Myocardial Infarction Injury in Patients with Chronic Lung Disease Entering Pulmonary Rehabilitation: Frequency and Association with Heart Rate Parameters

Carmen A. Sima, Benny C. Lau, Carolyn M. Taylor, Stephan F. van Eeden, W. Darlene Reid, Andrew W. Sheel, Ashley R. Kirkham, Pat. G. Camp

Submitted 19 July 2017
ABSTRACT

Background: Myocardial infarction (MI) remains under-recognized in chronic lung disease (CLD) patients. Rehabilitation health professionals need accessible clinical measurements to identify the presence of prior MI in order to determine appropriate training prescription.

Objectives: We aimed to estimate prior MI in CLD patients entering a pulmonary rehabilitation program, as well as its association with heart rate parameters such as resting heart rate and chronotropic response index.

Design: Retrospective cohort design.

Setting: Pulmonary rehabilitation outpatient clinic in a tertiary care university-affiliated hospital.

Patients: Eighty-five CLD patients were studied.

Methods: Electrocardiograms at rest and peak cardiopulmonary exercise testing, performed before pulmonary rehabilitation, were analyzed. Electrocardiographic evidence of prior MI, quantified by the cardiac infarction injury score (CIIS), was contrasted with reported myocardial events and then correlated with resting heart rate and chronotropic response index parameters.

Main outcome measurements: Cardiac infarction injury score, resting heart rate and chronotropic response index.

Results: Sixteen CLD patients (19%) demonstrated electrocardiographic evidence of prior MI, but less than half (8%) had a reported MI history (p <.05). The Cohen’s Kappa test revealed poor level of agreement between CIIS and medical records (kappa = 0.165), indicating that prior MI diagnosis was under-reported in the medical records. Simple and
multiple regression analyses showed that resting heart rate but not chronotropic response index was positively associated with CIIS in our population ($R^2 = 0.29, p < .001$). CLD patients with a resting heart rate over 80 beats/min had approximately 5 times higher odds of having prior MI, as evidenced by a CIIS $\geq 20$.

**Conclusions**: CLD patients entering pulmonary rehabilitation are at risk of unreported prior MI. Elevated resting heart rate seems to be an indicator of prior MI in CLD patients; therefore, careful adjustment of training intensity such as intermittent training is recommended under these circumstances.

**Level of evidence**: III

**Keywords**: chronic lung disease; pulmonary rehabilitation; myocardial infarction; cardiac infarction injury score; heart rate; chronotropic incompetence.
Ischemic heart disease is a major determinant of morbidity and mortality among individuals with chronic lung diseases (CLD), particularly those with chronic obstructive pulmonary disease (COPD) [1,2]. Moreover, myocardial infarction (MI), which is a serious manifestation of ischemic heart disease, remains commonly under-recognized in this population [3,4]. Given that survivors of MI are at high risk of poor outcomes and future cardiac events (with a relative risk of recurrent MI and cardiovascular mortality increased by more than 30% compared to general population) [5], overlooking this condition in CLD patients can lead to inadequate treatment decisions. This aspect is particularly relevant in a pulmonary rehabilitation setting where health care professionals should be aware of prior MI to determine appropriate training prescription and avoid adverse cardiac events associated with exercise such as arrhythmia, recurrent myocardial ischemia, or infarction [6,7].

Pulmonary rehabilitation is an evidence-based intervention that combines exercise training and education to improve physical condition and health related quality of life of patients with CLD [8]. Before starting a pulmonary rehabilitation program (PRP), patients with CLD undergo a health history to identify those at high risk for complications that may emerge during exercise training [8]. However, the history of comorbidities often relies on patients’ self-report rather than objective medical assessments. Exercise tests are also performed to evaluate patients’ exercise tolerance and prescribe exercise intensity [9]. Nevertheless, while symptom-limited incremental exercise tests, such as a cardiopulmonary exercise test (CPET), are useful for identifying myocardial ischemic injury, they are not
always available or routinely performed before pulmonary rehabilitation. With these limitations being recognized [10,11], rehabilitation health professionals must rely on other accessible clinical measurements to estimate the presence of prior MI.

A number of electrocardiographic (ECG) classification systems are currently available to estimate the presence and/or severity of prior MI. The Cardiac Infarction Injury Score (CIIS), which is a validated ECG score [12], has been shown to be highly accurate at detecting prior MI. Whether used as a categorical or continuous variable, the CIIS can provide useful information on myocardial damage and cardiac events [13]. Furthermore, a CIIS value equal or greater than 20 is a significant predictor of cardiovascular mortality in apparently healthy middle-aged individuals [14] and patients with COPD [3,15]. Therefore, the CIIS is a convenient, non-invasive diagnostic tool to detect prior MI.

