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Heart Rate Recovery as a Preoperative Test of Perioperative Complication Risk

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Abstract

The autonomic nervous system plays important physiologic roles in a variety of organ systems. Autonomic dysfunction has been shown to be predictive of increased mortality in patients with cardiovascular disease. Its importance in patients with chronic respiratory disorders has been described in recent years. Here, we summarize the prognostic value of autonomic dysfunction, as reflected by impaired heart rate recovery (HRR), in patients with chronic respiratory disorders, including chronic obstructive pulmonary disease, interstitial lung disease, and lung cancer. We suggest that HRR may be clinically useful in the preoperative physiologic evaluation, specifically in lung cancer patients being considered for surgery.

The preoperative evaluation of surgical candidates includes cardiovascular and pulmonary risk assessments. The autonomic nervous system (ANS) influences both cardiac and pulmonary function. Heart rate recovery (HRR), an indicator of parasympathetic nervous system (PNS) activity, is easily obtained following exercise testing. Here, we review the physiologic function of the ANS, focusing on HRR and its relationship to outcomes of cardiovascular and pulmonary diseases. In doing so, we propose a practical use for HRR evaluation as a metric assessed in the preoperative cardiopulmonary risk assessment of the surgical candidate.

Material and Methods

A qualitative review of the function of the ANS was performed, focusing on the cardiovascular and respiratory systems. To identify studies describing the prognostic implications of HRR, a PubMed search using the medical subject heading term “prognosis” and key words “heart rate recovery” was performed; all abstracts were reviewed, with a focus on respiratory disorders. In addition, to identify studies describing HRR in the preoperative risk assessment, PubMed searches using the key words “heart rate recovery”

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and the medical subject heading term “surgical complications,” or key words “cardiopulmonary complications,” or “surgical complications” were performed (Appendix).

Autonomic Dysfunction and Disease

Relevant to cardiorespiratory physiology, neurons of the sympathetic nervous system (SNS) innervate cardiac myocytes, vascular smooth muscle, and bronchial smooth muscle (Table 1). Activity of the SNS leads to increased heart rate (HR), cardiac conduction and contractility, and bronchodilation. Neurons of the PNS usually oppose the activity of SNS neurons, particularly at sites dually innervated by both the SNS and PNS. Using acetylcholine and norepinephrine as key neurotransmitters, these systems work in a complementary fashion to maintain homeostasis, a principal role for the ANS [1].

The cardiac chronotropic effects of the ANS can be assessed using various measures of HR, such as HRR, commonly defined as the difference between the HR at the end of exercise and at 1 min following cessation of exercise), resting HR, and HR variability (HRV) during inspiration at rest [2, 3].

Autonomic dysfunction (AD) is associated with adverse outcomes in many chronic illnesses. Impaired HRR following exercise testing, for instance, has been found to be associated with all-cause mortality, independent of the severity of coronary artery disease (CAD), in patients undergoing first-time coronary angiography [4]. In hypertensive patients, an elevated resting HR has been associated with higher mortality [3], while decreased HRV has been associated with an increased risk of major cardiac events in elderly patients [5], survivors of myocardial infarction [6], and patients with a reduced ejection fraction [7]. In addition, decreased parasympathetic tone and increased sympathetic tone have been associated with obesity, insulin resistance, diabetes, hypertension, hypercholesterolemia, depression, anxiety, heart failure, and peripheral vascular disease [8].

HRR as an Indicator of Parasympathetic Activity

The HR is controlled by the sinus node, modulated by input from the SNS and PNS. At the onset of exercise, HR increases primarily by parasympathetic withdrawal. As exercise reaches more vigorous levels, sympathetic activation contributes progressively more to help attain and maintain tachycardia [9]. When exercise is stopped, parasympathetic reactivation and sympathetic withdrawal begins. While the relative contribution of parasympathetic and sympathetic activity varies at different stages of recovery, animal [10–12] and human studies [13–15] suggest that parasympathetic activity plays a dominant role in modulating HR in the immediate, 1min period following cessation of exercise. HRR in the first minute, therefore, is considered reflective of parasympathetic tone, while HR and HRV, measured at rest, are reflective of a balance between both sympathetic and parasympathetic tone [2, 3].

Measurement and Interpretation of HRR

HRR can be reported as a continuous variable, divided into quantiles, or as binary variable (normal vs. impaired). In most epidemiologic studies, HRR is reported as the difference between the HR at the end of exercise and HR at 1 or 2 min after stopping exercise [16]. Currently, there is no standardized definition of impaired HRR [16].

Studies on HRR utilize different exercise protocols, most frequently with graded treadmill exercise testing (72% of 74 epidemiologic studies surveyed), followed by cycle ergometry (25%), and other methods (3%) [16] including the 6-min walk test (6MWT). HRR can vary according to the amount of exercise achieved, differences between arm and leg exercise, and supine, sitting, or upright position [16, 17]. The endpoints used for the protocols also vary, and include symptom limited maximum exercise, pre-defined goals (eg, 80% of maximum predicted heart rate), and anaerobic thresholds [16]. Currently, there is no standardized protocol for HRR evaluation. When possible, symptom limited maximal exercise is preferable, as it offers a reproducible endpoint for comparison between subjects.

