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Heart rate variability and heart rate recovery in lung cancer survivors eligible for long-term cure

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ABSTRACT

Lung cancer survivors are at risk for physical fitness and autonomic function impairments. In a cross-sectional study of consecutive lung cancer survivors post-curative intent therapy, we assessed and identified predictors of resting heart rate variability (HRV) and heart rate recovery (HRR), defined as standard deviation of normal-to-normal-R-to-R intervals (SDNN) and root-mean-square-of-successive-differences (rMSSD) from routine out-patient single 10-s electrocardiographs (ECGs) and difference in heart rate (HR) at 1-minute following and the end of the six-minute-walk-test (6MWT), respectively. In 69 participants, the mean (SD) HRR was -10.6 (6.7) *beats*. Significant independent predictors of HRR were age and HR change associated with the 6MWT. In a subset of 41 participants with available ECGs, the mean (SD) SDNN and rMSSD were 19.1 (15.6) and rMSSD 18.2 (14.6) *ms*, respectively. Significant independent predictors of HRV were supine HR, HRR, and total lung capacity. HRV/HRR may be useful physiological measures in studies aimed at improving physical fitness and/or autonomic function in lung cancer survivors.

1. Introduction

Lung cancer is the second-most commonly diagnosed cancer in the United States (US) (Siegel et al., 2018). The number of lung cancer survivors is increasing partly due to advances in therapy and possibly screening (Vachani et al., 2017). Lung cancer survivors suffer from the negative health consequences associated with aging, health behaviors, comorbidities, and/or lung cancer and its treatment (Pozo et al., 2014). Physiological evaluation in lung cancer is most commonly performed in the preoperative context to measure or estimate peak oxygen consumption – the gold-standard measure of cardiorespiratory fitness – which is an independent predictor of perioperative morbidity and mortality in patients being considered for major lung resection (Brunelli et al., 2013). More recently, the utility of physiological evaluation outside of the preoperative context has been described, including in post-treatment lung cancer survivors to identify health impairments (Ha et al., 2016).

Heart rate variability (HRV) and heart rate recovery (HRR) are interrelated measures of physical fitness and/or autonomic function (Kiviniemi et al., 2017) which plays important physiological roles in the homeostasis of important organs, including heart and lungs (Ha, Fuster et al., 2015). HRV is decreased in heavy smokers (Cagirci et al., 2009) and increases with reduction in cigarette smoking (Munjal et al., 2009). Impaired HRR has been reported in patients with chronic obstructive pulmonary disease (COPD), diabetes, and heart failure (Curtis and O'Keefe, 2002), the three-most common comorbidities in lung cancer (Islam et al., 2015). Moreover, antineoplastic therapy can also lead to neuropathy and autonomic dysfunction (Starobova and Vetter, 2017), further modulating heart rate measures. Critically, impaired HRR is associated with worse survival in patients undergoing exercise testing, independent of standard cardiac risk factors and workload achieved (Cole et al., 1999). Therefore, HRV and HRR may be additional domains

Abbreviations: 6MWD, six-minute walk distance; 6MWT, six-minute walk test; ATS, American Thoracic Society; CAD, coronary artery disease; CI, confidence interval; COPD, chronic obstructive pulmonary disease; DL_{CO}, diffusion capacity of the lung for carbon monoxide; DM, diabetes mellitus; ECG, electrocardiograph; FEV_1, forced expiratory volume in 1 second; HR, heart rate; HRR, heart rate recovery; HRV, heart rate variability; MVA, multivariable linear regression analysis; NSCLC, non-small cell lung cancer; O_2, oxygen; PAC, premature atrial contraction; PVC, premature ventricular contraction; QoL, quality of life; rMSSD, root mean square of successive differences; RPE, ratings of perceived exertion; SDNN, standard deviation of normal-to-normal R-R intervals; TLC, total lung capacity; UVA, univariable linear regression analysis; VASDHS, VA San Diego Healthcare System

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of physiological evaluation that have diagnostic, predictive, and prognostic utility in lung cancer survivors.

Traditionally, HRV is obtained from electrocardiographs (ECGs) of at least 240 *s* in duration (ESC, 1996) and HRR from maximal exercise testing (Adabag and Pierpont, 2013). In recent years, HRV obtained from routine, outpatient, 10-s ECGs is reported as more readily-available and has reference values available for interpretation (O'Neal et al., 2016). HRV obtained from 10-s ECGs, in single and repeated measures, has been validated (Munoz et al., 2015) and shown to be prognostic independent of cardiac risk factors (de Bruyne et al., 1999) and in individuals without cardiovascular disease (O'Neal et al., 2016). Also, HRR from submaximal (Cole et al., 2000) and functional exercise testing is associated with clinical outcomes in various patient populations including lung cancer (Ha et al., 2015).

The identification of predictors of HRV and HRR may provide important insights into factors that could be modified to improve lung cancer survivorship. In this study, we aimed to identify predictors of HRV and HRR in lung cancer survivors eligible for long-term cure. We hypothesized that resting HRV measured from a single, routine, outpatient 10-s ECG and HRR following functional exercise testing are inter-dependently associated and can be used to assess physical fitness and/or autonomic function in this patient population.

2. Methods

2.1. Study overview

We previously performed a cross-sectional study, in which we enrolled 87% of eligible lung cancer survivor following curative-intent treatment, to assess and analyze the relationship between functional exercise capacity and cancer-specific quality of life (QoL) (Ha et al., 2018). In the present study, we enrolled additional participants to identify predictors of HRV and HRR and explore their inter-dependence. In brief, we identified eligible patients from a tumor board list of consecutive lung cancer cases managed at the VA San Diego Healthcare System (VASDHS). Between July 2016 and March 2018, we mailed information letters to eligible patients diagnosed with/managed for lung cancer at the VASDHS since October 2010 and followed up with a telephone call approximately one week later to gauge their interest. We obtained written informed consent from all enrolled participants and followed standard recommendations to report our findings (von Elm et al., 2007). The VASDHS Institutional Review Board approved our protocol (no. H150158).

