Published in final edited form as:

Respirology. 2011 April ; 16(3): 439–445. doi:10.1111/j.1440-1843.2010.01877.x.

Heart rate recovery after six-minute walk test predicts pulmonary hypertension in patients with idiopathic pulmonary fibrosis

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Abstract

Background and objective—In patients with IPF, we sought to validate that abnormal heart rate recovery at 1 min (HRR1) after six-minute walk test (6MWT) predicts mortality and to explore the relationship between abnormal HRR1 and pulmonary hypertension (PH).

Methods—We identified IPF patients who performed a 6MWT as part of their clinical evaluation between 2006 and 2009 and were followed to lung transplantation or death. Right heart catheterization (RHC) data were collated and analysed for the subgroup who had this procedure.

Results—There were 160 subjects who qualified for the survival analysis, and those with an abnormal HRR1 had worse survival than subjects with normal HRR1 (log-rank $P = 0.01$). Eighty-two subjects had a right heart catheter (RHC); among them, abnormal HRR1 was associated with RHC-confirmed PH ($\chi^2 = 4.83$, $P = 0.03$) and had a sensitivity, specificity, positive predictive value and negative predictive value of 52%, 74%, 41% and 82%, respectively, for PH. In bivariate and multivariable analyses, abnormal HRR1 appeared to be the strongest predictor of RHC-confirmed PH (odds ratio (OR) = 4.0, 95% CI: 1.17–13.69, $P = 0.02$ in the multivariable analysis).

Conclusions—This study adds to data that support the validity of abnormal HRR1 as a predictor of mortality and of RHC-confirmed PH in IPF. Research is needed to further investigate the link between abnormal HRR1 and PH and to elucidate heart–lung interactions at work during exercise and recovery in patients with IPF.

Keywords

heart rate recovery; idiopathic pulmonary fibrosis; interstitial lung disease; pulmonary hypertension

INTRODUCTION

IPF is a progressive fibrosing interstitial lung disease (ILD) without effective therapy and a poor prognosis. Median survival rates have been observed to be as low as 2.5 years.¹

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Prognostic variables in IPF include age, gender, disease duration, symptom severity, radiologic features, functional capacity, and both baseline and serial changes in measures of pulmonary physiology and gas exchange.^{2–8}

We recently observed that the absence of a fall in heart rate by greater than 13 beats per minute 1 min after the performance of a six-minute walk test (6MWT) was associated with increased mortality in patients with IPF and added independent prognostic information beyond that provided by baseline demographic and physiologic data.⁹ Failure of the heart rate to fall after cessation of exertion, or what is called an abnormal heart rate recovery (HRR), has previously been found to be associated with increased mortality in a variety of conditions and clinical scenarios.^{10–12}

Given the lack of any reliably effective therapy for IPF, potentially modifiable comorbid conditions may be attractive therapeutic targets. In this regard, several investigators have focused their attention on IPF-related pulmonary hypertension (IPF-PH), a complication of IPF associated with functional impairment and a poor prognosis.^{13–20} Whether therapies effective for pulmonary arterial hypertension have a role in IPF-PH remains to be determined.^{21,22}

Although right heart catheterization (RHC) is the gold standard for determining whether PH is present, RHC is invasive and expensive. Transthoracic echocardiography is the most established of the non-invasive methods used to screen for PH, but it yields notoriously inaccurate estimates of RHC-derived systolic pulmonary artery pressure in patients with IPF.^{13,23} A variety of other non-invasive modalities to predict PH in patients with IPF, including pulmonary physiologic parameters, radiologic imaging findings, as well as rest and exercise gas exchange measures have also proved to be imperfect.^{14,19,22}

In our initial study of HRR in IPF, along with its prognostic power, an abnormal HRR was strongly associated with PH. To further investigate the implications of abnormal HRR in IPF, we conducted this study with the following aims: (i) to validate, in an entirely new cohort from a different institution, our prior observation that abnormal heart rate recovery at 1 min (HRR1) portends a poor prognosis in IPF; and (ii) to test the hypothesis that an abnormal HRR is associated with RHC-confirmed PH in patients with IPF.

