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ORIGINAL PAPER

Time-updated resting heart rate predicts mortality in patients with COPD

Albert J. Omlor[1] · Franziska C. Trudzinski[1] · Mohamad Alqudrah[1] · Frederik Seiler[1] · Frank Biertz[2] · Claus F. Vogelmeier[3] · Tobias Welte[4] · Henrik Watz[5] · Benjamin Waschki[5,6] · Titus J. Brinker[7] · Stefan Andreas[8,9] · Sebastian Fähndrich[1] · Peter Alter[3] · Rudolf A. Jörres[10] · Michael Böhm[11] · Robert Bals[1] on behalf of German COSYCONET Cohort

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Abstract
High resting heart rate (RHR) is associated with higher mortality in the general population and in cardiovascular disease. Less is known about the association of RHR with outcome in chronic obstructive pulmonary disease (COPD). In particular, the time-updated RHR (most recent value before the event) appears informative. This is the first study to investigate the association of time-updated RHR with mortality in COPD. We compared the baseline and time-updated RHR related to survival in 2218 COPD patients of the German COSYCONET cohort (COPD and Systemic Consequences—Comorbidities Network). Patients with a baseline RHR > 72 beats per minute (bmp) had a significantly ($p = 0.049$) higher all-cause mortality risk (adjusted hazard ratio (HR) of 1.37 (1.00–1.87) compared to baseline RHR ≤ 72 bpm. The time-updated RHR > 72 bpm was markedly superior (HR 1.79, 1.30–2.46, $p = 0.001$). Both, increased baseline and time-updated RHR, were independently associated with low FEV1, low TLCO, a history of diabetes, and medication with short-acting beta agonists (SABAs). In conclusion, increased time-updated RHR is associated with higher mortality in COPD independent of other predictors and superior to baseline RHR. Increased RHR is linked to lung function, comorbidities and medication. Whether RHR is an effective treatment target in COPD, needs to be proven in controlled trials.

Keywords COSYCONET · COPD · Heart rate · Comorbidity · Mortality

C. F. Vogelmeier, P. Alter, T. Welte, H. Watz, B. Waschki: Members of the German Center for Lung Research (DZL).

✉ Robert Bals
robert.bals@uks.eu

[1] Department of Internal Medicine V – Pulmonology, Allergology, Critical Care Medicine, Saarland University Medical Centre, Saarland University Hospital, 66421 Homburg/Saar, Germany

[2] Institute for Biostatistics, Hannover Medical School, Hannover, Germany

[3] Department of Medicine, Pulmonary and Critical Care Medicine, University Medical Center Giessen and Marburg, Philipps-University Marburg (UMR), Marburg, Germany

[4] Clinic for Pneumology, Hannover Medical School, Hannover, Germany

[5] Airway Research Center North, Pulmonary Research Institute at LungenClinic Grosshansdorf, Grosshansdorf, Germany

[6] Department of General and Interventional Cardiology, University Heart Center Hamburg, Hamburg, Germany

[7] Department of Dermatology, University Hospital Heidelberg, University of Heidelberg, Heidelberg, Germany

[8] Lungenfachklinik Immenhausen, Immenhausen, Germany

[9] Kardiologie und Pneumologie, Universitätsmedizin Göttingen, Göttingen, Germany

[10] Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine, University Hospital, LMU Munich, Munich, Germany

[11] Department of Internal Medicine III – Cardiology, Angiology and Intensive Care Medicine, Saarland University Hospital, Saarland University, Homburg, Germany

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Introduction

Chronic obstructive pulmonary disease (COPD) is one of the most important causes of death worldwide [1]. Patients with COPD often suffer from cardiovascular comorbidities such as coronary artery disease, heart failure, hypertension and peripheral artery disease [2–4]. A possible cause for comorbidity is the presence of risk factors such as smoking, male sex and advanced age. In addition, chronic inflammation may facilitate the progression of COPD and its comorbidities [5]. A low or incident decline of FEV_1 is associated with increased mortality from cardiovascular diseases [6, 7], rendering cardiovascular comorbidities the most important causes of mortality in moderate forms of COPD. In severe COPD, respiratory failure is the most frequent cause of death [3, 5, 8].

High resting heart rate (RHR) is associated with increased mortality in numerous conditions and has been shown to be both marker and modifiable risk factor. This is especially true for cardiovascular disorders but has also been reported for renal disease and neurological disorders. Moreover, an association of a high RHR with cardiovascular events [9–11], all-cause mortality [9, 12–14] and cognitive decline [15] has been demonstrated in previous trials. Similar results have been shown for patients with left ventricular hypertrophy [16]. Likewise, an increased incidence of coronary heart disease and death was reported for patients with an elevated RHR [17]. The mechanisms linking RHR to clinical outcomes are, however, still not sufficiently understood.

Studies in COPD have shown an association between an elevated RHR at baseline and mortality [18–20]. However, another investigation not referring to COPD found that time-updated RHR (the latest RHR measurement available) over multiple follow-up measurements provided a greater prognostic value compared to RHR at baseline [21]. Whether this also applies to COPD in view of the multiple known risk factors in this disease is unknown. The aim of our study was to compare time-updated RHR and baseline RHR as risk factors for COPD mortality including all-cause mortality. We further aimed to identify factors associated with higher RHR, both at baseline and time-updated.

Methods

Patients and procedures

The multicentre cohort study COSYCONET (German COPD and Systemic Consequences—Comorbidities Network) investigates the progression of COPD and its comorbidities. In 31 study centres, 2741 patients with physician-diagnosed COPD and an age of 40 years and older were recruited between 2010 and 2013. Inclusion was based on a physician's diagnosis of COPD (GOLD criteria of 2010 via a ratio of FEV1/FVC < 0.7 in standardized spirometry after bronchodilatation or in 430 cases based on typical symptoms such as chronical coughing and sputum production despite the absence of an airflow limitation). Exclusion criteria were lung cancer, surgical lung volume reduction, lung transplantation, severe exacerbation within the last 4 weeks and physical or cognitive inability to perform the assessments. The study was approved by the ethics committees of all study centres, and all participants gave their written informed consent. Further information on the study protocol has been previously published [22, 23].

Measurements and outcomes

At baseline, structured interviews were performed to assess comorbidities and demographics. COPD categorization was done according to the revised GOLD 2017 classification [24]. The BODE index was calculated using the algorithm created by Celli and colleagues [25]. Spirometry, the determination of the diffusing capacity for carbon monoxide (TLCO) and body plethysmography were conducted according to the ATS/ERS guidelines [26]. Reference values of the Global Lung Function Initiative (GLI) were used [27]. In all study centres, resting heart rate (RHR) was determined from ECG tracings via the device Mortara (WelchAllyn, Amsterdam, The Netherlands) after 10 min of rest in supine position as described in detailed SOPs [22]. ECGs were electronically transmitted to the central database and evaluated by a custom-made algorithm regarding RHR.