THE KINETICS OF HRR.—In healthy individuals, the kinetics of HRR following exercise depends of the level of exercise achieved. In 9 healthy volunteers age 24 to 46 years, HRR followed first-order decay following submaximal levels of exercise, but not maximal exercise [18]. In a different study of 6 sedentary young men exercising at submaximal levels, HR decreased monoexponentially during recovery from cycle ergometer exercise at ~ 20%, 40%, and 65% of peak oxygen consumption (VO_{2peak}), with tau values (the time it takes for all but ~ 37% of the HR to return to preexercise levels) of ~14 s, 33 s, and 56 s, respectively [14]. In the first minute, HR decreased ~35 beats, independent of the exercise intensity, thought to be mainly due to the prompt restoration of vagal tone [14].

In individuals with chronic medical illness, HRR appears to follow first-exponential decay, even following maximal exercise. In a study of older-age adults with hypertension, monoexponential modeling was found to be an excellent fit for HRR following symptom limited exercise treadmill testing, with tau values higher in the hypertensive group compared to controls without hypertension (tau, 126 vs. 102 s; $p = 0.047$) [19]. In a different study of 20 patients with chronic HF exercised at anaerobic threshold, the time constants for HRR was described in patients with HF and age-matched normal controls (~ 430 and ~ 180 s, respectively; $p < 0.01$) [13].

Many drugs have effects on HF. β -blocker use is common in candidates undergoing exercise testing. HRR is primarily modulated by the PNS as described previously (particularly if measured within 1 min following the cessation of exercise). β -blocker use, therefore, theoretically would have a minimally effect on HRR. In a diverse group of patients, HRR was unchanged in those whom β -blockers were continued, versus discontinued, or in those without β -blocker use [20]. In addition, HRR was not changed in patients with β -blockade who have normal findings on stress echocardiograms [21]. More importantly, β -blockade use has not been reported to have a significant impact on the relevant outcomes of epidemiologic studies on HRR.

A COMMON DEFINITION OF IMPAIRED HRR.—While curve fitting will likely offer more precise definitions of normal versus impaired HRR, in the clinical setting, the increased complexity and time required for curve fitting, as well as the relative lack of epidemiological validation for the results, make the rapidly and easily obtained binary HRR preferable [16]. In most epidemiologic studies, HRR is reported as the difference between the HR at the end of exercise and HR at 1 or 2 min after stopping exercise (in 83% of 74 surveyed studies) [16].

Impaired HRR has been variably defined as a decrease in HR at 1 min following cessation of exercise of 8 to 17 beats, though it is most commonly defined as 12 or 13 [16].

HRR in Cardiovascular Disease

Much of the literature regarding the prognostic significance of the ANS relies on measures of HRR. In a landmark study, in a cohort of 2,428 patients without a prior history of heart failure, coronary revascularization, or coronary angiography, impaired HRR (defined as a decrease in HR of 12 beats from peak exercise to 1 min into recovery) was found to be associated with a 4-fold risk of death [4]. After adjustment for age, gender, medications, cardiac perfusion defects on thallium scintigraphy, standard cardiac risk factors, resting HR, change in HR with exercise, and workload achieved, there was still a 2-fold risk of death in those with impaired HRR. Impaired HRR also has prognostic value after submaximal exercise. In one study, impaired HRR after submaximal exercise, defined as a decrease of 42 beats from peak HR to that measured 2 min into recovery, was associated with a 2.58-fold higher relative risk of death in a cohort of patients enrolled in a lipid research study; this increased risk remained after adjusting for baseline physical activity, and resting and exercise heart rates [22].

HRR in Respiratory Disease

In the respiratory system, intrathoracic airways receive autonomic innervation from both the SNS and PNS, carried exclusively by the left and right vagus nerves. Parasympathetic ganglionic neurons are found along extrapulmonary and intrapulmonary airways. They are largest and most numerous in the trachea and mainstem bronchi, with progressively diminishing size and quantity in more peripheral airways [23]. The parasympathetic branch of the ANS dominates the innervation of the lower respiratory tract in regulating airway smooth muscle tone, bronchial blood flow, and secretions [23]. In addition, pulmonary arterial tone is partly modulated by sympathetic innervation [24]. Cholinergic and adrenergic, as well as noncholinergic and nonadrenergic neurotransmitters (including nitric oxide) [25], modulated by the ANS, have been described to contribute to vasodilation, increased vascular permeability, and pulmonary inflammation and edema through recruitment and activation of inflammatory cells. Recently, noncholinergic and nonadrenergic neurotransmitters, released by pulmonary nerve fibers, have been shown to also contribute to bronchoconstriction, mucous secretion, and pulmonary vascular tone [26].

Among chronic pulmonary diseases, ANS involvement is most evident in asthma and chronic obstructive pulmonary disease (COPD). The reversible episodic wheezing and chest tightness of asthma is largely a consequence of bronchial narrowing due to the constriction of bronchial smooth muscle, the main regulator of which is the PNS [23]. The effect of beta-adrenergic receptor agonists in reversing airflow obstruction can be mimicked by muscarinic receptor antagonists [27], suggesting that the substance responsible for the majority of the smooth muscle contraction is acetylcholine [23]. In asthmatics with symptoms poorly controlled by inhaled corticosteroids, clinical trials show that the addition of an antimuscarinic drug is as efficacious as a long-acting beta-adrenoreceptor agonist [28]. In patients with COPD, long-acting antimuscarinic agents exert both the predicted effects on

airway smooth muscle tone and mucous secretion, as well as antiinflammatory markers [29, 30].