METHODS

Subjects

The study sample consisted of consecutive patients with IPF evaluated at a tertiary and lung transplantation referral centre from 2006–2009 and who performed a 6MWT as part of their clinical evaluation. None of the subjects in this study was included in our previously published study;⁹ the cohorts are from different institutions. The routine collection of data during recovery after the 6MWT was instituted at this centre only within the last 4 years, so patients evaluated before that time were not included in the study sample. The study was approved by the Inova Fairfax Hospital Institutional Review Board. The diagnosis of IPF was made in accordance with consensus guidelines from the American Thoracic Society/European Respiratory Society (ATS/ERS).^{24,25}

Testing

Pulmonary function tests, including FVC and DL_{CO}, were performed according to ATS/ERS criteria, and their results are reported as percentages of predicted (e.g. FVC% and DL_{CO}%).^{26–29} The 6MWT was performed according to ATS/ERS criteria with the following modifications: during the test and recovery period, subjects wore a finger probe connected to a pulse oximeter. Both heart rate and peripheral oxygen saturation (SpO₂) were

recorded at the end of each minute of the 6MWT, as well 1 min after completion of the test with the patient seated. Supplemental oxygen was used at the flow rate commensurate with the subjects' current oxygen prescriptions. The test was terminated if SpO₂ fell below 80%; however, patients were included in the study sample regardless of whether they walked for a full 6 min. RHC was performed at the discretion of the evaluating physician. Most subjects had RHC done as part of lung transplantation candidacy evaluation. We defined PH as present when the mean pulmonary artery systolic pressure was ≥ 25 mm Hg in the face of a pulmonary artery occlusion pressure that was ≤ 15 mm Hg.³⁰

Data collection

Clinical data were collected by chart review and database query. HRR1 was defined as the difference between a subject's heart rate at the end of walk test (could be <6 min if the test was terminated for low SpO₂) and 1 min into recovery.

Statistical analysis

Baseline data are presented as counts, percentages, or measures of central tendency. Continuous variables were compared by using *t*-tests or nonparametric equivalent where appropriate. Categorical variables were compared by using chi-square or Fisher's exact test where appropriate. We used the product-limit method to derive, and a Kaplan–Meier curve to display, survival for the entire study sample (whether RHC was performed or not) stratified on HRR1 (abnormal vs normal). Survival time was calculated from the time of the 6MWT to death or censoring (subjects were censored at the time of transplant or if they were alive at last contact). Vital status was ascertained on 20 April 2009 by either records review or query of the social security death index. For subjects who performed more than one 6MWT at the study centre, we chose the earliest test to allow for the longest follow up. But, for subjects who had RHC, we chose the 6MWT temporally closest to the date of the RHC. We used the chi-square test to assess the relationship between HRR1 (dichotomous variable: abnormal vs normal) and PH (dichotomous variable: yes vs no). We used logistic regression to examine the relationship between various predictor variables and the presence of RHC-confirmed PH. For the multivariable analysis of PH, to develop the most parsimonious model, we included as candidate variables any with a *P*-value of ≤ 0.1 on bivariate analysis, and we used both forward and backward selection techniques—to confirm model stability (i.e. that the models were the same regardless of the selection technique)—with *P* ≤ 0.1 for variable selection and *P* ≤ 0.1 for variable retainment in the final model. SAS version 9.2 (SAS Institute; Cary, NC, USA) was used to perform all statistical analyses, and we considered *P* < 0.05 to represent statistical significance.

RESULTS

There were 160 subjects enrolled for the survival analysis, 82 of whom had RHC a median 58 days before (interquartile range (IQR) 223 days prior to 28 days after) the 6MWT. Table 1 displays demographic and disease characteristics of the entire cohort stratified on HRR1.

Prediction of survival

Subjects with an abnormal HRR1 had significantly worse survival (*P* = 0.01) than subjects with a normal HRR1 (Fig. 1).

Prediction of PH

Demographics and disease characteristics for the 82 subjects who underwent RHC are presented in Table 2. Among those with an abnormal HRR1, 41% (11 of 27) had PH compared with only 18% (10 of 55) of subjects with a normal HRR1 ($\chi^2 = 4.83$, *P* = 0.03).

