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Respiratory Muscle Dysfunction in Congestive Heart Failure
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Background—In congestive heart failure (CHF), the prognostic significance of impaired respiratory muscle strength has not been established.

Methods and Results—Maximal inspiratory pressure (Pi_{max}) was prospectively determined in 244 consecutive patients (207 men) with CHF (ischemic, n=75; idiopathic dilated cardiomyopathy, n=169; age, 54±11 years; left ventricular ejection fraction [LVEF], 22±10%). Pi_{max} was lower in the 244 patients with CHF than in 25 control subjects (7.6±3.3 versus 10.5±3.7 kPa; $P=0.001$). The 57 patients (23%) who died during follow-up (23±16 months; range, 1 to 48 months) had an even more reduced Pi_{max} (6.3±3.2 versus 8.1±3.2 kPa in survivors; $P=0.001$). Kaplan-Meier survival curves differentiated between patients subdivided according to quartiles for Pi_{max} ($P=0.014$). Pi_{max} was a strong risk predictor in both univariate ($P=0.001$) and multivariate Cox proportional hazard analyses ($P=0.03$); multivariate analyses also included NYHA functional class, LVEF, peak oxygen consumption (peak $\dot{V}o_2$), and norepinephrine plasma concentration. The areas under the receiver-operating characteristic curves for prediction of 1-year survival were comparable for Pi_{max} and peak $\dot{V}o_2$ (area under the curve [AUC], 0.68 versus 0.73; $P=0.28$), and they improved with the triple combination of Pi_{max}, peak $\dot{V}o_2$, and LVEF (AUC, 0.82; $P=0.004$ compared with AUC of Pi_{max}).

Conclusions—In patients with CHF, inspiratory muscle strength is reduced and emerges as a novel, independent predictor of prognosis. Because testing for Pi_{max} is simple in clinical practice, it might serve as an additional factor to improve risk stratification and patient selection for cardiac transplantation. (***Circulation***. 2001;103:2153-2158.)

Key Words: heart failure ■ muscles ■ exercise ■ prognosis

In congestive heart failure (CHF), accurate assessment of disease severity and risk stratification are crucial for the optimal selection of candidates and the timing of cardiac transplantation. Currently, judgment of prognosis is primarily based on hemodynamic parameters and the impairment of functional capacity. In particular, peak oxygen consumption during cardiopulmonary exercise testing (peak $\dot{V}o_2$) has been widely recommended for risk stratification.[1,2] However, the existence of an optimal peak $\dot{V}o_2$ cut-off value for the prediction of survival in CHF remains a matter of debate.[2] The continuous parameter peak $\dot{V}o_2$ is determined by cardiac output and by pulmonary and skeletal muscle function.[3] In severe CHF, a general atrophic loss of skeletal muscle bulk in patients has been reported.[4] Moreover, even in early stages of CHF, peripheral muscle function is impaired due to structural and metabolic abnormalities of skeletal musculature.[5] Biopsies of respiratory muscles showed a variety of histological abnormalities in CHF,[6] including fiber type I atrophy of the diaphragm in experimental CHF in rats.[7] Both a generalized skeletal muscle dysfunction and a chronically increased workload may result in decreased strength and endurance of respiratory muscles in CHF.[8–16]

Thus far, respiratory muscle strength has not been evaluated as an indicator of prognosis in various degrees of CHF. Earlier data from our laboratory indicated that respiratory muscle strength might be reduced in CHF patients who have an unfavorable outcome.[8] Thus, it was hypothesized that respiratory muscle function might be a predictor of survival in patients with CHF. Therefore, maximal inspiratory pressure (Pi_{max}) was prospectively assessed in CHF patients with a wide range of exercise limitations, and the impact of Pi_{max} for prognosis was determined during long-term follow-up. This study sought to clarify whether Pi_{max} predicts survival independently of established predictors of prognosis (left ventricular ejection fraction [LVEF], peak $\dot{V}o_2$, and norepinephrine) and whether the combination of Pi_{max} with other noninvasive prognostic parameters improves risk stratification in patients with CHF.

Methods

A total of 244 consecutive patients (207 men, 85%) with stable CHF (NYHA functional class I, n=31 [13%]; class II, n=100 [41%]; class III, n=113 [46%]) were prospectively enrolled after they gave written, informed consent. The study was approved by the Ethical Committee for human research of the University of Heidelberg.