2.2. Participants

We included lung cancer survivors who completed curative-intent lung cancer treatment, defined as lung cancer resection surgery, definitive radiation, or concurrent chemoradiation for stage I-IIIA disease $\geq$1 month previously. We excluded patients who were unable to perform functional exercise testing, due to dementia (n = 2), bilateral below-knee amputation (n = 2), or quadriplegia (n = 1). For HRV measures, we additionally excluded patients with atrial arrhythmias, atrial or ventricular pacing, or frequent premature atrial or ventricular contractions (PAC/PVCs).

2.3. Heart rate variability

We used routine, outpatient, 12-lead, 10-ECGs obtained for clinical indications and within six months of study enrollment to assess HRV. We defined HRV as the standard deviation of normal-to-normal R-R intervals (SDNN) and root-mean-square of successive differences (rMSSD) from these 10-s ECGs, previously shown to correlate and agree well with the gold-standard 240-300-s tracings (Pearson's *r* 0.85-0.86, Bland-Altman limits of agreement 0.08-0.10, and Cohen's d 0.15-0.17 for rMSSD) (Munoz et al., 2015). We visually inspected all ECGs and excluded those with atrial arrhythmias or atrial or ventricular pacing, or contained > 50% beats that were PAC/PVCs (O'Neal et al., 2016). In any included ECG that had PAC/PVCs, we additionally excluded the beats before and after them from HRV measurements, as suggested by previous literature (O'Neal et al., 2016). We measured normal-to-normal R-R intervals manually using electronic calipers in the GE® MUSE editor software.

2.4. Heart rate recovery

We obtained HRR following the six-minute walk test (6MWT) as supported by existing literature (Minai et al., 2012; Ha et al., 2015). We performed the 6MWT according to the standard protocol at the VASDHS which follows the American Thoracic Society (ATS) Pulmonary Function Standards Committee recommendations (ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories, 2002), modified to include HRR evaluation. In brief, we obtained pre-6MWT vital signs with the patient in the upright, seated position. We then instructed participants to walk as far as possible for six minutes in a 130-ft (40-m) hallway. At the end of six minutes, we instructed participants to sit down for post-6MWT measures. We used a finger-probe pulse oximeter to obtain heart rate (HR) and oxygen (O_2) saturation levels, and defined HRR as the difference, in *beats*, in HR at 1-minute following completion of the 6MWT and at the end of the 6MWT. Participants who had supplemental O_2 prescribed used their own equipment at the same flow rate as their regular prescription. We did not conduct practice tests or ECG monitoring as per ATS recommendations (ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories, 2002). All HRV and HRR measurements were obtained by one observer (DH) blinded to all baseline characteristics and HRR or HRV measurements.

2.5. Covariates

We collected a thorough list of clinical characteristics related to physical fitness and/or autonomic function that included age, sex, ethnicity, smoking history, comorbidities (e.g. chronic cardiovascular and pulmonary diseases), medications (e.g. beta-blockers, inhibitors of the renin-angiotensin system), lung function [forced expiratory volume in 1 s (FEV_1), total lung capacity (TLC), diffusion capacity of the lung for carbon monoxide (DL_{CO})], and echocardiographic findings where available. Lung cancer characteristics included histologic subtype, stage, and treatment.

2.6. Statistical analyses

We summarized descriptive statistics as means and standard deviations (SDs) for all continuous variables and as counts and percentages for categorical variables. We used independent-sample t-tests and chi-square tests to compare differences in clinical characteristics between participants included for HRV and HRR measurements. Both HRV and HRR were recorded and analyzed as continuous variables. We interpreted SDNN and rMSSD using reference values for stage I-II non-small cell lung cancer (NSCLC) patients (De Couck and Gidron, 2013), the six-minute walk distance (6MWD) using reference equations in healthy adults (Enright and Sherrill, 1998), and HRR using a cutoff of $\leq$ 12-*beat* decrease to indicate impairment (Cole et al., 1999; Ha et al., 2015). We also used reference values provided in the literature to compare HRV measures between our cohort and historical controls.

We transformed SDNN and rMSSD into normal distribution using natural logarithms as supported by previous literature (De Couck and Gidron, 2013). We used correlation coefficients, and univariable (UVA) and multivariable (MVA) linear regressions to assess and analyze the relationship between baseline characteristics and HRV and HRR. For MVAs, we used stepwise, backward selection modeling starting with all baseline characteristics with $p < 0.20$ in UVAs. To identify predictors

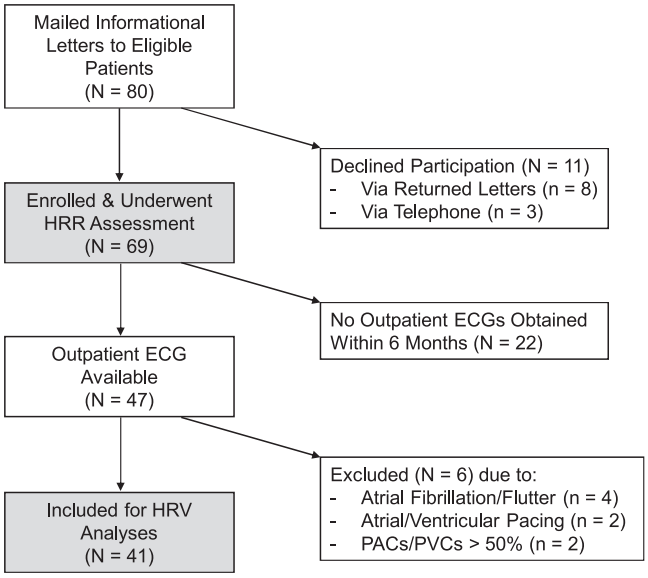

Fig. 1. Flow Diagram of Included Participants.
Shaded boxes indicate cohorts analyzed.
6MWT = six-minute walk test; ECG = electrocardiogram; HRR = heart rate recovery; HRV = heart rate variability; PAC = premature atrial contraction; PVC = premature ventricular contraction.

