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The Prognostic Role of Heart Rate Recovery after Exercise in Health and Disease

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Abstract

Autonomic nervous system abnormalities are strongly related to increased cardiovascular morbidity and mortality in both healthy and diseased populations. Stress exercise electrocardiogram is a valid diagnostic and prognostic tool for cardiovascular disease. It has been also demonstrated that heart rate profile during and after exercise reflects cardiac sympathetic and parasympathetic activation, which can be significantly affected in several diseases. More specifically, heart rate recovery after exercise is a valid index of parasympathetic function and a strong predictor of cardiovascular mortality. In this chapter, the prognostic role of heart rate recovery in general population and in cardiovascular disease will be discussed.

Introduction

Abnormalities of autonomic function are significantly related with major cardiovascular adverse events. As a result, numerous markers/indices of autonomic activity are used in everyday clinical practice in order to identify patients at high risk for sudden cardiac death [1-3]. Exercise stress test represents a diagnostic and prognostic tool that is widely used for evaluating cardiovascular function. It is also known that the response of acute exercise depends on the Autonomous Nervous System (ANS) activity with increased sympathetic and decreased parasympathetic activity during incremental exercise and combination of sympathetic withdrawal and parasympathetic reactivation at the recovery period after maximal exercise. Heart Rate Recovery (HRR) after maximal exercise, is one of the most commonly and easily used parameter that reflects autonomic activity and predicts cardiovascular events and mortality not only in disorders of the cardiovascular system, but also in other systemic disorders [1-3].

In this chapter, we focus on the definition, pathophysiology, clinical applications and the prognostic importance of heart rate recovery after exercise in various clinical settings in different healthy and diseased populations. The usefulness of this objective index for risk stratification in different populations of patients and its possible role in monitoring directed medical treatment will be also discussed.

Exercise, Heart Rate and Autonomic Nervous System

Heart Rate reflects the dynamic balance between sympathetic and parasympathetic autonomic nervous system. Parasympathetic activation retards HR via acetylcholine release from efferent vagal nerve discharge. In contrast, sympathetic activation accelerates HR via circulating epinephrine, neural release of nor epinephrine or both [4]. The intrinsic rate of sinoatrial node is 100 beats per minute (bpm) and is regulated by the pacemaker current, which establishes the slope of spontaneous diastolic depolarization. [5,6]. However the normal range is lower and oscillates from 60 to 80 bpm due to the predominant influence of parasympathetic nervous system efferent vagus nerve. The intrinsic rate decreases with increasing age [7]. The extrinsic regulation of sinoatrial node in response to physical, mental activity and sleep states [8] is also achieved by a tonic activity of both limbs of autonomic nervous system and hormones and the reflex regulation is associated with cardio respiratory and baroreceptor inputs.

During exercise, the activity of sympathetic system increases while parasympathetic activity decreases. As a result of this vagal withdrawal and adrenergic discharge, heart rate, cardiac contractility, alveolar ventilation and venous return increase during exercise which is vital for the adjustment of a subject's cardiac output to metabolic demands [9]. As exercise proceeds, sympathetic activation and catecholamine release reach at maximum level, resulting to vasoconstriction of circulatory system except for exercising muscles, as well as coronary and cerebral circulation [9]. During exercise, parasympathetic activities continue to modulate HR in a minor but significant way, as a consequence of myocardial perfusion occurring mainly at diastolic interval [10]. Heart rate recovery index represents the rate of decline in HR after the cessation of exercise test and is defined as the HR difference between maximal HR on exercise and HR during recovery phase. HRR measurement utilizes dynamic protocols, such as arm ergometry, bicycle ergometry and treadmill protocols. Although Bruce protocol is the most used protocol of treadmill, Naught on protocol is more suitable for debilitated patients or for those with limited exercise tolerance [11].

Concerning the recovery phase, HR returns to the pre-exercise rate after several minutes to hours, however the maximum reduction occurs at the first few minutes. HRR indices are calculated by subtracting first, second and third minute HRs from the maximal HR obtained during stress testing (HRR1, HRR2 and HRR3 respectively). Activity (e.g., complete cessation of exercise or cool-down) and position (supine, sitting or standing) influence heart rate recovery. HRR ≤12 bpm at 1st minute for upright position, ≤18 bpm at 1st minute for supine position and ≤ 22 bpm at 2 minutes for sitting position are considered abnormal [12]. Heart rate recovery after exercise represents the changes in autonomic tone that occur immediately after the cessation of exercise. There is increasing

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evidence that the recovery phase after exercise is a vulnerable phase for various cardiovascular events and this also seems to have prognostic significance. Autonomic evaluation during exercise and recovery may be prognostically important, because these are «high-risk periods» for sudden cardiac death, and autonomic changes that occur during exercise could modulate this high risk [1,12,3].

Prognostic and Clinical Data of Heart Rate Recovery

Heart rate recovery has been used in different populations as shown in (Table 1).