Resting heart rate and heart rate response to exercise are two hemodynamic parameters regularly monitored in the rehabilitation setting, which also carry prognostic information about cardiac ischemic risk [16,17]. A persistently elevated resting heart rate has been shown to be involved in the pathophysiology of atherosclerosis [18] and acute coronary events [19]. In particular, resting heart rates over 80 beats/minute have been associated with increased risk of all-cause and cardiovascular mortality in both general and high-risk populations [20,21]. An inadequate heart rate increase in response to exercise (e.g., chronotropic incompetence) has been also found correlated with the incidence of coronary disease and the risk of cardiovascular death [22,23]. Despite patients with CLD commonly displaying both elevated resting heart rate and chronotropic incompetence [24-26], there is
no study to date investigating the relationship between these two parameters and prior MI in this population.

We conducted a retrospective chart and a database review to estimate the presence of prior MI in CLD patients entering a PRP based on their CIIS, and to determine if a MI was reported in the medical records. Secondly, we evaluated whether resting heart rate and chronotropic response are associated with prior MI, as assessed by the CIIS, in this CLD population. Our hypothesis was that the frequency of prior MI quantified through the CIIS would be higher than that reported in the medical records, and a positive association between heart rate parameters and CIIS would be present in this population. Because CLD patients are a heterogeneous group, we also determined if the results differed in patients diagnosed with COPD compared to patients diagnosed with other CLD.

METHODS

Study design and population

This study used a retrospective cohort design and was conducted in a pulmonary rehabilitation outpatient clinic in a tertiary care university-affiliated hospital. The medical records of CLD patients referred for a PRP between January 2010 and December 2014 were reviewed. Data was collected from the patients who met the following inclusion criteria: over 35 years of age; a physician diagnosis of CLD confirmed by clinical, radiological, and pulmonary function examinations; an available symptom-limited cardiopulmonary exercise testing (CPET) performed on an electronic cycle ergometer using an individualized ramp protocol with 5 or 10 watts per minute increments, according to
published guidelines [27], before the start of the PRP; and twelve-lead ECG recordings obtained at rest and during the CPET. Patients were excluded if they had: uninterpretable or irretrievable ECGs; missing hemodynamic data at resting and peak exercise; or conditions altering CIIS calculation such as atrial fibrillation, ventricular paced rhythm, left bundle branch block, and left ventricular hypertrophy with repolarization abnormalities. For patients with more than one admission to PRP during the inclusion period, data collected from the latest admission was used. Ethical approval to conduct the study was obtained from the appropriate Research Ethics Board.

**Study procedure**

Two sources of data consisting of the patients’ medical record and PRP database contributed to the retrospective data collection. First, each patient’s medical record was electronically searched in order to retrieve information on the completion of a CPET before entering PRP and standard 12-lead ECGs recorded at rest and during the CPET. Next, the PRP database and CPET electronic records were reviewed to collect patients’ characteristics, medical history, and hemodynamic and functional measurements.

**Electrocardiographic classification of prior myocardial infarction**

To estimate the presence of prior myocardial events, the CIIS was calculated from the baseline ECGs obtained at rest, before commencing the CPET. A cardiologist and a trained health professional with expertise in electrocardiography, blind to any patient information, independently analyzed each ECG for recording accuracy. Twelve specific ECG features
including R, S and T wave amplitudes, Q wave duration, and Q/R amplitude ratios were measured, tabulated, and converted to a CIIS [12]. To avoid any interpretation errors in this process, a calculation protocol was developed a priori and refined until the inter-rater reliability exceeded 0.90. Any disagreements between the two assessors were resolved through discussion. Patients were classified as having prior MI if their CIIS was equal to or greater than 20, as this value accurately classifies a “probable infarction” in an adult population [12,28].

Heart rate measurements

Resting and peak heart rate were collected as values measured at rest prior to CPET and during the last minute of CPET, respectively. Chronotropic response index (CRI), which represents the capacity to increase the heart rate in response to exercise, was calculated as the percentage of heart rate reserve that was used during exercise: \[
\frac{(\text{peak heart rate} - \text{resting heart rate}) \times 100}{(220 - \text{age}) - (\text{resting heart rate})}
\] [29]. A cut-off point of ≤ 80% was considered as chronotropic incompetence [23], except for subjects on β-blockers where a cut-off point of ≤ 62% was applied [30]. Based on the CPET records, all patients took their medications including inhalers on the morning of the test.