of HRV, we performed MVAs with and without supine HR from routine outpatient ECGs, as HR has been shown to have both physiological and mathematical relationships with HRV measures (Sacha, 2014). We used regression coefficients (β), 95% confidence intervals (CIs), and coefficients of determination (R^2 and partial R^2) for interpretation, and defined statistical significance as $p < 0.05$ in two-tailed tests. IBM® SPSS® Statistics software versions 23.0 and 24.0 were used for analyses.

3. Results

3.1. Participants

We enrolled 69 lung cancer survivors following curative intent treatment to undergo 6MWT and HRR evaluation. Of these participants, a subset of 41 participants had routine outpatient ECGs obtained clinically within 6 months of enrollment and met inclusion criteria for HRV measurements (Fig. 1). The baseline clinical characteristics for both cohorts are described in Table 1; most participants were white males who were current or former smokers and underwent either lung cancer resection surgery or definitive radiation for treatment. There were no significant differences in clinical characteristics between cohorts except for those in the HRV cohort having a higher percentage of early stage (I-II) lung cancer and receipt of surgical treatment (Table 1).

3.2. Assessments and identifying predictors of HRV (N = 41)

The mean (SD) SDNN and rMSSD were 19.1 (15.6) and 18.2 (14.6) *ms*, respectively, and their natural logarithm transformed values 2.72 (0.64) and 2.69 (0.63). Twenty-four participants (59%) had impaired SDNN and rMSSD, defined as < the mean reference values derived from single 10-s ECGs for stage I-II NSCLC patients (E-Table 1) (De Couck and Gidron, 2013). There was no significant difference in SDNN ($p = 0.33$) or rMSSD ($p = 0.27$) between our cohort and historical stage I-II NSCLC patients (De Couck and Gidron, 2013). Compared to individuals without cardiovascular disease included in the Multi-Ethnic Study of Atherosclerosis (O'Neal et al., 2016), lung cancer survivors included in our cohort had a mean difference of -5.04 *ms* (95% CI -9.96, -0.12, $p = 0.045$) in SDNN and -9.08 *ms* (95% CI -13.7, -4.47, $p < 0.001$) in rMSSD.

Table 1
Participant Characteristics.

Participant Characteristic (VASDHS, 2016-2018)	HRR Cohort(N = 69)	HRV Subset(N = 41)	P-value‡
Age, *year*, mean (SD)	71.0 (8.4)	69.7 (8.4)	0.43
White race, n (%)	63 (91)	35 (85)	0.75
Male sex, n (%)	66 (96)	39 (95)	0.90
BMI, kg/m^2, mean (SD)	26.5 (4.8)	26.5 (5.1)	1.00
Smoking history, n (%)			0.92
Current	22 (32)	14 (34)	
Former	41 (59)	23 (56)	
Never	6 (9)	4(10)	
Pack years, mean (SD)	52.8 (32.2)	53.2 (36.4)	0.95
Comorbidities, n (%)			
Hypertension	57 (83)	31 (76)	0.38
Hyperlipidemia	57 (83)	33 (81)	0.78
Diabetes	18 (26)	11 (27)	0.93
Atrial arrhythmia*	17 (25)	Excluded	N/A
CAD	25 (36)	18 (44)	0.43
HF†	17 (25)	9 (22)	0.75
COPD/asthma	51 (74)	30 (73)	0.93
OSA	16 (23)	12 (29)	0.48
Anxiety/Depression/ PTSD	21 (30)	11 (27)	0.69
Other cancers	29 (42)	16 (39)	0.76
Medications, n (%)			
Beta-blockers	31 (45)	19 (46)	0.89
ACE-I/ARB	27 (39)	16 (39)	0.76
Pulmonary function, mean (SD)			
FEV_1/FVC, *%*	59.9 (14.9)	61.8 (13.8)	0.51
FEV_1, *% predicted*	71.1 (25.2)	71.6 (23.7)	0.92
TLC, *% predicted***	110.9 (22.3)	108.1 (22.8)	0.53
DL_{CO}, *% predicted*	78.6 (25.6)	79.8 (23.8)	0.81
Lung cancer characteristics			
Clinical stage, n (%)			**< 0.01**
I	55 (80)	30 (73)	
II	4 (6)	10 (24)	
IIIA	10 (15)	1 (2)	
Histologic subtype, n (%)			0.62
Adenocarcinoma	33 (48)	23 (56)	
Squamous cell carcinoma	17 (25)	9 (22)	
Presumed	14 (20)	6 (15)	
Primary treatment, n (%)			**< 0.001**
Surgical resection	34 (49)	31 (76)	
Definitive radiation	25 (36)	2 (5)	
Chemoradiation	10 (15)	8 (20)	

***Bolded** variables indicate statistically-significant differences between cohorts.*
ACE-I = angiotensin converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BMI = body-mass index; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; DL_{CO} = diffusion capacity of the lung for carbon monoxide; FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity; HF = heart failure; OSA = obstructive sleep apnea; PTSD = posttraumatic stress disorder; SD = standard deviation; TLC = total lung capacity.

