Heart rate and 123I-MIBG in heart failure with preserved ejection fraction: More variability and slower washout—A secret recipe for better survival

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AUTONOMIC NERVOUS SYSTEM

The autonomic nervous system (ANS) regulates physiological processes such as blood pressure and heart rate (HR) among many others, through two major divisions: the sympathetic and parasympathetic systems. The former activates the fight-or-flight mechanisms, while the latter conserves energy and restores it. A delicate homeostasis exists, and this relationship is known as sympathovagal balance.¹

The HR is an indirect manifestation of this sympathovagal balance and is an indicator of one's health. Indeed, higher variations in HR indicate a well-balanced autonomic function, while a steady HR with low variability indicates a low parasympathetic tone.² This balance can be offset in many diseases, involve any organ of the body, be peripheral or central in origin, due to primary or secondary causes, temporary or permanent.

Therefore, the ANS may serve as a barometer to one's health. In patients with heart failure (HF) for instance, the balance between the sympathetic and parasympathetic nervous system is offset in favor of an unchecked excess sympathetic tone though activation of the renin-angiotensin system, an increased norepinephrine levels (equally in patients with HF with

reduced and preserved ejection fraction),^{3,4} and withdrawal of parasympathetic tone.^{1,5}

AUTONOMIC DYSFUNCTION AND CARDIOVASCULAR DISEASE: A MISSING LINK?

Autonomic dysfunction, especially lower parasympathetic activity, is associated with the risk of development and progression of coronary heart disease.^{6,7} Low parasympathetic tone in particular, as evidenced by increased resting HR and decreased Valsalva ratio, is associated with high carotid intima media thickness and elevated coronary artery calcium score among diabetic patients⁸; this highlights the association between autonomic dysfunction and subclinical coronary artery disease. In addition, it has been hypothesized that increased cardiac sympathetic tone increases mitochondrial reactive oxygen species production that leads to myocardial apoptosis, promoting myocardial remodeling and decrease in myocardial vascularity, with subsequent reduction of the coronary blood flow reserve.⁹

Furthermore, reduced HR variability (HRV) was shown to be associated with blunted nocturnal blood pressure drop,¹⁰ paroxysmal atrial fibrillation,¹¹ and silent ischemia,⁷ which are associated with HF with preserved ejection fraction. Indeed, in the current manuscript by Hashimoto et al., 44% of patients with HF and preserved ejection fraction had low HRV and increased 123I-MIBG washout-rates, both indicators of autonomic dysfunction.¹² Given the increased evidence linking autonomic dysfunction with premature cardiovascular disease, silent ischemia and diastolic dysfunction, it is not surprising to see an association with increased cardiovascular events.

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AUTONOMIC DYSFUNCTION AND MAJOR CARDIOVASCULAR ADVERSE EVENTS

Epidemiological studies strengthen the association between cardiovascular autonomic dysfunction and mortality risk,¹³ with data showing incremental prognostic value beyond traditional risk factors, and consistent results across study groups, patient cohorts, disease spectrum, and testing modalities.¹⁴ Among elderly patients without known history of cardiac disease, Tsuji et al. showed increased risk for sudden cardiac events among those with reduced autonomic activity.² One of the proposed mechanism is that the excess sympathetic activity predisposes to malignant arrhythmia. This was latter on re-tested and validated using 123I-MIBG imaging, a direct tool to image autonomic function, in which low heart-to-mediastinal ratio was an independent predictor of ventricular arrhythmia.¹⁵

In addition, a decreased HRV, specifically very-low resting parasympathetic activity, was shown in several studies to be associated with worse outcomes.^{2,16} HR turbulence, a type of HRV analysis, was also shown in one of the first prospective studies to be associated with fatal and nonfatal cardiac arrest in seemingly low-risk post-acute myocardial infarction cohort.¹⁷ Therefore, abnormal cardiac autonomic activity is associated with a post-MI mortality, sudden cardiac and all-cause death. This highlights the need for autonomic testing to risk-stratify for major cardiovascular events.¹⁸

TESTING FOR AUTONOMIC DYSFUNCTION

Cardiac sympathetic nerve imaging allows direct assessment of the integrity of the adrenergic cardiac innervation.¹⁹ This is performed using hydroxyephedrine labeled with carbon-11 [¹¹C-HED] positron emission tomography (PET) or methylated 11carbon-labeled radiotracer 3-quinuclidinyl benzilate (11C-MQNB). The former is a sympathetic analog, while the latter, an atropine analog, evaluates the parasympathetic nervous system.²⁰ These tracers reflect the integrity of the autonomic system and have prognostic value.²¹