Additional clinical outcomes

Spirometric measurements [percent predicted forced expiratory volume in 1 second (FEV₁), forced vital capacity (FVC), and FEV₁/FVC ratio] were gathered from patient records along with age, height, weight, smoking status, and use of oxygen. Body mass
index (BMI) was calculated as weight divided by height squared. Indices of submaximal [e.g., distance walked during a six-minute walk test (6MWD)] and maximal/peak exercise capacity [e.g., oxygen uptake (VO$_2$), workload, and exercise time] were also collected along with information on medications and comorbidities. Both the 6MWD and the progressive incremental cycle ergometry CPET protocols were performed in the clinical setting following the standard guidelines [27,31]. Given that our data was collected from CLD patients before they commenced the pulmonary rehabilitation program, no description of the content of exercise training program is provided in the present manuscript. All comorbidities, including MI, were defined on the basis of self-report or physician reports.

**Statistical analysis**

For descriptive statistics, continuous variables were described using means and standard deviations, whereas categorical data were described using counts and percentages. Differences in patients’ baseline characteristics according to the patient groups (COPD versus non-COPD) were compared using parametric (Student’s t-test) or non-parametric (Wilcoxon Mann-Whitney) tests for continuous variables, and Chi-square or Fisher’s tests for categorical variables. The Cohen’s Kappa test was used to compare the agreement between CIIS and medical records of past myocardial events. Univariate correlations and multivariate regression analyses were performed to assess the relationship between CIIS and heart rate parameters in our CLD population, considering CIIS first as a continuous variable, then as a dichotomous variable (CIIS ≥ 20 versus CIIS < 20). Resting heart rate and chronotropic response index were also included in the analysis as continuous and
categorical variables. Stepwise regression was applied to select suitable variables for use in
the regression model. All statistical analyses were performed using the statistical software
.05 was considered statistically significant.

RESULTS
Population sample
In the considered time frame, one hundred and sixteen CLD patients with CPET were
identified. Of the 116 potential participants, 31 patients (27%) were excluded because they
either had uninterpretable or missing ECGs, pharmacological or treadmill stress testing, or
conditions known to alter CIIS interpretation. Therefore, 85 chronic lung disease patients
were included in the final analysis of whom 54 patients had a physician diagnosis of COPD
(COPD group) and 31 patients had a physician diagnosis of CLD other than COPD (non-
COPD group). Diagnoses in the non-COPD group included bronchiectasis (n=1), chronic
asthma (n=2), cystic fibrosis (n=2), combined obstructive-restrictive patterns
(FEV$_1$/FVC>70) (n=10), and interstitial lung diseases such as sarcoidosis, nonspecific
interstitial pneumonia, idiopathic pulmonary fibrosis, and hypersensitivity pneumonitis
(n=16). The study flow diagram is presented in Figure 1.

Participant characteristics
The study population had a mean age (± SD) of 64 ± 10 years and 52% were male. The
COPD and non-COPD groups did not differ significantly in patient characteristics except
for sex, smoking status, pulmonary function tests, and pulmonary medication prescription (Table 1). While the individuals in the COPD group were predominantly men (61%) with moderate-severe pulmonary obstruction (FEV₁ 50 ± 17% predicted; FEV₁/FVC 48 ± 12), the individuals in the non-COPD group were predominantly women (65%) with mild-moderate pulmonary restriction (FVC 73 ± 14% predicted; FEV₁/FVC 77 ± 12), and fewer pack-years. The COPD patients used significantly more lung medications than those in the non-COPD group, but no differences between the two groups were found in the use of cardiovascular medications. Renin-angiotensin system (RAS) antagonists were the most frequent, and beta-blockers the least frequent, cardiovascular medications prescribed in this population. Ischemic heart disease, hypertension, and dysrhythmias were the main cardiovascular diseases found in the patients’ medical records.