* *Defined as any history of, including paroxysmal atrial fibrillation or flutter, treated with medical therapy or ablation.*

** *Data available in 34 and 58 participants for HRV and HRR cohorts, respectively.*

† *Defined as ejection fraction < 50% or clinical documentation of systolic heart failure.*

‡ *Independent sample t-tests for continuous variables and chi-square likelihood ratio tests for categorical variables.*

In UVA (E-Table 2), clinical characteristics significantly/borderline associated with HRV were age, TLC *% predicted*, supine HR, pre-6MWT HR, HR change associated with the 6MWT, and HRR following the 6MWT (Table 2). Exploratory UVA in 27 participants with ECGs obtained post-lung cancer treatment showed no significant association between primary treatment modality and HRV ($p = 0.36$ for Ln-SDNN, and $p = 0.37$ for Ln-rMSSD). In MVAs including all clinical characteristics with $p < 0.20$ in UVAs, in a model that also contained age, TLC

Table 2
UVA – Statistically Significant or Borderline-Significant Predictors of HRV and HRR.

	HRV (Ln-SDNN) (N = 41)			HRV (Ln-rMSSD) (N = 41)			HRR (N = 69)		
Clinical Characteristic	β	R^2	P-value	β	R^2	P-value	β	R^2	P-value
Age, per *year*	**0.03**	**0.11**	**0.04**	0.02	0.09	0.052	NS/BS	NS/BS	NS/BS
Hyperlipidemia (*N/Y*)	NS/BS	NS/BS	NS/BS	NS/BS	NS/BS	NS/BS	**−4.95**	**0.08**	**0.02**
Atrial arrhythmia (*N/Y*)	N/A*	N/A*	N/A*	N/A*	N/A*	N/A*	**3.68**	**0.06**	**0.048**
TLC, *% predicted*	0.01	0.11	0.053	0.01	0.11	0.06	NS/BS	NS/BS	NS/BS
Supine† HR, *beats/min*	**−0.02**	**0.23**	**0.001**	**−0.02**	**0.24**	**0.001**	**0.19**	**0.21**	**0.003**
Pre-6MWT HR, *beats/min*	−0.01	0.08	0.08	−0.01	0.08	0.08	**0.16**	**0.11**	**0.01**
HR change, *beats*	**0.02**	**0.11**	**0.04**	**0.02**	**0.12**	**0.03**	**−0.40**	**0.45**	**< 0.001**
SBP change, *mmHg*	NS/BS	NS/BS	NS/BS	NS/BS	NS/BS	NS/BS	−0.08	0.04	0.09
6MWD, *m*	NS/BS	NS/BS	NS/BS	NS/BS	NS/BS	NS/BS	**−0.02**	**0.10**	**0.01**
HRR, *beat*	**−0.04**	**0.15**	**0.01**	**−0.04**	**0.16**	**0.01**	N/A	N/A	N/A

NS/BS = not significant or borderline significant (p ≥ 0.10).
***Bolded** values indicate statistically significant association at p < 0.05.*
6MWD = six-minute walk distance; 6MWT = six-minute walk test; ECG = electrocardiograph; HR = heart rate; HRR = heart rate recovery; HRV = heart rate variability; Ln = natural logarithm; SBP = systolic blood pressure; SDNN = standard deviation of normal-to-normal R-R intervals; rMSSD = root mean square of successive differences; TLC = total lung capacity; UVA = univariable linear regression analysis.
* *Excluded per inclusion/exclusion criteria.*
† *Obtained on routine outpatient ECGs.*

Table 3
MVA*–Independent Predictors of HRV (N = 41).

	(A) With Supine HR					
	Ln-SDNN[a]			Ln-rMSSD[b]		
Variable	β (95% CI)	Partial R^2	P-value	β (95% CI)	Partial R^2	P-value
Age, *year*	0.02 (-0.01, 0.04)	0.09	0.11	0.02 (-0.01, 0.04	0.06	0.18
TLC, *% predicted*	0.01 (0.00, 0.02)	0.10	0.10	0.01 (0.00, 0.03)	0.10	0.09
Pre-6MWT HR, *beats/min*	0.01 (0.00, 0.03)	0.09	0.12	0.01 (0.00, 0.03)	0.08	0.13
HR change, *beats*	0.02 (0.00, 0.04)	0.12	0.06	**0.02 (0.00, 0.04)**	**0.14**	**0.04**
Supine HR, *beats/min*	**−0.02 (-0.03, -0.01)**	**0.21**	**0.01**	**−0.02 (-0.03, -0.004)**	**0.21**	**0.01**
	(B) Without Supine HR					
	Ln-SDNN[c]			Ln-rMSSD[d]		
Age, *year*	0.02 (-0.01, 0.04)	0.07	0.14	0.01 (-0.01, 0.04	0.05	0.199
TLC, *% predicted*	**0.01 (0.00, 0.02)**	**0.13**	**0.047**	**0.01 (0.00, 0.02)**	**0.13**	**0.047**
HRR, *beat*	**−0.04 (-0.07, -0.003)**	**0.14**	**0.03**	**−0.04 (-0.07, -0.01)**	**0.16**	**0.02**