The prognostic role of HRR in these populations is analyzed below:

Sudden Cardiac Death and Apparently Healthy Subjects: Sudden and unexpected death of cardiac causes is an important health burden in western world. Its effect is accentuated by the fact that sudden death appears as the first manifestation of cardiovascular disease. Thus, identification of apparently normal people who actually are at high-than-average risk for sudden death is a major challenge. In a study of 5713 asymptomatic working men (between 42 to 53 years old), none of whom had clinically detectable cardiovascular disease, underwent a standardized graded exercise testing between 1967 and 1972. During a 23-year follow-up period, 81 subjects died suddenly. The risk of sudden death due to myocardial infarction was increased in subjects with a decrease in heart rate of less than 25 beats per minute after the termination of exercise [3]. In another pioneer study, myocardial ischemia was induced by a 2-min occlusion of the left circumflex artery during the last minute of exercise in mongrel dogs with myocardial infarction (105 dogs). Ventricular Fibrillation (VF) was induced in 66 animals (susceptible), whereas the remaining 39 dogs had no arrhythmias (resistant). This study showed that animals with higher HRR resulted from exercise of the previous day, were resistant to VF and demonstrated a specific relationship between heart rate recovery and a confirmed increased risk for VF [13].

Heart Failure

Neurohormonal activation and alterations in autonomic control are both compensatory mechanisms that provide valuable support to the heart to maintain circulatory homeostasis at the early stages of heart failure, despite the fact that the sustained and chronic neurohumoral hyperactivity activation plays a central role in the pathogenesis of chronic heart failure and is an important predictor of clinical outcomes among such patients. Adaptations of the autonomic nervous system, including excess sympathetic activity and concomitant sympathetic withdrawal, are among the main manifestations of this maladaptive neuroendocrine imbalance.

Heart failure patients with reduced ejection fraction

In a study conducted by our institute, ninety-two stable CHF patients performed an incremental symptom-limited cardiopulmonary exercise testing. HRR1 was lower in non-survivors (11.4+/-6.4 vs. 20.4+/-8.1; p<0.001). All cause-mortality rate was 65% in patients with HRR1<or=12 bpm versus 11% in patients with HRR1>12 bpm. Early heart rate recovery was an independent prognostic risk indicator in CHF patients and could be used in CHF risk stratification [14]. Sheppard et al., studied 78 HF patients and found that HRR was decreased and was correlated with known prognostic markers. Patients with a HRR<24 beats/min, 90 sec after maximum exercise were more likely to have a HF hospitalization [15]. In a prospective study among 202 subjects with chronic heart failure that were referred for maximal exercise testing, heart rate recovery was measured one minute after the cessation of exercise. Subjects at the lowest risk tertile based on post-exercise HRR (≥30 beats/min) had low risk for cardiac events irrespective of the risk predicted by the survival scores [16]. Another study among 1167 patients with heart failure, it was demonstrated that HRR <16 beats per minute was an independent predictor of mortality [17]. Noteworthy, an earlier study of the same group, demonstrated that HRR < 17bpm predicted sudden cardiac death in heart failure [18]. In a retrospective study, 712 patients underwent a CPET with an active recovery phase. They were followed up for all-cause mortality (5.9 ± 3.3 years follow-up). Groups were identified according to HRR: group-1 (HRR ≤ 4 bpm), group-2 (5 ≤ HRR ≤ 9 bpm), and group-3 (HRR ≥10). Kaplan–Meier analysis estimated survival of 91, 64, and 43% (group-1); 94, 76, and 63% (group-2); and 92, 82, and 70% (group-3) at 1, 5, and 10 years, respectively [19]. Furthermore, HF patients that presented a normal HRR at 2 minutes had a better survival compared to patients with an abnormal HRR at 2 minutes after adjustment for age and beta-blocker use [20]. A large cohort of 5438 patients with HF was followed up for/more than 3 years and found that HRR ≤18 bpm at 1st min after exercise was predictive for all-cause mortality independent of the LV Ejection Fraction (EF) [21].

Another study among 136 HF patients showed that HRR at the 3rd minute after the peak of the exercise was an independent predictor of mortality [22]. Finally, in a recent study of our institute, autonomic nervous system abnormalities expressed by HR profile during exercise in CHF patients were associated to peripheral skeletal muscle abnormalities [23].

Heart failure patients with preserved ejection fraction

Approximately 50% of patients who present clinical features of heart failure are found to have normal left ventricular ejection fraction (LVEF) and normal valvular function. The term heart failure with preserved LVEF (HFpEF) is applied to these patients. Typically, they are elderly women who frequently have associated hypertension, diabetes, and/or coronary artery disease. They have similar hospital length of stay, admission rates, and mortality rate to those patients with systolic heart failure. The prevalence of HFpEF seems to be increased, and in contrast to systolic heart failure the mortality rate of this disorder is not declined. In one recent study HRR<12 beats per minute was attenuated in HFpEF in relation to healthy subjects [24]. In 2.826 patients with normal wall motion responses to symptom-limited exercise testing, indices of abnormal diastolic function were also well correlated with abnormal HRR [25].