Myocardial infarction history

Sixteen CLD patients (19%) were classified as having prior MI based on a CIIS ≥ 20, compared to only seven patients (8%) who had reported acute myocardial events according to their medical records (p = .03). The Cohen’s Kappa test revealed poor level of agreement between CIIS and medical records (kappa = 0.165). This means that a significant percentage of patients with prior MI were detected only through CIIS, indicating that prior MI diagnosis was under-reported in the medical records. The percentages of patients with prior MI evidenced by CIIS ≥ 20 and medical records were similar in the COPD group (17% versus 11%, p = .37), but differed significantly in the non-COPD group (23% versus 3%, p = .02), as illustrated in Figure 2.
Relationship between CIIS and heart rate variables

Hemodynamic and functional capacity data are presented in Table 2. On average, the study population had a CIIS of 13.0 ± 8.1 with similar (non-significant differences) values in the COPD group (13.2 ± 6.8) and the non-COPD group (12.5 ± 10.1). While resting heart rate did not differ between the two groups, the COPD group manifested significantly lower peak heart rate and percent predicted heart rate (121 ± 18 beats/min and 78 ± 12%, respectively) compared to the non-COPD group (138 ± 19 beats/min and 87 ± 11%, respectively). The COPD group also had significantly lower chronotropic response (e.g., CRI 53 ± 22% versus 74 ± 21%), submaximal (6MWD 385 ± 106 meters versus 438 ± 92 meters) and maximal functional exercise capacity indices (e.g., relative peak VO\textsubscript{2} 16.6 ± 4.9 mL/kg/min versus 19.1 ± 4.5 mL/kg/min) compared to the non-COPD group.

Univariate correlations, employed to determine heart rate parameters significantly associated with CIIS, considered as a continuous variable, showed that resting heart rate (r=0.22, p = .04), but not chronotropic response index (r=0.12, p = .27) was positively associated with CIIS. Multivariate regression analyses indicated that resting heart rate remained significantly associated with CIIS even after adjusting for confounding factors such as diastolic blood pressure, FVC, and the use of cardiovascular medication (particularly the absence of RAS antagonist prescription) (R\textsuperscript{2}=0.29, p < .001). As illustrated in Table 3, these results were similar (R\textsuperscript{2}=0.27, p < .001) when resting heart rate was expressed as a dichotomous variable (HR>80 beats/min).

When CIIS was considered as a dichotomous variable (CIIS ≥ 20 versus CIIS < 20), the logistic regression indicated that the resting heart rate was a significant predictor of CIIS (p
only when resting heart rate was used as a dichotomous variable; patients with a 
resting heart rate over 80 beats/min had approximately 5 times higher odds of having a 
CIIS $\geq$ 20. In the same analysis the absence of RAS antagonist medication, but not diastolic 
blood pressure or FVC, reached significance (Table 4). The inclusion of the CLD diagnosis 
(COPD or non-COPD) as an independent variable did not improve any of the regression 
models.

DISCUSSION

We found that CLD patients entering pulmonary rehabilitation were at risk of 
unreported prior MI. Although the proportion of prior MI, as detected by the CIIS score, 
was similar in COPD and non-COPD patient groups, the COPD patients were more likely 
to have a reported MI in their medical history. In addition, resting heart rate, but not 
chronotropic response index, was significantly associated with CIIS in this CLD 
population. An elevated resting heart rate (e.g., over 80 beats/min) was found to be an 
indicator of prior MI in CLD patients, and therefore, it raises awareness for careful 
adjustments of training intensity under these circumstances.

Previous studies that investigated MI history in patients with COPD using ECG 
classification schemes reported frequency values ranging around 20%. Vanflleteren et al. 
[4], using the Minnesota scoring system, found that 21% of COPD patients entering a PRP 
presented ECG changes suggestive of silent MI, and 14% of these patients did not have any 
medical records of ischemic heart disease. With a CIIS cut-off value of 20, Sillen et al. [32] 
showed that approximately 10% of the COPD patients in Global Initiative for Chronic
Obstructive Lung Disease (GOLD)-D stage referred to PRP had prior MI. Similarly, Karoli et al. [15] found that 12.1% and 5.6% of the COPD patients in their study had a prior MI according to the ECG and medical records, respectively. Moreover, they found that a CIIS above 20 represented a risk factor for death in this population.

Although the prevalence values may vary with the population or the diagnosis method, our results are in line with these studies and show that 19% and 8% of CLD patients enrolled in the PRP had a prior MI according to the ECG and medical records, respectively. In addition, we found that the non-COPD patients were less likely to have a reported MI in their history compared to the COPD patients. Therefore, these results show the importance of screening for ischemic heart disease in all patients with CLD entering pulmonary rehabilitation.

We also found that CLD patients entering our PRP displayed elevated resting heart rate with values being about 20 beats/min higher than those reported in the literature for apparently healthy individuals of the same age [33]. Moreover, the resting heart rate in our CLD population was on average 85 beats/min, a value that has been shown to be associated with increased risk of all-cause and cardiovascular mortality in both general [20,21] and COPD [34] populations.

