Resting heart rate is a predictor of mortality in COPD

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ABSTRACT The clinical significance of high heart rate in chronic obstructive pulmonary disease (COPD) is unexplored. We investigated the association between resting heart rate, pulmonary function, and prognosis in subjects with COPD.

16 696 subjects aged ⩾40 years from the Copenhagen City Heart Study, a prospective study of the general population, were followed for 35.3 years, 10 986 deaths occurred. Analyses were performed using time-dependent Cox-models and net reclassification index (NRI).

Resting heart rate increased with severity of COPD ($p<0.001$). Resting heart rate was associated with both cardiovascular and all-cause mortality across all stages of COPD ($p<0.001$). Within each stage of COPD, resting heart rate improved prediction of median life expectancy; the difference between <65 bpm and >85 bpm was 5.5 years without COPD, 9.8 years in mild (Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage I), 6.7 years in moderate (GOLD stage II) and 5.9 years in severe/very severe COPD (GOLD stage III/IV), ($p<0.001$). Resting heart rate significantly improved risk prediction when added to GOLD stage (categorical NRI 4.9%, $p=0.01$; category less NRI 23.0%, $p<0.0001$) or forced expiratory volume in 1 s % predicted (categorical NRI 7.8%, $p=0.002$; category less NRI 24.1%, $p<0.0001$).

Resting heart rate increases with severity of COPD. Resting heart rate is a readily available clinical variable that improves risk prediction in patients with COPD above and beyond that of pulmonary function alone. Resting heart rate may be a potential target for intervention in COPD.

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In patients with COPD, an elevated resting heart rate predicts life expectancy and identifies patients at particular risk http://ow.ly/kFB4C

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Introduction

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death in the world [1] annually accounting for over 3 million deaths [2]. COPD is associated with increased resistance in the pulmonary vasculature, pulmonary hypertension, increased right ventricular workload and in advanced cases right heart failure (cor pulmonale). Pulmonary and cardiovascular dysfunction is, thus, intimately connected.

It is a common clinical experience that patients with COPD often have high resting heart rates. High resting heart rate is present and associated with poor outcome in other clinical syndromes, *e.g.* heart failure, a disease entity that shares many clinical features with COPD, such as decreased stroke volume, dyspnoea and fatigue.

Recent studies have suggested that beta-blockers may have a beneficial effect on all-cause mortality in patients with COPD [3]. One of the main properties of beta-blockers is heart rate reduction. Heart rate may, therefore, potentially be a prognostic marker and therapeutic target in COPD as in other patient groups such as coronary heart disease and heart failure [4, 5].

Although elevated resting heart rate has been shown to be associated with increased cardiovascular and all-cause mortality in normal subjects and in subjects with heart disease [6-8] the contribution of resting heart rate to mortality in patients with COPD has never been examined in the setting of a large-scale population study.

In the present study, the relationships between COPD, resting heart rate and prognosis were studied. First, we examined whether COPD severity was associated with an increase in resting heart rate; secondly, we examined whether resting heart rate was associated with cardiovascular and all-cause mortality in COPD; thirdly, we examined whether resting heart rate could improve prediction of median life expectancy beyond that of Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage [1]; and finally, using net reclassification index (NRI), we examined whether adding resting heart rate to models with GOLD stage alone or forced expiratory volume in 1 s (FEV_1) % predicted alone could reclassify subjects into clinically meaningful higher or lower risk categories of mortality.

Methods

Population

The Copenhagen City Heart Study is a prospective study of a random population sample of 18 974 males and females aged $\geqslant$20 years living in Copenhagen, Denmark. The study was initiated in 1976 and has so far included four examinations: the first survey lasted from 1976 to 1978; the second survey from 1981 to 1983; the third from 1991 to 1994; and the fourth from 2001 to 2003. The first cross-sectional survey included 14 223 individuals. Subjects aged between 20–49 years have subsequently been added throughout the following surveys to the current total number. The sampling background and methods have been described in detail in several publications [9–11].

Subjects

All subjects were of Caucasian descent. In the present study, only subjects aged $\geqslant$40 years were included. Subjects with atrial fibrillation or flutter were excluded from the analyses; also cases with missing data on resting heart rate or pulmonary function were excluded (n=375). Information on vital status and causes of death was obtained from national registers. Cardiovascular death was defined as International Classification of Diseases (ICD)-8 codes 390–458 and ICD-10 codes I00-I99. A total of 106 subjects were lost to follow-up due to emigration; follow-up was, therefore, 99.4% complete.

