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Impaired chronotropic response to 6-min walk test and reduced survival in interstitial lung disease

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Summary
Background: Reduced chronotropic response to maximal exercise has been associated with poor survival in people without respiratory disease. The contribution of chronotropic response to exercise limitation and survival in interstitial lung disease (ILD) is not well defined. This study investigated the relationships between chronotropic response during 6-min walk test, exercise capacity and survival in ILD.
Methods: Eligible participants had ILD, were ambulant and free of heart failure and beta blocker therapy. Chronotropic response during the 6-min walk test was defined as peak heart rate (HR) minus resting HR. Survival was recorded at four years.
Results: Sixty-two participants (40 idiopathic pulmonary fibrosis) were included, with mean (SD) TLCO 50(18)% predicted and 6-min walk distance (6MWD) 377 (127) metres. A smaller chronotropic response was associated with reduced 6MWD ($r = 0.65$, $p < 0.001$). Independent predictors of 6MWD were chronotropic response, peak oxygen uptake on cardiopulmonary exercise test; right ventricular systolic pressure on echocardiogram; and age. This model explained 83% of the variance in 6MWD, with 24% of the variance attributable to chronotropic response. A chronotropic response during 6-min walk test of less than 20 beats per minute was an independent predictor of death at four years (odds ratio 10.71, 95% confidence interval 2.67–42.94) in a model that also included oxygen desaturation and forced vital capacity.
Conclusions: Impaired chronotropic response to 6-min walk test is associated with reduced 6MWD and reduced survival in ILD, independent of physical fitness and pulmonary

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hypertension. Investigation of the mechanisms underlying attenuated HR response to exercise in ILD is warranted.

Background

Exercise intolerance is a cardinal feature of the interstitial lung diseases (ILDs). Reduced exercise capacity is associated with significant exertional dyspnoea, fatigue and poor quality of life.[1,2] Exercise performance is a strong predictor of prognosis, with increased mortality associated with lower peak oxygen capacity, shorter 6-min walk distance (6MWD) and greater exercise-induced hypoxaemia.[3–5] The mechanisms of exercise intolerance are not fully understood, but include altered ventilatory mechanics, impaired gas exchange, peripheral muscle dysfunction and circulatory dysfunction.[6] The relative contribution of these factors to exercise performance and survival has not been established.

An increase in heart rate during exercise is a crucial contributor to aerobic exercise capacity in healthy individuals.[7] The heart rate response to exercise reflects the integrated response of many physiologic processes related to age, physical fitness, resting heart rate, coronary artery disease, autonomic nervous system function and use of medications.[8] Chronotropic incompetence occurs when an individual does not achieve 80% of heart rate reserve, calculated as the change in heart rate (HR) from rest to peak exercise on a maximum symptom-limited exercise test.[9] Chronotropic incompetence predicts all-cause and cardiovascular mortality in large studies of apparently healthy men.[10,11] The association between chronotropic incompetence and mortality is independent of physical fitness,[12] coronary artery disease[13] and myocardial perfusion.[14]

The contribution of chronotropic response to exercise limitation in ILD is not well defined. The current definition of chronotropic incompetence may not be applicable in this group, where ventilatory limitation frequently limits maximal exercise performance[6] and may reduce the maximal heart rate that can be achieved.[15] Recent studies have examined HR responses to submaximal exercise, showing that heart rate recovery following a 6-min walk test predicts survival in patients with idiopathic pulmonary fibrosis,[16,17] however the relevance of HR responses during exercise was not evaluated. In pulmonary arterial hypertension, chronotropic response to 6-min walk test (degree of change in HR during exercise) predicts 6MWD, independently of stroke volume.[18] It is not known whether chronotropic response to 6MWD is useful to predict exercise capacity or survival in ILD.

The aims of this study were to (1) evaluate the contribution of chronotropic response to functional exercise capacity in ILD; (2) assess the relationship of chronotropic response to mortality; and (3) compare indices of chronotropic response obtained from maximal and sub-maximal exercise testing in ILD. We hypothesised that impaired chronotropic response would be associated with reduced functional exercise capacity, independent of physical fitness; impaired chronotropic response would be associated with poorer survival; and chronotropic response measured on 6-min walk test was a more sensitive marker of survival than chronotropic incompetence measured on a cardiopulmonary exercise test.