Much of the literature relating AD and outcomes in chronic respiratory disorders also utilizes measures of HRR. For instance, in a study of 147 patients, those with COPD tended to have lower HRR at 1 min compared to healthy subjects (11 ± 9 beats vs. 20 ± 9 beats; $p < 0.0001$) [31]. Impaired HRR, defined as a 14-beat decrease in HR at 1 min following cardiopulmonary exercise testing, was prevalent in 66% of patients with COPD [31]. In this group of patients, HRR was also an independent predictor of all-cause mortality in multivariable survival analysis (hazard ratio, 5.12; 95% confidence interval [CI], 1.54 to 17.00) [31]. In a large series of patients with idiopathic pulmonary fibrosis (IPF), impaired HRR, defined as a decrease of 13 beats at 1 min following the 6MWT, was found to be associated with a 4.5-fold risk of death (95% CI, 1.5 to 13.7) [32]. In a smaller series of 49 patients with medically inoperable, early-stage lung cancer, we reported an association between impaired HRR, defined as a 12-beat decrease at 1 min following the 6MWT, with all-cause mortality (hazard ratio, 15.8; 95% CI, 1.96 to 128.0) [33]. In addition to its prognostic value, impaired HRR has been predictive of various adverse clinical outcomes in other groups of respiratory diseases. For instance, in a series of patients with pulmonary arterial hypertension, impaired HRR, defined as a <16 beat-decrease at 1 min following the 6MWT, was found to be prognostic of clinical worsening (hazard ratio, 5.2; 95% CI, 1.8 to 14.8) [34]. Impaired HRR has also been shown to be predictive of the severity of apnea in patients with obstructive sleep apnea [35, 36] and functional capacity in long-term survivors of pulmonary embolism [37].

The ANS, therefore, plays an important role in both cardiovascular and respiratory disorders. Impaired HRR is common in a variety of cardiorespiratory conditions, which in recent years, has been shown to have prognostic values for worse survival and outcomes for several chronic pulmonary conditions (Table 2).

Possible Mechanisms for Adverse Cardiopulmonary Outcomes

Investigators have attempted to elucidate the mechanism of the increased risk of death in individuals with impaired HRR. Impaired HRR has been proposed to be associated with underlying ischemic CAD, and therefore potentially acute myocardial infarction [38]. However, in a large prospective study of 2,935 patients, impaired HRR was associated with mortality independent of the severity of CAD seen on angiography [39]. In a 12-year follow up study, impaired HRR was found to be associated with sudden cardiac death, suggesting that cardiac arrhythmias could play an important role [40].

Much of the literature on the impaired physiologic responses of AD comes from studies involving left heart failure [41]. Contributing mechanisms include dysfunction of carotid, aortic, and cardiopulmonary baroreceptors [42]; impaired sensitivity of central and peripheral chemoreceptors [43, 44]; and abnormal response from metaboreceptors located in skeletal muscles [45]. In addition, neurohumoral pathways, mediated by catecholamines released from the adrenal medullae and the reninangiotensin-aldosterone system also contribute [46].

In patients with chronic respiratory disorders, the exact mechanism(s) of how AD leads to adverse outcomes remains speculative. In patients with COPD, AD can lead to increased airway resistance, work of breathing, and muscle wasting [31]. In patients with pulmonary arterial hypertension, impaired HRR could indicate underlying chronotropic incompetence and therefore worsening clinical outcomes [34, 41]. Baroreceptor dysfunction in pulmonary arteries could lead to an imbalance in the baroreflex, leading to worsening pulmonary hypertension and related clinical outcomes. In patients with IPF, hypoxemia could lead to SNS hyperactivity, which is known to increase pulmonary vascular resistance and therefore the development of pulmonary hypertension [24]. In obstructive sleep apnea patients, AD could lead to decreased sensitivity of central and peripheral chemoreceptors (which detect changes in pH, PaO₂, PaCO₂, and regulate ventilation) and therefore worsening apnea-hypopnea indices [36]. In patients with sarcoidosis, small fiber neuropathy could lead to AD, and therefore its clinical manifestations (eg, sudden death, ventricular and atrial arrhythmias, and heart failure) [47]; in those without neuropathy, AD could reflect the degree of impairment of pulmonary [26] and systemic [48] inflammatory responses (eg, increased macrophage activation) and, therefore, disease severity (Table 3).

An overlying possibility is that AD could lead to impairment in gas exchange, resulting in adverse outcomes in chronic lung diseases. Maldistribution of ventilation-perfusion (V_A/Q) ratios has been well established as the underlying basis of pulmonary gas exchange impairment during exercise in patients with asthma, COPD, and interstitial lung disease [49]. In patients with asthma, hypoxemia, when present, is primarily due to areas of lung with low V_A/Q ratios [49]. Patients with COPD have more fixed peripheral airway obstruction and destruction of the pulmonary vascular bed. Therefore, in these patients, hypoxemia during exercise is most associated with an inability to increase alveolar ventilation in line with the increasing cardiac output. Hypoxic hypercapnia in COPD is related to reduced ventilation and increase in alveolar dead space due to a loss of hypoxic vasoconstriction. In patients with interstitial lung disease, V_A/Q inequality is the most important underlying cause of gas exchange impairment, and in patients with IPF, impaired oxygen diffusion across the alveolar-capillary barrier during exercise [49]. Hypoxic vasoconstriction is an important mechanism of gas exchange regulation in patients with pulmonary hypertension. Blood gas changes on exercise therefore, can be explained by different relative increases in oxygen consumption and carbon dioxide elimination, alveolar ventilation, diffusion limitation, and cardiac output [50], all of which can be modulated by the ANS through the chemoreceptors, baroreceptors, and cardiac chronotropic effects as described previously. Other possibilities include excessive mucous production or an inability to clear secretions, leading to mucous impaction in airways of patients with excessive airway secretions.