***Bolded** variables indicate statistically significant association at p < 0.05.*
6MWT = six-minute walk test; CI = confidence interval; HR = heart rate; HRR = heart rate recovery; HRV = heart rate variability; HRV = heart rate variability; Ln = natural logarithm; MVA = multivariable linear regression analysis; O_2 = oxygen; SDNN = standard deviation of normal-to-normal R-R intervals; rMSSD = root mean square of successive differences; TLC = total lung capacity; UVA = univariable linear regression analysis.
* *Step-wise backwards selection using variables with p < 0.20 from UVA (E-Table 2): age,* TLC% *predicted, Pre-6MWT HR, HR change, O_2 saturation change, and HRR, with and without supine HR as covariate.*
[a] *Overall model R^2 = 0.42, P < 0.01; no significant interaction between age and supine HR (p = 0.96), supine HR and pre-6MWT HR (p = 0.68), or supine HR and HR change (p = 0.95).*
[b] *Overall model R^2 = 0.42, P < 0.01; no significant interaction between HR change and supine HR (p = 0.98).*
[c] *Overall model R^2 = 0.31, P = 0.01; no significant interaction between* TLC% *predicted and HRR (p = 0.46).*
[d] *Overall model R^2 = 0.30, P = 0.01; no significant interaction between* TLC% *predicted and HRR (p = 0.41).*

% predicted, and pre-6MWT HR, and HR change associated with the 6MWT, supine HRR was a consistent significant independent predictor of HRV (Table 3A, Fig. 2 Ai-ii & E-Figure 1A). When supine HR was not included, MVAs showed that total lung capacity and HRR were significant independent predictors of HRV (Table 3B, Fig. 2 Aiii-iv & E-Fig. 1B-C).

3.3. Assessments and identifying predictors of HRR (N = 69)

The mean (SD) 6MWD was 342 (123) *m*, 66 (24) % predicted, with 40 participants (58%) having impaired functional exercise capacity as defined by standard equations for normal healthy adults (Enright and Sherrill, 1998). Following the 6MWT, the mean (SD) HRR was -10.6 (6.7) *beats*; 45 participants (65%) had impaired HRR as defined by a cutoff of ≤12-*beat* decrease (E-Table 1) (Cole et al., 1999; Ha et al., 2015).

In UVA (E-Table 3), hyperlipidemia, atrial arrhythmia, pre-6MWT HR, HR change associated with the 6MWT, and 6MWD were associated with HRR (Table 2); lung cancer histologic subtype, stage, and primary treatment modality (surgical resection, definitive radiation, or chemoradiation) were not associated with HRR (E-Table 3). In MVAs and a final model (Table 4) that also included hyperlipidemia and pre-6MWT, age and HR change associated with the 6MWT were significant independent predictors of HRR (Fig. 2B). When patients with a history of paroxysmal, persistent, or permanent atrial arrhythmia managed with medical and/or ablation therapy were excluded (UVA results are shown in E-Table 3), similar results were obtained; heart failure with reduced ejection fraction was additionally found to be a significant predictor of HRR (Table 4).

3.4. HRR-HRV inter-dependence

Heart rate recovery following the 6MWT correlated moderately-well with HRV (Spearman's ρ -0.38, p = 0.01 for SDNN and -0.41, p = 0.008 for rMSSD, respectively). Impaired SDNN/rMSSD was concordant with HRR in 69% of cases. Overall, the mean HRR for participants with

