients, whereas ACE inhibitors/angiotensin receptor blockers (95.6 \%), diuretics (92.4 \%), and oral anticoagulation were (78.7 \%) widely used. Concomitant conditions that could influence respiratory muscles were diabetes mellitus (20.1 \%), chronic renal failure (18.5 \%), previous sternotomy (17.3 \%), 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 characteristic 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.

### 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]. \( P_{\text{imax}} \) 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 \( P_{\text{imax}} \) and P0.1 are expressed as positive values, although they are negative with respect to atmosphere. The ratio P0.1/\( P_{\text{imax}} \) 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

| 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 (\( n, \% \))                  | 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  |
| peakVO2 (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 |
| \( P_{\text{imax}} \) (kPa)                                   | 6.3±2.7  |
| P0.1 (kPa)                                                    | 0.18 [0.17] |
| P0.1/P0.1\(_{\text{max}}\) (%)                                 | 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, \( P_{\text{imax}} \) maximum inspiratory pressure, P0.1 inspiratory pressure at 0.1 s after inspiration start, P0.1/P0.1\(_{\text{max}}\) relation of inspiratory pressure 0.1 after inspiration to pressure at maximum inspiration.

*Weight loss was defined as unintended loss >6 \% of body weight within 6 months.

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 \( p_{\text{ETO}}\) and \( p_{\text{ETCO}}\)\(_2\), 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 VCO₂, values due to hyper-ventilation (acidosis) in the last minutes of exercise were excluded, and the slope of the revealed linear relationship (VE/VCO₂ 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 cause. 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/VCO₂ slope, LVEF, P0.1, and P0.1/Pimax). 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 “$\rho$”. 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, peakVO₂, 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 $P_{\text{imax}}$

Higher anthropometric measures (height, weight, and BMI) were formally correlated with respiratory muscle strength $P_{\text{imax}}$ (cf. to BMI $r=0.19$, cf. to weight $r=0.29$, cf. to height $0.25$, all $p<0.003$, see Fig. 1). A division of patients in quintiles proved an increase in $P_{\text{imax}}$ from low BMI (1st quintile BMI<23.2 kg/m² and $P_{\text{imax}}=5.6±2.5$ kPa) to high BMI (5th quintile BMI>29.4 kg/m² and $P_{\text{imax}}=7.4±2.9$ kPa, ANOVA $p=0.03$, Fig. 2). $P_{\text{imax}}$ of cachectic patients, i.e. with BMI<21 kg/m² 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 ($p=0.23$).

$P_{\text{imax}}$ correlated with most parameters of pulmonary function, such as VC ($r=0.36$), FEV1 ($r=0.34$), TLCOVA ($r=0.2$; all $p<0.002$). There was no correlation of $P_{\text{imax}}$ with any of the cardiac parameters (blood pressure, heart rate, PAPm, PCWP, cardiac index, LVEF, LVEDd, all $r$ resp. $p<0.06$; $p>0.1$).

$P_{\text{imax}}$ 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, PCWP, LVEDP), and in percentage of predicted values of pulmonary function (VC, FEV1, TLCOVA), and of exercise parameters (peakVO₂, VE/VCO₂ slope). Concomitant diseases as COPD, diabetes mellitus, chronic renal failure, or previous sternotomy revealed no differences in $P_{\text{imax}}$, P0.1, or P0.1/Pimax. 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]($P_{\text{imax}}$ as a function of BMI. $P_{\text{imax}}=BMI 0.13+2.8$; $r=0.19$; $p=0.003$. Continuous line, mean regression. Dotted line, 95 % confidence intervals)
3.2 Ventilatory drive P0.1 and inspiratory effort per breath P0.1/Pimax

Neither body mass index nor its constituents height and weight correlated with $P=0.1$ or $P0.1/Pimax$ ($\rho=-0.1$ 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 $P0.1/Pimax$ [4 % (1.4 %) vs. 3 % (1.1 %); all $p>0.3$].

The ventilatory drive $P0.1$ depended on pulmonary pressure ($PAPm\rho=0.2$; $p=0.002$). A higher ratio $P0.1/Pimax$ correlated with lower respiratory efficiency ($VE/VCO_2$ slope, $\rho=0.16$, $p=0.015$) and a higher exhaustion of the breathing reserve peakVE/MVV ($\rho=0.26$, $p<0.001$), and $P0.1/Pimax$ was inversely correlated with peakVO$_2$ ($\rho=-0.16$, $p=0.011$). As to $Pimax$, 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 [$P0.1/Pimax$ 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 ($\chi^2=0.04$; $p=0.8$), as well as the concomitant diseases diabetes mellitus ($\chi^2=3.4$; $p=0.06$), renal failure ($\chi^2=1.7$; $p=0.2$), and previous sternotomy ($\chi^2=3.7$; $p=0.053$), whereas only COPD ($\chi^2=4.5$; $p=0.03$) 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 $\chi^2=13.5$; $p=0.009$; 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 $\chi^2=9.4$; $p=0.002$; Fig. 4). Additionally, peakVO$_2$ was able to predict survival if patients were grouped by peakVO$_2\leq$14 and $>14$ ml/min/kg (Log rank $\chi^2=3.8$; $p=0.05$).

3.4 Univariate analysis of survival

Neither $Pimax$ [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 $Pimax$. The parameters correlating to respiratory muscle strength $Pimax$ 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 ($Pimax$) 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 $Pimax$ and is apart from gender and lung volume the only determinate of $Pimax$. 

Fig. 2 $Pimax$ 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.
but this relation between body mass and Pimax 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 Pimax 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 Pimax if BMI falls below a critical value, e.g. <21 kg/m², and for this reason, the difference in Pimax of cachectic and non-cachectic patients did not reach significance. Nevertheless, we think that former studies on Pimax and prognosis have to be corrected insofar that Pimax 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 scope 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/VCO₂ slope) in our study correlated with P0.1 (representing more the neural drive) but not with Pimax.

| Parameter, unit | Survivors | Nonsurvivors (death/assist) | p |
|----------------|-----------|----------------------------|---|
| Age (years)    | 53.9 [11.9] | 54.2 [12.3] | NS² |
| 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/m²)    | 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/m²)  | 2.2 [0.97] | 2.3 [0.52] | NS |
| FVC (%)        | 77.1±14.6 | 73.5±14.0 | NS |
| FEV1 (%)       | 76.1±17.1 | 68.7±17.1 | 0.007 |
| FEV1% FVC      | 73.1±19.7 | 63.0±20.7 | 0.002 |
| TLC/VA (%)     | 14.6±16.1 | 11.4±16.0 | NS |
| PeakVO₂ (mL/min/kg) | 33.0 [13.0] | 38.0 [16.5] | 0.02² |
| PeakVE/MVV (%) | 43.0±16.1 | 44.6±16.0 | NS |
| Pimax (kPa)    | 6.4±2.8 | 6.1±2.6 | NS |
| P0.1 (kPa)     | 0.18 [0.18] | 0.18 [0.13] | NS² |
| P0.1/Pimax (%) | 0.18 [0.18] | 0.18 [0.13] | NS² |
| eGFR (mL/min/1.73 m²) | 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

²Mann–Whitney test, all other p unpaired t test
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.

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 $\text{Pi}_{\text{max}}$ correlates weakly with body mass index, $\text{peakVO}_2$, 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 $\text{Pi}_{\text{max}}$ cannot be regarded as a predictive factor in itself because muscle function becomes more determined 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;1:7–284 (von Haehling S, Morley JE, Coats AJ and Anker SD).

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