Despite similar resting heart rate values, we found that the COPD group displayed significantly lower heart rate values at peak exercise than the non-COPD group. This hemodynamic feature, paralleled by significant lower submaximal and maximal functional capacities, can be explained by the higher pulmonary function impairment in the COPD group compared to the non-COPD group. Nevertheless, both COPD and non-COPD
patients in our study showed limited capacity to increase their heart rate in response to exercise, as evidenced by the presence of impaired chronotropic response in more than three-quarters of all CLD patients. These results reinforce the opinion that in addition to ventilatory limitation, which is recognized as a primary determinant of exercise tolerance [35], the hemodynamic limitations, which have also been reported as exercise tolerance predictors [36], should be taken into consideration in this population.

Finally, our results indicated that higher resting heart rate along with lower resting diastolic blood pressure, higher FVC, and absence of RAS antagonist medication were significantly associated with the CIIS in our CLD population. While the relationship between elevated resting heart rate and cardiovascular ischemic risk is clearly established [16,21], there are also studies that have reported an association between low diastolic blood pressure and increased risk of MI in elderly people [37,38]. Our data also indicated that in the absence of RAS antagonist medication, CLD patients were more likely to have had a past myocardial event. These findings are in agreement with studies reporting that RAS antagonists (particularly, angiotensin-converting enzyme inhibitors) have an important role in the management of patients at increased cardiovascular risk by reducing MI, stroke, and new-onset congestive heart failure [39]. Similar to other investigators [3], we were not able to confirm the association between FEV$_1$ and CIIS; however, we found that FVC was one of the parameters of the model.

In summary, the weak but statistically significant association between resting heart rate and CIIS found in this study cannot be excluded from consideration due to the magnitude of risk associated with MI history. Moreover, elevated resting heart rate (e.g., over 80
beats/min) seems to be an indicator of prior MI in CLD patients, and therefore, a number of
training guiding principles can be applied under these circumstances. Based on the
literature addressing models of pulmonary rehabilitation for cardiovascular diseases [40,41], starting a light-to-moderate exercise intensity (40-60% peak VO$_2$) with a focus on
endurance is recommended in this population. After a duration of 20-30 minutes of aerobic
exercise is achieved, the intensity can be gradually increased to moderate-to-high levels
(60-80% peak VO$_2$). Interval training can be also applied, in which moderate exercise
intensity of 0.5 - 4 seconds alternates with resting periods of 2 - 4 seconds. Finally,
providing oxygen supplementation during endurance training as well as reducing strength
training could prevent any further myocardial injury.

A number of limitations need to be considered in the interpretation of these results.
First, the study had a retrospective design, which might have introduced bias related to
accuracy and completeness of data from the medical records. Moreover, we excluded
patients with ventricular paced rhythm, left bundle branch block, and left ventricular
hypertrophy with repolarization abnormalities, that are known to alter the CIIS
interpretation. Since these conditions commonly co-exist with ischemic heart disease, our
findings might actually underestimate the real proportion of myocardial injury or infarction
in this population. Other limitations of our study could be related to the nature of the ECG
recordings. Some resting ECG recordings may have been performed with the patients in a
sitting position instead of supine, which could have introduced motion artifacts that could
alter the CIIS calculation. However, our total CIIS (13.0 ± 8.1) was similar to Brekke et al.
study (13.5 ± 11.6), which was performed supine in a population of patients with acute
exacerbation of COPD [3], giving us confidence that the patients’ position did not
significantly alter the CIIS. Since the resting heart rate values were measured before the
CPET, one could infer that neural impulses from the central command in anticipation of the
onset of exercise, use of inhaled bronchodilators (e.g., beta-adrenergic agonists), and/or
specific disease conditions (e.g., hypoxemia, dyspnea) could have lowered the accuracy of
data. However, the strength of this study is represented by the fact that even in the presence
of these potential influencing factors, we were able to detect a clinically relevant
association between elevated resting heart and prior MI in patients with CLD, and provide
physiotherapists with a resting heart rate threshold (e.g., 80 beats/min) that would enable
them to make informed and safe clinical decisions.