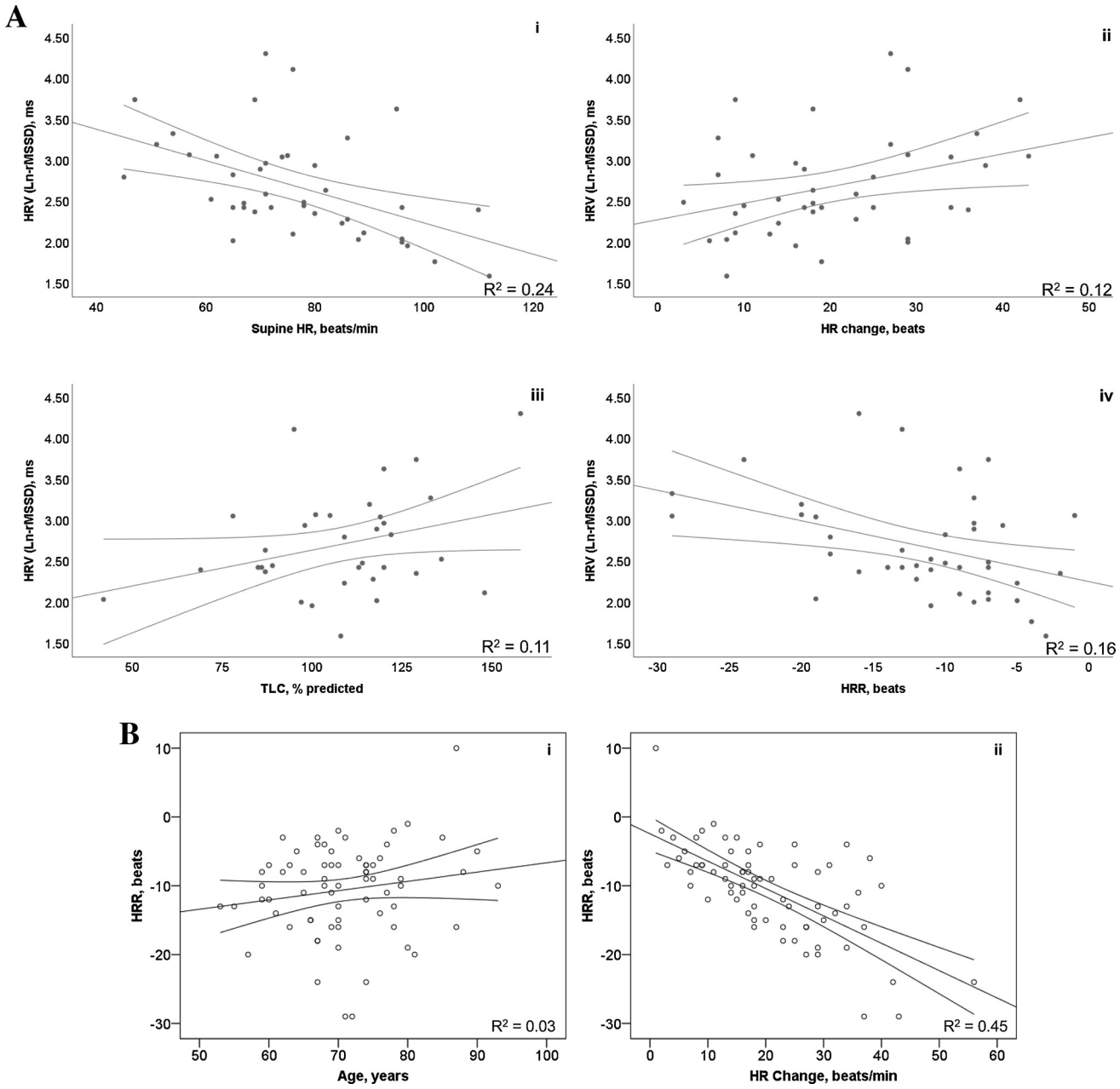

Fig. 2. A Significant Independent Predictors of HRV (Ln-rMSSD).
R^2 values from univariable linear regression analyses; bands indicate 95% confidence intervals.
HR = heart rate; HRR = heart rate recovery; HRV = heart rate variability; Ln = natural logarithm; rMSSD = root mean square of successive differences; TLC = total lung capacity.
Fig. 2 B: Significant Independent Predictors of HRR.
R^2 values from univariable linear regression analyses; bands indicate 95% confidence intervals.
6MWD = six-minute walk distance; 6MWT = six-minute walk test; HR = heart rate; HRR = heart rate recovery.

normal compared to impaired SDNN and rMSSD, respectively were -14.4 *vs*. -9.7 *beats* (p = 0.04) and -15.6 vs. -9.8 *beats* (p = 0.04) (Fig. 3).

4. Discussion

In lung cancer survivors eligible for long-term cure, we assessed HRV and HRR and found impairments in 59% and 65% of patients, respectively and identified their predictors. In addition, HRV and HRR were inter-dependently associated, supporting their utility in assessing physical fitness and/or autonomic function in the lung cancer population. To the best of our knowledge, our study is the first to identify predictors of HRV and HRR in lung cancer survivors eligible for long-term cure and characterize their inter-relationship. Similar to a previous study (Danieli et al., 2014), we report a moderate correlation (correlation coefficient 0.3-0.7) between SDNN/rMSSD and HRR.

Lung cancer survivors face many health issues that may affect their physical fitness and/or autonomic function, including due to aging (Kingwell et al., 1994), tobacco exposure (Niedermaier et al., 1993), comorbidities including COPD (Heindl et al., 2001), heart failure (Barretto et al., 2009), and diabetes (Karjalainen et al., 2014), and chemotherapy treatment (Barutcu et al., 2004). In our multivariable models, HRR explains approximately 15% of the variances in HRV, suggesting caution against exchanging HRR for HRV. Notably, HRR can

Table 4
MVA – Independent Predictors of HRR.

	All Participants (N = 69)[a]			Excluding Atrial Arrhythmia (N = 52)[b]		
Variable	β (95% CI)	Partial R^2	P-value	β (95% CI)	Partial R^2	P-value
Age, *year*	**0.17 (0.04, 0.30)**	**0.10**	**0.01**	**0.26 (0.13, 0.39)**	**0.25**	**< 0.001**
Hyperlipidemia (*N/Y*)	−2.30 (-4.98, 0.39)	0.05	0.09	N/A*	N/A*	N/A*
HFrEF (*N/Y*)	N/A	N/A	N/A	**−3.32 (-5.78, -0.86)**	**0.14**	**0.01**
Pre-6MWT HR, *beats/min*	−0.15 (-0.31, 0.007)	0.06	0.06	−0.08 (-0.25, 0.08)	0.02	0.32
HR change, *beats/min*	**−1.32 (-1.82, -0.81)**	**0.31**	**< 0.001**	**−1.31 (-1.92, -0.69)**	**0.29**	**< 0.001**
Pre-6MWT HR × HR change	**0.01 (0.007, 0.02)**	**0.19**	**< 0.001**	**0.01 (0.004, 0.02)**	**0.16**	**0.01**

***Bolded** variables indicate statistically significant association at $p < 0.05$.*

6MWD = six-minute walk distance; 6MWT = six-minute walk test; ACE-I = angiotensin converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BMI = body-mass index; CI = confidence interval; DBP = diastolic blood pressure; DL_{CO} = diffusion capacity of the lung for carbon monoxide; HFrEF = heart failure with reduced ejection fraction; HR = heart rate; HRR = heart rate recovery; MVA = multivariable linear regression analysis; SBP = systolic blood pressure; UVA = univariable linear regression analysis.

