

Original Scientific Paper

Is serial determination of inspiratory muscle strength a useful prognostic marker in chronic heart failure?

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Background Little data exists on the prognostic role of inspiratory muscle strength (P_Imax) in chronic heart failure (CHF). Training studies, however, frequently use it as a therapeutic target and surrogate marker for prognosis. The prognostic value of changes of P_Imax that allow this extrapolation is unknown.

Design Patients with stable CHF were prospectively included and 1-year and all-time event rates recorded for endpoint analysis.

Methods In 158 patients (85% men; New York Heart Association functional class: 2.4 ± 0.6), P_Imax was measured along with clinical evaluations at two visits, the initial visit and the second visit, 6.4 ± 1.4 months apart. The mean follow-up was 59 ± 34 months.

Results Overall, 59 patients (37%) reached the primary endpoint of death or hospitalization (endpoint positive), and overall mortality rate (secondary endpoint) was 26% (42 patients). P_Imax did not differ between endpoint-negative and endpoint-positive patients, both at the initial and at the second visit (8.3 ± 5.6 vs. 7.3 ± 3.4 kPa and 8.8 ± 6.0 vs. 7.9 ± 3.6 kPa, respectively; $P=NS$), and both groups showed increased P_Imax (0.6 ± 2.6 vs. 0.6 ± 2.8 kPa; $P=NS$). Cox analyses found neither the absolute nor the relative change of P_Imax to be significant predictors for the primary and secondary endpoints ($P=NS$ for both), both for the 1-year and for the all-time event rates. Endpoint rates did not differ between patients showing increasing or decreasing P_Imax ($P=NS$; relative risk (RR): 0.77; 95% confidence interval: 0.47–1.27).

Conclusion Trials focusing on inspiratory muscle function should use the actual levels of P_Imax as a surrogate marker to represent prognostic information, rather than relative or absolute changes. This is the first study to investigate the prognostic information of the changes of P_Imax over time, regarding both short-term and long-term morbidity and mortality in patients with stable CHF. *Eur J Cardiovasc Prev Rehabil* 15:156–161 © 2008 The European Society of Cardiology

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Introduction

Evaluation of markers for risk prediction in chronic heart failure (CHF) is commonly carried out at a defined point of time during its clinical course (static markers); interventional studies mostly evaluate the time course of such markers (dynamic markers) [1]. Only very few studies, nevertheless, have addressed the link between dynamic measurement and prognostic information.

Although some [2–4] reported a benefit from serial analyses, others [5] were not able to confirm this.

Dysfunction of skeletal and respiratory muscle has been described as a comorbid status, reflecting the systemic impact of heart failure [6–9]. Inspiratory muscle strength representing respiratory muscle function is estimated through maximum inspiratory mouth occlusion pressure (P_Imax). It is reduced early in CHF [10], and a reduction is associated with a poor outcome [9]. P_Imax is an established surrogate marker and a therapeutic target for interventions in many trials [11,12]. If, however, changes of P_Imax resulting from interventions are to be

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interpreted correctly, the link between these changes and their possible prognostic information needs to be established. So far, only two studies [9,13] with a total of 389 patients have addressed the prognostic value of P_Imax, demonstrating its independence from earlier established prognostic markers [13]; however, the prognostic value of serial estimates of P_Imax has never been addressed before.

Analysis of parameter changes during a certain follow-up period requires a homogeneous state of patients. Therefore, this study prospectively evaluated the prognostic significance of P_Imax and the potential additional value of P_Imax changes during a 6-month period in a large cohort of stable CHF patients.

Methods

We prospectively included 168 patients (85% men) with stable CHF. At inclusion (initial visit, V1), P_Imax was determined, and a baseline clinical evaluation performed. A second evaluation (second visit, V2) including the determination of P_Imax was performed after 6 months (mean: 6.4 ± 1.4 months). For V2, this study design mirrors the common outpatient setting, in which the clinician judges the individual course of a patient in the light of previous data.

All patients were followed up for at least 12 months after V2, the mean follow-up period being 59 ± 34 months. Patients had to be on stable medication for more than 4 weeks prior to inclusion. Patients with an endpoint between V1 and V2 were excluded from the final analysis because they no longer fulfilled the entry criterion of stability of CHF.

Exclusion criteria were a positive history for primary pulmonary disease, uncorrected valvular defects, cardiac decompensation requiring inotropic support within the last 3 months prior to study inclusion, and conditions that could possibly affect respiratory muscle function (e.g. thyroid dysfunction and electrolyte disturbance). The study conformed to the principles outlined in the Declaration of Helsinki and was approved by the local Ethics Committee. All patients gave their written informed consent.