TABLE 1.   Baseline Clinical and Functional Characteristics of Patients With CHF and Control Subjects

	CHF Patients (n=244)	Control Subjects (n=25)	P
Age, y	54±11	47±14	NS
Height, cm	174±8.7	180±5	NS
Weight, kg	79±14	90±13	NS
IVC, % of predicted	83.7±15.9	101.9±9.5	0.001
FEV$_1$, % of predicted	85.9±19.3	107.3±14.3	0.001
FEV$_1$/IVC	0.79±0.09	0.82±0.07	NS
Pi$_{max}$, kPa	7.6±3.3	10.5±3.7	0.001
Pe$_{max}$, kPa	9.5±3.4	10.1±4.0	NS
P$_{0.1}$, kPa	0.3±0.2	0.2±0.1	NS
LVEF, %	22±10		
NYHA functional class	2.4±0.7		
Workload, W	82±38		
Peak V̇o$_2$ mL · min^{-1} · kg^{-1}	14.6±5.2		

Value are mean±SD. NS indicates not significant; FEV$_1$, forced expiratory volume in 1 s.

The cardiac diagnosis was based on left heart catheterization and coronary angiograms taken before study inclusion. LVEF at rest was <40%, as determined by radionuclide ventriculography.[17] Standard medical treatment was optimized for the individual patient before inclusion into the study and included angiotensin-converting enzyme inhibitors (97% of patients), diuretics (87%), digitalis (72%), and β-blockers (34%). Patients were studied while on stable doses of their medications. Blood samples were taken to exclude conditions that could possibly affect respiratory muscle function (eg, thyroid dysfunction, electrolyte disturbance) and to determine blood gases and plasma concentrations of norepinephrine, as described elsewhere.[17]

Patients with valvular defects, a history of pulmonary disease, or an episode of deterioration requiring intravenous inotropic support within 4 weeks before enrollment were excluded. Patients meeting the recently described criteria for cachexia or wasting[4] or with symptoms at rest (NYHA functional class IV) were excluded, because particularly poor prognosis has been well established for these CHF subgroups.

Pulmonary and Respiratory Muscle Function Testing

A technician who was unaware of other variables in the study and who was blinded to the status of the patient determined inspiratory vital capacity (IVC) and forced expiratory volume in 1 s using a pneumotachograph (Erich Jaeger, MasterLabPro 4.2). Predicted values corrected for sex, age, and height were used.[18]

Pi$_{max}$ was determined through a flanged mouthpiece in deep inspiration from functional residual capacity against a shutter with a minor air leak preventing undesirable glottis closure (Erich Jaeger, MasterLabPro 4.2).[19] Maximal expiratory pressure (Pe$_{max}$) was measured at total lung capacity during a maximal expiratory effort. Of 3 measurements with <5% variability, the highest pressure was used for analysis. Two minutes of rest were allowed between the 2 maneuvers when necessary. Mouth occlusion pressure (P$_{0.1}$) was assessed 0.1 s after the onset of inspiration during spontaneous breathing at rest.[20] Pi$_{max}$ and P$_{0.1}$ are expressed as positive values, although they are negative pressures with respect to atmosphere. Because published reference values for Pi$_{max}$, Pe$_{max}$, and P$_{0.1}$ vary considerably,[19,20] they were determined in 25 control subjects who were not on medication and who had normal left ventricular function, as determined by echocardiography (Table 1).

Cardiopulmonary Exercise Testing

Patients underwent symptom-limited exercise testing in a semisupine position on a bicycle ergometer until exhaustion, according to a modified Bruce protocol.[8,17] Briefly, after 5 minutes of sample collection at rest, exercise started with 2 minutes at 0 W. Workload was increased in steps of 15 W every 2 minutes. Airflow and expiratory O$_2$ concentrations were continuously analyzed and averaged online from 8 consecutive breaths (OxyconAlpha, Jaeger; face mask by Hans Rudolph, Wyandotte).

Follow-Up

Patients were included and followed from March 1996 until January 2000 at regular outpatient visits or by telephone calls to the patients' home or family physician.

The predefined end point was all-cause mortality. Aortocoronary bypass grafts and left ventricular assist devices were not inserted in the studied patients. Those patients who underwent orthotopic heart transplantation were followed until the surgical procedure. Regardless of the postoperative outcome, these patients were classified as survivors.