The limited availability of PET and high cost, however, limit its routine use. Single photon emission computed tomography (SPECT) imaging with 123-iodine metaiodobenzylguanidine [123-I MIBG] on the other hand, is an attractive alternative. 123I-MIBG is a false neurotransmitter that uses the same uptake and storage mechanisms as the endogenously produced neurotransmitter norepinephrine; hence, its kinetics reflects the integrity and function of cardiac presynaptic sympathetic nerve terminals.²² The most commonly

used semi-quantitative parameters of 123-I MIBG uptake are the heart-to-mediastinum ratio and washout-rate; reduced heart-to-mediastinum ratio and high washout-rate are indicators of autonomic dysfunction and have prognostic value,²³⁻²⁵ including sudden cardiac death.^{15,26,27} They also correlate with the degree of coronary artery stenosis, which suggests that the cardiac adrenergic nerve endings function is modified even in mild coronary artery disease before denervation occurs.²⁸ This explains why cardiac 123I-MIBG scintigraphy may diagnose autonomic dysfunction in early stages before clinical manifestations such as reduced HRV^{29,30}

While direct imaging of the ANS is more accurate, there is a need for simpler and more accessible tools to evaluate the ANS. These includes: (1) cardiovagal innervation testing, which evaluates the integrity of the parasympathetic system through heart rate response to deep breathing and to the Valsalva maneuver; and (2) vasomotor adrenergic innervation that evaluates the integrity of the sympathetic system through beat-to-beat blood pressure response to the head-up tilt and Valsalva maneuver. A list of tools to measure ANS is summarized in Table 1.

To that effect, the HR which is affected by the balance of sympathetic and parasympathetic tones, is an indirect non-invasive reflection of the integrity of ANS. Patients with elevated resting heart rate have lower parasympathetic tone. However, in isolation, a resting HR is not accurate enough to detect autonomic dysfunction. HRV which is a measure of the variation in beat-to-beat intervals in heart rate, is a more powerful tool in assessment of the autonomic function; it is non-invasive, accurate, reproducible, reliable, simple, and quick to process. It is a reflection of the heart-brain interactions and autonomic nervous system dynamics.³¹ In addition, functional imbalances between the sympathetic and parasympathetic nervous systems are further unmasked through respiratory; hence, coupling of HRV with respiratory activity helps identify further the cardiovagal response.³²

Other tools to detect autonomic dysfunction include heart rate QT variability which can detect subclinical cardiac autonomic neuropathy in diabetic patients,³³ and HR fragmentation, a marker of sinoatrial node instability and autonomic dysfunction, that also provides incremental prognostic value beyond Framingham in the MESA study.³⁴

While HRV analysis requires software analysis and some expertise, there are simpler variables that are readily available and routinely measured that also reflect the integrity of the ANS. HR recovery after exercise stress testing (maximal HR achieved—HR at one minute recovery) and HR reserve, are indicators of the

Table 1. Assessment tools of autonomic nervous system

Direct ANS imaging	
11C-HED	PET tracer Sympathetic analog Low retention index associated with increased mortality
11C-MQNB	PET tracer Atropine analog Assesses integrity of the parasympathetic system
123I-MIBG	SPECT tracer Norepinephrine analog Assesses integrity of the presynaptic sympathetic neurons. Detects early autonomic dysfunction Low heart-mediastinum ratio and high washout-rate correlate with sudden death, arrhythmia, and mortality Add-on risk stratification on top of HRV
Indirect ANS assessment	
Heart rate	High resting heart rate reflects low parasympathetic tone Lacks accuracy and specificity
Heart rate variability	Derived from Holter ECG analysis Non-invasive, reproducible, quantifiable Very-low frequency power reflects low parasympathetic tone Risk factor for cardiovascular disease Coupling with respiratory changes gives more in depth analysis of the cardiovagal response Risk-stratify seemingly low-risk cohort Established prognostic value Improves with exercise and lifestyle changes
Heart rate fragmentation	Marker of sinoatrial instability Prognostic value
Heart rate QT variability	Marker of subclinical autonomic dysfunction in diabetic patients
Heart rate recovery	Derived from exercise stress testing Detects autonomic dysfunction when blunted Prognostic value Improves with cardiac rehabilitation with parallel improvement in survival
Heart rate response	Derived from pharmacological stress myocardial perfusion imaging Blunted in patients with diabetes, heart failure, or renal failure Reflects autonomic dysfunction Risk-stratify patients Prognostic value

sympathovagal balance. Blunted HR recovery and reserve are associated with increased cardiovascular risk such as hypertension,³⁵ coronary artery calcification,³⁶ subclinical atherosclerosis,³⁷ inflammation and insulin resistance,³⁸ and arrhythmia.³⁹ In addition, they reflect autonomic dysfunction,⁴⁰ and predict major cardiovascular events.^{41,42}