Inspiratory muscle-function testing

Measurements of P_Imax were performed by a technician blinded to the status of the patient and unaware of the other variables in the study. P_Imax was determined through a flanged mouthpiece in deep inspiration from functional residual capacity against a shutter with a minor air leak to prevent undesirable glottis closure (Master-LabPro 4.2; Erich Jaeger, Wuerzburg, Germany) [14]. Out of three measurements with < 5% variability, the highest pressure was used for analysis. A short rest was allowed

between manoeuvres when necessary. P_Imax is expressed in kPa as positive values, although they are negative pressures with respect to atmosphere.

Follow-up and endpoint

Patient follow-up was performed by either regular outpatient visits or telephone calls to patients' homes or to their respective physicians. The combined endpoint of death or hospitalization due to cardiac reasons within 1 year was defined as the primary endpoint, and 1-year mortality was defined as the secondary endpoint. Analyses were further extended to overall follow-up for both endpoints. Patients were classified as endpoint positive (EPP) if they had an event after V2; otherwise they were classified as endpoint negative (EPN). No patient underwent coronary artery bypass grafting or implantation of a left-ventricular assist device during follow-up. Patients receiving orthotopic heart transplantation were censored at the date of transplantation.

Statistics

Statistical tools such as the χ^2 analysis, the *t*-test and the two-sample Wilcoxon test were used wherever appropriate. All tests are two-tailed, and a *P* value of less than 5% was regarded as being statistically significant. Differences in event-free survival were detected by the Cox proportional-hazard model and depicted by the Kaplan–Meier product-limit method. The data are presented as mean \pm SD, except when specified otherwise. Calculations were performed with SAS version 6.12 (SAS Institute Inc., Cary, North Carolina, USA).

Results

Of the 168 patients included, 10 patients reached a predefined endpoint between V1 and V2. According to the study protocol, they were excluded from the analysis because they no longer fulfilled the criterion of stable CHF. Therefore, 158 patients were retained for the final analysis and followed up for a mean period of 59 ± 34 months. Of this final study population, 19 patients (12%) reached the primary endpoint of death or hospitalization within 1 year, and the 1-year mortality rate was 8% (12 patients). The profiles of the patients included at V1 and V2 for the study population analysed are shown in Table 1.

Patient profile

Both at V1 and V2, P_Imax was higher in EPN than in EPP, the difference not reaching statistical significance. At V1, EPN differed from EPP only in mean age and in the left-ventricular ejection fraction (LVEF). At V2, the difference for LVEF was no longer significant, but the mean result for the 6-min walk test had become significant. No other difference between EPN and EPP was noted for other clinical characteristics. For complete results, see Table 2.

Table 1 Clinical characteristics of the patients included and of the actual study population retained at the initial and follow-up visits

	Included (V1) n=168	Retained (V1) n=158	Retained (V2) n=158
Age, years	53.1 ± 9.8	52.9 ± 9.9	53.4 ± 9.9
Men (n %)	143 (85)	134 (85)	134 (85)
ICMP (n %)	56 (33)	54 (34)	54 (34)
NYHA class I (n)	12	12	19
II	74	71	76
III	82	75	62
IV	0	0	1
MAP (mmHg)	87 ± 20	87 ± 21	83 ± 25
Heart rate (1/min)	77 ± 21	76 ± 21*	71 ± 19
LVEF (%)	25 ± 10	25 ± 10**	32 ± 12
BMI (kg/m ²)	26.6 ± 4.6	26.6 ± 4.5	26.7 ± 4.5
NTproBNP (ng/l)	2382 ± 2491	2296 ± 2420	1783 ± 1790
6WT (m)	463 ± 107	464 ± 109	473 ± 129
PI _{max} (kPa)	8.1 ± 5.3	8.1 ± 5.4	8.7 ± 5.8
ACEI or ARB (n %)	139 (88)	149 (94)	139 (88)
BBL (n %)	112 (67)	108 (68)	111 (70)
Aldactone (n %)	83 (53)	76 (48)	83 (53)
Diuretics (n %)	124 (79)	131 (83)	124 (79)

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BBL, β-blocker; BMI, body mass index; ICMP, ischemic cardiomyopathy; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; NTproBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association functional class; PI_{max}, maximum mouth occlusion pressure; V1, first visit; V2, second visit; 6WT, 6-min walk test. **P*<0.05; ***P*<0.01.