Statistics

Statistical analysis was performed with standard software (SAS version 6.09 and Microsoft Excel version 1997). The Spearman rank correlation coefficient was used as a measure of association. To test for differences between groups, a 2-sample-Wilcoxon-test was used.

Survival curves were calculated using the Kaplan-Meier method. Cox proportional hazard linear regression analysis was used to determine the prognostic value for a given independent continuous variable on time to death. Receiver-operating characteristic curves were constructed by means of plotting true-positive rates (sensitivity) against false-positive rates (1/specificity). $P<0.05$ was considered significant. Values are expressed as mean±SD.

Results

Clinical Correlation

The duration of CHF before inclusion into the study was 59±62 months (range, 1 to 300 months). Compared with control subjects, Pi$_{max}$ was reduced by 23% in CHF, whereas Pe$_{max}$ (Table 1) and arterial carbon dioxide pressure (PaCO$_2$; 37±4 versus 38±3 mm Hg; $P=$NS) did not differ. In CHF patients, IVC and forced expiratory volume in 1 s were correlated ($r=0.9$; $P=0.0001$) and were significantly lower than in controls, indicating a mild restrictive pattern in CHF (Table 1). NYHA functional class III patients had a lower Pi$_{max}$ (6.9±3.1 kPa) than NYHA class I (8.4±3.2 kPa; $P=0.02$) and II patients (8.1±3.4; $P=0.01$). Pi$_{max}$ correlated weakly with peak V̇o$_2$ ($r=0.32$; $P=0.005$), plasma norepinephrine ($r=-0.14$; $P=0.05$), and age ($r=-0.23$; $P=0.001$); it correlated moderately with IVC ($r=0.37$; $P=0.0001$) and not at all with LVEF ($r=0.01$; $P=$NS) or PaCO$_2$ ($r=0.04$; $P=$NS).

When subgroups with different causes of CHF (ischemic, n=75 [31%]; dilated cardiomyopathy, n=169 [69%]) were compared, no differences in age, height, weight, NYHA functional class, lung volumes, PaCO$_2$, or plasma norepinephrine concentration were found (data not shown). Moreover, Pi$_{max}$ (7.7±3.4 versus 7.6±3.3 kPa; $P=$NS) and Pe$_{max}$ (9.9±3.5 versus 9.2±3.4 kPa, $P=$NS) did not differ between patients in either group. Compared with patients with dilated cardiomyopathy, patients with ischemic heart disease were characterized by a slightly higher NYHA functional class (2.5±0.6 versus 2.3±0.8; $P<0.05$) but a lower peak V̇o$_2$

TABLE 2.   Clinical and Functional Characteristics of Patients With CHF: Survivors Versus Nonsurvivors

	Survivors (n=187)	Nonsurvivors (n=57)	P
Age, y	54±11	56±11	NS
Height, cm	174±9	174±7	NS
Weight, kg	79±14	77±15	NS
IVC, % of predicted	85.4±15.9	77.9±14.9	0.003
FEV_1, % of predicted	85.9±19.3	76.8±19.24	0.002
FEV_1/IVC	0.79±0.08	0.76±0.11	NS
Pi_{max}, kPa	8.1±3.2	6.3±3.2	0.0005
Pe_{max}, kPa	9.6±3.5	9.0±3.4	NS
$P_{0.1}$, kPa	0.3±0.2	0.3±0.2	NS
LVEF, %	23±10	18±9	0.001
NYHA functional class	2.3±0.7	2.5±0.7	NS
Workload, W	86±39	70±32	0.001
Peak $\dot{V}O_2$ mL · min^{-1} · kg^{-1}	15.1±5.1	12.9±5.3	0.007
Norepinephrine, nmol/L	2.3±1.8	3.4±2.1	0.001

Abbreviations as in Table 1.

(13.2±4.3 versus 15.2±5.5 mL · min^{-1} · kg^{-1}; $P<0.004$), despite a comparable LVEF (23±9% versus 21±10%, NS).

Survival Analysis

During follow-up (23±16 months; range, 1 to 46 months) 57 patients died (mean time to death, 16±12 months; range, 1 to 44 months), all from cardiovascular causes. The 1-, 2-, and 3-year mortality was 12%, 23%, and 30%, respectively. Thirty-eight patients underwent cardiac transplantation after 13±9 months (range, 1 to 37 months).