The regional ethical committee approved the study (H-KF-01-144/01). All participants gave written informed consent.

Measurements

All subjects underwent physical examinations as well as a self-administered questionnaire providing medical history, smoking (never, former, current) and alcohol consumption habits (never, monthly, weekly, or everyday drinker), leisure time physical activity (sedentary, referring to light activity $<$2 h per week; moderate, referring to light activity 2–4 h per week; and high, referring to light activity $>$4 h per week or high activity $>$2 h per week), medication, and history of contacts with the healthcare system. Blood pressure was measured with the London School of Hygiene sphygmomanometer. Plasma cholesterol, high-sensitivity C-reactive protein (CRP), fibrinogen and blood glucose values were measured on non-fasting venous blood samples [12]. A 12-lead ECG was recorded at rest in a supine position and coded according to the Minnesota code. Resting heart rate was read from the ECG.

In surveys one and two, FEV_1 and forced vital capacity (FVC) were measured with an electronic spirometer (Monaghan N 403; Monaghan, Littleton, CO, USA), which was calibrated daily. In surveys three and four, a dry wedge spirometer (Vitalograph, Maidenhead, UK), which was calibrated weekly, was used. The best

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FEV_1 and FVC of three were used in the analyses. Lung function data are reported as a percentage of predicted value according to age, sex and height (FEV_1 % pred) [13].

Severity of COPD was classified according to the GOLD classification [1]: mild COPD (GOLD stage I), FEV_1/FVC <70% and FEV_1 % pred ⩾80; moderate COPD (GOLD stage II) FEV_1/FVC <70% and 50⩽ FEV_1 % pred <80; severe COPD (GOLD stage III) FEV_1/FVC <70% and 30⩽ FEV_1 % pred <50; very severe COPD (GOLD stage IV) FEV_1/FVC <70% and FEV_1 % pred <30%.

Statistics

All statistical analyses were carried out using the statistical software R, version 2.13.1. (R Foundation for Statistical Computing, Vienna, Austria). For demographics, the Kruskal–Wallis test was used for continuous variables and Fischer's exact test for categorical variables.

First, we studied the association between resting heart rate and severity of COPD (GOLD stage). For each subject, only observations from the first study visit were used. The robustness of the association was examined by performing two analyses: 1) univariate; and 2) adjusted for age, sex, smoking, systolic blood pressure, cholesterol, body mass index (BMI), physical activity, alcohol consumption habits, use of heart medication, use of antihypertensives, use of nitrates, previous ischaemic heart disease, electrocardiographic evidence of ischaemic heart disease (Minnesota codes 1-1 and 1-2), previous stroke, previous diagnosis of any cancer (information from the Danish Cancer Registry), and self-reported diabetes or fasting glucose >11.1 $mmol \cdot L^{-1}$. Additional subanalyses were performed in the fully adjusted model that also included covariates only available in surveys three and four. These covariates were high-sensitivity CRP, fibrinogen, use of statins, use of medication for asthma or bronchitis, and dyspnoea (Medical Research Council (MRC) scale).

Secondly, the association between resting heart rate and cardiovascular and all-cause mortality was studied using both uni- and multivariate models (as stated previously) in a Cox proportional hazards model with time-dependent covariates. The assumption of proportionality in the Cox regression models was tested with the score process test.

Thirdly, to assess if resting heart rate in addition to GOLD stage predicts mortality better than GOLD stage alone, Kaplan–Meier survival curves for all-cause mortality were fitted and median life expectancy calculated for GOLD stage alone, and for GOLD stage stratified by resting heart rate.

Finally, we studied whether the addition of resting heart rate to pulmonary function (GOLD stage or FEV_1 % pred) would improve the predictive accuracy for mortality. Firstly, we calculated Harrell's C-statistic with and without resting heart rate. C-statistics assess the prognostic ability of a variable using a binary outcome. Since C-statistics are not developed for risk prediction models [14], we also assessed the NRI [15, 16]. The dataset was split in half, one half for developing the models and the other half for validating the models [16]. For the NRI, risk categories for mortality during a 10-year follow-up period based on GOLD stages in the development dataset were determined as <25%; 25%–35%; 35%–50%; and ⩾50%. Only subjects with GOLD stage 2 or higher were included. The categorical NRI provides information about how adding resting heart rate to GOLD stage or FEV_1 % pred correctly reclassifies subjects who do not have an event into a lower risk category and subjects who get an event into a higher risk category. The category less NRI provides information on improved reclassification into higher or lower risk without predefined risk categories; *i.e.* a subject for whom risk estimation is improved from 26% to 33% would, in the categorical analysis, not be considered reclassified due to the limits of the categories, whereas in the category less analysis this person would be registered as correctly reclassified. Statistical significance was assumed at a value of $p<0.05$.