Methods

Patients with documented ILD were recruited from two tertiary hospitals for two investigator-initiated studies examining exercise responses in ILD.[19,20] All participants gave written informed consent and the study was approved by the human ethics committees at both sites (210/04, 15/07). Diagnostic criteria for IPF were consistent with the International Consensus Statement.[21] For this study, participants were excluded if they were non-ambulant, had co-existent heart failure, were currently taking beta-blockers or digitalis, reported a history of syncope on exertion or had any comorbidities precluding exercise testing.

Functional exercise capacity was assessed using the 6-min walk test (6MWT).[22] Two tests were performed, with the best distance used for analysis. Use of oxygen during the test was standardised.[23] Participants were permitted to stop during the test if their symptoms became intolerable, but were encouraged to resume walking as soon as possible. Borg dyspnoea scores were recorded at the end of the test.[24] Heart rate and oxygen saturation were recorded continuously during the test using a pulse oximeter (Palm-SAT 2055; Nonin Medical, Plymouth, MN, USA). Chronotropic response was defined as peak HR minus resting HR.[18] In 54 participants an incremental exercise test (IET) was performed on a cycle ergometer.[25] Chronotropic incompetence was defined as failure to achieve 80% of heart rate reserve during the incremental test.[7] Measurements of spirometry, diffusing capacity and plethysmographic lung volumes were obtained and a trans-thoracic echocardiogram was performed.

Participants were followed for a minimum of four years, with vital status ascertained on 11th May 2009 by medical record review or individual patient follow up as required. Survival time was calculated as the time of the 6MWT to the time of death or censoring.

The relationship of demographic and clinical variables, including chronotropic response, to 6MWD was assessed using multiple regression analysis. Prior to developing the model we assessed univariate relationships between 6MWD and possible predictors, which included demographic variables (age, BMI, IPF diagnosis yes/no); resting physiology (FVC, TLCO, RVSP, resting HR); and exercise responses from the 6-min walk test and IET. Exercise variables evaluated were chronotropic response, maximum HR and end-walk Borg score on 6-min walk test; VO_2 peak and peak ventilation (VEpeak) on IET; and peak oxygen pulse (VO_2 peak/

peak HR), a measure of cardiac efficiency on IET. Variables with $p < 0.1$ on univariate testing were included in the multivariate model and the forward conditional method was used to determine independent predictors of 6MWD. An a priori decision was made to include VO_2 peak in the model, to assess the contribution of chronotropic response to 6MWD whilst controlling for physical fitness.

Differences in chronotropic response on 6-min walk test between survivors and non-survivors at four years were evaluated with the Mann Whitney *U* test. The performance of chronotropic response in predicting survival was assessed using receiver operating characteristic (ROC) curves. The effect of impaired chronotropic response on survival time was evaluated using Kaplan Meier survival curves and groups were compared using the log rank test.[10] The impact of impaired chronotropic response and other clinical variables on survival at four years was assessed using logistic regression analysis. Prior to developing the model we assessed univariate relationships between survival and markers of disease severity and survival, as described in the 6MWD analyses above. Variables with a univariate relationship to survival ($p < 0.1$) were included in the model. Forced vital capacity was also included in the model, to assess the performance of chronotropic response as a predictor of survival when compared to a more established marker. The Hosmer and Lemeshow test was used to evaluate model fit. We performed a sensitivity analysis by excluding those who stopped during the 6-min walk test, to assess the effects of test cessation on the relationship between chronotropic response and study outcomes (6MWD and survival). The analysis of chronotropic response was repeated using heart rate data obtained from the ECG on IET, to assess the accuracy of this model compared to that obtained using heart rate data from the 6-min walk test. Statistical significance was determined by a *p* value of <0.05. All analyses were undertaken using SPSS version 19.0 (SPSS Inc; Chicago, IL).