Coronary Artery Disease

Exercise testing is used in clinical practice in order to detect the presence of Coronary Artery Disease (CAD) through evaluation of ST segment abnormalities, angina or abnormal blood pressure response to exercise. Another important index of exercise testing with important prognostic impact on this population is HRR. A significant study showed that when HRR decreases to less than 10/min to 12/min, risk of death increases markedly [26]. Among patients who underwent an exercise stress testing and who had a coronary

Table 1: List of Clinical conditions investigated in association with Heart Rate Recovery.

1. **Sudden Cardiac death**
2. **Heart failure patients**
   - *Heart failure patients with reduced ejection fraction*
   - *Heart failure patients with preserved ejection fraction*
1. **Coronary Artery Disease**
2. **Atrial fibrillation**
3. **COPD**
4. **Obstructive sleep apnea (OSA)**
5. **Pulmonary arterial hypertension**
6. **Idiopathic pulmonary fibrosis (IPF)**
7. **Autoimmune disorders**
   - *Systemic lupus erythematosus (SLE)*
   - *Ankylosing spondylitis (AS)*
   - *Sarcoidosis*
   - *Fibromyalgia (FM)*
   - *Familial Mediterranean Fever (FMF)*
   - *Behçet's disease*
1. **Renal disease**
2. **Thyroid disorders**
3. **Arterial Hypertension**
4. **Diabetes**
5. **Metabolic syndrome**
6. **Cancer**
7. **Elderly**
8. **Physical activity**
9. **Depression**
10. **Medical treatments and interventions**
    - *Left ventricle assist device (LVAD)*
    - *Cardiac resynchronization therapy (CRT)*
    - *Resistance exercise training*
    - *Renal sympathetic denervation*
    - *Cardiac rehabilitation (CR)*
    - *Continuous positive airway pressure (CPAP)*
    - *Weight loss*
    - *Medical treatment*

angiography within 90 days, an attenuated HRR after exercise predicted mortality. Mortality risk of abnormal HRR was comparable to angiographic ally confirmed severe CAD and abnormal HRR provided additive prognostic information to the angiographic severity of CAD [27]. Another study of 208 patients showed that abnormal HRR is related to the extent and severity of coronary artery disease, the calculated risk score for the exercise test, and smoking. After adjusting for confounders, abnormal HRR was independently associated with extensive CAD. These results suggest that abnormal HRR alone noted at stress ECG testing may have an independent value in predicting the extent of underlying CAD [28]. A study of 509 subjects showed that abnormal HRR of exercise treadmill testing was associated with a high prevalence of abnormal and high-risk stress Myocardial Perfusion Imaging (MPI) findings, even in patients without other exercise treadmill testing findings that would traditionally prompt further testing. These findings suggested that further testing with stress MPI should be taken into consideration in patients with abnormal HRR at routine exercise treadmill testing [29]. In another study, slower HRR in young adulthood was not associated with the presence of Coronary Artery Calcium (CAC) when assessed 15 years later in middle aged (average age 40 years) [30]. However, HRR at 3 minutes independently predicted long-term follow-up (14.7 years) all-cause and CV mortality in 4097 patients with stable CAD. The authors suggested that measurement of HRR for 3 minutes during passive recovery could be used as a complementary tool to identify patients with a higher total and CV risk [31]. Additionally, in an indian study of 390 positive patients for CAD, demonstrated that the abnormal HRR after exercise is an adverse prognostic indicator for patients with symptomatic CAD on long term follow-up [32].

Atrial Fibrillation

Atrial Fibrillation (AF) is a rapidly evolving epidemic, representing a multi-factorial, dynamic disorder with different underlying substrates, serious health consequences and economic burden of health care systems of western world. Aging of population and increased incidence of risk factors were responsible for the increase of AF in the past decades. It is also well-known that AF is independently associated with increased morbidity and mortality, mainly due to an increased incidence of thromboembolic events. Although its etiology is multi-factorial, prior studies have demonstrated that autonomic dysfunction in general, and decreased parasympathetic function in particular, may play a significant role in its development [33]. In a prospective cohort study, Maddox found that patients with an impaired HRR on Exercise Testing (ET) were more likely to experience new-onset AF than patients without impaired HRR, independently of demographic and clinical factors. It was also demonstrated a trend between increasing severity of HRR and new-onset AF, and that adjustment for ACEI, beta-blocker, or statin use did not alter the primary association. This information provides further clinical support to prior studies, demonstrating associations between autonomic dysfunction and AF, and identifies ET as an additional tool to explore this relationship [34].