Results

A total of 16 696 subjects were included. During the 35.3 years of follow-up (mean 20.1 years), 5394 cardiovascular deaths and 10 986 all-cause deaths occurred. Clinical characteristics are shown in table 1.

COPD severity and levels of resting heart rate

Resting heart rate increased with severity of COPD (fig. 1a and 1b).

Compared to subjects with no COPD mean (95% CI) resting heart rate was 0.5 (-1.2–0.2) $beats \cdot min^{-1}$ higher in subjects with stage I COPD, 1.4 (1.0–1.9) $beats \cdot min^{-1}$ higher in subjects with stage II COPD, 4.5 (3.7–5.2) $beats \cdot min^{-1}$ higher in subjects with stage III COPD, and 10.4 (8.9–11.9) $beats \cdot min^{-1}$ higher in subjects with stage IV COPD (fig. 1a). In the multivariate model including age, sex, smoking, blood pressure, cholesterol, BMI, physical activity, alcohol, medication, diabetes, previous cardiovascular disease and cancer (see statistics) the difference in resting heart rates was -0.3 (-1.0–0.3) $beats \cdot min^{-1}$, 0.9 (0.4–1.3) $beats \cdot min^{-1}$, 3.9 (3.1–4.6) $beats \cdot min^{-1}$, and 9.9 (8.4–11.4) $beats \cdot min^{-1}$, respectively for each GOLD stage (fig. 1b). The p-value for trend was <0.001 in both analyses.

TABLE 1 Clinical characteristics of the 16 696 subjects included in the study

	GOLD stage					p-value
	No COPD	I	II	III	IV	
Subjects n	14051	516	1564	457	108	
Male n (%)	6251 (44.5)	313 (60.7)	866 (55.4)	261 (57.1)	75 (69.4)	<0.001
Age years	54±9	57±10	57±10	59±9	62±9	<0.001
Resting heart rate beats·min^{-1}	73.4±13	72.6±12	74.6±13	77.5±13	84.9±14	<0.001
Systolic blood pressure mmHg	137±22	138±22	141±23	141±22	144±20	<0.001
Body mass index kg·m^{-2}	25.5±4.2	24.4±3.2	25.1±4.2	25.1±4.8	24.6±5.1	0.894
FEV1 % pred	89±17	89±16	65± 8	42±6	24±5	<0.001
Sedentary physical activity	17.6	21.4	24.3	31.1	47.7	<0.001
Smoking status						
Never	21.9	15.6	10.9	7.3	7.5	<0.001
Former	19.2	19.9	12.9	15.4	34.9	<0.001
Current	58.9	64.5	76.2	77.3	57.5	<0.001
Daily alcohol consumption	24.3	32.5	33.6	34.4	38.3	<0.001
Cholesterol mmol·L^{-1}	6.1±1.2	6.0±1.2	6.0±1.2	6.0±1.1	5.9±1.2	0.009
Use of heart medication	9.0	7.8	10.1	15.0	16.8	<0.001
Previous coronary heart disease	2.2	1.7	3.0	2.8	3.7	0.219
Previous stroke	1.0	1.4	1.5	1.5	2.8	0.152
Previous cancer	4.1	2.9	5.4	5.9	8.3	0.004
Diabetes	3.1	1.8	4.2	5.4	10.6	<0.001

Data are presented as mean±SD or %, unless otherwise stated. GOLD: Global Initiative for Chronic Obstructive Lung Disease; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 s; % pred: % predicted.

In a subanalysis also including use of asthma or bronchitis medication, MRC class, high-sensitivity CRP, fibrinogen and use of statins in the full multivariate model the positive relationship between resting heart rate and COPD severity remained highly significant (p<0.001).