A Practical Application: Preoperative Cardiopulmonary Evaluation

Traditionally, cardiopulmonary fitness is evaluated with measures of oxygen consumption. During exercise, ventilation, cardiac output, and systemic and pulmonary blood-flow change to meet the metabolic demands of contracting muscles, with the end goal of preserving cellular oxygenation and acid-base homeostasis [51]. Assessment of peak exercise capacity relies on measurement of oxygen uptake (VO_{2peak} , measured in liters per minute), reflecting

the peak or maximal ability to take in, transport, and use oxygen. $\text{VO}_{2\text{peak}}$ has become the gold standard measurement of cardiopulmonary fitness, and is the most important parameter measured during functional exercise testing [51, 52]. A normal $\text{VO}_{2\text{peak}}$ usually excludes significant pulmonary, cardiovascular, and neuromuscular diseases [51, 52].

Along with pulmonary function, $\text{VO}_{2\text{peak}}$ is often measured in the preoperative evaluation of lung cancer patients being considered for major lung resection surgery. In this group of patients, $\text{VO}_{2\text{peak}}$ predicts postoperative cardiopulmonary complications [53, 54] and improves the risk-stratification [55]. In addition, the performance on less technologically involved exercise tests (eg, the distance walked during a shuttle walk test (SWT) and the height climbed during a stair climbing test [SCT]), has been shown to predict postoperative complications [56], and have a linear relationship with $\text{VO}_{2\text{peak}}$ [57]. These measures, therefore, can also be used to risk-stratify patients.

Guideline-based cardiopulmonary physiologic assessment of lung cancer patients currently uses a combination of lung function testing (ie, forced expiratory volume in the first second, diffusion limitation of carbon monoxide (DLCO), their respective predicted postoperative values) and functional assessments (ie, the distance walked on a SWT, the height climbed during a formal SCT, and $\text{VO}_{2\text{peak}}$ during a cardiopulmonary exercise test) to risk-stratify patients undergoing evaluation for lung resection surgery [58–60] (Fig 1). Simple exercise tests (SWT, SCT) are recommended to help risk-stratify patients with impaired lung function and to determine the need to formally measure $\text{VO}_{2\text{peak}}$ [61]. Measures of autonomic function, including HRR, are not included in guidelines for assessment, despite having significant consequences on health as laid out previously. In addition, the recovery phase after exercise, despite the potential to provide insight into the postoperative course, has also been neglected in the literature.

Recently, we evaluated the association between impaired HRR and postoperative cardiopulmonary complications in 96 lung cancer patients undergoing lung resection surgery. Impaired HRR (defined as a 12-beat decrease at 1 min following the 6MWT), present in 32% of patients, was found to be an independent predictor of postoperative cardiopulmonary complications (odds ratio, 4.9; 95% CI, 1.79 to 13.8). This was notable because this group of patients was already highly selected based on traditional measures of cardiopulmonary fitness [62].

In a separate series of 160 patients undergoing noncardiac surgery, HRR at 1 min following preoperative exercise testing was significantly lower in patients who developed intraoperative hypotension compared to those without intraoperative hypotension (22 ± 6 beats vs. 29 ± 5 beats, $p = 0.001$) [63]. HRR was found to be an independent predictor of intraoperative hypotension (odds ratio, 0.82; 95% CI, 0.73 to 0.92) [63]. HRR appears to be able to help identify patients with AD and increased risk of perioperative cardiopulmonary complications with elective surgery.

AD, specifically as reflected by impaired HRR, appears to be a domain of functional assessment, which can provide useful preoperative information over and above currently used tests. The concept has physiologic and clinical merits, as traditional measures of fitness

aim to estimate VO_{2peak} during active exercise (modulated mainly by the SNS), while HRR is measured during the recovery phase of exercise (modulated mainly by the PNS) as outlined previously.

Implications for Future Research

There are several important questions for future research: What is the mechanism of how impaired HRR leads to increased mortality? Does improvement in HRR secondary to exercise training, such as during cardiopulmonary rehabilitation, reduce the risk of postoperative complications? What is the relationship (or lack thereof) between HRR and VO_{2peak} ? Do measures of HRR add to the accuracy of current guideline-based algorithms in predicting perioperative cardiopulmonary complications?