All-cause death was defined as primary endpoint in this analysis. COSYCONET comprises visits at baseline (visit 1), and after 6, 18, 36, 54, and 72 months. In the present analysis, we evaluated mortality data up to 72 months (visit 6). The time variable for the regression analysis was based on either the date of death (for deceased patients) or the date of the most recent follow-up visit up to visit 6 (confirming survival for non-deceased patients). In cases where death was confirmed but the exact date of death was not documented, the 15th of the month was chosen if only month and year were known, the 1st July of the year was chosen if only the year was known, and the day of report was chosen if neither year nor month were documented.

Statistical analysis

Patients were divided into two groups according to RHR (≤ 72 bpm, and > 72 bpm) representing a value close to the

median (71 bpm for baseline and 72 bpm for time-updated RHR). The number of groups based on RHR was limited to two, as three or more groups led to oversampling (data not shown). RHR categories were formed based on the baseline rate which was defined as the last available value before death or the value at the last visit if the patient was alive. In all analyses (except descriptive statistics), patients with missing data for either baseline or time-updated RHR were excluded from the analysis for both groups.

Descriptive statistics were calculated for demographics, the distribution of COPD severity, comorbidities and relevant medication at baseline. For the comparison between the RHR groups, the *t* test was used for continuous, and the chi-squared statistics for categorical variables. This was done separately for the groups defined by the cut-off value of 72 bpm for either baseline RHR (A) or time-updated RHR (B).

Hazard ratios for all-cause death for high RHR and the covariates age, sex, pack years, FEV_1 percent predicted, obesity (BMI > 30), the diagnoses of arterial hypertension, history of myocardial infarction, history of stroke, history of diabetes, as well as education level and the presence of relevant medication (LAMA, LABA, SABA, ICS, systemic steroids, beta blocker, ACE inhibitors) were estimated using COX regression and adjusted survival curves were plotted. The influence of the RHR category on the hazard ratios was sequentially evaluated by adjustment with different sets of covariates. In addition, COX regression with the same covariates was also performed with either baseline or time-updated RHR as a continuous variable with increments of 5 bmp and 10 bpm.

Multiple linear regression analysis was performed with baseline RHR and time-updated RHR as dependent variable. As predictors in this model, the covariates already used for COX regression (age, sex category, pack years, FEV_1 percent predicted, obesity, arterial hypertension, myocardial infarction, stroke, diabetes, education level and relevant medication) were combined with intrathoracic gas volume (ITGV), TLCO as well as right ventricular thickness and right ventricular function. The regression models were obtained with stepwise forward selection of the above-mentioned predictors.

Histograms were created to compare the distributions of time-updated and baseline RHR between survivors and deceased patients with a baseline RHR ≤ 72 bbm or > 72 bpm, respectively. Mann–Whitney U test was used to test the distributions for survivors and deceased patients for significant differences.

Statistical analyses were performed using SPSS software (version 23; IBM Corp., Armonk, NY, USA). A *p* value of 0.05 or less was considered significant.

Results

RHR is associated with mortality

Of the 2741 patients at baseline 2669 with a documented baseline RHR and 2729 patients with a documented time-updated RHR were eligible for descriptive statistics. Detailed patient characteristics at baseline are shown in Tables 1 and 2.

2218 patients with complete datasets for both baseline and time-updated RHR were included into the COX regression analysis with baseline RHR, and 2218 patients into the COX analysis with time-updated RHR. Of those patients, 185 died. A baseline RHR of > 72 bpm was associated with a hazard ratio of 1.37 (1.00–1.87), which was significantly ($p = 0.049$) increased versus RHR < 72 bpm. In the COX regression analysis based on time-updated RHR, the high RHR group had a hazard ratio of 1.79 (1.30–2.46, $p = 0.001$). For time-updated RHR, the curves for low and high RHR tended to show a stronger separation (Fig. 1).

A significantly increased risk was associated with the covariates male sex, higher baseline age, pack years, and medication with beta blocker, long-acting muscarinic agonists or systemic steroids, while a lower risk was associated with obesity. The hazard ratios with 5% confidence interval are shown in Fig. 2.

For both baseline and time-updated RHR, the hazard ratio rose with stepwise inclusion of covariates into the model (Fig. 3). Stepwise addition of more adjustment parameters (age and sex in the first step, then additionally comorbidities and education level, then additionally medication) to the crude unadjusted regression increased the hazard ratios for RHR > 72 bpm. However, the final addition of FEV_1 as adjustment parameter to the model caused the hazard ratio for RHR > 72 bpm to decrease again significantly.

In the COX regression with baseline and time-updated RHR as continuous variables, different crude and adjusted (maximum set of covariates as described in the previous paragraph) hazard ratios were obtained for steps of 5 bpm and 10 bpm (Table 3).

In addition, subpopulations were analysed with a RHR step size of 10 bpm. For patients with no beta blocker intake, the hazard ratios were slightly higher in the adjusted models. COX regressions with a subset of patients with a RHR ≤ 100 bpm resulted in smaller hazard ratios. The adjusted hazard ratio for time-updated RHR > 72 bpm remained significantly elevated (Table 3).

Table 1 Patient characteristics at baseline with categories based on baseline RHR