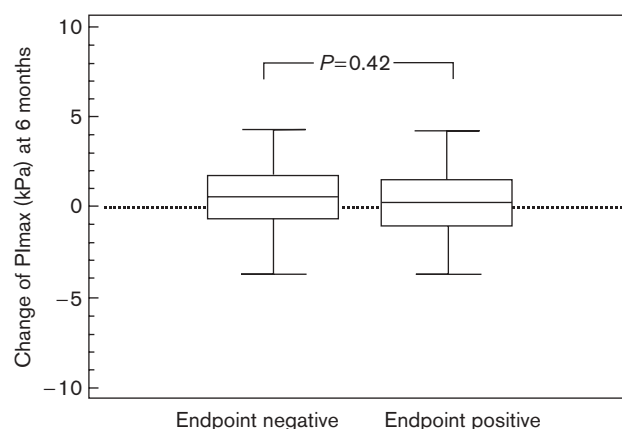
Table 2 Endpoint-positive and endpoint-negative patients for 1-year follow-up, at the initial visit and the follow-up visit after 6.4 ± 1.4 months

	EPN (n=139)		EPP (n=19)	
	V1	V2	V1	V2
n	139	139	19	19
NYHA-class I (n)	12	19	0	0
II	60	66	11	10
III	67	50	8	9
IV	0	1	0	0
LVEF (%)	26 ± 10*,**	33 ± 12	18 ± 4	26 ± 17
HR (bpm)	76 ± 21**	71 ± 19	75 ± 25	77 ± 17
MAP (mmHg)	88 ± 20	83 ± 26	86 ± 25	83 ± 24
6WT	466 ± 105	479 ± 130*	448 ± 139	420 ± 102
NTproBNP (ng/l)	2228 ± 2418	1765 ± 1825	3506 ± 2453	2154 ± 883
PI _{max} (kPa)	8.3 ± 5.6	8.8 ± 6.0	7.3 ± 3.4	7.9 ± 3.6
Delta PI _{max} (kPa)		0.6 ± 2.6		0.6 ± 2.8
Delta PI _{max} (%)		17.6 ± 63.0		15.3 ± 44.2

EPN, endpoint negative; EPP, endpoint positive; HR, heart rate; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; NTproBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association functional class; PI_{max}, maximum mouth occlusion pressure; 6WT, 6-min walk test. **P*<0.05 between groups at that visit; ***P*<0.05 between visits in that group.

Changes over time

Both EPN and EPP increased the mean PI_{max} between visits. This increase, however, was not significant for either of the groups. Furthermore, no significant difference was noted when comparing the mean change of PI_{max} between groups, both as absolute values and as percentages of the initial value (Fig. 1). EPN significantly increased LVEF and decreased heart rate, whereas the decrease in New York Heart Association functional class, mean arterial pressure and serum N-terminal pro-brain natriuretic peptide, as well as the increase in the 6-minute walk test were not statistically significant. No

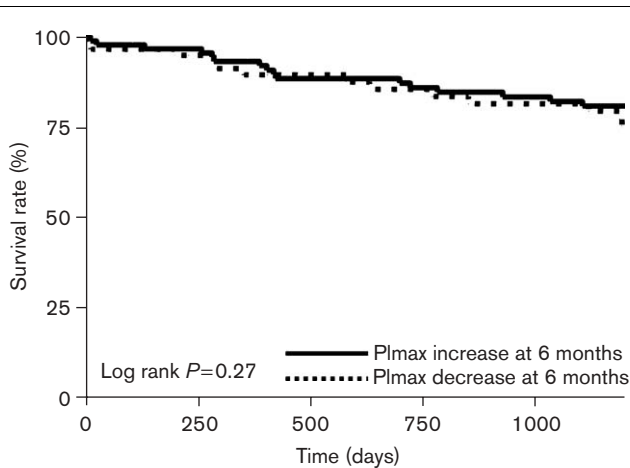
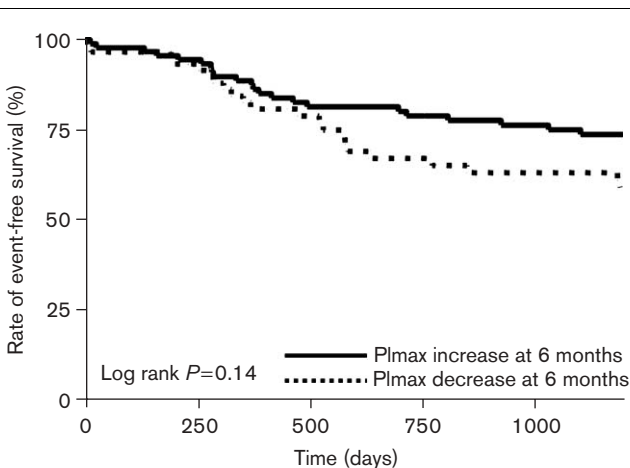
Fig. 1

Box plot depicting the absolute change of PI_{max} in patients, with and without the combined endpoint of death or hospitalization.

significant changes were noted for EPP between visits (Table 2).