So, HRR1 had a sensitivity, specificity, positive predictive value and negative predictive value of 52%, 74%, 41% and 82%, respectively, for the prediction of PH.

Table 3 displays the association between various predictor variables and the presence of RHC-confirmed PH. In multivariable analysis using either a forward or backward selection technique, and including all candidate variables with $P \leq 0.1$ from the bivariate analysis, abnormal HRR1 was the only variable retained in the model (OR 4.0, 95% CI: 1.17–13.69, $P = 0.02$). We performed similar analyses for the subgroup of subjects who underwent RHC and walked for the full 6 min during the 6MWT, and the results were the same—abnormal HRR1 was the only variable retained.

Table 4 shows the correlations between several variable pairs among subjects who underwent RHC. There was a strong positive correlation ($r = 0.83$, $P < 0.0001$) between the rise from baseline in HR during the 6MWT (i.e. Δ HR) and HRR1 (i.e. greater Δ HR was associated with greater HR recovery). There were weak-moderate correlations between 6MWD and Δ HR ($r = 0.48$, $P < 0.0001$) and between 6MWD and HRR1 ($r = 0.38$, $P = 0.0005$). Table 5 shows comparisons of values for several variables between subjects with or without PH.

DISCUSSION

In this study, we examined 160 subjects with IPF and observed that the failure of the heart rate to decline by more than 13 beats at 1 min after a 6MWT was a potent predictor of mortality, confirming our previous observation and building on the validity of abnormal HRR1 as a prognostic marker in IPF. We also observed abnormal HRR1 was a predictor of RHC-confirmed PH, with a specificity of 74% and a negative predictive value of 82%.

Recently, there has been a groundswell of interest in IPF-PH, specifically, its prevalence, treatment and non-invasive markers of its presence.^{13–19} Measures of pulmonary function,¹⁶ findings on high-resolution chest CT,¹⁹ and estimates of right ventricular systolic pressure (RVSP) derived from transthoracic echocardiography¹³ have proved to be unreliable predictors of RHC-confirmed PH in patients with IPF. HRR1 is a simple, inexpensive, easy-to-collect variable that can be captured at the time a patient performs a 6MWT—a measure of functional capacity that is itself simple, inexpensive, and used with increasing frequency in the evaluation and follow up of patients with IPF.

Exactly as in our prior study, we observed that the further a subject walks during the 6MWT, the greater the Δ HR from baseline; again as in our prior study, the greater the Δ HR, the greater HR recovers at 1 min post 6MWT. All of these HR findings are independent of exertion-related changes in peripheral oxygen saturation. Although the value of HRR1 was related to HR at the end of the 6MWT (end HR was positively correlated with HRR1), end HR explained only 23% of the variance in HRR1, meaning factors beside peak HR and oxygenation during the 6MWT, are playing a major role in determining HRR1.

Provencher and colleagues³¹ assessed heart rate response during 6MWT in subjects with pulmonary arterial hypertension and observed a significant association between 6MWD and Δ HR. Their results tell that for any increase of one in Δ HR, 6MWD increased by 3.12 m. We observed similar results among the 82 subjects who underwent RHC: for any one beat/min increase in Δ HR during the 6MWT, 6MWD increased by 4.15 m. The similarities in results bolster the validity of our findings.

One potential reason for the increased likelihood of abnormal HRR in patients with IPF-PH centres on chronotropic incompetence. Elevated pulmonary artery pressures, even at borderline high levels, can impair right ventricular diastolic function.^{32,33} That impairment

could induce chronic sympathetic nervous system hyperactivity, resulting in chronotropic incompetence—elevated resting heart rate, decreased maximal heart rate, decreased heart rate variability and (as relates to this study) impaired HRR. Sympathetic activation is known to participate in the cardiovascular perturbations in idiopathic pulmonary arterial hypertension³⁴ and could certainly do so here.