Nonsurvivors and survivors did not differ in age, height, weight, NYHA functional class, or $PaCO_2$ (37±4 versus 37±4 mm Hg; $P=NS$). However, nonsurvivors were characterized by a reduced LVEF, a decreased exercise capacity (as reflected by a reduction in maximal workload and peak $\dot{V}O_2$), and increased plasma concentrations of norepinephrine (Table 2). Furthermore, nonsurvivors had significantly smaller lung volumes than survivors, but no signs of airflow obstruction (Table 2). Although $P_{0.1}$, an index of respiratory center output, did not differ in survivors and nonsurvivors (Tables 1 and 2), Pi_{max} was reduced by 22% in nonsurvivors compared with survivors (Table 2).

Kaplan-Meier survival curves for patients subdivided in quartiles according to Pi_{max} allowed accurate prognostic stratification (Figure 1). A high Pi_{max} (>9.8 kPa) indicated the best prognosis at 12, 24, and 36 months of follow-up compared with lower Pi_{max} quartiles. Survival in this highest Pi_{max} quartile group was 3-fold higher than in patients in the lowest Pi_{max} quartile (<5.3 kPa; Figure 1). When patients with an intermediate peak $\dot{V}O_2$ of 10 to 20 mL · min^{-1} · kg^{-1} were analyzed separately, a low Pi_{max} (<5.3 kPa) indicated a 20% and 40% reduction in survival rate at 12 and 36 months, respectively, compared with a high Pi_{max} (>9.8 kPa; Figure 2).

Sensitivity and specificity of Pi_{max} for predicting survival at 12 and 36 months was assessed for different arbitrary thresholds (Table 3). Of all nonsurvivors, 64% and 59% had a $Pi_{max} \leq 7$ kPa (sensitivity) at 12 and 36 months follow-up,
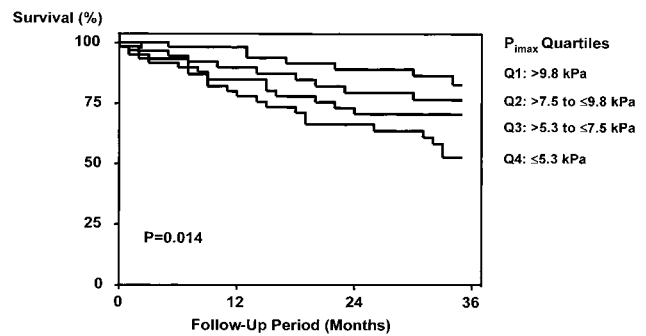

Figure 1. Kaplan-Meier survival curves of the total study population subdivided into quartiles (n=61 each) according to Pi_{max}: quartile 1 (Q1), ≤5.3 kPa; quartile 2 (Q2), >5.3 to ≤7.5 kPa; quartile 3 (Q3), >7.5 to ≤9.8 kPa; and quartile 4 (Q4), >9.8 kPa. Significant differences in survival are shown (log-rank $\chi^2=11$; df=3; $P=0.014$). There were 183, 168, and 127 individuals at risk at 12, 24, and 36 months follow-up, respectively.

respectively. In 58% and 60% of survivors, Pi_{max} was >7 kPa (specificity) after 12 and 36 months, respectively. Lower thresholds provided a higher sensitivity but a lower specificity and vice versa.

Univariate and Multivariate Analysis

In the univariate Cox regression analysis, Pi_{max}, LVEF, peak $\dot{V}O_2$ (Table 4), norepinephrine ($\chi^2=8.92$; hazard ratio [HR], 1.14; 95% confidence interval [CI], 1.05 to 1.24; $P=0.003$), and NYHA functional class ($\chi^2=4.56$; HR, 1.55, 95% CI, 1.04 to 2.32; $P=0.03$) were all significant prognostic indicators with descending statistical significance; Pe_{max} was not a significant prognostic indicator ($\chi^2=0.62$; HR, 0.97, 95% CI, 0.90 to 1.04; $P=0.43$).

Multivariate analysis using 3 variables indicated that Pi_{max} provided independent prognostic information that was comparable to peak $\dot{V}O_2$ (Table 4).