[a] *Step-wise backwards selection using variables with $p < 0.20$ from UVA (E-Table 3): age, BMI, hyperlipidemia, atrial arrhythmia, DL_{CO} % predicted, pre-6MWT HR, HR change, SBP change, 6MWD; overall model $R^2 = 0.66$, $p < 0.001$; no significant interaction between age and pre-6MWT HR ($p = 0.22$).*

[b] *Step-wise backwards selection using variables with $p < 0.20$ from UVA (E-Table 3): age,* white *race, sex, hyperlipidemia, HFrEF, ACE-I/ARB, pre-6MWT HR, pre-6MWT DBP, HR change, SBP change, 6MWD; overall model $R^2 = 0.71$, $p < 0.001$; no significant interaction between age and pre-6MWT HR ($p = 0.57$), or HFrEF and pre-6MWT HR ($p = 0.49$).*

* *Variable not included in final model (excluded in step-wise backwards selection).*

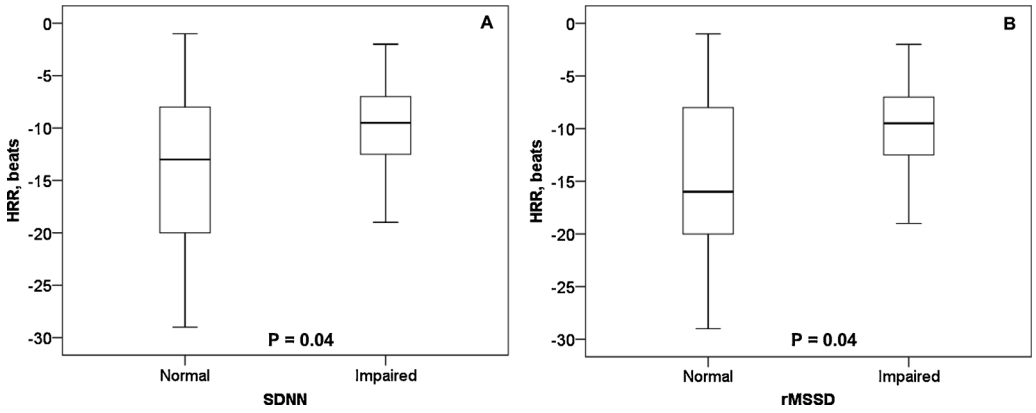

Fig. 3. Differences in HRR between Impaired and Normal HRV (A: SDNN and B: rMSSD).
P-values from independent sample t-tests (equal variances not assumed as determined by Levene's test for equality of variances); horizontal lines inside the boxes represent the median values, ends of boxes upper and lower quartiles, and whiskers highest and lowest observations.
HRR = heart rate recovery; HRV = heart rate variability; SDNN = standard deviation of normal-to-normal R-R intervals; rMSSD = root mean square of successive differences.

vary depending on cardiopulmonary fitness, exertional levels achieved, and changes in HR associated with exercise testing (Pierpont and Voth, 2004), including in cancer survivors (Niederer et al., 2015). Variations in HRR may also be related to chronotropic incompetence (Lauer et al., 1999) which may be present in some participants included. In addition, HRV from 10-s ECGs have increased agreement with the gold-standard 240-300-s tracings when repeated measurements are obtained (up to 3 times) (Munoz et al., 2015); we obtained HRV from single 10-s ECGs which may additionally explain some of the variances between HRR and HRV.

Similar to previous studies, we found HRR to be associated with age, resting and peak HR, exercise capacity, but not with beta-blocker or renin-angiotensin system inhibitor use (Cole et al., 1999; Karjalainen et al., 2014). Like a previously study involving 154 COPD patients (van Gestel et al., 2012), we found no association between HRV and functional capacity; this is in contrast to another study (Karjalainen et al., 2014) which reported a significant independent association between HRV as reflected by SDNN and rMSSD and exercise capacity in 1060 patients with coronary artery disease (CAD) with and without type 2 diabetes (DM). Differences in comorbidities (all/predominantly COPD vs. CAD with/without DM) and sample size may explain these contrasting findings. We found a positive association in TLC and HRV, similar to a previous report involving 30 patients with stable COPD (Corbo et al., 2013). This finding may have important implications in future studies aimed at assessing HRV in the lung cancer population in which COPD is highly prevalent (Islam et al., 2015) and could reflect alterations in vagal and pulmonary stretch receptor activities associated with chronic hyperinflation (Undem and Kollarik, 2005). As well, we found HR to be significantly associated with HRV, potentially due to physiological autonomic nervous system activity and/or the mathematical nonlinear relationship between HR and R−R intervals (Sacha, 2014). Interestingly, a recent review suggests that the removal of the HR impact on HRV may make HRV more predictive of non-cardiac death, while the enhancement of HR on HRV may increase predictive power for cardiac death (Sacha, 2014). Unlike existing literature (Umetani et al., 1998; Tsuji et al., 1996), age was not associated with HRV in multivariable analyses, possibly due to the inclusion of age in TLC *% predicted* which adjusts for age in our models or a small sample size.

Our study also suggests that on average, those with normal HRV have an average HRR of 14- to 16-*beat* decreases which are significantly higher than those with impaired HRV. Previous studies in the cardiovascular and chronic lung disease populations have suggested cutoff ranges of 12- to 18-*beat* decreases in HRR following exercise testing to predict outcomes (Ha et al., 2015). Based on our data, a HRR cutoff of -14 to -16 *beats* or less may indicate attenuated parasympathetic nervous system function in lung cancer survivors eligible for long-term cure, similar to previous studies involving HRR following the 6MWT to predict acute exacerbations in COPD (Rodriguez et al., 2017) and clinical worsening in pulmonary arterial hypertension (Minai et al., 2012) patients. However, our goal was not to draw firm conclusions about autonomic physiology but rather identify useful biomarkers for further study and possibly for easy clinical assessment.

Traditionally, evaluation of exercise performance focuses on muscle and cardiovascular function. The nervous system is often under-recognized despite having important physiological bases: somatic

innervations facilitate voluntary motor control, the sympathetic nervous system activates a "fight-or-flight" response at the beginning of exercise, and parasympathetic system a "rest-and-digest" state in recovery. While HRR is associated with exercise capacity partly due to the nature of the test (exercise is needed to assess recovery), a blunted HRR may be more closely related to physical inactivity than comorbidities according to one study (Karjalainen et al., 2014). Therefore, HRR may reflect another domain of fitness that is useful in the lung cancer population. We previously reported associations between impaired HRR and perioperative cardiopulmonary complications following lung cancer resection surgery (Ha et al., 2015b), and survival in patients undergoing stereotactic body radiotherapy for early-stage lung cancer (Ha et al., 2015a). Others have also reported an association between HRV and survival in cancer patients in a systematic review and meta-analysis (Zhou et al., 2016). Together, these data provide supporting evidence on the importance of these measures in the lung cancer population.