COPD

Chronic Obstructive Pulmonary Disease (COPD) is a chronic life-threatening lung disease characterized by chronic obstruction of lung airflow that interferes with normal breathing and is not fully reversible. Chick et al., showed that in patients with COPD, post exercise relative hyperpnea, hyper metabolism and tachycardia were significantly prolonged [35]. In a study of 627 patients with COPD, it was demostrated that spirometric abnormalities were associated with abnormal HRR, which may reflect an altered autonomic tone associated with pulmonary dysfunction, either obstructive or restrictive in nature [36]. Lacasse et al., showed that HRR in 147 COPD patients was attenuated in contrast to healthy people and a cut-off of abnormal HRR1 (≤14 beats) was a strong predictor of mortality in COPD patients [37]. In another interesting study, heart failure patients with and without concomitant chronic obstructive pulmonary disease were well matched, had impaired CPX responses and HRR1 was slower in patients with both HF and COPD (12.1 ± 2.5 vs 14.2 ± 2.9 bpm, $P < .001$) [38].

Obstructive Sleep Apnea (OSA)

Obstructive Sleep Apnea (OSA) is characterized by repetitive night-time obstructions of the upper airway that induce hypoxemia, hypercapnia, sympathetic activation, and arousals. This disorder induces cardiovascular autonomic imbalance and contributes to the increase of hypertension, to HF and death. In a study, the severity of OSAS was expressed by a higher Apnea-Hypopnea Index [AHI] and was independently associated with lower HRR-1 [39]. The same authors showed that HRR may provide extra information on the evaluation of the severity of OSA [40]. Our institute also confirmed that the HRR and VO2 recovery kinetics were impaired in patients suffering from OSA, and that the magnitude of this impairment is

correlated with disease severity [41]. Blunted HRR was shown in 30 middle-aged men with severe OSA, and it was significantly associated with high hs-CRP levels [42].

Pulmonary Arterial Hypertension (PAH)

Pulmonary Arterial Hypertension (PAH) is a rare, under diagnosed condition that is defined as an elevation of mean pulmonary arterial pressure. In patients with PAH, the average pulmonary arterial pressure is greater than 25 mm Hg at rest or 30 mm Hg during physical activity, as measured by right heart catheterization. The prevalence of PAH varies among specific populations, but one study estimated that it affects 15 in 1 million adults. Just recently it was demonstrated that autonomic nervous system abnormalities occur in PAH and may play a significant clinical and prognostic role. In a study held in our institute it was shown that HRR1 was markedly attenuated in patients with PAH in relation to healthy subjects (10+/-5 vs 29+/-6, beats/min, $P < 0.001$) and correlated well with peak oxygen uptake (VO2 peak), ($r=0.85$; $P < .001$), indicating profound autonomic nervous system abnormalities [43]. In a more recent study, during 6Min Walking Distance (6MWD) test, patients with HRR1 ≥ 16 were more likely to have clinical aggravation and shorter time to first clinical aggravating event during follow-up than those with HRR1<16bpm [44]. In another recent larger study among 72 patients, preserved HRR1 (>18 beats) was associated with less impaired responses to incremental exercise in patients with PAH [45].

Idiopathic Pulmonary Fibrosis (IPF)

Idiopathic Pulmonary Fibrosis (IPF) is a severe, progressive, fibro sing interstitial lung disease without effective therapy and a poor prognosis. Median survival times have been found as low as 2.5 years. Abnormal HRR after 6MWD test predicts mortality in 76 IPF patients and the cut-off values were 13 beats for abnormal HRR1 and 22 beats for HRR2 [46]. In another study of 160 patients of the same group, abnormal HRR1 was a predictor of mortality and HRR1 appeared to be the strongest predictor of Right Heart Catheterization Pulmonary Hypertension confirmed in IPF [47].

Autoimmune Disorders

Systemic lupus erythematosus (SLE)

Systemic Lupus Erythematosus (SLE) is an autoimmune disorder that results to multisystemic inflammatory damage and affects multiple organ systems, including the skin, joints, kidneys, heart, and the nervous system. It is reported that Cardio Vascular Diseases (CVD) are responsible for 20%-30% of deaths in patients with SLE. In a case-control study, a treadmill cardio respiratory test was performed in 22 women with SLE and in 20 controls. This study showed lower HRR1 (22.1 ± 2.5 vs. 32.4 ± 2.2, bpm, $p = 0.004$) and HRR2 (39.1 ± 2.9 vs. 50.8 ± 2.5, $p = 0.001$) than HRR of healthy subjects respectively [48]. In another study of 48 patients with SLE (35 women, mean age 46.3 ± 12.8 yrs) and 44 healthy controls significant differences were found in HRR1 and HRR2 between patients with SLE and control group (24.1 ± 6.5 vs 33.3 ± 9.3, bpm; $p < 0.001$, and 44.6 ± 13.3 vs 53.7 ± 9.9, bpm; $p < 0.001$, respectively) [49].

Ankylosing spondylitis (AS)

Ankylosing Spondylitis (AS) is a seronegative arthritis that mainly affects young men which present axial and peripheral enthesitis and arthritis, certain extra articular manifestations, family aggregation, and HLA-B27 association. Clinically, common manifestations are aortitis causing aortic regurgitation, myocarditis and increased myocardial fibrosis causing conduction disturbances. The last ones could be observed as sinus node dysfunction. Atrial and ventricular arrhythmias have been reported infrequently. In a study of 28 patients with AS and 30 volunteers, mean HRR1 (24.8 ± 4.2 vs. 28.8 ± 5.5 bpm, $p = 0.001$) and HRR2 (42.0 ± 4.4 vs. 48.0 ± 6.3 bpm, $p = 0.001$) values were significantly lower in patients than the control group and it was suggested that these patients should be followed up closely for adverse cardiovascular outcomes [50].