With 4 variables, including LVEF, peak $\dot{V}O_2$, NYHA class, and Pi_{max}, only LVEF ($\chi^2=9.04$; HR, 0.95, 95% CI, 0.87 to 1.04; $P=0.003$), peak $\dot{V}O_2$ ($\chi^2=5.23$; HR, 0.92, 95% CI, 0.84 to 1.01; $P=0.02$), and Pi_{max} ($\chi^2=4.97$; HR, 0.90; 95% CI, 0.82 to 0.99; $P=0.03$), but not NYHA class ($\chi^2=0.18$; HR, 0.91; 95% CI, 0.83 to 0.99; $P=0.67$), were significant independent prognostic indicators. Norepinephrine ($\chi^2=1.84$; HR, 1.07; 95% CI, 0.97 to 1.19; $P=0.17$) was not a significant prognostic predictor in a multivariate analysis including LVEF
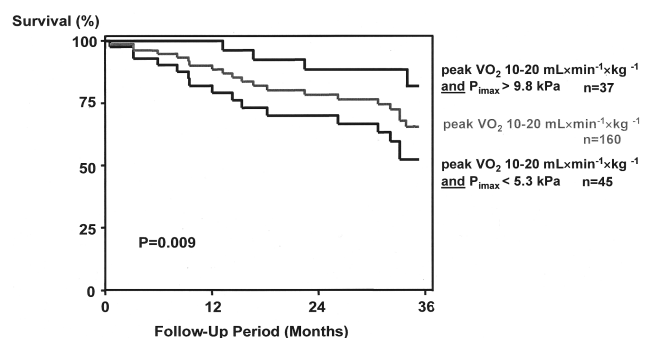

Figure 2. Risk stratification among patients with an intermediate peak $\dot{V}O_2$ of 10 to 20 mL · min^{-1} · kg^{-1} is significantly improved by combination with Pi_{max} (log-rank $\chi^2=8$; df=2; $P=0.018$).

TABLE 3. Sensitivity and Specificity of Thresholds in Pi_{max} for Predicting Survival at 12 and 36 Months

Threshold, kPa	12 Months		36 Months	
	Sensitivity	Specificity	Sensitivity	Specificity
≤4	32%	82%	30%	85%
≤5	44%	78%	39%	81%
≤6	56%	68%	48%	69%
≤7	64%	58%	59%	60%
≤8	80%	47%	73%	43%
≤9	88%	37%	82%	39%
≤10	96%	25%	91%	26%
≤11	96%	18%	96%	19%
≤12	100%	12%	100%	12%

($\chi^2=7.06$; HR, 0.95, 95% CI, 0.92 to 0.98; $P=0.008$), peak $\dot{V}O_2$ ($\chi^2=4.43$; HR, 0.93, 95% CI, 0.88 to 0.99; $P=0.04$), and Pi_{max} ($\chi^2=4.68$; HR, 0.90; 95% CI, 0.82 to 0.99; $P=0.03$).

Receiver-Operating Characteristic Curves for Survival at 12 Months

Parameters identified as independent predictors by multivariate Cox regression analysis were entered into receiver-operating characteristic analysis: peak $\dot{V}O_2$ (area under the curve [AUC], 0.73) and Pi_{max} (AUC, 0.68; $P=0.28$) were comparable. However, prediction of survival was weakly improved by combining Pi_{max} and peak $\dot{V}O_2$ (AUC, 0.75). By using a triple combination of Pi_{max}, peak $\dot{V}O_2$, and LVEF, risk stratification was most accurate (Figure 3). Addition of plasma norepinephrine did not further improve risk prediction.

Discussion

The major findings of this prospective study in 244 CHF patients are as follows. (1) Pi_{max}, but not Pe_{max}, decreases with NYHA functional class, and it correlates weakly with peak $\dot{V}O_2$ and plasma norepinephrine but not with LVEF. (2) Pi_{max} and Pe_{max} are not different between subgroups with ischemic and dilated cardiomyopathy. (3) During follow-up, nonsurvivors are characterized by a lower Pi_{max}. (4) Pi_{max} predicts prognosis independently from the established predictors peak $\dot{V}O_2$, LVEF, plasma norepinephrine, and NYHA functional class. (5) Pi_{max} improves risk stratification in candidates for cardiac transplantation, especially when combined with other prognostic parameters such as peak $\dot{V}O_2$ and LVEF.