Results

Sixty-two participants with ILD (32 males) were recruited. Forty participants (65%) had a confident diagnosis of IPF, whilst other participants had diagnoses of connective tissue related ILD ($n = 9$), dust-related ILD ($n = 4$), granulomatous ILD ($n = 4$), drug-related ILD ($n = 2$), hypersensitivity pneumonitis ($n = 2$) and Langerhans cell histiocytosis ($n = 1$). Forced vital capacity ranged from 32 to 102% predicted and the 6MWD ranged from 49 to 681 m (Table 1). Eight participants stopped at least once during the 6-min walk test. Participants with IPF had more severe impairment of TLCO and 6MWD than those with other ILDs, but did not differ for right ventricular systolic pressure (RVSP), HR response to exercise or VO_2 peak. On the IET, 39 of 54 participants (72%) failed to achieve 80% of their HR reserve and were designated as chronotropically incompetent.

The mean increase in HR during the 6-min walk test was 28 beats per minute (bpm), with a range of 5–55 bpm. A smaller chronotropic response was associated with a shorter 6MWD ($r = 0.65$, $p < 0.001$, Fig. 1). A significant relationship was also observed between 6MWD and peak HR ($r = 0.41$, $p = 0.001$) but not resting HR ($r = -0.11$, $p = 0.40$). There was no relationship between 6MWD and Borg scores at the end of the test ($r_S = 0.16$, $p = 0.27$). As expected, a lower VO_2 peak on IET was also associated with a lower 6MWD ($r = 0.72$, $p < 0.01$). In the stepwise regression analysis, independent predictors of 6MWD were VO_2 peak, chronotropic response, age and RVSP on echocardiogram. This indicates that lower physical fitness, a smaller HR response during the walk test, older age and a greater degree of pulmonary hypertension were independently associated with a lower 6MWD. This model explained 83% of the variance in 6MWD, with 24% of the variance attributable to chronotropic response (Table 2). When those who stopped during the 6MWT were excluded from the analysis, there was no change in the predictors of 6MWD (model not shown).

Table 1 Demographic characteristics of participants.

	All participants	IPF	Other ILD	*p* Value
Age, years	71 (11)	73 (7)	66 (14)	0.02
BMI, kg m^{-2}	29 (5)	30 (5)	27 (5)	0.06
FVC % pred	77 (22)	74 (20)	82 (25)	0.19
TLCO % pred	50 (18)	46 (17)	56 (17)	0.05
RVSP, mmHg	37 (13)	39 (15)	33 (9)	0.22
6MWD, metres	378 (127)	350 (124)	424 (121)	0.03
Nadir SpO_2, %	87 (7)	86(8)	90 (5)	0.04
HR at rest, bpm	79 (14)	80 (14)	78 (12)	0.55
HR maximum on 6MWT, bpm	107 (16)	106 (17)	108 (16)	0.72
Chronotropic response, bpm	28 (13)	26 (12)	30 (14)	0.26
VO_2 peak % predicted	57 (18)	57 (19)	58 (16)	0.74

Data are mean (standard deviation). *P* values are comparison of IPF and non-IPF participants. BMI – body mass index; bpm – beats per minute; FVC – forced vital capacity; TLCO – diffusing capacity for carbon monoxide; RVSP – right ventricular systolic pressure measured on echocardiography; 6MWD – 6-min walk distance; SpO_2 – oxyhaemoglobin saturation during 6-min walk test; HR – heart rate; VO_2 peak – peak oxygen uptake measured on cardiopulmonary exercise test.

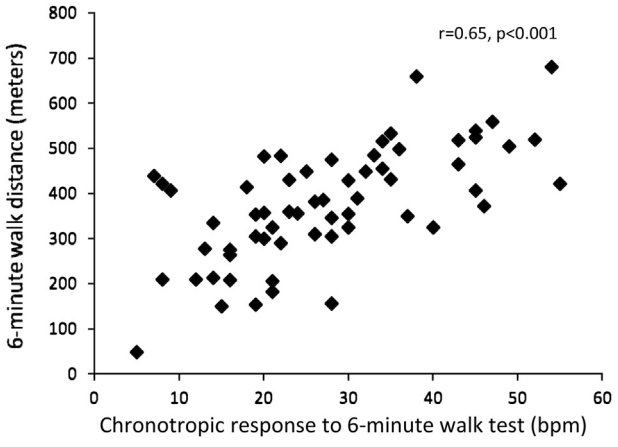

Figure 1 Relationship between chronotropic response and 6-min walk distance.