Sarcoidosis

Sarcoidosis is an inflammatory granulomatous disease of unknown cause that involves multiple organ systems, including the lungs, heart, nervous system, eyes, liver, and skin. Involvement of the heart in sarcoidosis includes heart block, congestive heart failure, diastolic dysfunction, left ventricular wall motion abnormalities, pericardial and valvular heart disease, ventricular arrhythmias, and sudden cardiac death. A study of 56 patients with sarcoidosis and 54 healthy control subjects, showed significant differences in HRR1 and HRR2 indices between patients with sarcoidosis and control group (25 ± 6 vs 34 ± 11bpm; $p=0.001$ and 45 ± 10 vs 53 ± 12 bpm; $p=0.001$, respectively). They also suggested that HRR index may be clinically helpful in identifying high-risk patients with sarcoidosis especially in terms of increased occurrence of arrhythmias and sudden cardiac death [51].

Fibromyalgia (FM)

Fibromyalgia (FM) is a chronic syndrome characterized by widespread pain and discomfort. In general, FM is accompanied by other symptoms such as fatigue, sleep disorders, reduced muscular strength and endurance, paresthesias, irritable bowel and joint stiffness. Fourteen women with FM (age: 46 ± 3 years) and 14 healthy individuals (controls) took part in a cross-sectional study and performed a treadmill cardio respiratory exercise testing. Significant differences were showed at the HRR2 (34.3 ± 4 versus 50.8 ± 3 bpm, $P = 0.002$) and a trend to a decreased HRR1 (24.5 ± 3 versus 32.6 ± 2 pbm, $P = 0.059$) respectively. The key messages from this study were that patients with fibromyalgia present cardiac autonomic impairment in response to exercise and that chronotropic incompetence and delayed heart-rate recovery may predispose fibromyalgic patients to a higher mortality risk [52].

Familial mediterranean fever (FMF)

Familial Mediterranean Fever (FMF) is a systemic inflammatory disease which is characterized by sporadic, acute attacks of fever and serositis. Cardiovascular involvement is one of the leading causes of morbidity and mortality among FMF patients. In a study that icluded 38 patients with FMF (14 men; mean age: 36.2 ± 12.1 years) and 35 healthy control subjects (12 men, mean age: 34.1 ± 9.9 years), significant differences in HRR1 and HRR2 indices between patients with FMF and control group were noted (26.4 ± 7.4 vs. 35.0 ± 8.0 bpm, $P = 0.001$ and 47.3 ± 11.8 vs. 54.8 ± 10.3 bpm, $P = 0.002$, respectively). The investigators concluded that the heart rate recovery index may be considered as a useful, simple, and non-invasive test, clinically helpful to the recognition of high-risk patients with FMF [53].

Behcet's disease

Behçet's disease, described as a triad of relapsing uveitis, recurrent aphthous ulcers of the mouth and genitalia and arthritis, is a multisystemic inflammatory disorder that has been associated with a number of cardiovascular dysfunctions such as endocarditis, myocarditis, pericarditis, intracardiac thrombosis, endomyocardial fibrosis, coronary arteritis, myocardial infarction, and valvular diseases, including ventricular arrhythmias and sudden cardiac death. Apart from cardiovascular system clinical manifestations, involvement of the mucocutaneous, ocular, gastrointestinal, respiratory, neurologic, urogenital, articular systems also occurs. In a recent study, HRR index was found impaired in patients with Behcet's disease. These results could explain the increased occurrence of arrhythmias and sudden cardiac death in patients with Behçet's disease, if the prognostic significance of HRR index is taken into consideration. The investigators suggested that it is crucial for Behçet's patients to be followed up closely for cardiovascular problems, especially rhythmic abnormalities that can be fatal and that heart rate recovery index may be clinically useful to the identification of high-risk patients [54].

Renal Disease

Impaired renal function is a strong predictor for cardiac and total mortality. Patients with IgA nephropathy have a relatively homogeneous type of renal disease. Patients suffering from chronic renal disease of any cause often develop insulin resistance, dyslipidaemia, hypertension and other features of metabolic syndrome. HRR was studied among 107 patients with chronic IgA nephropathy. They found that IgA nephropathy patients with Chronic Kidney Disease (CKD) [Estimated Glomerular Filtration Rate (eGFR) < 60 ml/min] have significantly lower HRR (<16 bpm) than those with higher eGFR. Furthermore, they demonstrated a robust inverse correlation between eGFR and HR [55]. Another study has recently evaluated the status of autonomic nervous system among patients with Autosomal-Dominant Polycystic Kidney Disease (ADPKD) who were normotensive and had normal renal function. A total of 28 normotensive ADPKD patients with normal renal function and 30 healthy control subjects participated in the study. HRR which was calculated at the 1st, 2nd, 3rd, 4th and 5th minute of recovery period after exercise was lower in ADPKD patients compared to healthy control group (27.1±7.9 vs 32.0±7.9; p=0.023, 46.9±11.5 vs 53.0±9.0; p=0.029, 56.7±12.0 vs 65.1±11.2; p=0.008 and 62.5±13.8 vs 76.6±15.5; p =0.001, respectively). The authors suggested that increased renal ischemia and the activation of the Renin-Angiotensin-Aldosterone System (RAAS) may contribute to the impairment of autonomic nervous system in these patients [56].