During pharmacological stress myocardial perfusion imaging, HR response can be calculated as percentage change from baseline. It is blunted in patients with diabetes and chronic kidney disease, which is thought to be a reflection

of autonomic dysfunction.^{43,44} Similar to other markers of autonomic dysfunction, blunted HR response is also an independent predictor of mortality with incremental value beyond traditional risk factors.⁴⁵⁻⁴⁹

INTEGRATING HRV AND 123I-MIBG WASHOUT-RATE

HRV and 123I-MIBG washout-rate are both markers of ANS and with an inverse relationship; they detect early autonomic dysfunction among those without

known coronary artery disease²² and asymptomatic patients with end-stage renal disease.⁵⁰

In the current manuscript, Hashimoto et al. identified 133 patients with HF and preserved ejection fraction who underwent HRV analysis of Holter electrocardiogram and 123I-MIBG SPECT imaging.¹² Each test was interpreted in a blinded manner, and the results were not available to the treating physician since this was a retrospective study. While low HRV, particularly very-low frequency power [cut-off 825 ms²], and high 123I-MIBG washout-rate [cut-off value 42%] were individually associated with increased major adverse cardiovascular events (MACE) in concordance with prior studies (described previously), the addition of the two parameters in the same model was even more predictive of outcomes, as they complimented each other. Indeed, when compared to those with high HRV and low washout-rate (very low-risk group, 55/133 of the cohort, 2% had MACE after 5.4 years follow-up), those with both low HRV and high washout-rates (very-high risk group, 36/133 of the cohort, 61% had MACE) had significantly higher risk (hazard ratio 40 [5.4-310], $p < 0.01$). Also, among patients with preserved ejection fraction and mild HF symptoms (74% NYHA I-II), the combination of HRV and 123I-MIBG washout-rate risk stratified two-third of the cohort into either a very-low or very-high risk groups, leaving only a third in the intermediate risk zone.¹² It is noteworthy that the MACE was driven by hospitalization for HF (21/39), and less so by cardiac death (16/39 with 12/39 related to pump failure). The incidence of sudden cardiac death however, was not clear but likely lower than expected. The selection bias, the small sample size, and the fact that the mean EF of the cohort was 63% could in part explain why hospitalization and death from heart failure were driving the outcomes with less impact from arrhythmia. In contrast, among patients with reduced ejection fraction undergoing both HRV and 123I-MIBG imaging, HRV was predictor of sudden cardiac death, while 123I-MIBG washout-rate predicted all-cause mortality.⁵¹

Biologically feasible mechanisms, epidemiological data, and clinical studies support the need to test for autonomic dysfunction, not only in diabetics, but also in the general population as they age and the incidence of heart disease increases. It is well established that autonomic dysfunction, whether measured indirectly (HR variability, response, recovery, etc...) or directly (neuronal imaging), is a cardiovascular risk factor with associated increased cardiac morbidity and mortality. Identifying early autonomic dysfunction can risk-stratify patients, particularly when combining data from both HRV analysis and 123I-MIBG imaging. Indeed, DePace et al. have shown that autonomic dysfunction can be

treated if the correction information on the sympatho-vagal balance is available.¹ Resuming exercise and daily life activities, or even a simple walk in nature, can improve HRV.^{52,53} Also, HR recovery can be restored back to normal among patients undergoing cardiac rehabilitation, and so does their survival curve.⁵⁴

Therefore, physical and pharmaceutical interventions that improve or restore autonomic function may lead to better prognosis. Early detection and risk stratification remain a key element.

Disclosure

None.