Resting heart rate and mortality

Resting heart rate was highly significantly associated with both cardiovascular and all-cause mortality in both uni- and multivariate models (table 2). There was no interaction between COPD severity and heart rate with

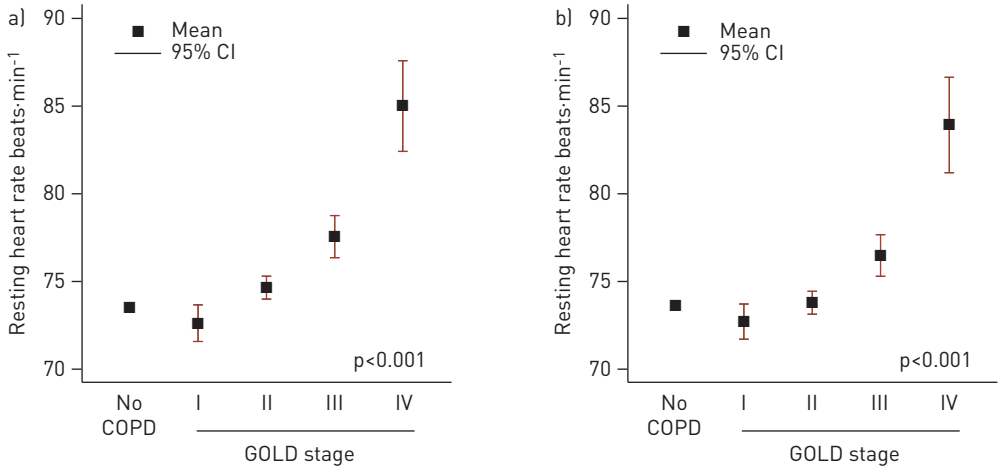

FIGURE 1 Resting heart rate and severity of chronic obstructive lung disease (COPD). Resting heart rate increase significantly with severity of COPD (p<0.001). a) Unadjusted analysis. b) Multivariate analysis adjusted for age, sex, smoking, systolic blood pressure, cholesterol, body mass index, physical activity, alcohol drinking habits, use of heart medication, use of antihypertensives, use of nitrates, previous ischaemic heart disease, electrocardiographic evidence of ischaemic heart disease, previous stroke, previous diagnosis of any cancer, self-reported diabetes or fasting glucose >11.1 mmol·L^{-1}. Data are presented as mean with error bars representing 95% CI. No COPD n=14051, Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage I n=516, GOLD stage II n=1564, GOLD stage III n=457, GOLD stage IV n=108.

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TABLE 2 Resting heart rate, all-cause and cardiovascular mortality

	Resting heart rate beats·min^{-1}			
	<64	65–74	75–84	⩾85
All-cause mortality				
Univariate	1¶	1.11 (1.05–1.17)	1.30 (1.23–1.37)	1.51 (1.42–1.60)
Multivariate#	1¶	1.16 (1.10–1.22)	1.31 (1.24–1.38)	1.51 (1.43–1.60)
Cardiovascular mortality				
Univariate	1¶	1.08 (1.00–1.17)	1.34 (1.24–1.45)	1.57 (1.45–1.70)
Multivariate#	1¶	1.16 (1.07–1.25)	1.36 (1.26–1.48)	1.57 (1.45–1.71)

Data are presented as hazard ratio (95% CI). #: multivariate analysis adjusted for age, sex, smoking, systolic blood pressure, cholesterol, body mass index, physical activity, alcohol consumption habits, use of heart medication, use of antihypertensives, use of nitrates, previous ischaemic heart disease, electrocardiographic evidence of ischaemic heart disease, previous stroke, previous diagnosis of any cancer, self-reported diabetes or fasting glucose >11.1 mmol·L^{-1}; ¶: reference.

regard to mortality. However, there was a significant interaction with smoking; elevated heart rate was associated with greater risk in current and former smokers. This has previously been discussed in detail [7].

GOLD stage, resting heart rate, and median life expectancy

Pulmonary function according to the GOLD staging was highly predictive of mortality. Median life expectancy (95% CI) was 78.8 (78.4–79.2) years in the no COPD group, 77.9 (75.6–79.5) years in GOLD stage I COPD, 73.4 (72.2–74.4) years in GOLD stage II COPD and 67.2 (65.2–68.9) years in GOLD stage III/IV COPD.