Table 2 Predictors of 6-min walk distance on stepwise multiple regression analysis.

Variable	B	SE	Standardised beta	*p* Value	R^2 change
VO_2 peak, ml kg min^{-1}	14.39	2.63	0.43	<0.001	0.51
Chronotropic response, bpm	3.64	0.77	0.36	<0.001	0.24
Age, years	−3.34	0.90	−0.28	0.001	0.05
RVSP, mmHg	−2.05	0.76	−0.21	0.10	0.03
Constant	390.34	105.78		0.001	
R^2					0.83

VO_2 peak — peak oxygen uptake on incremental cycle ergometer test; bpm — beats per minute; RVSP — right ventricular systolic pressure on transthoracic echocardiogram; B — unstandardised coefficient; SE — standard error of the coefficient; R^2 — proportion of observed variance in 6-min walk distance explained by the model.

After four years there were 20 deaths (32%), 15 of whom had IPF. The median chronotropic response to 6-min walk test in those who survived at four years was 30 bpm, compared to 16 bpm in non-survivors ($p < 0.001$). The ROC curve identified a chronotropic response of ≤20 bpm as the best threshold for predicting death at four years, with a sensitivity of 0.85 and specificity of 0.70. When only those with IPF were included, the thresholds for sensitivity and specificity were 0.67 and 0.92 respectively. Kaplan Meier survival curves comparing those with chronotropic response of ≤20 bpm to those with chronotropic response > 20 bpm are shown in Fig. 2 (log rank test $p < 0.001$ for difference between groups).

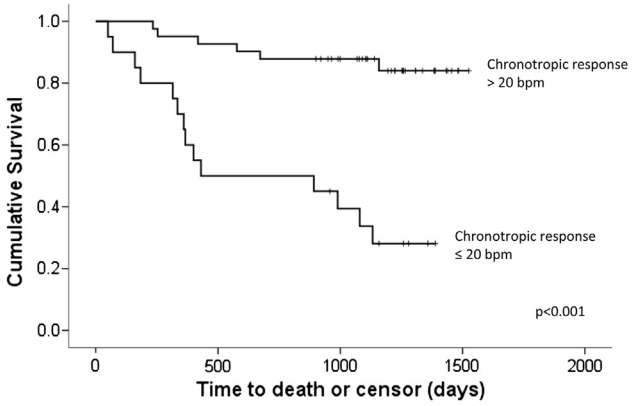

Figure 2 Kaplan Meier survival curves for those with a chronotropic response ≤20 bpm compared to those with chronotropic response >20 bpm.

Forty-one percent of those who were assessed as chronotropically incompetent on the IET using standard criteria[7] were deceased at four years, whilst all of those who did not have chronotropic incompetence were still alive ($p = 0.002$). Chronotropic incompetence on IET was therefore highly sensitive for predicting survival (sensitivity = 1.0), however specificity was 0.39. When only those with IPF were included, sensitivity and specificity were 1.0 and 0.5 respectively.

Variables associated with survival at four years were impaired chronotropic response to 6-min walk test ($p < 0.001$), RVSP ($p = 0.001$), nadir SpO_2 on 6MWT ($p = 0.006$), 6MWD ($p = 0.011$) and FVC ($p = 0.012$). A diagnosis of IPF was not significantly associated with survival ($p = 0.23$). The final model is shown in Table 3. The Hosmer and Lemeshow test indicated good model fit ($\chi^2 = 10.41$, $p = 0.24$). Impaired chronotropic response was an independent predictor of survival; those with a chronotropic response of ≤20 bpm on 6MWT were almost 11 times more likely to have died at four years. When those who stopped during the 6MWT were excluded from the analysis ($n = 8$), there was no change in the predictors of survival; those with impaired chronotropic response were almost 10 times more likely to have died at four years (model not shown).