An alternative explanation, as proposed to occur in COPD,³⁵ is that the ventilatory or gas exchange abnormalities of IPF directly induce autonomic dysfunction. Heindl and colleagues noted abnormal sympathetic activation in patients with chronic respiratory failure, including some with pulmonary fibrosis.³⁶ And sympathetic activation is known to increase pulmonary vascular resistance³⁷; thus sympathetic activity could be a cause of IPF-PH rather than simply an effect (via the mechanisms outlined in the previous paragraph). However, this explanation seems unlikely: if ventilatory and gas exchange abnormalities were the trigger for the development of PH, then all IPF patients would develop PH when their disease reaches a certain severity. That is not the case; thus, this explanation seems unlikely.

Another potential reason for an abnormal HRR1 besides resting PH, and one that we believe merits further study, is exercise-induced PH. Whether any of our subjects with normal resting MPAP by RHC (or those who did not undergo RHC) had exercise-induced PH is unknown but possible.

Our study has limitations, including its retrospective design, with the consequence that data collection was not systematically implemented. We have no data on chronotropically or vaso-active medications; however, these have been found in previous studies not to influence HRR findings.^{9,35} The number of subjects who died was small. Furthermore, with only 82 subjects undergoing RHC (21 with PH, and among those, only 5 with MPAP >45 mm Hg), the study did not have power to adequately investigate mechanisms for our observations. The low number of events limited the number of variables that we could include in our multivariable statistical analyses. However, the fact that HRR1 held up as a significant predictor while adjusting for other important variables (in limited-sized models) supports the robustness of our findings. Finally, the time between 6MWT and RHC was variable; obviously, having both tests performed on the same day (or at least within a week of each other) would be ideal.

Despite the limitations, this study advances our understanding of IPF by building on the validity of a simple, inexpensive prognostic variable in a sample with very well-defined IPF. In addition, these results show that in patients with IPF, abnormal HRR1 is a marker for resting PH that might merit confirmation with a RHC. Indeed, the aim of this study was not to prove that variables from the 6MWT could take the place of confirmatory RHC in IPF patients; rather, the goal was to identify a simple variable, obtained from an easily administered, clinical test that might improve our ability to detect IPF patients with complicating PH. We believe the data to derive HRR1 (e.g. HR at 1 min after test completion) should be routinely collected any time a patient with IPF performs a 6MWT. Moreover, the finding of an abnormal HRR1 should be viewed as a poor prognostic sign and should spark consideration for investigation of IPF-related PH. Future studies should prospectively investigate the association between abnormal HRR1 and resting, as well as exercise-induced PH and further tease out the mechanisms leading to an abnormal HRR1. We welcome the collaboration of any investigators interested in pursuing these goals.

In summary, among patients with IPF, the failure of the heart rate to drop by more than 13 beats/min at 1 min after the completion of a 6MWT is a poor prognostic marker. Further, abnormal HRR1 is associated with resting PH, and the detection of an abnormal HRR1

should initiate consideration for further evaluation. We believe HRR1 should be used as an outcome measure in trials of therapy for IPF and IPF-related PH. Future prospective studies are needed to examine the relationship between abnormal HRR1 and PH; to decipher whether exercise-induced PH or other physiologic mechanisms play any role; and to determine whether modulating HRR1 alters outcomes.

Acknowledgments

We appreciate the thoughtful comments of Robert Naeije (Department of Physiology, Free University of Brussels, Brussels, Belgium) on potential mechanisms of abnormal heart rate recovery in IPF patients. Dr Swigris is supported in part by a Career Development Award from the NIH (K23 HL092227).

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SUMMARY AT A GLANCE

For patients with IPF, a failure of heart rate to reduce by at least 14 beats/min after the first minute of recovery following completion of a six-minute walk test is an independent predictor of mortality and of pulmonary hypertension.

Figure 1. Kaplan–Meier survival curve for entire cohort stratified on heart rate recovery at 1 min (HRR1). Solid line represents curve for subjects with normal HRR1. Dashed line represents curve for subjects with abnormal HRR1. Tics represent censored observations.