Figure 2 shows median life expectancy by GOLD class and resting heart rate. As shown, median life expectancy decreased with increase in resting heart rate across all GOLD stages. Median life expectancies (95% CI) in no COPD were 80.9 (80.2–81.6) years in subjects with resting heart rate <65 beats·min^{-1}, 79.7 (79.1–80.2) years in resting heart rates 65–74 beats·min^{-1}, 78.2 (77.6–79.0) years in resting heart rates 75–84 beats·min^{-1}, and 75.4 (74.5–76.3) years in resting heart rate ⩾85 beats·min^{-1}. In subjects with GOLD stage I COPD median life expectancies were 80.5 (77.9–84.2) years, 79.5 (74.4–82.8) years, 78.9 (74.7–81.4) years, and 70.7 (67.0–75.6) years, respectively. In GOLD stage II COPD median life expectancies were 76.2 (73.3–78.7), 74.1 (72.4–75.8), 73.1 (70.8–74.9), and 69.5 (67.2–71.6). In GOLD stage III/IV COPD median life expectancies were 70.4 (65.3–74.0), 68.2 (61.9–73.1), 68.0 (63.9–69.4), and 64.5 (62.7–67.7), respectively. Thus, the difference in median life expectancy between a subject with a resting heart rate <65 beats·min^{-1} compared to a subject with resting heart rate ⩾85 beats·min^{-1} was 5.5 years in subjects with no COPD, 9.8 years in subjects with stage I COPD, 6.7 years in subjects with stage II COPD and 5.9 years in subjects with stage III/IV COPD.

Risk reclassification, adding resting heart rate to pulmonary function

The addition of resting heart rate to models with pulmonary function alone significantly improved risk prediction.

In a model where pulmonary function was determined as GOLD stage, C-statistics for GOLD stage alone were 0.54 (0.53–0.56) *versus* 0.57 (0.55–0.60) ($p<0.001$) with GOLD stage and resting heart rate. The categorical NRI was 4.9% ($p=0.01$) (fig. 3) and the categoryless NRI was 23.0% ($p<0.0001$). In a model where pulmonary function was determined as FEV_1 % pred, C-statistics were 0.57 (0.54–0.59) *versus* 0.59 (0.56–0.61) with both FEV_1 % pred and resting heart rate ($p<0.001$). The categorical NRI was 7.8% ($p=0.002$) (fig. 4) and the categoryless NRI was 24.1% ($p<0.0001$).

Resting heart rate correctly reclassified subjects across all COPD stages, 76.4% were GOLD stage II, 19.7% GOLD stage III and 3.9% GOLD stage IV which was similar to the general distribution of COPD (77.9% GOLD stage II, 18.3% GOLD stage III and 3.8% GOLD stage IV). Resting heart rate especially improved the prediction of non-events indicating that subjects with lower resting heart rates had a better survival than expected on the basis of their level of FEV_1.

Discussion

Resting heart rate increases with severity of pulmonary dysfunction in COPD, and improves prediction of mortality above and beyond knowledge of pulmonary function alone. These findings raise the question whether heart rate could be a target for intervention in COPD.

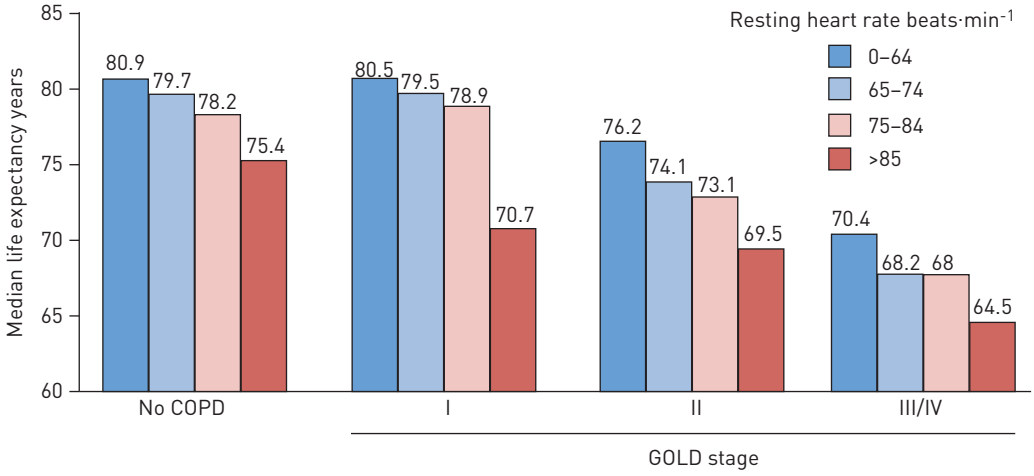

FIGURE 2 Life expectancy by Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage and resting heart rate.