When the analysis was repeated using heart rate (ECG) and SpO_2 data from the IET, there was little change in the model. Chronotropic response remained an independent predictor of survival and those with impaired response were almost 10 times more likely to have died at four years (Table 4). The ROC curve identified a chronotropic response on IET of ≤40 bpm as the best threshold for predicting

Table 3 Predictors of four year survival in interstitial lung disease using 6-min walk test.

	Estimate	SE	*p* Value	Odds ratio	95% CI
Impaired chronotropic response to 6-min walk test	2.37	0.71	0.001	10.71	2.67—42.94
Nadir SpO_2 on 6-min walk test	−0.10	0.05	0.058	0.91	0.82—1.003
FVC	−0.42	0.44	0.35	0.66	0.28—1.57
Constant	7.97	4.43	0.07		

SpO_2 — oxyhaempoglobin saturation; 6MWT — 6-min walk test; FVC — forced vital capacity; SE — standard error; CI — confidence interval.

Table 4 Predictors of four year survival in interstitial lung disease using incremental exercise test.

	Estimate	SE	*p* Value	Odds ratio	95% CI
Impaired chronotropic response to IET	2.29	0.76	0.003	9.85	2.21–43.90
Nadir SpO_2 on IET	−0.01	0.05	0.83	0.99	0.89–1.10
FVC	−0.52	0.46	0.26	0.60	0.24–1.49
Constant	0.16	4.61	0.97		

IET — incremental exercise test; SpO_2 — oxyhaempoglobin saturation; 6MWT — 6-min walk test; FVC — forced vital capacity; SE — standard error; CI — confidence interval.

death at four years, with a sensitivity of 0.74 and specificity of 0.81.

Discussion

This study has shown that in individuals with ILD, a smaller chronotropic response to 6-min walk test is associated with lower functional exercise capacity and reduced survival at four years. These effects were independent of physical fitness and the usual markers of disease severity. A chronotropic response of $\leq$20 bpm on 6-min walk test identified a high risk patient group with adequate sensitivity and specificity.

In healthy individuals, the increase in HR during exercise is the largest contributor to aerobic exercise performance, having a larger role than stroke volume or oxygen extraction.[26] Our study has shown that chronotropic response is an independent contributor to 6MWD in ILD, suggesting that HR response has a similarly important role during submaximal exercise capacity in this patient group. Our model explained 83% of the observed variation in 6MWD, with 24% of the variance attributable to chronotropic response (Table 2). Whilst peak HR also showed a strong relationship to 6MWD, the same relationship was not evident for resting HR, indicating that it is the failure to increase HR during exertion that impacts on exercise capacity, rather than an elevation in the resting heart rate. These results confirm previous observations in IPF[15,17] and PAH,[18] where smaller elevations in heart rate during submaximal and maximal exercise testing have been associated with lower exercise capacity. Our work extends these observations by confirming that this relationship is independent of measured VO_2 peak and age, indicating that reduced chronotropic response is not simply a function of lower physical fitness and age-related changes in heart rate.[7] The 6MWD has prognostic significance in ILD,[4] so the large proportion of variance in this measure that is explained by the chronotropic response further supports the significance of an inadequate HR increase during exercise in this population.

Failure to increase HR more than 20 bpm during the 6-min walk test was a strong predictor of survival at four years. The relationship between impaired heart rate response and poor outcome is well established in the cardiovascular literature.[11,12] Few studies have investigated the prognostic importance of heart rate changes during exercise in ILD, perhaps because of the predominance of ventilatory and circulatory limitations to exercise in this group. In IPF, previous authors have shown that abnormal heart rate recovery at 1 min and 2 min after a 6-min walk test was associated with reduced survival.[16] These authors also showed that a smaller chronotropic response was associated with a slower heart rate recovery, however its relationship to survival was not investigated. Predictors of survival are important for informing clinical care and as endpoints in clinical trials.[27] In this cohort, a chronotropic response to 6-min walk test of $\leq$20 bpm performed well as a predictor of survival when compared to FVC, a commonly used surrogate for survival in ILD (Table 3). The relative utility of chronotropic response compared to other predictors of survival, including FVC and heart rate recovery, should be evaluated in future studies.