Conclusions

AD, particularly as reflected by impaired HRR, is common in patients with cardiovascular and pulmonary diseases. Measures of HRR are simple to perform, and have both predictive and prognostic values. The usefulness of including impaired HRR in algorithms of physiologic evaluation of patients undergoing elective surgery, such as those with lung cancer being considered for lung resection surgery, should be studied (Fig 1).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviations and Acronyms

AD	autonomic dysfunction
ANS	autonomic nervous system
CAD	coronary artery disease
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CPET	cardiopulmonary exercise testing
HR	heart rate
HRR	heart rate recovery
HRV	heart rate variability
IPF	idiopathic pulmonary fibrosis
PNS	parasympathetic nervous system
SCT	stair climbing test
SNS	sympathetic nervous system

SWT	shuttle walk test
VO_{2peak}	peak oxygen consumption
6MWT	6-min walk test

References

1. McCorry LK. Physiology of the autonomic nervous system. *Am J Pharm Educ* 2007;71:78. [PubMed: 17786266]
2. Lahiri MK, Kannankeril PJ, Goldberger JJ. Assessment of autonomic function in cardiovascular disease: physiological basis and prognostic implications. *J Am Coll Cardiol* 2008;51: 1725–33. [PubMed: 18452777]
3. Lauer MS. Autonomic function and prognosis. *Cleve Clin J Med* 2009;76:S18–22. [PubMed: 19376976]
4. Cole CR, Blackstone EH, Pashkow FJ, Snader CE, Lauer MS. Heart-rate recovery immediately after exercise as a predictor of mortality. *N Engl J Med* 1999;341:1351–7. [PubMed: 10536127]
5. Tsuji H, Larson MG, Venditti FJ Jr, et al. Impact of reduced heart rate variability on risk for cardiac events. The Framingham Heart Study. *Circulation* 1996;94:2850–5. [PubMed: 8941112]
6. La Rovere MT, Bigger JT Jr, Marcus FI, Mortara A, Schwartz PJ. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators. *Lancet* 1998;351:478–84. [PubMed: 9482439]
7. Makikallio TH, Hoiber S, Kober L, et al. Fractal analysis of heart rate dynamics as a predictor of mortality in patients with depressed left ventricular function after acute myocardial infarction. TRACE Investigators. TRAndolapril Cardiac Evaluation. *Am J Cardiol* 1999;83:836–9. [PubMed: 10190395]
8. Curtis BM, O'Keefe JH Jr. Autonomic tone as a cardiovascular risk factor: the dangers of chronic fight or flight. *Mayo Clin Proc* 2002;77:45–54. [PubMed: 11794458]
9. Pierpont GL, Adabag S, Yannopoulos D. Pathophysiology of exercise heart rate recovery: a comprehensive analysis. *Ann Noninvasive Electrocardiol* 2013;18:107–17. [PubMed: 23530480]
10. Warner HR, Cox A. A mathematical model of heart rate control by sympathetic and vagus efferent information. *J Appl Physiol* 1962;17:349–55. [PubMed: 14005012]
11. Levy MN, Zieske H. Autonomic control of cardiac pacemaker activity and atrioventricular transmission. *J Appl Physiol* 1969;27:465–70. [PubMed: 5822553]
12. Brack KE, Coote JH, Ng GA. Interaction between direct sympathetic and vagus nerve stimulation on heart rate in the isolated rabbit heart. *Exp Physiol* 2004;89:128–39. [PubMed: 15109218]
13. Imai K, Sato H, Hori M, et al. Vagally mediated heart rate recovery after exercise is accelerated in athletes but blunted in patients with chronic heart failure. *J Am Coll Cardiol* 1994;24:1529–35. [PubMed: 7930286]
14. Perini R, Orizio C, Comandè A, et al. Plasma norepinephrine and heart rate dynamics during recovery from submaximal exercise in man. *Eur J Appl Physiol Occup Physiol* 1989;58: 879–83. [PubMed: 2767070]
15. Pierpont GL, Voth EJ. Assessing autonomic function by analysis of heart rate recovery from exercise in healthy subjects. *Am J Cardiol* 2004;94:64–8. [PubMed: 15219511]
16. Adabag S, Pierpont GL. Exercise heart rate recovery: analysis of methods and call for standards. *Heart* 2013;99:1711–2. [PubMed: 23591670]
17. Barak OF, Ovcin ZB, Jakovljevic DG, Lozanov-Crvenkovic Z, Brodie DA, Grujic NG. Heart rate recovery after submaximal exercise in four different recovery protocols in male athletes and non-athletes. *J Sports Sci Med* 2011;10:369–75. [PubMed: 24149885]
18. Pierpont GL, Stolpman DR, Gornick CC. Heart rate recovery post-exercise as an index of parasympathetic activity. *J Auton Nerv Syst* 2000;80:169–74. [PubMed: 10785283]