Respiratory Muscle Dysfunction is Related to Severity of CHF

As shown previously, the reduction in respiratory muscle strength as determined by Pi_{max} is related to the severity of
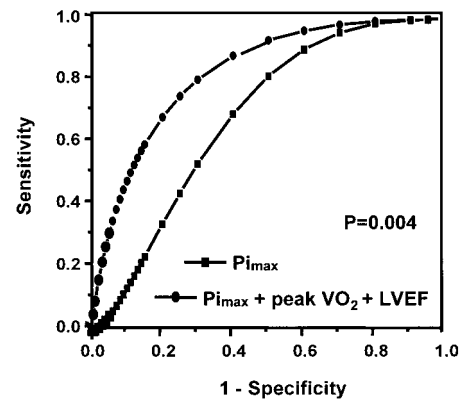

Figure 3. Receiver-operating characteristic curves for Pi_{max} for prediction of survival at 12 months (AUC, 0.68). The triple combination of Pi_{max}, peak $\dot{V}O_2$, and LVEF yields significantly increased prognostic information (AUC, 0.82).

CHF.[8,9,14–16] This is confirmed by the decline in Pi_{max} with increasing NYHA functional class and the correlation between Pi_{max} and peak $\dot{V}O_2$ in the present and previous reports.[8,9,21]

In the CHF patients, Pi_{max} was related to IVC. However, a restrictive ventilatory pattern does not seem to be responsible for changes in Pi_{max}, because the decline of Pi_{max} with increasing severity of CHF was still observed when Pi_{max} was corrected for IVC (data not shown).

Increased respiratory muscle strain did not play a major role in the observed reduction in Pi_{max} in CHF, because $P_{0.1}$ (an index of respiratory center output[20]) was not augmented. This finding is consistent with previous observations.[8,10] When $P_{0.1}$ was corrected for individual respiratory muscle strength ($P_{0.1}/Pi_{max}$), again no difference between groups was found (data not shown).

Respiratory Muscle Strength and Survival

Because Pi_{max} is a continuous parameter, values obtained in the present cohort were divided into 4 quartiles corresponding to 4 risk strata (Figure 1). For the lowest Pi_{max} quartile of the cohort, mortality was increased 3-fold compared with patients who had CHF but preserved respiratory muscle strength (Pi_{max} >9.8 kPa; Figure 1). Approximately 50% of patients with Pi_{max} ≤5 kPa died during follow-up, but only 15% of those with Pi_{max} >10 kPa died (Figure 1 and Table 3). These data provide the first evidence that respiratory muscle strength may be a powerful indicator of prognosis in CHF. Because in CHF patients with an intermediate peak $\dot{V}O_2$ of 10 to 20 mL · min^{-1} · kg^{-1} risk stratification solely based on peak $\dot{V}O_2$ is often inaccurate,[22] the use of Pi_{max} as an additional factor for

TABLE 4. Univariate and Multivariate Cox Regression Analysis of Study Variables and Survival

	Univariate			Multivariate		
	χ^2	P	HR (95% CI)	χ^2	P	HR (95% CI)
LVEF	15.04	0.0001	0.93 (0.90–0.97)	8.99	0.003	0.95 (0.92–0.98)
Peak $\dot{V}O_2$	12.39	0.0004	0.89 (0.83–0.95)	5.51	0.019	0.93 (0.87–0.99)
Pi_{max}	10.32	0.001	0.87 (0.80–0.95)	5.02	0.025	0.90 (0.82–0.99)

risk stratification is particularly important. Of the 244 patients in this study, 160 belonged to that group. Those belonging to the highest Pi_{max} quartile (n=37) had a 1-year survival rate of 100%, whereas 22% of those in the lowest quartile (n=45) died within the first year. Therefore, in the majority of the patients with an intermediate peak $\dot{V}O_2$, Pi_{max} allowed significantly better risk stratification than peak $\dot{V}O_2$ alone.