Change of PI_{max}, resultant event rates and Cox analyses

During the 1-year follow-up, patients with increasing PI_{max} between visits had a primary endpoint rate of 11% (10 patients) for death or hospitalization in contrast to 14% (nine patients) for patients with decreasing PI_{max} [*P*=NS; RR: 0.77; 95% confidence interval (CI): 0.47–1.27]. During the entire follow-up period, 32% (30 patients) of patients with increasing PI_{max} and 45% (29 patients) of patients with decreasing PI_{max} reached the combined endpoint (*P*=NS; RR: 0.79; 95% CI: 0.59–1.05) during follow-up. Patients with increasing

Fig. 2Kaplan-Meier curve depicting the 3-year survival of patients with increasing P_Imax, compared with those with decreasing P_Imax.**Fig. 3**Kaplan-Meier curve depicting the 3-year event rate for death or hospitalization of patients with increasing P_Imax vs. decreasing P_Imax.

P_Imax had a 1-year mortality rate of 6% (six patients). In contrast, patients with decreasing P_Imax had a 1-year mortality rate of 9% (six patients; $P = \text{NS}$; RR: 0.83; 95% CI: 0.46–1.48). The overall mortality rate was 22% (21 patients) for patients with increasing P_Imax and 33% (21 patients) for patients with decreasing P_Imax ($P = \text{NS}$; RR: 0.79; 95% CI: 0.57–1.11) (Figs 2 and 3).

Cox analysis showed that neither the absolute (d_{PImax}) nor the relative change of P_Imax ($d_{\text{PImax}}\%$) were significant predictors for the primary and secondary endpoints ($P = \text{NS}$ for both). Furthermore, the predictive accuracies of d_{PImax} and $d_{\text{PImax}}\%$ (as judged by the

area under the curve of the receiver-operating curve) were not superior to P_Imax, both for the prediction of the primary and the secondary endpoints. The same results were obtained for overall mortality or the all-time combined endpoint. In contrast, P_Imax was a significant predictor for death or hospitalization both at V1 and V2 (χ^2 : 7.83, $P < 0.01$; χ^2 : 9.73, $P < 0.01$; respectively) as well as for death both at V1 and V2 (χ^2 : 8.13, $P < 0.01$; χ^2 : 5.37, $P < 0.05$; respectively).

Discussion

Although P_Imax is frequently used as a surrogate marker and therapeutic target for interventions in many trials of CHF, the prognostic value of serial determinations of P_Imax has not been addressed before. This, however, seems to be crucial if one wants to correctly interpret the changes of P_Imax resulting from intervention, or to use them as a surrogate for prognosis. We sought to provide this link in a prospective setting without intervention between visits, to differentiate the prognostic information relating to the level of change of P_Imax from that relating to the intervention performed. The main findings of our study are as follows:

1. Without any intervention targeting inspiratory muscles, neither the absolute nor the relative changes of P_Imax predict the 1-year or overall mortality in stable CHF.
2. Without any intervention targeting inspiratory muscles, neither the absolute nor the relative changes of P_Imax predict the 1-year or overall event rate for the combined endpoint of death and hospitalization for cardiac reasons in stable CHF.
3. Neither the absolute nor the relative changes of P_Imax were found to be additional significant predictors with respect to P_Imax.

We were able to confirm previous reports [9,13] regarding the prognostic value of P_Imax. Even though no information is available with regard to the prognostic value of serial measurements of P_Imax, the issue of change over time of other predictive variables in CHF has been addressed before. Although Gullestad *et al.* [5] were not able to demonstrate any additional benefit from serial determination of echocardiography parameters or pV_O₂, Florea *et al.* [3] found that the change of exercise parameters and LVEF significantly added to the prognostic value of single measurements. Grigioni *et al.* [2] extended these findings to ECG parameters, but changes in these failed to gain significance in their study. Recently, Corra *et al.* [4] reported that a combination of single and time-related functional variables would enhance the prognostication process.