References

- DePace NL, Mears JP, Yayac M, Colombo J. Cardiac autonomic testing and diagnosing heart disease. "A clinical perspective". *Heart Int* 2014;9:37-44.
- Tsuji H, Venditti FJ Jr, Manders ES, Evans JC, Larson MG, Feldman CL, et al. Reduced heart rate variability and mortality risk in an elderly cohort. The framingham heart study. *Circulation*. 1994;90:878-83.
- Kitzman DW, Little WC, Brubaker PH, Anderson RT, Hundley WG, Marburger CT, et al. Pathophysiological characterization of isolated diastolic heart failure in comparison to systolic heart failure. *JAMA* 2002;288:2144-50.
- Levi R, Silver RB, Mackins CJ, Seyedi N, Koyama M. Activation of a renin-angiotensin system in ischemic cardiac sympathetic nerve endings and its association with norepinephrine release. *Int Immunopharmacol* 2002;2:1965-73.
- Packer M. The neurohormonal hypothesis: A theory to explain the mechanism of disease progression in heart failure. *J Am Coll Cardiol*. 1992;20:248-54.
- Liao D, Cai J, Rosamond WD, Barnes RW, Hutchinson RG, Whitset EA, et al. Cardiac autonomic function and incident coronary heart disease: A population-based case-cohort study. The alic study. Atherosclerosis risk in communities study. *Am J Epidemiol*. 1997;145:696-706.
- Huikuri HV, Jokinen V, Syvanne M, Nieminen MS, Airaksinen KE, Ikaheimo MJ, et al. Heart rate variability and progression of coronary atherosclerosis. *Arterioscler Thromb Vasc Biol*. 1999;19:1979-85.
- Fakhrzadeh H, Yamini-Sharif A, Sharifi F, Tajalizadekhoob Y, Mirarefin M, Mohammadzadeh M, et al. Cardiac autonomic neuropathy measured by heart rate variability and markers of subclinical atherosclerosis in early type 2 diabetes. *ISRN Endocrinol* 2012;2012:168264.
- Pop-Busui R, Kirkwood I, Schmid H, Marinescu V, Schroeder J, Larkin D, et al. Sympathetic dysfunction in type 1 diabetes: Association with impaired myocardial blood flow reserve and diastolic dysfunction. *J Am Coll Cardiol* 2004;44:2368-74.
- Salles GF, Ribeiro FM, Guimaraes GM, Muxfeldt ES, Cardoso CR. A reduced heart rate variability is independently associated with a blunted nocturnal blood pressure fall in patients with resistant hypertension. *J Hypertens* 2014;32:644-51.
- Raman D, Kaffashi F, Lui LY, Sauer WH, Redline S, Stone P, et al. Polysomnographic heart rate variability indices and atrial