For example, in subjects with moderate COPD, resting heart rate predicts up to 10 years difference in median life expectancy between subjects with resting heart rate <65 and $\geqslant 85$ beats·min^{-1}; in fact, the difference between high and low resting heart rate within the same GOLD stage is of a greater magnitude than the differences in life expectancy between adjacent GOLD stages, thus, the difference in median life expectancies between mild COPD and moderate COPD was 4.5 years. Hence, resting heart rate improves the identification of subjects with COPD at risk. Monitoring resting heart rate can readily be implemented into clinical practice and day-to-day patient care.

Also, in terms of differences in absolute risk two important points can be inferred from our findings. First, in subjects within the same GOLD stage classification but with different resting heart rates an elevated resting heart rate is associated with poor prognosis and, in relation to absolute risk, the greater the severity of pulmonary dysfunction the greater is the difference in absolute risk between high and low heart rate categories. For example, in individuals without COPD the absolute mortality risk in a 10-year period is 17% in the low heart rate groups and 25% in the high heart rate groups and the absolute risk difference is, therefore, 8%. In comparison, participants with GOLD stage IV COPD have a poor prognosis and the corresponding absolute mortality risk during a 10-year period is 49% in the low resting heart rate group and

	Model with GOLD stage and resting heart rate				
Model with GOLD stage	<25%	25–35%	35–50%	≥50%	Total
Subjects without event					
<25%	0	0	0	0	0
25–35%	55	900	82	0	1037
35–50%	0	49	179	4	232
≥50%	0	0	1	36	37
Total	55	949	262	40	1306
Subjects with event					
<25%	0	0	0	0	0
25–35%	7	329	51	0	387
35–50%	0	25	110	0	135
≥50%	0	0	0	35	35
Total	7	354	161	35	557

FIGURE 3 Risk reclassification: Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage *versus* GOLD stage with resting heart rate. Resting heart rate improves the risk prediction when added to a model with GOLD stage alone. This is shown by the greater number of subjects in the blue squares compared with the number of subjects in the red squares for both non-events and events. White squares: subjects classified in the same risk category by both models; blue squares: subjects without events reclassified into a lower risk category and subjects with events reclassified into a higher risk category after inclusion of resting heart rate to the model with GOLD stage alone; red squares: subjects without events reclassified into a higher risk category and subjects with events reclassified into a lower risk category after inclusion of resting heart rate to the model with GOLD stage alone.

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	Model with FEV_1 % pred and resting heart rate				
Model with FEV_1 % pred	<25%	25–35%	35–50%	≥50%	Total
Subjects without event					
<25%	111	35	1	0	147
25–35%	117	613	60	1	791
35–50%	0	65	250	21	336
≥50%	0	0	10	22	32
Total	228	713	321	44	1306
Subjects with event					
<25%	25	20	0	0	45
25–35%	25	216	45	0	286
35–50%	0	36	144	15	195
≥50%	0	0	7	24	31
Total	50	272	196	39	557

FIGURE 4 Risk reclassification: forced expiratory volume in 1 s (FEV_1) % predicted *versus* FEV_1 % pred with resting heart rate. Resting heart rate improves the risk prediction when added to a model with FEV_1 % pred alone. This is shown by the greater number of subjects in the blue squares compared with the number of subjects in the red squares for both non-events and events. White squares: subjects classified in the same risk category by both models; blue squares: subjects without events reclassified into a lower risk category and subjects with events reclassified into a higher risk category after inclusion of resting heart rate to the model with FEV_1 % pred alone; red squares: subjects without events reclassified into a higher risk category and subjects with events reclassified into a lower risk category after inclusion of resting heart rate to the model with FEV_1 % pred alone.

72% in the high resting heart rate group, giving an increased absolute risk of mortality of 23%. Secondly, the proportion of subjects with high heart rate is far greater in GOLD stages III and IV and this implies that a far greater proportion of subjects with severe COPD are at risk compared with subjects with no or less pulmonary dysfunction.