CONCLUSIONS
The present study showed that patients with chronic lung disease entering pulmonary
rehabilitation are at risk of unreported prior myocardial infarction. Both COPD and non-
COPD patients should receive the same attention regarding myocardial infarction history.
An elevated resting heart rate (particularly over 80 beats/min) appears to be an indicator of
prior myocardial infarction injury in chronic lung disease patients, and it raises awareness
for careful adjustments of training intensity under these circumstances. Further studies are
needed to explore this association under rigorously controlled conditions along with the
effect of pulmonary rehabilitation in lowering resting heart rate and cardiovascular risk in
this population.
REFERENCES


(31) ATS statement: Guidelines for the six-minute walk test. Am J Respir Crit Care

(32) Sillen MJH, Franssen FME, Delbressine JML, et al. Heterogeneity in clinical
characteristics and co-morbidities in dyspneic individuals with COPD GOLD D: Findings

(33) Miyai N, Arita M, Miyashita K, Morioka I, Shiraishi T, Nishio I. Blood pressure
response to heart rate during exercise test and risk of future hypertension. Hypertension:

(34) Jensen M, Marott JL, Lange P, Vestbo J. Resting heart rate is a predictor of mortality


(36) van Gestel AJR, Kohler M, Steier J, et al. Cardiac autonomic function and
cardiovascular response to exercise in patients with Chronic Obstructive Pulmonary

blood pressure to coronary heart disease death in presence of myocardial infarction: The

(38) Franklin SS, Larson MG, Khan SA, et al. Does the relation of blood pressure to
coronary heart disease risk change with aging? The Framingham Heart Study. Circulation
2001;103(9):1245-1249.


Table 1. Characteristics of the study participants

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total (n=85)</th>
<th>COPD (n=54)</th>
<th>Non-COPD (n=31)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>64 ± 10</td>
<td>65 ± 8</td>
<td>62 ± 13</td>
<td>.19</td>
</tr>
<tr>
<td>Male/female (%)</td>
<td>52/48</td>
<td>61/39</td>
<td>35/65</td>
<td>.02</td>
</tr>
<tr>
<td>BMI (kg/m^2)</td>
<td>27.3 ± 6.4</td>
<td>26.4 ± 6.4</td>
<td>28.7 ± 6.3</td>
<td>.08</td>
</tr>
<tr>
<td>Smoking history (pack-year)</td>
<td>34 ± 26</td>
<td>44 ± 23</td>
<td>17 ± 22</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Current smokers, n (%)</td>
<td>16 (19)</td>
<td>14 (26)</td>
<td>2 (6)</td>
<td>.04</td>
</tr>
<tr>
<td><strong>Pulmonary function test</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁ (% predicted)</td>
<td>57 ± 19</td>
<td>50 ± 17</td>
<td>70 ± 15</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>FVC (% predicted)</td>
<td>77 ± 17</td>
<td>79 ± 18</td>
<td>73 ± 14</td>
<td>.07</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>59 ± 19</td>
<td>48 ± 12</td>
<td>77 ± 12</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Long-term oxygen therapy, n (%)</td>
<td>8 (9)</td>
<td>7 (13)</td>
<td>1 (3)</td>
<td>.24</td>
</tr>
<tr>
<td><strong>Lung medications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of lung medications</td>
<td>3 ± 2</td>
<td>4 ± 2</td>
<td>2 ± 2</td>
<td>.002</td>
</tr>
<tr>
<td>Short/long muscarinic antagonists, n (%)</td>
<td>43 (51)</td>
<td>34 (63)</td>
<td>9 (29)</td>
<td>.003</td>
</tr>
<tr>
<td>Short/long beta agonists, n (%)</td>
<td>61 (72)</td>
<td>46 (85)</td>
<td>15 (48)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Inhaled/oral corticosteroids, n (%)</td>
<td>56 (66)</td>
<td>36 (67)</td>
<td>20 (65)</td>
<td>.84</td>
</tr>
<tr>
<td><strong>Cardiovascular medications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of medications</td>
<td>1 ± 2</td>
<td>1 ± 2</td>
<td>1 ± 2</td>
<td>.98</td>
</tr>
<tr>
<td>RAS antagonists, n (%)</td>
<td>29 (34)</td>
<td>18 (33)</td>
<td>11 (35)</td>
<td>.84</td>
</tr>
<tr>
<td>Anticoagulants, n (%)</td>
<td>19 (22)</td>
<td>12 (22)</td>
<td>7 (23)</td>
<td>.97</td>
</tr>
<tr>
<td>Medication</td>
<td>COPD (n, %)</td>
<td>Non-COPD (n, %)</td>
<td>p值</td>
<td>Non-COPD (n, %)</td>
</tr>
<tr>
<td>----------------------------</td>
<td>-------------</td>
<td>-----------------</td>
<td>-----</td>
<td>----------------</td>
</tr>
<tr>
<td>Diuretics, n (%)</td>
<td>17 (20)</td>
<td>11 (20)</td>
<td>0.91</td>
<td>6 (19)</td>
</tr>
<tr>
<td>Statins, n (%)</td>
<td>15 (18)</td>
<td>9 (17)</td>
<td>0.75</td>
<td>6 (19)</td>
</tr>
<tr>
<td>Calcium antagonists, n (%)</td>
<td>14 (16)</td>
<td>9 (17)</td>
<td>0.94</td>
<td>5 (16)</td>
</tr>
<tr>
<td>Beta-blockers, n (%)</td>
<td>9 (11)</td>
<td>6 (11)</td>
<td>&gt;0.99</td>
<td>3 (10)</td>
</tr>
<tr>
<td><strong>Cardiovascular comorbidities</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic heart disease, n (%)</td>
<td>29 (34)</td>
<td>18 (33)</td>
<td>0.84</td>
<td>11 (35)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>27 (32)</td>
<td>14 (26)</td>
<td>0.12</td>
<td>13 (42)</td>
</tr>
<tr>
<td>Dysrhythmias, n (%)</td>
<td>24 (28)</td>
<td>18 (33)</td>
<td>0.16</td>
<td>6 (19)</td>
</tr>
</tbody>
</table>