	N	All	RHR ≤ 72	RHR > 72	*p* value
Demographics					
Age (years)	2669	65.0 ± 8.60	65.3 ± 8.81	64.7 ± 8.37	ns
Male	2669	1574/2669 (59%)	855/1435 (60%)	719/1234 (58%)	ns
BMI (kg/m^2)	2667	27.1 ± 5.38	26.8 ± 5.05	27.3 ± 5.75	$p < 0.05$
Pack years	2444	48.0 ± 35.8	46.9 ± 35.6	49.4 ± 36.1	ns
Current smoker	2668	657/2668 (25%)	377/1435 (26%)	280/1233 (23%)	$p = 0.034$
FEV1 (% predicted GLI)	2654	56.8 ± 20.6	61.4 ± 21.0	51.5 ± 20.1	$p = 0.001$
TLCO (% predicted GLI)	2518	55.5 ± 21.7	58.3 ± 20.9	52.1 ± 22.1	$p = 0.001$
ITGV (% predicted GLI)	2595	144.1 ± 37.5	138.3 ± 34.9	150.8 ± 39.3	$p = 0.001$
COPD GOLD 2017	2654				
Group A		294/2654 (11%)	198/1428 (14%)	96/1226 (8%)	$p = 0.001$
Group B		1423/2654 (54%)	784/1428 (55%)	639/1226 (52%)	
Group C		48/2654 (2%)	27/1428 (2%)	21/1226 (2%)	
Group D		889/2654 (33%)	419/1428 (29%)	470/1226 (38%)	
Increased alcohol consumption	2668	265/2668 (10%)	129/1435 (9%)	136/1233 (11%)	ns
Education level	2602				$p = 0.01$
Basic school education		1414/2602 (54%)	729/1398 (52%)	685/1204 (57%)	
Secondary school education		727/2602 (28%)	394/1398 (28%)	333/1204 (28%)	
Higher School Education		461/2602 (18%)	275/1398 (20%)	186/1204 (15%)	
COPD morbidity					
BODE	2558	2.12 ± 1.91	1.69 ± 1.74	2.64 ± 2.11	$p = 0.001$
SQRQ	2643	42.6 ± 19.7	39.4 ± 19.2	46.4 ± 20.1	$p = 0.001$
Comorbidity					
Myocardial Infarction	2669	219/2669 (8%)	145/1435 (10%)	74/1234 (6%)	$p = 0.001$
Hypertension	2669	1435/2669 (54%)	801/1435 (56%)	699/1234 (57%)	ns
Stroke	2669	117/2669 (4%)	65/1435 (5%)	52/1234 (4%)	ns
Diabetes	2669				$p = 0.001$
Non-insulin-dependent		232/2669 (9%)	107/1435 (7%)	125/1234 (10%)	
Insulin-dependent		141/2669 (5%)	56/1435 (4%)	85/1234 (7%)	
Obesity	2667	1651/2667 (62%)	888/1434 (62%)	763/1233 (62%)	ns
Medication					
LABA	2544	2144/2544 (84%)	1149/1362 (84%)	995/1182 (84%)	ns
LAMA	2544	1906/2544 (75%)	1037/1362 (76%)	869/1182 (74%)	ns
SABA	2544	1525/2544 (60%)	791/1362 (58%)	734/1182 (62%)	$p = 0.043$
ACE inhibitor	2669	1217/2669 (46%)	641/1435 (45%)	576/1234 (47%)	ns
Beta blocker	2669	602/2669 (23%)	408/1435 (28%)	194/1234 (16%)	$p = 0.001$
ICS	2544	1680/2544 (66%)	905/1362 (66%)	775/1182 (66%)	ns
Systemic steroids	2669	318/2669 (12%)	135/1435 (9%)	183/1234 (15%)	$p = 0.001$
Echocardiography					
Right ventricular wall thickness (mm)	1940	5.79 ± 3.26	5.69 ± 2.91	5.90 ± 3.64	ns
Right ventricular function	2335				ns
Normal		2189/2335 (93%)	1182/1255 (94%)	1007/1080 (93%)	
Mildely reduced		92/2335 (4%)	42/1255 (3%)	50/1080 (5%)	
Moderately reduced		13/2335 (< 1%)	8/1255 (< 1%)	5/1080 (< 1%)	
Severely reduced		1/2335 (< 1%)	0/1255 (0%)	1/1080 (< 1%)	
Not assessable		40/2335 (2%)	23/1255 (2%)	17/1080 (2%)	

Table 2 Patient characteristics at baseline with categories based on time-updated RHR

	N	All	RHR ≤ 72	RHR > 72	*p* value
Demographics					
Age (years)	2729	65.0 ± 8.62	65.1 ± 8.92	65.0 ± 8.31	ns
Male	2729	1609/2729 (59%)	826/1401 (59%)	783/1328 (59%)	ns
BMI (kg/m^2)	2727	27.0 ± 5.39	27.0 ± 5.22	27.0 ± 5.56	ns
Pack years	2496	47.9 ± 35.7	46.4 ± 34.9	49.5 ± 36.6	$p = 0.026$
Current smoker	2728	665/2728 (24%)	351/1401 (25%)	314/1327 (24%)	ns
FEV1 (% predicted GLI)	2714	57.0 ± 20.7	61.6 ± 21.1	52.0 ± 20.2	$p = 0.001$
TLCO (% predicted GLI)	2518	55.5 ± 21.7	59.1 ± 21.4	51.6 ± 21.3	$p = 0.001$
ITGV (% predicted GLI)	2595	144.1 ± 37.5	137.7 ± 35.1	150.8 ± 38.8	$p = 0.001$
COPD GOLD 2017	2714				
Group A		301/2714 (11%)	189/1395 (14%)	112/1319 (8%)	$p = 0.001$
Group B		1454/2714 (53%)	761/1395 (55%)	693/1319 (53%)	
Group C		48/2714 (2%)	27/1395 (2%)	21/1319 (2%)	
Group D		911/2714 (34%)	418/1395 (30%)	493/1319 (37%)	
Increased alcohol consumption	2728	269/2728 (10%)	125/1401 (9%)	144/1327 (11%)	ns
Education level	2660				ns
Basic school education		1445/2660 (54%)	719/1363 (53%)	726/1297 (56%)	
Secondary school education		738/2660 (28%)	382/1363 (28%)	356/1297 (27%)	
Higher school education		477/2660 (18%)	262/1363 (19%)	215/1297 (17%)	
COPD morbidity					
BODE	2615	2.11 ± 1.92	1.69 ± 1.75	2.56 ± 2.11	$p = 0.001$
SQRQ	2702	42.6 ± 19.7	39.6 ± 19.3	45.8 ± 20.2	$p = 0.001$
Comorbidity					
Myocardial Infarction	2729	223/2729 (8%)	139/1401 (10%)	84/1328 (6%)	$p = 0.001$
Hypertension	2729	1536/2729 (56%)	779/1401 (56%)	757/1328 (57%)	ns
Stroke	2729	118/2729 (4%)	67/1401 (5%)	51/1328 (4%)	ns
Diabetes	2353				ns
Non-insulin-dependent		233/2729 (9%)	110/1401 (8%)	123/1328 (9%)	
Insulin-dependent		143/2729 (5%)	61/1401 (4%)	82/1328 (6%)	
Obesity	2727	1689/2727 (62%)	869/1400 (62%)	820/1327 (62%)	ns
Medication					
LABA	2600	2193/2600 (84%)	1119/1329 (84%)	1074/1271 (85%)	ns
LAMA	2600	1949/2600 (75%)	991/1329 (75%)	958/1271 (75%)	ns
SABA	2600	1558/2600 (60%)	770/1329 (58%)	788/1271 (62%)	$p = 0.037$
ACE inhibitor	2729	1239/2729 (45%)	627/1401 (45%)	612/1328 (46%)	ns
Beta blocker	2729	619/2729 (23%)	384/1401 (27%)	235/1328 (18%)	$p = 0.001$
ICS	2600	1716/2600 (66%)	868/1329 (65%)	848/1271 (67%)	ns
Systemic steroids	2729	326/2729 (12%)	141/1401 (10%)	185/1328 (14%)	$p = 0.002$
Echocardiography					
Right ventricular wall thickness (mm)	1984	5.83 ± 3.49	5.87 ± 3.41	5.79 ± 3.58	ns
Right ventricular function	2388				ns
Normal		2236/2388 (94%)	1160/1233 (94%)	1076/1155 (93%)	
Mildely reduced		96/2388 (4%)	49/1233 (4%)	47/1155 (4%)	
Moderately reduced		14/2388 (< 1%)	8/1233 (< 1%)	6/1155 (< 1%)	
Severely reduced		1/2388 (< 1%)	0/1233 (0%)	1/1155 (< 1%)	
Not assessable		41/2388 (2%)	16/1233 (1%)	25/1155 (2%)	