The relationship between elevated heart rate and severity of COPD has never previously been established in a large-scale study. The most important issue is whether high resting heart rate is a feature of the pulmonary disease and, therefore, not a focus for a specific intervention, or whether increased heart rate plays an independent pathophysiological role and, therefore, might be a goal for intervention to improve the prognosis in COPD.

Resting heart rate has been shown to be a risk factor in both the general population [6, 7, 17–19] and in populations with cardiovascular disease [4, 8]. COPD and heart failure share many of the same features. Both are characterised by dyspnoea, fatigue, decreased stroke volume and increased heart rate. However, in contrast to the clinical classification of heart failure [20], heart rate has so far played no role in the risk stratification or management of patients with COPD.

Heart rate-reducing agents such as beta-blockers have, in cardiovascular clinical medicine, long proven beneficial effects on mortality and morbidity, but the effect of heart rate-reducing agents specifically for COPD is unexplored. Clinicians commonly avoid the use of beta-blockers in subjects with COPD [21]. However, a recent retrospective study of 6000 patients with COPD suggested that beta-blockers may have a beneficial effect on mortality [3]. New agents (I_f -inhibitors) with selective sinus node inhibition and heart rate-reducing properties without systemic effects have recently been introduced in heart failure and ischaemic heart disease [22, 23]. It is possible, that reducing heart rate in subjects with COPD could increase myocardial performance and thereby improve symptoms and prognosis. A clinical trial of heart rate reduction in COPD seems warranted at this point in time.

Several haemodynamic factors, such as hypoxia and decreased stroke volume, probably play a role in the relationship between high resting heart rate and COPD. Low arterial oxygen saturation leads to an increase in cardiac output [24]. Furthermore, pulmonary dysfunction in COPD is associated with an incremental decrease in left ventricular size and stroke volume [25, 26]. When stroke volume is decreased, cardiac output can be maintained by an increase in heart rate. COPD is additionally known to be associated with autonomic dysfunction resulting in decreased parasympathetic and increased sympathetic activity [27, 28]. Smoking is the leading cause of COPD. We have recently shown that former and current smokers are at increased risk of elevated heart rate compared to never-smokers [7]. These findings are in line with BARR *et al.* [25] who found a significant interaction between smoking status and stroke volume in subjects with pulmonary dysfunction; smokers were found to have lower ventricular dimensions compared to

nonsmokers. Vascular abnormalities with intimal hypertrophy, endothelial dysfunction, decreased vascular relaxation and, as a consequence, an increase in pulmonary pressure and myocardial impairment may play a role. This has been observed in both subjects with COPD as well as in smokers with normal pulmonary function [29]. However, this subject needs further investigation.

Study limitations

Resting heart rate was assessed from the ECG. It is possible that other assessments of heart rate, *e.g.* 24-hour ambulatory ECG, could provide more accurate heart rate measurements. However, the current findings can easily be translated into a normal clinical setting. Also, misclassification of resting heart rate from a single ECG would bias the results toward the null hypothesis.

A possible limitation may also be that diagnosis of asthma in our study was made by an affirmative answer to the question ''Do you have asthma?''. We have no data on reversibility of FEV_1 and, thus, some misclassification between asthma and COPD is possible. Yet, we do not think that this possibility affects our general findings regarding heart rate and mortality.

Bronchodilators are known to increase heart rate and could be an important confounder in this study; however, we found that adjusting for use of asthma or bronchitis medication in addition to other possible confounding factors did not change the association between elevated heart rate and severity of pulmonary dysfunction.

In epidemiological studies residual confounding factors can never be excluded. Inflammatory markers have previously been shown to be associated with subclinical disease [30–32]; including these markers of chronic low-grade inflammation in the multivariate adjustments did not change the results. The possible contribution from underlying subclinical disease may, therefore, have been minimised.

In conclusion, we demonstrate that resting heart rate increases with the severity of COPD. In multivariate analyses, resting heart rate is associated with both cardiovascular and all-cause mortality in subjects with COPD. High resting heart rate is associated with decreased median life expectancies across all stages of COPD and provides improved risk prediction above that of pulmonary function alone, measured either as GOLD stage or FEV_1 % pred.

Resting heart rate can easily, with minimal clinical training, and without cost be included in the clinical assessment of patients with COPD as a risk marker. Resting heart rate is a potentially modifiable risk factor. Clinical trials of heart rate lowering in COPD seem warranted.

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