Because peak $\dot{V}O_2$ is dependent on patients' motivation to endure an incremental exercise test, it frequently underestimates exercise capacity in candidates for cardiac transplantation.[22] Moreover, peak $\dot{V}O_2$ globally assesses cardiac, respiratory, and peripheral muscle function during exercise,[3] which may all contribute to exercise limitation. Therefore, selected parameters derived from exercise testing, such as ventilatory and heart rate response, have recently been suggested as better predictors of CHF mortality than peak $\dot{V}O_2$.[23]

In a different approach to improve risk stratification in CHF, a heart failure survival score (HFSS) was recently proposed. The HFSS would combine multiple, independent, noninvasive variables.[24] Peak $\dot{V}O_2$ alone predicted freedom of an outcome event (death, urgent transplantation, or implantation of ventricular assist device within 12 months) with an AUC of 0.62, whereas the HFSS noninvasive multivariate model provided an AUC of 0.76.[24] The patients analyzed by HFSS and the present cohort are comparable in size and baseline clinical parameters. In the present study, peak $\dot{V}O_2$ alone predicted 1-year survival with an AUC of 0.73. When Pi_{max} was added, AUC increased to 0.75. With the combination of the significant predictors identified by multivariate Cox regression analysis (Pi_{max}, peak $\dot{V}O_2$, and LVEF), the AUC increased to 0.82 (Figure 3). These findings underline the fact that a multivariable model is preferable to risk stratification relying on a single parameter only. Moreover, the present data suggest including respiratory muscle function in comprehensive prognostic models as an independent predictor.

Clinical Implications and Further Investigation

The present findings are of major clinical importance because the measurement of Pi_{max} is noninvasive and independent of the patients' ability to walk or cycle. The determination of Pi_{max} is easily performed during routine pulmonary function testing.[19] Although Pi_{max} depends on patients' cooperation, repeated measurements revealed good reproducibility after 3 days[19] and after 3 months.[25] Although Pi_{max} values in the present control group are comparable to data published elsewhere,[19,20] substantial variation in Pi_{max} between different laboratories, depending on equipment and technique, may occur. Thus, risk stratification using the Pi_{max} strata observed in the present study depends on reference values of individual laboratories.

The reduction in respiratory muscle strength may reflect increased work of breathing in CHF.[12] As shown previously, restrictive ventilatory pattern, ventilatory inefficiency, and increased dead space ventilation may occur in CHF and partially contribute to the overload of the respiratory musculature in CHF, although respiratory drive as assessed by $P_{0.1}$ and $PaCO_2$ at rest are not increased.[8] Alternatively, the reduction in Pi_{max} may be due to a generalized skeletal muscle

disorder in CHF.[4,5,9] However, the unchanged Pe_{max} is a strong argument against this hypothesis.

It has been shown that the reduction in inspiratory muscle strength in CHF is associated with a significant decline in respiratory muscle endurance, as measured by various techniques.[21,26,27] Therefore, the assessment of respiratory muscle endurance, eg, by measuring maximal voluntary ventilation, might be another valuable parameter for risk stratification in CHF. As opposed to Pi_{max}, however, maximal voluntary ventilation is influenced by reduced static lung volumes, thus reflecting respiratory muscle capacity less accurately than Pi_{max}.

Respiratory muscle function can be improved by selective respiratory muscle training[25] or by unloading respiratory muscles with noninvasive continuous positive airway pressure ventilation during acute training and long-term disease in selected patients.[28,29]

In conclusion, CHF is characterized by respiratory muscle dysfunction. For the first time, respiratory muscle strength has been characterized as an independent predictor of prognosis in CHF. The easily obtainable Pi_{max} might thus serve as a new parameter to further improve risk stratification in patients with CHF.