19. Best SA, Bivens TB, Dean Palmer M, et al. Heart rate recovery after maximal exercise is blunted in hypertensive seniors. *J Appl Physiol* (1985) 2014;117:1302–7. [PubMed: 25301897]
20. Maeder MT, Duerring C, Engel RP, Boesch C, Pfisterer ME, Myers J, Muller-Brand J, Zellweger MJ. Predictors of impaired heart rate recovery: a myocardial perfusion SPECT study. *Eur J Cardiovasc Prev Rehabil* 2010;17:303–8. [PubMed: 19940778]
21. Karnik RS, Lewis W, Miles P, Baker L. The effect of betablockade on heart rate recovery following exercise stress echocardiography. *Prev Cardiol* 2008;11:26–8. [PubMed: 18174788]
22. Cole CR, Foody JM, Blackstone EH, Lauer MS. Heart rate recovery after submaximal exercise testing as a predictor of mortality in a cardiovascularly healthy cohort. *Ann Intern Med* 2000;132:552–5. [PubMed: 10744592]
23. Undem BJ, Potenzieri C. Autonomic neural control of intrathoracic airways. *Compr Physiol* 2012;2:1241–67. [PubMed: 23798300]
24. Barnes PJ, Liu SF. Regulation of pulmonary vascular tone. *Pharmacol Rev* 1995;47:87–131. [PubMed: 7784481]
25. van der Velden VH, Hulsman AR. Autonomic innervation of human airways: structure, function, and pathophysiology in asthma. *Neuroimmunomodulation* 1999;6:145–59. [PubMed: 10213912]
26. McGovern AE, Mazzone SB. Neural regulation of inflammation in the airways and lungs. *Auton Neurosci* 2014;182: 95–101. [PubMed: 24411267]
27. Chapman KR. The role of anticholinergic bronchodilators in adult asthma and chronic obstructive pulmonary disease. *Lung* 1990;168:295–303. [PubMed: 2143551]
28. Peters SP, Kunselman SJ, Icitovic N, et al. National Heart, Lung, and Blood Institute Asthma Clinical Research Network. Tiotropium bromide step-up therapy for adults with uncontrolled asthma. *N Engl J Med* 2010;363:1715–26. [PubMed: 20979471]
29. Buels KS, Fryer AD. Muscarinic receptor antagonists: effects on pulmonary function. *Handb Exp Pharmacol* 2012;(208): 317–41.
30. Wollin L, Pieper MP. Tiotropium bromide exerts anti-inflammatory activity in a cigarette smoke mouse model of COPD. *Pulm Pharmacol Ther* 2010;23:345–54. [PubMed: 20362689]
31. Lacasse M, Maltais F, Poirier P, et al. Post-exercise heart rate recovery and mortality in chronic obstructive pulmonary disease. *Respir Med* 2005;99:877–86. [PubMed: 15939250]
32. Swigris JJ, Swick J, Wamboldt FS, et al. Heart rate recovery after 6-min walk test predicts survival in patients with idiopathic pulmonary fibrosis. *Chest* 2009;136:841–8. [PubMed: 19395579]
33. Ha D, Stephens K, Choi H, et al. Heart rate recovery and survival in patients undergoing stereotactic body radiotherapy for treatment of early-stage lung cancer. *JRSBRT* 2015;3:193–201. [PubMed: 29296402]
34. Minai OA, Gudavalli R, Mummadi S, Liu X, McCarthy K, Dweik RA. Heart rate recovery predicts clinical worsening in patients with pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2012;185:400–8. [PubMed: 22108205]
35. Cholidou KG, Manali ED, Kapsimalis F, et al. Heart rate recovery post 6-minute walking test in obstructive sleep apnea: cycle ergometry versus 6-minute walking test in OSA patients. *Clin Res Cardiol* 2014;103:805–15. [PubMed: 24820928]
36. Maeder MT, Munzer T, Rickli H, et al. Association between heart rate recovery and severity of obstructive sleep apnea syndrome. *Sleep Med* 2008;9:753–61. [PubMed: 17980656]
37. Chow V, Ng AC, Seccombe L, et al. Impaired 6-min walk test, heart rate recovery and cardiac function post pulmonary embolism in long-term survivors. *Respir Med* 2014;108: 1556–65. [PubMed: 25154698]
38. Georgoulas P, Orfanakis A, Demakopoulos N, et al. Abnormal heart rate recovery immediately after treadmill testing: correlation with clinical, exercise testing, and myocardial perfusion parameters. *J Nucl Cardiol* 2003;10: 498–505. [PubMed: 14569243]
39. Vivekananthan DP, Blackstone EH, Pothier CE, Lauer MS. Heart rate recovery after exercise is a predictor of mortality, independent of the angiographic severity of coronary disease. *J Am Coll Cardiol* 2003;42:831–8. [PubMed: 12957428]
40. Jouven X, Empana JP, Schwartz PJ, Desnos M, Courbon D, Ducimetiere P. Heart-rate profile during exercise as a predictor of sudden death. *N Engl J Med* 2005;352:1951–8. [PubMed: 15888695]