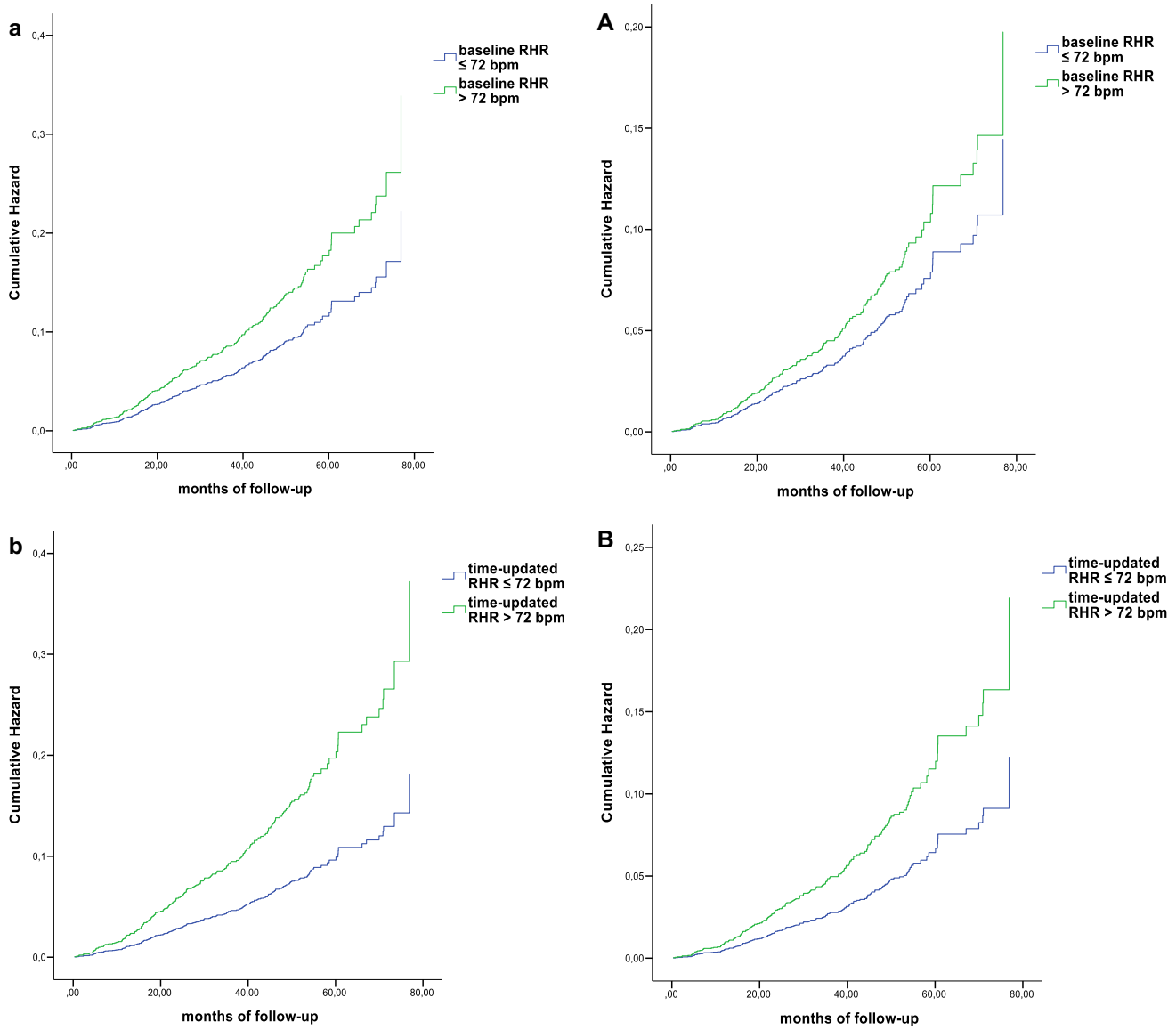

Fig. 1 COX regression models with two RHR categories (≤ 72 bpm (blue) and > 72 bpm (green)). Unadjusted hazard curves for baseline RHR (**a**) and time-updated RHR **b** in comparison to adjusted cox hazard curves for baseline RHR (**A**) and time-updated RHR (**B**). **A** and **B** were adjusted for age, sex category, packyears, FEV1, obesity, arterial hypertension, myocardial infarction, stroke, diabetes, education level, LAMA, LABA, SABA, ICS, systemic steroids, beta blockers and ACE inhibitors

Factors associated with increased RHR

To gain a better understanding why time-updated RHR was a better predictor for mortality than baseline RHR, multiple linear regression analyses were performed. Predictors that were significantly associated with an increased baseline RHR were diabetes and a medication with short-acting beta agonists (SABAs). In contrast, a high FEV_1, a medication with beta blockers, a high diffusing capacity (TLCO) and a medication with long-acting muscarinic antagonists (LAMAs) were associated with a lower baseline RHR.

Regarding time-updated RHR, also a high FEV_1, a medication with beta blockers, a high diffusing capacity (TLCO) and a history of stroke were associated with a lower heart rate, while a high intrathoracic gas volume (ITGV), a history of diabetes and obesity, a medication with short-acting beta agonists (SABAs) and male sex were associated with a higher heart rate.

Moreover, to understand the kind of shift in RHR, we established histograms of the differences between time-updated RHR and baseline RHR for the groups of survivors and non-survivors, stratified according to higher (> 72 bpm) versus lower (≤ 72 bpm) baseline RHR (Fig. 4). Survivors