Chronotropic incompetence, as defined by failure to achieve a set percentage of the age-predicted maximum heart rate, requires an incremental exercise test for definitive diagnosis.[7] However in this study, 72% of participants were defined as chronotropically incompetent, which reduced the specificity of the test in predicting survival. The chronotropic response calculated from ECG data on IET proved to be a useful marker of survival, but provided no more information than if it was calculated from the 6-min walk test. In IPF, the role of laboratory-based, incremental exercise testing is not well defined and it is not recommended for routine monitoring.[28] In contrast, 6-min walk tests are routinely performed to monitor functional status and oxygenation in people with ILD. Our study suggests that evaluation of heart rate responses during a 6MWT is both feasible and meaningful in this population. Our data reinforce the need for new ways to assess the contribution of heart rate to exercise performance in individuals with respiratory and circulatory limitations to exercise.

The mechanisms responsible for reduced chronotropic response in our sample are not known. Data from other groups with chronic disease suggests a contribution from chronically elevated sympathetic nervous system activity and resulting downregulation of β-adrenergic receptors. Increased sympathetic nervous system activation has been demonstrated in pulmonary arterial hypertension, where it is associated with increased heart rate and reduced 6MWD.[29] Sympathetic nervous system activation was a better predictor of clinical deterioration than HR or 6MWD. In people with heart failure, where circulating catecholamines are known to be chronically elevated, a lower density of endomyocardial β-adrenergic receptors was associated with impaired chronotropic response and reduced VO_2 peak.[30] Preliminary data indicate increased sympathetic activation in a small group of patients with lung fibrosis and chronic hypoxaemia.[31] The authors postulated that alterations in the chemoreceptor activation

of sympathetic outflow may play a role, however other mechanisms, such as the impact of elevated pulmonary pressures on the myocardium, could also contribute.

If the reduction in chronotropic response to exercise in ILD is common and clinically significant, as suggested by our results, new treatment strategies should be considered. In heart failure, endurance exercise training has been shown to reduce sympathetic outflow and circulating catecholamines.[32] This is associated with an increase in peak heart rate.[33] However, preliminary data on a combination of endurance and strength training in ILD do not suggest any effect on peak HR.[19] Whether other training modes might prove more effective in addressing chronotropic response in ILD is not known. The impact of treating hypoxaemia or pulmonary hypertension on autonomic function and heart rate responses in ILD should also be studied.

This study has a number of limitations, including a modest sample size and inclusion of participants with a variety of ILDs. These results need to be validated in a larger sample, where potential for differing effects in diagnostic groups can be more clearly delineated. We were not able to determine the exact cause of death for our participants, so we cannot specify how many deaths were due to cardiac or respiratory causes. However, a recent suggests that all-cause mortality is the most relevant endpoint in IPF trials, as it retains all clinically relevant information.[27] Due to the extended time period required to collect information about mortality, our participants were recruited some years ago, when different diagnostic criteria were used[21] compared to those in use today.[28] It is possible that the use of modern diagnostic criteria might have affected our subgroup analyses; however the consistent relationship between chronotropic response and survival in this study, regardless of diagnosis, suggests that any effect would be small. Our heart rate data during the 6-min walk test were obtained by pulse oximetry rather than electrocardiogram (ECG), which may have increased the error associated with this measure. However, previous authors have reported that heart rate obtained from a pulse oximeter during exercise is highly accurate when compared to ECG at heart rates up to 155 bpm.[34] The maximum heart rate recorded during the 6-min walk test in this study was 149 bpm, suggesting that accurate heart rate data were obtained. Use of a pulse oximeter to record heart rate during a walk test reflects usual clinical practice and chronotropic response collected in this manner proved to be a sensitive predictor of outcome.

In conclusion, a reduced chronotropic response during the 6MWT is associated with reduced exercise tolerance and increased mortality in ILD. Failure of the HR to rise more than 20 bpm during a 6MWT may be a simple predictor of outcome. Future studies should investigate the mechanism of reduced HR response and whether it can be modified by emerging treatments.

Conflict of interest statement

The authors have no conflict of interest to declare in relation to this manuscript.

The study sponsors had no role in the collection, analysis and interpretation of data; in the writing of the manuscript; or in the decision to submit the manuscript for publication.

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