Thyroid Disorders

As far as the human body physiology is concerned, thyroid hormones - thyroxine (T4) and triiodothyronine (T3) are responsible for an overall increase in the basal metabolism which is accompanied by greater tissue oxygen consumption. These effects are due to vasodilation and the concomitant increase in cardiac output, which are facilitated by enhanced chronotropism and inotropism. In a study that included 25 patients with Subclinical Hypothyroidism (SCH), it was shown that both HRR and chronotropic incompetence CI were significantly lower during exercise testing in SCH patients compared to controls (P < 0.003; P < 0.03, respectively) [57]. Another unique cross-sectional study was carried out among 29 patients on TSH-suppressive therapy with levothyroxine for thyroid carcinoma (subclinical hyperthyroidism) and 35 euthyroid subjects. All volunteers underwent a cardiopulmonary exercise testing on a treadmill. Heart-rate and blood pressure recovery immediately after exercise were slower among patients when compared to euthyroid subjects. Subclinical hyperthyroidism was associated with impaired functional and hemodynamic responses during exercise and its recovery. The authors suggested that autonomic disorders expressed by HRR should be taken into account in the treatment strategy [58].

Arterial Hypertension

Cardiovascular functions, including Blood Pressure (BP), and heart rate present diurnal oscillation. Circadian type blood pressure rhythm refers to the daily variation of BP that is generally higher during the day rather than the night. Most of people present a decline in arterial BP between 10- 20% during night-time intervals which is called dipper pattern. Blunted decline in nighttime BP (non-dipping pattern) indicates abnormal parasympathetic and sympathetic activities associated with an increased risk for overall mortality [59]. In mild-moderate hypertensive patients (n = 219, age 55 +/- 3, 77% men) who underwent a maximal exercise, blunting of the BP nocturnal fall was associated with a delayed recovery in heart rate after graded maximal exercise and with greater aortic stiffness and ventricular mass. The authors suggested that in non-dipper subjects a relative decrease of parasympathetic reactivation after exercise was related to the failure of BP night-time fall, which might contribute to target-organ damage [60]. Blunting of the BP nocturnal fall is associated with a delayed HRR after graded maximal exercise in both normotensive and hypertensive groups but it was exaggerated in the hypertensive group [61].

Diabetes Mellitus

Patients with Coronary Artery Disease (CAD) and type 2 diabetes mellitus (T2DM), are suffering with higher incidence of cardiovascular events than CAD patients without T2D. Cardiac autonomic neuropathy is a common complication in DM which represents a serious, but often unrecognized complication of T2D [62,63]. Previous studies suggest that a decreased HRR is a significant independent predictor of mild and high risk cardiac events. The cut off points for HRR1 and HRR2 were 12 bpm and 28 bpm respectively [62,63]. However, in another recent study cut-offs for heart-rate recoveries at 1st, 2nd and 3rd min were 28, 50 and 52≤ beats/min, respectively [64]. More studies are needed to elucidate the optimal cut-off for HRR in such population.

Silent Myocardial Ischemia (SMI) is defined as myocardial ischemia without typical chest pain. SMI occurs in more than 20% of asymptomatic patients with type 2 diabetes. It was recently shown that silent myocardial ischemic patients have statistically significant impaired HRR indices than patients without silent myocardial ischemia [65]. In another population-based cohort of healthy adults, fasting plasma glucose was strongly associated with an abnormal HRR, even after adjusting for confounding factors [66].

The Cardiac study prospectively examined whether autonomic nervous system dysfunction was associated with an increase in

insulin and glucose over time and the development of type 2 diabetes in healthy young subjects. This study showed that there may be a complex association among insulin, glucose, and autonomic dysfunction [67]. Another study detected an independent association of diabetic retinopathy with HRR and suggested that the redetection of HR changes during and after exercise could be a simple, feasible and practical tool to identify a high-risk group for the presence of diabetic retinopathy [68].