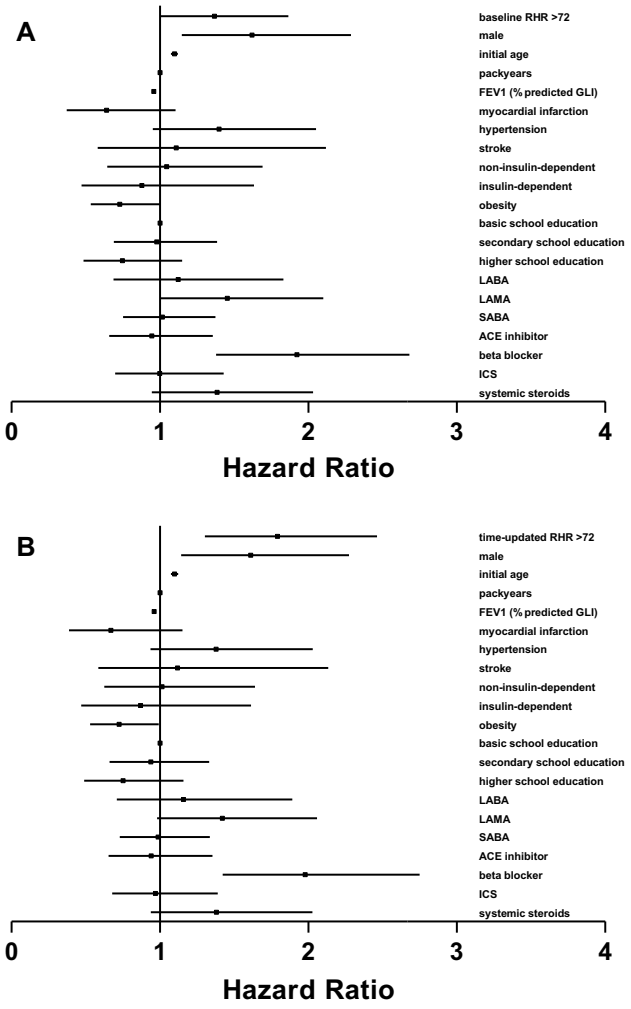

Fig. 2 Forest plot of the hazard ratios from the COX regression models with **A** baseline RHR > 72 bpm and **B** time-updated RHR > 72 bpm

with higher (> 72 bpm) baseline RHR tended to shift towards a lower time-updated RHR, while the deceased patients showed no such trend (significant difference between the distributions in Mann–Whitney U test, $p = 0.001$). In contrast, the lower baseline RHR group (≤ 72 bpm) showed comparable shift to a higher time-updated RHR for both survivors and deceased patients (no significant difference between the distributions in Mann–Whitney U test).

Discussion

Herein, we report that elevated values of the time-updated RHR are not only associated with clinical outcomes and comorbidities in patients with COPD, but also a predictor of mortality that is superior to baseline RHR. The observation, that the most recent RHR is the best predictor, is compatible with the assumption that a marked elevation of RHR has short-term rather than long-term clinical implications. A similar result has been reported for patients with left ventricular systolic dysfunction [21]. In our statistical model for baseline RHR, we took all data from the baseline visit. In contrast, the analysis for time-updated RHR contains additional data from later visits at 6, 18 and 36 months [22]. With 10 min, our study chose a rather short period of supine rest compared to other studies. Overall, there is much variation in the resting heart rate protocols across different studies [28]. In our study, the short time period was chosen as the schedule of the visits was quite loaded and we had to optimize time durations for each examination. In linear regression analysis, time-updated differed from baseline RHR in the association with obesity and medication with systemic steroids and long-acting muscarinic antagonists (LAMAs), thereby indicating its relation to other significant predictors of the worsening of COPD over time. Moreover,

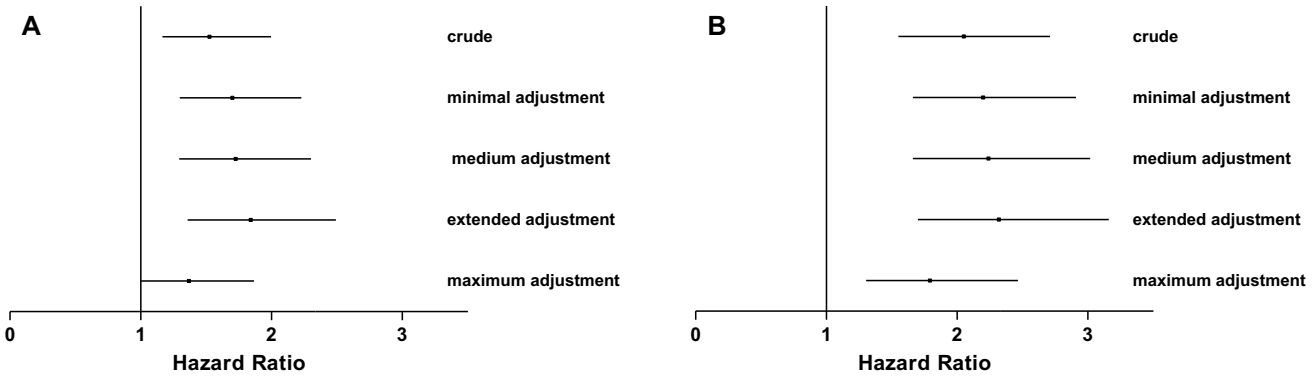

Fig. 3 Hazard ratios for baseline RHR > 72 bpm (**A**) and time-updated RHR > 72 bpm (**B**) with different adjustments. Crude: no adjustment. Minimal adjustment: age and sex. Medium adjustment: minimal adjustment + packyears, comorbidity (myocardial infarction, hypertension, stroke, obesity, diabetes) and education. Extended adjustment: medium adjustment + relevant medication (LABA, LAMA, SABA, ACE Inhibitor, beta blocker, ICS, systemic steroids). Maximum adjustment: extended adjustment + FEV1

Table 3 Adjusted hazard ratios for baseline and time-updated RHR as a continuous variable with different step sizes

Step size (bbm)	Baseline RHR	Time-updated RHR
	Adjusted hazard ratio	Adjusted hazard ratio
5	1.096 (1.038–1.157) $p=0.001$	1.156 (1.094–1.221) $p=0.001$
10	1.202 (1.078–1.340) $p=0.001$	1.335 (1.197–1.490) $p=0.001$
10*	1.217 (1.066–1.389) $p=0.004$	1.410 (1.230–1.618) $p=0.001$
10**	1.067 (0.929–1.226) $p=0.357$	1.225 (1.083–1.385) $p=0.001$

*Analysis with subset of patients without beta blocker therapy. $N=1707$. **Analysis with subset of patients with heartrate ≤ 100 bpm. $N=2135$