Table 1

Baseline characteristics of entire study sample stratified on HRR1

	HRR1 13 (n = 48)	HRR1 > 13 (n = 112)	P-value
Age in years [†]	69.7 (7.9)	66.6 (9.6)	0.04
Male, %	78	74	0.7
FVC% [†]	59.4 (16.2)	64.5 (14.3)	0.07
DL _{CO} % [†]	36.4 (21.8)	41.2 (14.9)	0.2
6MWD in meters [†]	253.6 (141.4)	362.1 (130.5)	<0.0001
Baseline SpO ₂	97.0 (3.5)	97.7 (3.0)	0.2
ΔSpO ₂	−6.6 (6.3)	−8.3 (5.0)	0.1
6MWT Nadir SpO ₂ <89%, %	42	49	0.4
Baseline HR [†]	91.3 (16.0)	81.8 (15.2)	0.001
HR at end of 6MWT [†]	105.0 (16.6)	113.9 (17.2)	0.003
ΔHR	13.7 (10.0)	32.1 (13.7)	<0.0001
HR 1 min post 6MWT [†]	98.6 (16.3)	86.7 (16.5)	<0.0001
Supplemental O ₂ flow rate			
None, <i>n</i>	29	89	0.02 [§]
1–3 L/min, <i>n</i>	7	9	
4–5 L/min, <i>n</i>	4	5	
6 L/min, <i>n</i>	8	9	
Walked for <6 min, %	21	14	0.2
Months of follow up [‡]	12.0 (6.2–19.2)	12.6 (6.7–18.1)	0.9

P-values for comparison between groups stratified on HRR.Data are counts (*n*), percentages, mean (SD)[†], or median (interquartile range).[‡][§]For none versus any oxygen comparison between groups.HR, heart rate; HRR1, heart rate 1 min into recovery after 6MWT; RHC, right heart catheterization; SpO₂, peripheral oxygen saturation; ΔHR, HR at the end of the 6MWT minus HR at baseline; ΔSpO₂, SpO₂ at the end of the 6MWT minus SpO₂ at baseline.

Table 2

Baseline characteristics of subjects who underwent RHC stratified on HRR1

	HRR1 13 (<i>n</i> = 27)	HRR1 > 13 (<i>n</i> = 55)	<i>P</i> -value
Age in years [†]	66.9 (5.8)	64.2 (9.3)	0.1
Male, %	78	74	0.7
FVC% [†]	57.6 (15.5)	62.8 (14.9)	0.2
DL _{CO} % [†]	28.0 (21.2)	40.3 (12.5)	0.003
6MWD in meters [†]	230.9 (144.9)	360.2 (138.7)	0.003
Baseline SpO ₂	96.6 (4.1)	97.2 (3.7)	0.5
ΔSpO ₂	−7.5 (7.3)	−8.7 (5.5)	0.5
6MWT Nadir SpO ₂ <89%, %	59	56	0.8
Baseline HR [†]	92.1 (18.5)	82.3 (18.5)	0.01
HR at end of 6MWT [†]	103.4 (19.1)	116.5 (19.3)	0.005
ΔHR	11.2 (12.1)	34.3 (14.8)	<0.0001
HR 1 min post 6MWT [†]	99.1 (18.2)	87.0 (18.6)	0.007
Supplemental O ₂ flow rate			
None, <i>n</i>	12	40	0.06 [§]
1–3 L/min, <i>n</i>	6	4	
4–5 L/min, <i>n</i>	2	3	
6 L/min, <i>n</i>	7	8	
Walked for <6 min, %	67	82	0.2
Months of follow up [‡]	12.6 (7.8–20.4)	13.5 (7.7–18.4)	0.9

P-values for comparison between groups stratified on HRR.[†]Data are counts (*n*), percentages, mean (SD) or[‡]median (interquartile range).[§]For none versus any oxygen comparison between groups.

HR, heart rate; HRR1, heart rate 1 min into recovery after 6MWT; RHC, right heart catheterization; SpO₂, peripheral oxygen saturation; ΔHR, HR at the end of the 6MWT minus HR at baseline; ΔSpO₂, SpO₂ at the end of the 6MWT minus SpO₂ at baseline.