References

1. Constanzo M, Augustine S, Bourge R, et al. Selection and treatment of candidates for heart transplantation. *Circulation*. 1995;92:3593–3612.
2. Myers JL, Gullestad L, Vagelos R, et al. Clinical, hemodynamic, and cardiopulmonary exercise test determinants of survival in patients referred for evaluation of heart failure. *Ann Intern Med*. 1998;129: 286–293.
3. Jones NL. *Clinical Exercise Testing*. 4th ed. Philadelphia: Saunders; 1997.
4. Anker SD, Ponikowski P, Varney S, et al. Wasting as independent risk factor for mortality in chronic heart failure. *Lancet*. 1997;349: 1050–1053.
5. Coats AJS. The "muscle hypothesis" of chronic heart failure. *J Mol Cell Cardiol*. 1996;28:2255–2262.
6. Lindsay DC, Lovegrove CA, Dunn MJ, et al. Histological abnormalities of muscle from limb, thorax and diaphragm in chronic heart failure. *Eur Heart J*. 1996;17:1239–1250.
7. Stassijns GA, Gayan-Ramirez G, DeLeyn P, et al. Effects of dilated cardiomyopathy on the diaphragm in the Syrian hamster. *Eur Respir J*. 1999;13:391–397.
8. Meyer FJ, Zugck C, Haass M, et al. Inefficient ventilation and reduced respiratory muscle capacity in congestive heart failure. *Basic Res Cardiol*. 2000;95:333–342.
9. Opasich C, Ambrosino N, Felicetti G, et al. Heart failure-related myopathy. *Eur Heart J*. 1999;20:1191–1200.
10. Witt C, Borges AC, Haake H, et al. Respiratory muscle weakness and normal ventilatory drive in dilative cardiomyopathy. *Eur Heart J*. 1997; 18:1322–1328.
11. McParland C, Krishan B, Wang Y, et al. Inspiratory muscle weakness and dyspnoea in chronic heart failure. *Am Rev Respir Dis*. 1992;146:467–472.
12. Mancini DM, Henson D, LaManca J, et al. Respiratory muscle function and dyspnea in patients with chronic congestive heart failure. *Circulation*. 1992;86:909–918.
13. Ambrosino N, Opasich C, Crotti P, et al. Breathing pattern, ventilatory drive and respiratory muscle strength in patients with chronic heart failure. *Eur Respir J*. 1994;7:17–22.

14. Chua TP, Anker SD, Harrington D, et al. Inspiratory muscle strength is a determinant of maximum oxygen consumption in chronic heart failure. *Br Heart J*. 1995;74:381–385.

15. Nishimura Y, Maeda H, Tanaka K, et al. Respiratory muscle strength and hemodynamics in chronic heart failure. *Chest*. 1994;105:355–359.

16. Hammond MD, Bauer KA, Sharp JT, et al. Respiratory muscle function in congestive heart failure. *Chest*. 1990;98:1091–1094.

17. Zugck C, Krüger C, Dürr S, et al. Is the six minutes walk test a reliable substitute for peak oxygen uptake in patients with dilated cardiomyopathy? *Eur Heart J*. 2000;21:540–549.

18. Quanjer PH, Tammeling GJ, Cotes JE, et al. Lung volumes and forced ventilatory flows: European Community for Steel and Coal. *Eur Respir J*. 1993;6:5–10.

19. Black LF, Hyatt RE. Maximal respiratory pressures: normal values and relationship to age and sex. *Am Rev Respir Dis*. 1969;99:696–702.

20. Milic-Emili J, Whitelaw WA, Derenne JP. New tests to assess lung function: occlusion pressure-a simple measure of the respiratory center's output. *N Engl J Med*. 1975;293:1029–1030.

21. Nanas SN, Nanas J, Kassiotis Ch et al. Respiratory muscles performance is related to oxygen kinetics during maximal exercise and early recovery in patients with congestive heart failure. *Circulation*. 1999;100:503–508.

22. Ramos-Barbon D, Fitchett D, Gibbons WJ, et al. Maximal exercise testing for the selection of heart transplantation candidates: limitation of peak oxygen consumption. *Chest*. 1999;115:410–417.

23. Robbins MR, Francis G, Pashkow FJ, et al. Ventilatory and heart rate response to exercise. *Circulation*. 1999;100:2411–2417.

24. Aaronson K, Schwartz JS, Chen T, et al. Development and prospective validation of a clinical index to predict survival in ambulatory patients referred for cardiac transplant evaluation. *Circulation*. 1997;95:2660–2667.

25. Mancini DM, Henson D, La MJ, et al. Benefit of selective respiratory muscle training on exercise capacity in patients with chronic congestive heart failure. *Circulation*. 1995;91:320–329.

26. Mancini DM, Henson D, LaManca J, et al. Evidence of reduced respiratory muscle endurance in patients with heart failure. *J Am Coll Cardiol*. 1994;24:972–981.

27. Walsh JT, Andrews R, Johnson P, et al. Inspiratory muscle endurance in patients with chronic heart failure. *Heart*. 1996;76:332–336.

28. Granton JT, Naughton MT, Benard DC, et al. CPAP improves inspiratory muscle strength in patients with heart failure and central sleep apnea. *Am J Respir Crit Care Med*. 1996;153:277–282.

29. Naughton MT, Rahman A, Hara K, et al. Effect of continuous positive airway pressure on intrathoracic and left ventricular transmural pressures in patients with congestive heart failure. *Circulation*. 1995;91:1725–1731.