Legend: BMI = body mass index, FEV1 = forced expiratory volume in one second, FVC = forced vital capacity, RAS = renin angiotensin system; Values are described as mean ± standard deviation, except for sex, smoking status, medication, and comorbidities, which are described as counts and percentage; p < .05 significantly different between COPD and non-COPD patients
<table>
<thead>
<tr>
<th>Variables</th>
<th>Total (n=85)</th>
<th>COPD (n=54)</th>
<th>Non-COPD (n=31)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac infarction injury score</td>
<td>13.0 ± 8.1</td>
<td>13.2 ± 6.8</td>
<td>12.5 ± 10.1</td>
<td>.75</td>
</tr>
<tr>
<td>Resting HR (bpm)</td>
<td>85 ± 13</td>
<td>85 ± 14</td>
<td>85 ± 11</td>
<td>.80</td>
</tr>
<tr>
<td>Resting HR &gt; 80, n (%)</td>
<td>55 (65)</td>
<td>33 (61)</td>
<td>22 (71)</td>
<td>.36</td>
</tr>
<tr>
<td>Resting SBP (mmHg)</td>
<td>128 ± 20</td>
<td>127 ± 20</td>
<td>128 ± 22</td>
<td>.83</td>
</tr>
<tr>
<td>Resting DBP (mmHg)</td>
<td>78 ± 12</td>
<td>78 ± 13</td>
<td>77 ± 12</td>
<td>.83</td>
</tr>
<tr>
<td>Resting SpO₂ (%)</td>
<td>97 ± 2</td>
<td>96 ± 2</td>
<td>97 ± 3</td>
<td>.01</td>
</tr>
<tr>
<td>Peak HR (bpm)</td>
<td>127 ± 20</td>
<td>121 ± 18</td>
<td>138 ± 19</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Peak HR (% predicted)</td>
<td>81 ± 12</td>
<td>78 ± 12</td>
<td>87 ± 11</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Peak SBP (mmHg)</td>
<td>176 ± 25</td>
<td>175 ± 26</td>
<td>179 ± 23</td>
<td>.45</td>
</tr>
<tr>
<td>Peak DBP (mmHg)</td>
<td>85 ± 13</td>
<td>85 ± 14</td>
<td>84 ± 12</td>
<td>.69</td>
</tr>
<tr>
<td>Relative Peak VO₂ (mL/kg/min)</td>
<td>17.5 ± 4.9</td>
<td>16.6 ± 4.9</td>
<td>19.1 ± 4.5</td>
<td>.02</td>
</tr>
<tr>
<td>Relative Peak VO₂ (% predicted)</td>
<td>72 ± 20</td>
<td>70 ± 20</td>
<td>77 ± 20</td>
<td>.09</td>
</tr>
<tr>
<td>Peak workload (Watts)</td>
<td>71 ± 27</td>
<td>68 ± 29</td>
<td>78 ± 23</td>
<td>.04</td>
</tr>
<tr>
<td>Exercise time (min)</td>
<td>6 ± 3</td>
<td>6 ± 3</td>
<td>7 ± 2</td>
<td>.03</td>
</tr>
<tr>
<td>CRI (%)</td>
<td>60 ± 24</td>
<td>53 ± 22</td>
<td>74 ± 21</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CRI ≤ 80, n (%)</td>
<td>67 (79)</td>
<td>47 (87)</td>
<td>20 (65)</td>
<td>.01</td>
</tr>
<tr>
<td>6 MWD (meters)</td>
<td>405 ± 104</td>
<td>385 ± 106</td>
<td>438 ± 92</td>
<td>.04</td>
</tr>
</tbody>
</table>
Legend: HR = heart rate, bpm = beats/min, SBP = systolic blood pressure, DBP = diastolic blood pressure, SpO2 = blood oxygen saturation, VO2 = oxygen uptake, CRI = chronotropic response index, 6MWD = six minute walk distance test; Values are described as mean ± standard deviation, except for CRI, which is described as counts and percentage; p < .05 significantly different between COPD and non-COPD patients.
Table 3. Multiple regression analysis for cardiac infarction injury score as continuous variable