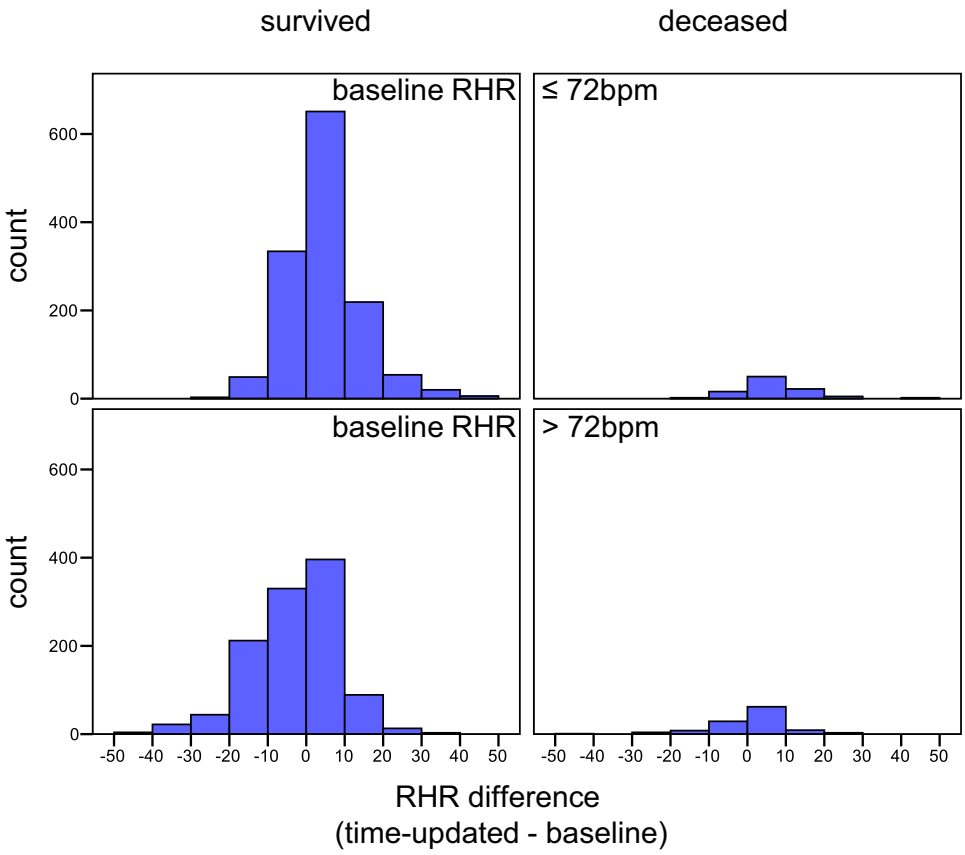

Fig. 4 Heartrate-difference between baseline RHR and time-updated RHR for survivors and deceased patients with low or high baseline RHR

the histograms of the RHR difference (time-updated RHR minus baseline RHR) showed, that patients from the higher baseline RHR group (> 72 bpm) who survived tended to shift to a lower time-updated RHR, while the deceased patients showed no such trend. In contrast, the lower baseline RHR group (≤ 72 bpm) showed comparable shift to a higher time-updated RHR for both survivors and deceased patients (Fig. 4). This might account to the better separation for time-updated RHR.

Using baseline RHR only, Warnier et al. [19], Jensen et al. [18] and Byrd et al. [20] observed similar associations in other COPD cohorts. In comparison to our approach, dividing a sample of 2218 patients into 2 RHR groups with a cut-off of 72 bpm, Warnier et al. divided a sample of 405 patients into 2 groups based on a cut-off of 85 bpm, while Jensen et al. analysed data of 16,696 subjects from a random population, of whom 2645 had a diagnosis of COPD. These patients were divided into four groups based on RHR (< 65, 65–74, 75–84, > 84). In contrast, Byrd et al. divided 16,485 patients with COPD into 3 groups based on RHR (< 70, 70–79, > 79). Because of the different number of groups, only Warnier's study with its two groups was directly comparable to our results. The hazard ratio for a RHR > 80 bpm in Warnier's study (1.6) ranged between our adjusted hazard ratio for baseline RHR > 72 bpm (1.37) and that for a time-updated RHR > 72 bpm (1.79).

Beyond RHR, our analysis revealed further parameters that are associated with mortality. The higher mortality for

male and older patients is in line with the expectations and literature findings. Medication with long-acting muscarinic antagonists and beta blockers is associated with increased mortality. Especially, the high hazard ratio for beta blockers seems to conflict with previous studies in COPD [29, 30], however, beta blocker treatment was not randomized in our study, and the patients with beta blockers probably were a less healthy group due to cardiovascular disease. Despite the inclusion of medication, the major important associations remained significant, indicating that they were not a statistical artefact.

The better survival of obese patients could be due to the known association of underweight with higher COPD stages [31], but obesity also might have an impact on autonomic dysfunction, as a major risk factor in COPD [32]. This complex interaction could be part of an obesity paradox and needs further investigation in COPD, in comparison with chronic heart failure [33, 34].

An important question is which factors could elevate baseline RHR in COPD. Impaired pulmonary function and the presence of comorbidities were identified as factors associated with increased values for baseline RHR as well as time-updated RHR. Both RHRs also increased with an increased intrathoracic gas volume, as a measure of lung hyperinflation. On the other hand, a high FEV_1 and a high TLCO, as indicators of less severe COPD, were associated with lower RHR. Accordingly, an association between an impaired lung function in COPD patients and an increased left ventricular wall strain has been described [35]. This association between lung function and RHR might also explain, why adjustment for FEV_1 markedly reduced the hazard ratio, while the addition of most adjustment parameters made the association between a high RHR and mortality stronger. Apparently, RHR is elevated in parallel with other markers of disease severity in COPD and might represent an integrative, easy-to-measure marker associated with mortality risk.

Autonomic dysfunction in COPD, with sympathy-vagal disbalance, could be a central factor for elevated RHR [32, 36]. Recent studies have linked autonomic dysfunction to exposure to particulate matter found in polluted air and cigarette smoke [37, 38]. Moreover, nicotine in cigarette smoke also increases sympathetic activity [38, 39]. Chronic hypoxemia seems to be another cause for autonomic dysfunction. Autonomic dysfunction was also shown to be associated with arrhythmia and sudden cardiac death [40]. Cardiovascular comorbidity caused by impaired endothelial function due to a long smoking history might be another factor [41]. Moreover, mechanical effects of obstruction and hyperinflation on cardiac filling seem to be an important factor, leading for compensation to an elevated RHR [35, 42, 43]. Thus, there are a multitude of pathophysiological factors potentially involved in an elevated RHR, rendering this measure a relevant marker of mortality risk in COPD.

Our study has some limitations and strengths. The analysis is not randomized and as a result observational and hypothesis generating. Moreover, the comorbidities are derived from the patients' reports; however, there is a high concordance of reports with disease-specific medication in COSYCONET [44]. On the other hand, our study has a large number of 2218 patients with more detailed information on comorbidities than many previous studies not focused on comorbid conditions. The actual hazard ratios for an increased RHR could be even higher than the overall results, as beta blockers shift patients with more severe disease to the lower RHR category [45]. The higher hazard ratios we found in the subpopulation of patients without beta blockers support this assumption.

In conclusion, we report that the time-updated resting heart rate RHR, i.e. the most recent value before an event, shows a closer association with mortality than baseline RHR in COPD patients. This is in line with observations in patients with other clinical conditions than COPD. The most important factors linked to elevated baseline and time-updated RHR were pulmonary function and comorbidities. Irrespective of these links, RHR, in particular time-adjusted RHR, turned out to be an independent and robust predictor of mortality.