41. Ciarka A, Doan V, Velez-Roa S, Naeije R, van de Borne P. Prognostic significance of sympathetic nervous system activation in pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2010;181:1269–75. [PubMed: 20194810]
42. Grassi G, Seravalle G, Cattaneo BM, et al. Sympathetic activation and loss of reflex sympathetic control in mild congestive heart failure. *Circulation* 1995;92:3206–11. [PubMed: 7586305]
43. Narkiewicz K, Pesek CA, van de Borne PJ, Kato M, Somers VK. Enhanced sympathetic and ventilatory responses to central chemoreflex activation in heart failure. *Circulation* 1999;100:262–7. [PubMed: 10411850]
44. Ponikowski P, Chua TP, Piepoli M, et al. Augmented peripheral chemosensitivity as a potential input to baroreflex impairment and autonomic imbalance in chronic heart failure. *Circulation* 1997;96:2586–94. [PubMed: 9355898]
45. Notarius CF, Atchison DJ, Floras JS. Impact of heart failure and exercise capacity on sympathetic response to handgrip exercise. *Am J Physiol Heart Circ Physiol* 2001;280:H969–76. [PubMed: 11179037]
46. Thomas GD. Neural control of the circulation. *Adv Physiol Educ* 2011;35:28–32. [PubMed: 21385998]
47. Hoitsma E, Marziniak M, Faber CG, et al. Small fibre neuropathy in sarcoidosis. *Lancet* 2002;359:2085–6. [PubMed: 12086764]
48. Janig W Sympathetic nervous system and inflammation: a conceptual view. *Auton Neurosci* 2014;182:4–14. [PubMed: 24525016]
49. Young IH, Bye PT. Gas exchange in disease: asthma, chronic obstructive pulmonary disease, cystic fibrosis, and interstitial lung disease. *Compr Physiol* 2011;1:663–97. [PubMed: 23737199]
50. Wagner PD. Ventilation-perfusion matching during exercise. *Chest* 1992;101:192–198S.
51. Arena R, Sietsema KE. Cardiopulmonary exercise testing in the clinical evaluation of patients with heart and lung disease. *Circulation* 2011;123:668–80. [PubMed: 21321183]
52. Fishman RS, Systrom DM. Preoperative cardiopulmonary exercise testing: determining the limit to exercise and predicting outcome after thoracotomy. *J Cardiothorac Vasc Anesth* 1991;5:614–26. [PubMed: 1768827]
53. Loewen GM, Watson D, Kohman L, et al., Cancer and Leukemia Group B. Preoperative exercise Vo₂ measurement for lung resection candidates: results of Cancer and Leukemia Group B Protocol 9238. *J Thorac Oncol* 2007;2:619–25. [PubMed: 17607117]
54. Benzo R, Kelley GA, Recchi L, Hofman A, Sciruba F. Complications of lung resection and exercise capacity: a meta-analysis. *Respir Med* 2007;101:1790–7. [PubMed: 17408941]
55. Brunelli A, Belardinelli R, Refai M, et al. Peak oxygen consumption during cardiopulmonary exercise test improves risk stratification in candidates to major lung resection. *Chest* 2009;135:1260–7. [PubMed: 19029436]
56. Brunelli A, Refai M, Xiume F, et al. Performance at symptom-limited stair-climbing test is associated with increased cardiopulmonary complications, mortality, and costs after major lung resection. *Ann Thorac Surg* 2008;86:240–7; discussion 247–8. [PubMed: 18573431]
57. Win T, Jackson A, Groves AM, Sharples LD, Charman SC, Laroche CM. Comparison of shuttle walk with measured peak oxygen consumption in patients with operable lung cancer. *Thorax* 2006;61:57–60. [PubMed: 16244091]
58. Brunelli A, Charloux A, Bolliger CT, et al. European Respiratory Society and European Society of Thoracic Surgeons joint task force on fitness for radical therapy. ERS/ESTS clinical guidelines on fitness for radical therapy in lung cancer patients (surgery and chemo-radiotherapy). *Eur Respir J* 2009;34:17–41. [PubMed: 19567600]
59. Howington JA, Blum MG, Chang AC, Balekian AA, Murthy SC. Treatment of stage I and II non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013;143: e278–313S.
60. Lim E, Baldwin D, Beckles M, et al., British Thoracic Society, Society for Cardiothoracic Surgery in Great Britain and Ireland. Guidelines on the radical management of patients with lung cancer. *Thorax* 2010;65(Suppl 3):iii1–27. [PubMed: 20940263]
61. Brunelli A, Kim AW, Berger KI, Addrizzo-Harris DJ. Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: diagnosis and management of lung cancer,

- 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143:e166S–90S. [PubMed: 23649437]
62. Ha D, Choi H, Zell K, et al. Association of impaired heart rate recovery with cardiopulmonary complications after lung cancer resection surgery. J Thorac Cardiovasc Surg 2014;149: 1168–73.e3. [PubMed: 25583106]
63. Kose EA, Kabul HK, Yildirim V, Tulmac M. Preoperative exercise heart rate recovery predicts intraoperative hypotension in patients undergoing noncardiac surgery. J Clin Anesth 2012;24:471–6. [PubMed: 22986319]
64. Swigris JJ, Olson AL, Shlobin OA, Ahmad S, Brown KK, Nathan SD. Heart rate recovery after six-minute walk test predicts pulmonary hypertension in patients with idiopathic pulmonary fibrosis. Respirology 2011;16:439–45. [PubMed: 20946337]
65. Maeder MT, Ammann P, Schoch OD, et al. Determinants of postexercise heart rate recovery in patients with the obstructive sleep apnea syndrome. Chest 2010;137:310–7. [PubMed: 19837829]
66. Ardic I, Kaya MG, Yarlioglues M, et al. Impaired heart rate recovery index in patients with sarcoidosis. Chest 2011;139: 60–8. [PubMed: 20595456]

Fig 1.

Potential addition of HRR to the physiologic evaluation of lung cancer patients worthy of further study. (CPET = cardiopulmonary exercise testing; HRR = heart rate recovery; ppoDL_{CO} = predicted postoperative DL_{CO}; ppoFEV₁ = predicted postoperative FEV₁; SCT = stair climbing test; SWT = shuttle walk test; VO_{2max} = maximal oxygen consumption; 6MWT = 6-min walk test.)

Table 1.