Metabolic Syndrome

Metabolic syndrome is characterized by autonomic dysfunction and is associated with cardiovascular events. In a Korean study of 1434 patients with metabolic syndrome a slowed HRR was found [69]. In another study, HRR was strongly associated with the metabolic syndrome, waist circumference, and insulin sensitivity in women than in men among the population [70]. HRR was also impaired in young adult males with metabolic syndrome [71]. Patients with coexisting coronary artery disease and metabolic syndrome had also lower HRR (23 ± 12 vs 27 ± 13 bpm, p <0.0001) than those without MS [72]. Epicardial Fat Thickness (EFT) is a recent identified cardiovascular risk factor among patients with metabolic syndrome (MS). Patients that presented an increased EFT had a diminished HRR compared to control group (21 ± 8 vs. 26 ± 9; p = 0.006) [73].

BNP

Brain Natriuretic Peptide (BNP) is a hormone that is released from the ventricles in response to an increase in left ventricular pressure and volume. Plasma BNP levels have a major diagnostic and prognostic role especially in HF patients [74]. Increased BNP levels have been observed in patients with arterial hypertension (HTN), atrial fibrillation, vascular heart disease, ST-segment elevation of myocardial infarction and myocardial ischemia without extensive necrosis [75]. A pioneer study demonstrated the association between HRR and plasma BNP levels during exercise. In this study 105 patients were included that referred for chest pain and had a normal left ventricular systolic function. HRR2 was defined as the difference between the peak heart rate and the rate measured two minutes after completing a treadmill exercise test. Plasma BNP levels were measured before exercise, 5 minutes after completing exercise, and during exercise (absolute value of difference between pre- and post-exercise BNP levels). The results showed that patients with abnormal HRR2 values (≤24 beats) had lower high-density lipoprotein, lower peak HR, and higher pre- and post-exercise BNP levels than patients with normal HRR2 values. The patients with demonstrated CAD had also an abnormal HRR2. The study concluded that HRR2 was independently associated with pre-exercise and post-exercise BNP levels, even among patients with normal myocardial systolic function [76].

Cancer

Whether abnormalities of autonomous nervous system are related to cancer, it is still under investigation. In an interesting study (Paris Prospective Study I), 6101 asymptomatic French working men aged from 42 to 53 years old, free of clinically detectable cardiovascular disease or cancer, underwent a standardized graded exercise test from 1967 to 1972. A graded- increased risk for no cardiovascular and cancer mortality was observed in patients with: (i) a higher resting heart-rate, (ii) a poorer heart-rate increase during exercise and (iii) a slower decrease of heart-rate during recovery, although the relationship was not statistical significant for the last one. Investigators suggested that heart rate is a general integrator of many physiologic systems such as cardiovascular, respiratory and neuro-psychologic system. Abnormalities in heart-rate before, during and after exercise are generally interpreted as mediated by an imbalance of vagal and adrenergic tone, which may in turn be related to cancer risk [77].

Octogenarians

Cardiovascular disease is common among elderly patients. As a consequence, they are in high risk for arteriosclerosis. Several treadmill exercise testing prognostic parameters have been identified in elderly populations. However, despite the widespread use of treadmill exercise testing, its prognostic value among elderly patients has not been well characterized yet. In a study which included 97 consecutive octogenarians (age, 81.1+1.8 years; 66% male) who were submitted to a treadmill exercise testing with a follow-up period (2.6+1.6 years), abnormal HRR was the only independent predictor of all-cause deaths [78].

Physical Activity

Habitual leisure-time Physical Activity (PA) improves cardio respiratory fitness and is associated with adverse cardiovascular events such as cardiovascular morbidity and mortality. In a large study of 30.594 men from the Aerobics Center Longitudinal Study, habitual physical activity such as walking, but especially swimming and running, when performed with adequate volume had better HRR in relation to sedentary participants [79]. In another study of nineteen endurance athletes who participated the study, HRR was significantly correlated with PA and VO_2 max, (r = 0.67, P = 0.003 and 0.51, P = 0.039, respectively), and the authors suggested that HRR may be a better indicator of fitness-related differences in autonomic control in this population [80].

Depression

Depression is associated with increased risk of death among patients with coronary artery disease. A study of 22 patients with Major Depressive Disorder (MDD) resulted that physical fitness was decreased and HRR was more blunted, among these patients compared to matched healthy controls which may imply a high cardiovascular risk and autonomic dysfunction [81].

Monitoring Interventions

LVADs in heart failure patients

Mechanical circulatory support via Left Ventricular Assist Devices (LVADs) has recently become a matter of great interest for end stage heart failure patients instead of heart transplantation (BTT) These devices have a myocardial recovery function (BTR) while offering long-term chronic support. Continuous development of LVAD, has decreased their production cost and improvements in associated health care have made their usage even wide. In a small study that was realized in our institute LVAD patients present an impaired CR and an abnormal HRR1 immediately after implantation, indicating significant cardiac autonomic abnormalities. These alterations seem to remain stable 3 months after LVAD implantation [82].

Cardiac resynchronization therapy (CRT)

Cardiac Resynchronization Therapy (CRT) improves functional capacity, left ventricular myocardial functions, and survival in patients with refractory HF and left bundle branch block. It is also known that CRT can exert a favorable effect on the mechanism that sustains the harmful autonomic dysfunction state. Improvement in ventricular performance via CRT shifts the cardiac autonomic balance towards a more favorable profile of a more parasympathetic activation enhancement. HRR improved six months after CRT and the beneficial effect was observed in both responders and non-responders in CRT. However, the degree of improvement in HRR indices was correlated with LV reverse "remodeling" [83].