These contradictory studies possibly demonstrate some of the pitfalls that occur with serial evaluation of markers,

such as the interval between visits and the range of this interval. The larger the interval, the more obvious will be the change, although clinical consequences might already have necessitated interventions. Furthermore, if the interval range is large, individual changes might no longer be comparable. In daily routine, however, it is rather difficult for the clinician to organize follow-ups in predefined periods of time outside controlled trials. Therefore, a certain range is unavoidable. In addition to these limiting factors, the value of the changes over time might be blunted if the clinical characteristics already differed at the initial visit [5]; hence, the results of the above studies might not be entirely comparable.

As far as soft endpoints such as functional capacity or quality of life are concerned, the link between change and result seems to be established for P_Imax. Already general training not specifically targeting the respiratory muscle alleviates dyspnoea and improves exercise performance in patients with CHF [15,16]. Training interventions and trials focusing on respiratory muscle function consistently showed improved muscle endurance and strength, resulting in enhanced exercise capacity, significantly less dyspnoea and improved functional status [12,17,18]. This, however, was not related to either the increased cardiac output or stroke volume [19]. The functional improvement resulted in less frequent periods of rest, fatigue, greater self-confidence, maintenance of independence and enhanced quality of life [11,19].

None of these trials or interventions focusing on respiratory muscle function reported any effect on survival. In contrast, a recent meta-analysis [20] confirmed the positive effect on survival of general physical training. Furthermore, skeletal muscle dysfunction and wasting responds to physical training [21]. Therefore, one would expect a positive link between the changes of P_Imax and survival. Given that we were unable to establish this link both for short-term and long-term mortality or morbidity, the prognostic impact of interventions and studies solely targeting respiratory muscles needs to be addressed.

It is known [20,21] that general physical training exerts positive effects on the different aspects of heart failure – ranging from cardiopulmonary, skeletal muscle and endothelial function to changes in neurohumoral activation patterns [22]. As a hypothesis, it is therefore possible for respiratory muscle function in the context of general physical training to reflect a more systemic positive modification. Inversely, respiratory muscle training alone can certainly improve respiratory function, leading to positive functional effects, without the more systemic effects of general physical training including improved survival.

To omit this possible bias regarding the kind of intervention performed, this study investigated the

changes of P_Imax in stable patients without any intervention, thus separating the possible prognostic effect of training from the prognostic information of the measurement. Patients were followed up on a regular basis at our specialized CHF clinic, and no intervention was performed by us. Had patients been registered with any kind of training programme, the general practitioner concerned would have informed the doctor in charge. In addition, patients had been questioned accordingly during the determination of endpoints. Consequent to our results, we suggest that trials focusing on inspiratory muscle function should use the actual levels of P_Imax as a surrogate marker rather than the relative or the absolute changes to represent prognostic information. P_Imax represents a marker of severity in itself [9,13]. Therefore, the risk would be more related to the actual level of P_Imax, rather than to the change from earlier measurements.

Limitations

To the best of our knowledge, we included one of the largest cohorts so far regarding the serial evaluation of inspiratory muscle force. The number of patients might, nevertheless, represent a limiting factor. It might have precluded the effect of time-related changes of P_Imax from becoming statistically significant. A nonconservative size estimate performed, using the data on the changes of P_Imax derived from this study by applying a type I error (α) of 0.05 and a type II error (β) of 0.10, however, indicates that the number of patients required would be 3836. For the reasons stated above, this study investigates the relationship between the changes of P_Imax and prognosis without any intervention between visits. Therefore, the question as to what extent these changes of P_Imax might reflect the beneficial effects of general physical training cannot be fully answered. Here, we postulate the need for a randomized interventional trial. Last, the interval chosen for our study might limit the results obtained, but we chose an interval of 6 months because we consider this to be appropriate in the general clinical follow-up of patients with stable CHF.

Conclusion

Trials focusing on inspiratory muscle function should use actual levels of P_Imax as a surrogate marker to represent prognostic information rather than the relative or the absolute change. In this first study to address the prognostic usefulness of the changes of P_Imax over time regarding both short-term and long-term morbidity and mortality in patients with stable CHF, change in P_Imax was not found to be an additional significant predictor. Furthermore, this is the first study giving a size estimate of potential randomized trials targeting a possible survival benefit of interventions on inspiratory muscles.

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Conflict of interest: none.

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