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References

1. Agusti AG (2005) Systemic effects of chronic obstructive pulmonary disease. Proc Am Thorac Soc 2(4):367–370
2. Chen W, Thomas J, Sadatsafavi M, FitzGerald JM (2015) Risk of cardiovascular comorbidity in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. Lancet Respir Med 3(8):631–639. https://doi.org/10.1016/S2213-2600(15)00241-6
3. Mannino DM, Thorn D, Swensen A, Holguin F (2008) Prevalence and outcomes of diabetes, hypertension and cardiovascular

disease in COPD. Eur Respir J 32(4):962–969. https://doi.org/10.1183/09031936.00012408
4. Cuthbert JJ, Kearsley JW, Kazmi S, Kallvikbakka-Bennett A, Weston J, Davis J, Rimmer S, Clark AL (2019) The impact of heart failure and chronic obstructive pulmonary disease on mortality in patients presenting with breathlessness. Clin Res Cardiol 108(2):185–193. https://doi.org/10.1007/s00392-018-1342-z
5. Ukena C, Mahfoud F, Kindermann M, Kindermann I, Bals R, Voors AA, van Veldhuisen DJ, Böhm M (2010) The cardiopulmonary continuum systemic inflammation as 'common soil' of heart and lung disease. Int J Cardiol 145(2):172–176. https://doi.org/10.1016/j.ijcard.2010.04.082
6. Divo M, Cote C, de Torres JP, Casanova C, Marin JM, Pinto-Plata V, Zulueta J, Cabrera C, Zagaceta J, Hunninghake G, Celli B (2012) Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 186(2):155–161
7. Tockman MS, Pearson JAYD, Fleg JL, Metter EJ, Kao SY, Pal KGRAM, Cruise LJ, Fozard JL (1995) Rapid decline in FEV 1 a new risk factor for coronary heart disease mortality. Am J Respir Crit Care Med 151:390–398
8. Sin DD, Anthonisen NR, Soriano JB, Agusti AG (2006) Mortality in COPD: role of comorbidities. Eur Respir J 28(6):1245–1257. https://doi.org/10.1183/09031936.00133805
9. Lonn EM, Rambihar S, Gao P, Custodis FF, Sliwa K, Teo KK, Yusuf S, Böhm M (2014) Heart rate is associated with increased risk of major cardiovascular events, cardiovascular and all-cause death in patients with stable chronic cardiovascular disease: an analysis of ONTARGET/TRANSCEND. Clin Res Cardiol 103(2):149–159. https://doi.org/10.1007/s00392-013-0644-4
10. Munzel T, Hahad O, Gori T, Hollmann S, Arnold N, Prochaska JH, Schulz A, Beutel M, Pfeiffer N, Schmidtmann I, Lackner KJ, Keaney JF Jr, Wild PS (2019) Heart rate, mortality, and the relation with clinical and subclinical cardiovascular diseases: results from the Gutenberg Health Study. Clin Res Cardiol. https://doi.org/10.1007/s00392-019-01466-2
11. Chin KL, Collier T, Pocock S, Pitt B, McMurray JJV, van Veldhuisen DJ, Swedberg K, Vincent J, Zannad F, Liew D (2019) Impact of eplerenone on major cardiovascular outcomes in patients with systolic heart failure according to baseline heart rate. Clin Res Cardiol 108(7):806–814. https://doi.org/10.1007/s00392-018-1410-4
12. Böhm M, Swedberg K, Komajda M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L, Investigators S (2010) Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial. Lancet 376(9744):886–894. https://doi.org/10.1016/S0140-6736(10)61259-7
13. Böhm M, Borer J, Ford I, Gonzalez-Juanatey JR, Komajda M, Lopez-Sendon J, Reil JC, Swedberg K, Tavazzi L (2013) Heart rate at baseline influences the effect of ivabradine on cardiovascular outcomes in chronic heart failure: analysis from the SHIFT study. Clin Res Cardiol 102(1):11–22. https://doi.org/10.1007/s00392-012-0467-8
14. Dyer AR, Persky V, Stamler J, Paul O, Shekelle RB, Berkson DM, Lepper M, Schoenberger JA, Lindberg HA (1980) Heart rate as a prognostic factor for coronary heart disease and mortality: findings in three Chicago epidemiologic studies. Am J Epidemiol 112(6):736–749
15. Böhm M, Schumacher H, Leong D, Mancia G, Unger T, Schmieder R, Custodis F, Diener HC, Laufs U, Lonn E, Sliwa K, Teo K, Fagard R, Redon J, Sleight P, Anderson C, O'Donnell M, Yusuf S (2015) Systolic blood pressure variation and mean heart rate is associated with cognitive dysfunction in patients with high cardiovascular risk. Hypertension 65(3):651–661. https://doi.org/10.1161/HYPERTENSIONAHA.114.04568
16. Okin PM, Kjeldsen SE, Julius S, Hille DA, Dahlof B, Edelman JM, Devereux RB (2010) All-cause and cardiovascular mortality in relation to changing heart rate during treatment of hypertensive patients with electrocardiographic left ventricular hypertrophy. Eur Heart J 31(18):2271–2279. https://doi.org/10.1093/eurheartj/ehq225
17. Gillum RF, Makuc DM, Feldman JJ (1991) Pulse rate, coronary heart disease, and death: the NHANES I epidemiologic follow-up study. Am Heart J 121(1 Pt 1):172–177
18. Jensen MT, Marott JL, Lange P, Vestbo J, Schnohr P, Nielsen OW, Jensen JS, Jensen GB (2013) Resting heart rate is a predictor of mortality in COPD. Eur Respir J 42(2):341–349. https://doi.org/10.1183/09031936.00072212
19. Warnier MJ, Rutten FH, de Boer A, Hoes AW, De Bruin ML (2014) Resting heart rate is a risk factor for mortality in chronic obstructive pulmonary disease, but not for exacerbations or pneumonia. PLoS ONE 9(8):e105152. https://doi.org/10.1371/journal.pone.0105152
20. Byrd JB, Newby DE, Anderson JA, Calverley PMA, Celli BR, Cowans NJ, Crim C, Martinez FJ, Vestbo J, Yates J, Brook RD, Investigators S (2018) Blood pressure, heart rate, and mortality in chronic obstructive pulmonary disease: the SUMMIT trial. Eur Heart J 39(33):3128–3134. https://doi.org/10.1093/eurheartj/ehy451
21. Hamill V, Ford I, Fox K, Böhm M, Borer JS, Ferrari R, Komajda M, Steg PG, Tavazzi L, Tendera M, Swedberg K (2015) Repeated heart rate measurement and cardiovascular outcomes in left ventricular systolic dysfunction. Am J Med 128(10):1102–1108. https://doi.org/10.1016/j.amjmed.2015.04.042 **e1106**
22. Karch A, Vogelmeier C, Welte T, Bals R, Kauczor HU, Biederer J, Heinrich J, Schulz H, Glaser S, Holle R, Watz H, Korn S, Adaskina N, Biertz F, Vogel C, Vestbo J, Wouters EF, Rabe KF, Sohler S, Koch A, Jorres RA (2016) The German COPD cohort COSYCONET: aims, methods and descriptive analysis of the study population at baseline. Respir Med 114:27–37. https://doi.org/10.1016/j.rmed.2016.03.008
23. Fahndrich S, Biertz F, Karch A, Kleibrink B, Koch A, Teschler H, Welte T, Kauczor HU, Janciauskiene S, Jorres RA, Greulich T, Vogelmeier CF, Bals R (2017) Cardiovascular risk in patients with alpha-1-antitrypsin deficiency. Respir Res 18(1):171. https://doi.org/10.1186/s12931-017-0655-1
24. Kahnert K, Alter P, Young D, Lucke T, Heinrich J, Huber RM, Behr J, Wacker M, Biertz F, Watz H, Bals R, Welte T, Wirtz H, Herth F, Vestbo J, Wouters EF, Vogelmeier CF, Jorres RA (2018) The revised GOLD 2017 COPD categorization in relation to comorbidities. Respir Med 134:79–85. https://doi.org/10.1016/j.rmed.2017.12.003
25. Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA, Pinto Plata V, Cabral HJ (2004) The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med 350(10):1005–1012. https://doi.org/10.1056/NEJMoa021322
26. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J, Force AET (2005) Standardisation of spirometry. Eur Respir J 26(2):319–338. https://doi.org/10.1183/09031936.05.00034805
27. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, Enright PL, Hankinson JL, Ip MS, Zheng J, Stocks J, Initiative ERSGLF (2012) Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. Eur Respir J 40(6):1324–1343. https://doi.org/10.1183/09031936.00080312