Resistance exercise training and detraining in young men

In a prospective study, fourteen young men (25.0 +/-1.1 year of age) completed a crossover design consisted of a 4-week time-control period, a 6–week time of resistance training (3 days/week), and a 4-week time of detraining. The results showed that short term resistance exercise training increased HRR and after exercise detraining period, cardiac autonomic parameters returned to pre training values [84].

Renal sympathetic denervation

Renal Sympathetic Denervation (RD) in patients with resistant arterial hypertension is a new but not widely used method. In a series of 46 patients, RD reduced blood pressure during exercise without compromising chronotropic competence in patients with resistant hypertension. Heart rate at rest decreased and HRR improved after the procedure by 4 ± 7 bpm [85].

COPD cardiopulmonary rehabilitation program

In a study held in our institute consisted of 45 COPD patients, cardiopulmonary rehabilitation program (consisted of 36 exercise-based sessions) enhanced their heart rate recovery (from 16.2±8.0 to 18.4±8.4 bpm, $p<0.05$) indicating a degree of improved cardiac parasympathetic function [86].

Cardiac rehabilitation (CR) program

In a large retrospective study, 1070 consecutive patients referred for exercise testing were evaluated before and after completion of a cardiac rehabilitation program. In the sample of patients that completed cardiac rehabilitation, there was an improvement in HRR and there was also a strong association between abnormal HRR after training and all cause mortality. Patients that normalized HRR through rehabilitation program had a similar mortality rate to those with baseline normal HRR [87]. In another study, a 12-week unsupervised walking program of 40-minute walking (five days per week) had a significant HRR amelioration in stable CHF patients [88]. In a previous randomized study held in our institute, 29 stable CHF patients participated in a rehabilitation program of 36 sessions, three times per week. Patients who exercised by a continuous training regime had a significant increase in HRR1 (15.0+/-9.0 to 24.0+/-12 bpm; P=0.02) in contrast to those who assigned to interval training (HRR1: 21+/-11 to 21+/-8 bpm; P=NS). We concluded that despite similar beneficial effects in aerobic capacity continuous exercise training conferred greater improvement at the cardiac autonomic nervous system activity compared to interval training in CHF patients [89]. In another study it was demonstrated a significantly more rapid decline of HRR after exercise training compared to inactive control group (main effect 12.6 vs 2.6 beat/min in the trained and control groups, respectively, P =0.005) [90]. Exercise training irrespective of modality of exercise can improve HRR in CHF patients with abnormal baseline HRR comparing to normal HRR as a recent study shows [91]. Focusing exercise training particularly in those patients with abnormal HRR might be an important target of exercise training in these patients [92].

CABG patients and cardiac rehabilitation

HRR was also significantly improved after cardiac rehabilitation in CABG patients consistent with an autonomic improvement [93]. In another study, 15 patients after bypass cardiac surgery that participated at a cardiac rehabilitation program presented a significantly higher HRR1 (16.38+/-6.32 versus 11.38+4.81 bpm, p = 0.03) compared to the control group and improved HRR [94].

Continuous positive airway pressure (nCPAP)

Forty patients with recently diagnosed OSA underwent cardiopulmonary exercise testing before and after 7.9+/-1.4 months of effective continuous positive airway pressure (nCPAP) (nightly usage>3.5 h). The results showed a marked increase of HRR1 in severe OSA [95].

Weight loss

One hundred and twenty-five obese subjects with no past history of stroke, cardiovascular events, or use of medications underwent and an exercise plus weight loss program of 3 months. In these patients there was a significant an improvement in HRR (from 36+/-13 to 45+/-14 bpm, $p<0.0001$) [96]. Similarly, in a previous study it was demonstrated that HRR improved (from 33.1 +/- 1.4 to 36.9 +/- 1.3 bpm, $P < 0.001$) after weight loss [97]. In 57 overweight women with polycystic ovary syndrome after a 10-week of approximately 30% energy restricted diet there was also a significant increase in HRR (from 30.9 +/- 1.1 to 38.0 +/- 1.1 bpm, $p<0.05$) [98]. Furthermore, in severe obese patients that underwent sub maximal exercise testing (80% predicted maximum HR) at baseline and 2 years after Gastric bypass surgery an improvement in HRR (up to 13 bpm) was observed [99].

Conclusion

Heart rate recovery is a potent marker of cardiac parasympathetic activity that can be used in order to identify patients at high risk for cardiovascular and all-cause mortality. Different stress test exercise protocols may create confusion about the value of heart rate recovery, so the technique should be standardized and cut-off values of abnormality should be set out. HRR is a considerable simple, useful clinical objective index for risk stratification in different disease populations with an important role in monitoring interventions that should be added in the physicians' routine clinical practice.

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