Exercise has been shown to be effective in improving QoL and function in cancer survivors (Buffart et al., 2017). However, the evidence of effectiveness is not as consistent in lung cancer survivors compared to other cancers (Bade et al., 2015), possibly due to unique characteristics in lung cancer as discussed above. Physiological evaluation in lung cancer survivors may help identify patients at risk for clinical worsening who may benefit from additional health services (e.g. rehabilitation and/or exercise programs) to improve health. Physiological measures that are readily available may help identify at-risk individuals, monitor their health changes, and evaluate the effectiveness of health interventions. HRR and HRV from 10-s ECGs are relatively easy to obtain, have been demonstrated to be responsive to exercise training (Bellenger et al., 2016; Snoek et al., 2013), and therefore may have such utility in lung cancer patients. Unlike HRR, HRV can be obtained at rest and therefore is not subjected to variations in patient effort associated with exercise testing. In our study, a higher number of early stage lung cancer survivors who underwent surgical resection had HRV measurements, suggesting that HRV can be readily assessed from routine pre-operative ECGs.

Our study has limitations. First, our small sample size may not be adequately powered to detect significant associations between lung cancer-specific characteristics including stage and treatment modality and these heart rate measures; however a previous analysis of 133 NSCLC patients reported that HRV on 10-s ECGs were lower in stage I-II compared to stage III-IV NSCLC [mean (SD) rMSSD = 15.6 (11.5) vs 20.3 (23.5) *ms*, respectively, p = 0.01] (De Couck and Gidron, 2013), suggesting lung cancer-specific effects. Second, we did include other factors including ratings of perceived exertion (RPE) during the 6MWT which may limit our interpretation of the predictors of HRR; however the change in HR during exercise testing has been shown to correlate very well (correlation coefficient 0.74) with RPE (Scherr et al., 2013) and therefore could be an indirect measure. Third, we did not measure HRV using the gold-standard 240-300-s or longer (e.g. 10-20-min) tracings; however, HRV measures from single 10-s ECGs have been shown to correlate and agree very well with the gold-standard as analyzed by correlation coefficients (r = 0.758 – 0.764 and 0.853 – 0.862 for SDNN and rMSSD, respectively), Bland-Altman 95% limits of agreements (bias = 0.398 – 0.416 and 0.079 – 0.096), and Cohen's d statistics (d = 0.855 – 0.894 and 0.150 – 0.171) (Munoz et al., 2015). In addition, a recent review of HRV in cancer patients identified five studies involving 1396 patients showed that HRV measures from 10-s ECGs are predictive of survival, associated with tumor burden/cancer stage, and low compared to healthy controls (Kloter et al., 2018). As well, HRV from 10-s ECGs has been shown to be predictive of cardiac death in a population of 5272 patients aged ≥ 55 years (de Bruyne et al., 1999) and overall survival in 1175 patients aged ≥ 45 years and free of cardiovascular disease and risk factors included in the Multi-Ethnic Study of Atherosclerosis (O'Neal et al., 2016). Equally important, reference norms and ranges for HRV measures from 10-s ECGs have been proposed for cancer (De Couck and Gidron, 2013) and non-cancer (O'Neal et al., 2016) patient populations. Therefore, HRV measures from 10-s ECG have concurrent, predictive, and discriminant validity. While there is supporting evidence for HRV metrics from ECG including 10-s tracings, we also recognize that temporal analyses for HRV are susceptible to non-stationarities and may be better addressed using techniques such as phase-rectified signal averaging (Campana et al., 2010), which was not performed in our study. Fourth, we did not assess other measures of autonomic function (e.g. baroreflex sensitivity, muscle sympathetic nerve activity, plasma catecholamines) or cardiorespiratory fitness [e.g. maximal oxygen consumption (VO_{2max})] and cannot give insights into its pathophysiological mechanisms in lung cancer survivors due to the descriptive nature of our study and the absence of related clinical outcomes. Fifth, the single-institutional nature involving a predominantly white male veteran population and/or referral and survivor bias may limit the generalizability of our findings.

The strengths of our study include a thorough list of comorbidities and potential confounders relevant in the lung cancer population including tobacco exposure history and lung function. Also, all baseline characteristics were collected and verified by a board-certified physician to maximize accuracy, and all physiological assessments including the HRV, 6MWT, and HRR measurements were performed by one observer, limiting inter-operator variability. In addition, we performed thorough analyses to identify predictors of HRV and HRR that included adjustments for resting supine and upright HR measures, facilitating interpretation of our findings. Last, we detected a moderate correlation/association between HRV and HRR, further providing evidence for their inter-relationship.

In conclusion, we assessed and identified predictors of HRV and HRR in lung cancer survivors eligible for long-term cure. HRV and HRR are interrelated measures, are relatively easy to obtain, and may have diagnostic, predictive, and prognostic value in the lung cancer population. Studies aimed at improving lung cancer survivorship including through rehabilitation and exercise training may consider these measures for stratification and/or as physiological outcomes.

Informed consent

Written informed consent was obtained from all participants included in this study.

Ethical standards

All human studies have been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The contents included in this manuscript were previously made available in a pre-print publication (Ha et al., 2019) and are revised and updated in this current version.

Declaration of Competing Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the

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