28. Vogel CU, Wolpert C, Wehling M (2004) How to measure heart rate? Eur J Clin Pharmacol 60(7):461–466. https://doi.org/10.1007/s00228-004-0795-3
29. Leitao Filho FS, Alotaibi NM, Yamasaki K, Ngan DA, Sin DD (2018) The role of beta-blockers in the management of chronic obstructive pulmonary disease. Expert Rev Respir Med 12(2):125–135. https://doi.org/10.1080/17476348.2018.1419869
30. Lipworth B, Wedzicha J, Devereux G, Vestbo J, Dransfield MT (2016) Beta-blockers in COPD: time for reappraisal. Eur Respir J 48(3):880–888. https://doi.org/10.1183/13993003.01847-2015
31. Sami R, Sadegh R, Esmailzadehha N, Mortazian S, Nazem M, Zohal M (2018) Association of anthropometric indexes with disease severity in male patients with chronic obstructive pulmonary disease in Qazvin, Iran. Am J Mens Health. https://doi.org/10.1177/1557988318760053
32. Ricci F, Wollmer P, Engstrom G, Fedorowski A, Hamrefors V (2018) Markers of cardiovascular autonomic dysfunction predict COPD in middle-aged subjects. Eur Respir J. https://doi.org/10.1183/13993003.02481-2017
33. Anker SD, von Haehling S (2011) The obesity paradox in heart failure: accepting reality and making rational decisions. Clin Pharmacol Ther 90(1):188–190. https://doi.org/10.1038/clpt.2011.72
34. Horwich TB, Fonarow GC, Clark AL (2018) Obesity and the obesity paradox in heart failure. Prog Cardiovasc Dis 61(2):151–156. https://doi.org/10.1016/j.pcad.2018.05.005
35. Alter P, Jorres RA, Watz H, Welte T, Glaser S, Schulz H, Bals R, Karch A, Wouters EFM, Vestbo J, Young D, Vogelmeier CF (2018) Left ventricular volume and wall stress are linked to lung function impairment in COPD. Int J Cardiol 261:172–178. https://doi.org/10.1016/j.ijcard.2018.02.074
36. Andreas S, Anker SD, Scanlon PD, Somers VK (2005) Neurohumoral activation as a link to systemic manifestations of chronic lung disease. Chest 128(5):3618–3624. https://doi.org/10.1378/chest.128.5.3618
37. Pan L, Dong W, Li H, Miller MR, Chen Y, Loh M, Wu S, Xu J, Yang X, Shima M, Deng F, Guo X (2018) Association patterns for size-fractioned indoor particulate matter and black carbon and autonomic function differ between patients with chronic obstructive pulmonary disease and their healthy spouses. Environ Pollut 236:40–48. https://doi.org/10.1016/j.envpol.2018.01.064
38. Middlekauff HR, Park J, Moheimani RS (2014) Adverse effects of cigarette and noncigarette smoke exposure on the autonomic nervous system: mechanisms and implications for cardiovascular risk. J Am Coll Cardiol 64(16):1740–1750. https://doi.org/10.1016/j.jacc.2014.06.1201
39. Lombardo TW, Epstein LH (1986) The nicotine paradox: effect of smoking on autonomic discrimination. Addict Behav 11(3):341–344
40. Wang X, Jiang Z, Chen B, Zhou L, Kong Z, Zuo S, Liu H, Yin S (2016) Cardiac autonomic function in patients with acute exacerbation of chronic obstructive pulmonary disease with and without ventricular tachycardia. BMC Pulm Med 16(1):124. https://doi.org/10.1186/s12890-016-0287-0
41. Andreas S, Haarmann H, Klarner S, Hasenfuss G, Raupach T (2014) Increased sympathetic nerve activity in COPD is associated with morbidity and mortality. Lung 192(2):235–241. https://doi.org/10.1007/s00408-013-9544-7
42. Watz H, Waschki B, Meyer T, Kretschmar G, Kirsten A, Claussen M, Magnussen H (2010) Decreasing cardiac chamber sizes and associated heart dysfunction in COPD: role of hyperinflation. Chest 138(1):32–38. https://doi.org/10.1378/chest.09-2810
43. Smith BM, Prince MR, Hoffman EA, Bluemke DA, Liu CY, Rabinowitz D, Hueper K, Parikh MA, Gomes AS, Michos ED, Lima JAC, Barr RG (2013) Impaired left ventricular filling in COPD and emphysema: is it the heart or the lungs? The multi-ethnic study of atherosclerosis COPD study. Chest 144(4):1143–1151. https://doi.org/10.1378/chest.13-0183
44. Lucke T, Herrera R, Wacker M, Holle R, Biertz F, Nowak D, Huber RM, Sohler S, Vogelmeier C, Ficker JH, Muckter H, Jorres RA, Consortium C (2016) Systematic analysis of self-reported comorbidities in large cohort studies—a novel stepwise approach by evaluation of medication. PLoS One 11(10):e0163408. https://doi.org/10.1371/journal.pone.0163408
45. Rivinius R, Helmschrott M, Ruhparwar A, Rahm AK, Darche FF, Thomas D, Bruckner T, Ehlermann P, Katus HA, Doesch AO (2018) Control of cardiac chronotropic function in patients after heart transplantation: effects of ivabradine and metoprolol succinate on resting heart rate in the denervated heart. Clin Res Cardiol 107(2):138–147. https://doi.org/10.1007/s00392-017-1165-3