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>β</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Model 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting HR (bpm)</td>
<td>0.17</td>
<td>(0.05, 0.28)</td>
<td>.004</td>
</tr>
<tr>
<td>Resting DBP (mmHg)</td>
<td>-0.17</td>
<td>(-0.29, -0.04)</td>
<td>.008</td>
</tr>
<tr>
<td>FVC (% predicted)</td>
<td>0.13</td>
<td>(0.04, 0.22)</td>
<td>.005</td>
</tr>
<tr>
<td>RAS antagonists (0)</td>
<td>4.64</td>
<td>(1.53, 7.75)</td>
<td>.003</td>
</tr>
<tr>
<td>R-square</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Model 2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting HR &gt; 80 (bpm)</td>
<td>3.92</td>
<td>(0.59, 7.25)</td>
<td>.02</td>
</tr>
<tr>
<td>Resting DBP (mmHg)</td>
<td>-0.16</td>
<td>(-0.29, -0.03)</td>
<td>.01</td>
</tr>
<tr>
<td>FVC (% predicted)</td>
<td>0.14</td>
<td>(0.04, 0.23)</td>
<td>.006</td>
</tr>
<tr>
<td>RAS antagonists (0)</td>
<td>4.44</td>
<td>(1.12, 7.76)</td>
<td>.009</td>
</tr>
<tr>
<td>R-square</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Legend: HR = heart rate, bpm = beats/min, DBP = diastolic blood pressure, FVC = forced vital capacity, RAS (0) = absence of RAS antagonist prescriptions
Table 4. Logistic regression analysis for cardiac infarction injury score as categorical variable

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>β</th>
<th>Wald Chi-square</th>
<th>Point estimate</th>
<th>95% Wald confidence limits</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Model 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting HR (bpm)</td>
<td>0.05</td>
<td>3.4</td>
<td>1.1</td>
<td>(0.99, 1.11)</td>
<td>.06</td>
</tr>
<tr>
<td>Resting DBP (mmHg)</td>
<td>-0.05</td>
<td>3.6</td>
<td>0.9</td>
<td>(0.90, 1.00)</td>
<td>.05</td>
</tr>
<tr>
<td>FVC (% predicted)</td>
<td>0.03</td>
<td>2.3</td>
<td>1.0</td>
<td>(0.99, 1.07)</td>
<td>.13</td>
</tr>
<tr>
<td>RAS antagonists (0)</td>
<td>2.29</td>
<td>4.3</td>
<td>9.8</td>
<td>(1.14, 85.03)</td>
<td>.03</td>
</tr>
<tr>
<td><strong>Model 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting HR &gt; 80 (bpm)</td>
<td>1.56</td>
<td>3.9</td>
<td>4.7</td>
<td>(1.01, 22.24)</td>
<td>.04</td>
</tr>
<tr>
<td>Resting DBP (mmHg)</td>
<td>-0.06</td>
<td>3.7</td>
<td>0.9</td>
<td>(0.89, 1.00)</td>
<td>.05</td>
</tr>
<tr>
<td>FVC (% predicted)</td>
<td>0.03</td>
<td>2.7</td>
<td>1.0</td>
<td>(0.99, 1.07)</td>
<td>.09</td>
</tr>
<tr>
<td>RAS antagonists (0)</td>
<td>2.20</td>
<td>4.1</td>
<td>9.2</td>
<td>(1.06, 76.08)</td>
<td>.04</td>
</tr>
</tbody>
</table>

Legend: HR = heart rate, bpm = beats/min, DBP = diastolic blood pressure, FVC = forced vital capacity, RAS (0) = absence of RAS antagonist prescriptions
**Figure 1.** Study flow diagram

**Figure 2.** Percentage of patients with myocardial infarction based on the medical records (gray bars) and Cardiac Infarction Injury Score (black bars); all chronic lung disease (CLD) patients; COPD; and non-COPD; *p < .05