Table 3

Bivariate analyses: predictors of PH

	Odds ratio	95% CI	P-value
Abnormal HRR	3.09	1.11–8.66	0.03
Age	1.02	0.96–1.09	0.44
Male gender	0.57	0.19–1.68	0.31
FVC%	0.99	0.96–1.03	0.81
DL _{CO} %	0.96	0.92–1.00	0.07
Δ HR	0.98	0.94–1.00	0.12
Baseline SpO ₂	0.99	0.87–1.12	0.84
Δ SpO ₂	0.99	0.92–1.08	0.95
SpO ₂ recovery	0.89	0.79–0.99	0.04
6MWD	0.99	0.99–1.00	0.04

HR, heart rate; HRR, heart rate recovery at 1 min after the 6MWT; RHC, right heart catheterization; SpO₂, peripheral oxygen saturation; Δ HR, HR at the end of the 6MWT minus HR at baseline; Δ SpO₂, SpO₂ at the end of the 6MWT minus SpO₂ at baseline.

Table 4
Correlations and *P*-values for associations among variables for subjects who underwent RHC

	BaseHR	EndHR	ΔHR	HRR1	BaseSp	NadirSp	ΔSpO ₂	6MWD	MPAP
BaseHR	1.0	0.56 <0.0001	-0.34 0.002	-0.29 0.01	-0.22 0.05	-0.20 0.07	-0.05 0.68	-0.35 0.001	0.07 0.53
EndHR		1.0	0.58 <0.0001	0.48 <0.0001	0.05 0.67	0.03 0.79	-0.15 0.18	0.12 0.28	-0.10 0.38
ΔHR			1.0	0.83 <0.0001	0.27 0.02	0.21 0.10	-0.12 0.27	0.48 <0.0001	-0.18 0.11
HRR1				1.0	0.22 0.04	0.23 0.04	-0.14 0.20	0.38 0.0005	-0.18 0.11
BaseSp					1.0	0.48 <0.0001	-0.17 0.14	0.40 0.0002	0.07 0.56
NadirSpO ₂						1.0	0.57 <0.0001	0.35 0.001	-0.10 0.40
ΔSpO ₂							1.0	0.03 0.80	0.12 0.30
6MWD								1.0	-0.46 <0.0001
MPAP									1.0

BaseHR, HR at start of 6MWT; EndHR, HR at end of 6MWT; HR, heart rate; HRR1, heart rate recovery (continuous variable) at 1 min after the 6MWT; MPAP, mean pulmonary artery pressure; RHC, right heart catheterization; Sp, peripheral oxygen saturation; ΔHR, HR at the end of the 6MWT minus HR at baseline; ΔSpO₂, SpO₂ at the end of the 6MWT minus SpO₂ at baseline.

Table 5

Characteristics of subjects who underwent RHC stratified on the presence or absence of RHC-confirmed PH

	Subjects without PH (<i>n</i> = 61)	Subjects with PH (<i>n</i> = 21)	<i>P</i> -value
Age in years [†]	64.6 (8.5)	66.2 (7.6)	0.4
Male, %	79%	68%	0.3
FVC% [†]	61.1 (15.8)	60.1 (14.8)	0.8
DL _{CO} % [†]	38.4 (14.1)	30.1 (16.2)	0.07
6MWD in meters [†]	337.4 (148.7)	260.2 (153.0)	0.04
Baseline SpO ₂ [†]	97.0 (3.8)	96.9 (4.1)	0.8
SpO ₂ at end of 6MWT [†]	88.2 (5.9)	86.8 (5.3)	0.3
SpO ₂ difference (end 6MWT-rest) [†]	-8.28 (6.0)	-8.4 (6.6)	0.9
Baseline HR [†]	84.4 (17.9)	88.6 (15.7)	0.4
HR at end of 6MWT [†]	112.9 (21.2)	110.3 (16.9)	0.6
HR difference (end 6MWT-rest) [†]	28.5 (18.2)	21.5 (15.2)	0.12
HR 1 min post 6MWT [†]	89.7 (19.7)	94.6 (17.6)	0.3

[†]Data are counts (*n*), percentages or means (SD).HR, heart rate; SpO₂, peripheral oxygen saturation.