Physiologic Autonomic Nervous System Function [1, 48]

Organ	Target Cells/Tissue	Receptor	SNS Function	PNS Function
Heart	Cardiac muscle	β_1 β_2	↑ Heart rate ↑ Contraction ↑ Conduction	↓ Heart rate ↓ Conduction
Arterioles (skin, abdominal viscera, kidneys)	Smooth muscle Skeletal muscle	α_1 α_1, β_2	Vasoconstriction Vasoconstriction	N/A N/A
Lungs	Airway smooth muscle Glands	β_2 α_1, β_2	Bronchodilation ↓ Secretions	Bronchoconstriction ↑ Secretions
Gastrointestinal tract	Stomach and intestinal smooth muscles Secretory cells/glands Sphincters	α_1, β_2 α_1	↓ Motility Contraction	↑ Motility ↑ Secretion Relaxation
Pancreas	Exocrine Islets β cells	α α	↓ Digestive enzymes ↓ Insulin	↑ Digestive enzymes ↑ Insulin
Liver	Hepatocytes	α_1, β_2	Glycogenolysis Gluconeogenesis	N/A
Kidneys	Juxtaglomerular apparatus	β_1	↑ Renin	N/A
Adrenal glands	Adrenal medullae	Nicotinic	↑ Epinephrine ↑ Norepinephrine	N/A
Urinary bladder	Detrusor muscle Urethral sphincter	β_2	Relaxation Contraction	Contraction Relaxation
Lymphoid organs	Inflammatory cells	Adrenergic receptors	↑ Inflammatory markers	N/A

PNS = parasympathetic nervous system; SNS = sympathetic nervous system.

Table 2.

HRR and Outcomes in Pulmonary Disorders

Patient Population	Number of Patients	Definition of Impaired HRR (beats) ^a	Method of Exercise	Prevalence of Impaired HRR	Outcomes	Hazard Ratio (95% Confidence Interval, <i>p</i> Value)
COPD [31]	147	14	CPET	66%	All-cause mortality	5.12 (1.54–17.00, <i>p</i> = 0.008)
IPF [32]	76	13	6MWT	38%	All-cause mortality	4.5 (1.5–13.7, <i>p</i> = 0.008)
IPF [64]	160	13	6MWT	30%	Development of pulmonary hypertension	4.0 (1.17–13.69, <i>p</i> = 0.02)
Medically inoperable early-stage lung cancer [33]	49	12	6MWT	65%	All-cause mortality	15.8 (1.96–128.0, <i>p</i> = 0.01)
Obstructive sleep apnea [35, 36, 65] ^b	63, 54, 74	N/A	CPET	N/A	Apnea-hypopnea index	Inverse relationship
Pulmonary arterial hypertension [34]	75	<16	6MWT	40%	Clinical worsening	5.2 (1.8–14.8, <i>p</i> = 0.002)
Pulmonary embolism long-term survivors [37] ^b	104	N/A <16	6MWT	N/A 30%	Abnormal (<85% pred) vs. normal 6MWD Charlson comorbidity index 0 vs 1	18 ± 13 vs. 28 ± 13, <i>p</i> = 0.002 29 ± 14 vs. 22 ± 12, <i>p</i> = 0.014
Sarcoidosis [66] ^b	56	N/A	ETT	N/A	Healthy age-matched controls Scadding stage	25 ± 6 vs. 34 ± 11, <i>p</i> < 0.001 Stage 0: II, 31 ± 6 vs. 25 ± 4, <i>p</i> = 0.01 Stage 0: III, 31 ± 6 vs. IV, 18 ± 7, <i>p</i> < 0.001
Surgery, noncardiac [63]	157	23	ETT	N/A	Intraoperative hypotension	0.82 (0.72–0.92, <i>p</i> = 0.001)
Lung cancer resection [62]	96	12	6MWT	32%	Cardiopulmonary complications	4.97 (1.79–13.8, <i>p</i> = 0.002)

^aDefined as the difference in heart rate at the end of exercise and at 1 min following cessation of exercise.^bHRR analyzed as a continuous variable.

COPD = chronic obstructive lung disease; CPET = cardiopulmonary exercise testing; ETT = exercise treadmill test; HRR = heart rate recovery; IPF = idiopathic pulmonary fibrosis; 6MWT = 6-min walk test.

Table 3.
Possible Mechanisms for the Association of Autonomic Dysfunction and Adverse Outcomes in Respiratory Disorders

Respiratory Disorder	Adverse Clinical Outcome	Possible Mechanisms
Idiopathic pulmonary fibrosis	Development of pulmonary hypertension, all-cause mortality	Hypoxemia SNS hyperactivity leading to increased pulmonary vascular resistance
Obstructive lung disease (asthma, chronic obstructive pulmonary disease)	All-cause mortality	Decreased sensitivity of central and peripheral chemoreceptors, leading to respiratory failure Increased-airway resistance, work of breathing, muscle wasting
Obstructive sleep apnea	Apnea-hypopnea index	Decreased sensitivity of central and peripheral chemoreceptors
Pulmonary vascular disease (pulmonary arterial hypertension, pulmonary embolism survivors)	Worsening clinical outcomes, decreased functional capacity	Chronotropic incompetence SNS hyperactivity
Sarcoidosis	Severity of disease	Impaired pulmonary and systemic inflammatory responses
Thoracic surgery	Cardiopulmonary complications, intraoperative hypotension	Chronotropic incompetence Decreased sensitivity of chemoreceptors and baroreceptors SNS hyperactivity

SNS = sympathetic nervous system.