- ectopy associated with incident atrial fibrillation risk in older community-dwelling men. *JACC Clin Electrophysiol* 2017;3:451-60.
12. Hashimoto H, Nakanishi R, Mizumura S, Hashimoto Y, Okamura Y, Yamanaka K, et al. Prognostic values of 123i-mibg myocardial scintigraphy and heart rate variability in patients with heart failure with preserved ejection fraction. *J Nucl Cardiol* 2018
13. Astrup AS, Tarnow L, Rossing P, Hansen BV, Hilsted J, Parving HH. Cardiac autonomic neuropathy predicts cardiovascular morbidity and mortality in type 1 diabetic patients with diabetic nephropathy. *Diabetes Care* 2006;29:334-9.
14. 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.
15. Marshall A, Cheetham A, George RS, Mason M, Kelion AD. Cardiac iodine-123 metaiodobenzylguanidine imaging predicts ventricular arrhythmia in heart failure patients receiving an implantable cardioverter-defibrillator for primary prevention. *Heart* 2012;98:1359-65.
16. Maser RE, Mitchell BD, Vinik AI, Freeman R. The association between cardiovascular autonomic neuropathy and mortality in individuals with diabetes: A meta-analysis. *Diabetes Care* 2003;26:1895-901.
17. Bilchick KC, Fetis B, Djoukeng R, Fisher SG, Fletcher RD, Singh SN, et al. Prognostic value of heart rate variability in chronic congestive heart failure (veterans affairs' survival trial of antiarrhythmic therapy in congestive heart failure). *Am J Cardiol* 2002;90:24-8.
18. Barthel P, Bauer A, Muller A, Junk N, Huster KM, Ulm K, et al. Reflex and tonic autonomic markers for risk stratification in patients with type 2 diabetes surviving acute myocardial infarction. *Diabetes Care* 2011;34:1833-7.
19. Jb M, Ev C, Jb J. Cardiac autonomic nervous system in heart failure: Imaging technique and clinical implications. *Curr Cardiol Rev* 2011;7:35-42.
20. Jamali HK, Waqar F, Gerson MC. Cardiac autonomic innervation. *J Nucl Cardiol* 2017;24:1558-70.
21. Pietila M, Malminiemi K, Ukkonen H, Saraste M, Nagren K, Lehtikoinen P, et al. Reduced myocardial carbon-11 hydroxyephedrine retention is associated with poor prognosis in chronic heart failure. *Eur J Nucl Med* 2001;28:373-6.
22. Simula S, Vanninen E, Hedman A, Lehto S, Kuikka J, Hartikainen J. Myocardial (123) i-metaiodobenzylguanidine washout and heart rate variability in asymptomatic subjects. *Ann Noninvasive Electrocardiol* 2012;17:8-13.
23. Merlet P, Valette H, Dubois-Rande JL, Moyse D, Duboc D, Dove P, et al. Prognostic value of cardiac metaiodobenzylguanidine imaging in patients with heart failure. *J Nucl Med*. 1992;33:471-7.
24. Agostini D, Verberne HJ, Burchert W, Knuuti J, Povinec P, Sambucetti G, et al. I-123-mibg myocardial imaging for assessment of risk for a major cardiac event in heart failure patients: Insights from a retrospective european multicenter study. *Eur J Nucl Med Mol Imaging* 2008;35:535-46.
25. Ogita H, Shimonagata T, Fukunami M, Kumagai K, Yamada T, Asano Y, et al. Prognostic significance of cardiac (123)i metaiodobenzylguanidine imaging for mortality and morbidity in patients with chronic heart failure: A prospective study. *Heart* 2001;86:656-60.
26. Tamaki S, Yamada T, Okuyama Y, Morita T, Sanada S, Tsukamoto Y, et al. Cardiac iodine-123 metaiodobenzylguanidine imaging predicts sudden cardiac death independently of left ventricular ejection fraction in patients with chronic heart failure and left ventricular systolic dysfunction: Results from a comparative study with signal-averaged electrocardiogram, heart rate variability, and qt dispersion. *J Am Coll Cardiol* 2009;53:426-35.
27. Boogers MJ, Borleffs CJ, Henneman MM, van Bommel RJ, van Ramshorst J, Boersma E, et al. Cardiac sympathetic denervation assessed with 123-iodine metaiodobenzylguanidine imaging predicts ventricular arrhythmias in implantable cardioverter-defibrillator patients. *J Am Coll Cardiol* 2010;55:2769-77.
28. Simula S, Vanninen E, Viitanen L, Kareinen A, Lehto S, Pajunen P, et al. Cardiac adrenergic innervation is affected in asymptomatic subjects with very early stage of coronary artery disease. *J Nucl Med* 2002;43:1-7.
29. Murata K, Sumida Y, Murashima S, Matsumura K, Takeda H, Nakagawa T, et al. A novel method for the assessment of autonomic neuropathy in type 2 diabetic patients: A comparative evaluation of 123i-mibg myocardial scintigraphy and power spectral analysis of heart rate variability. *Diabet Med*. 1996;13:266-72.
30. Kreiner G, Wolzt M, Fasching P, Leitha T, Edlmayer A, Korn A, et al. Myocardial m-[123i]iodobenzylguanidine scintigraphy for the assessment of adrenergic cardiac innervation in patients with iddm. Comparison with cardiovascular reflex tests and relationship to left ventricular function. *Diabetes*. 1995;44:543-549
31. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task force of the european society of cardiology and the north american society of pacing and electrophysiology. *Eur Heart J*. 1996;17:354-381
32. Badra LJ, Cooke WH, Hoag JB, Crossman AA, Kuusela TA, Tahvanainen KU, et al. Respiratory modulation of human autonomic rhythms. *Am J Physiol Heart Circ Physiol* 2001;280:H2674-88.
33. Imam MH, Karmakar CK, Khandoker AH, Jelinek HF, Palaniswami M. Heart rate independent qt variability component can detect subclinical cardiac autonomic neuropathy in diabetes. *Conf Proc IEEE Eng Med Biol Soc* 2016;928:31.
34. Costa MD, Redline S, Davis RB, Heckbert SR, Soliman EZ, Goldberger AL. Heart rate fragmentation as a novel biomarker of adverse cardiovascular events: The multi-ethnic study of atherosclerosis. *Front Physiol* 2018;9:1117.
35. Jae SY, Bunsawat K, Fadel PJ, Fernhall B, Choi YH, Park JB, et al. Attenuated heart rate recovery after exercise testing and risk of incident hypertension in men. *Am J Hypertens* 2016;29:1103-8.
36. Jae SY, Kurl S, Laukkanen JA, Yoon ES, Choi YH, Fernhall B, et al. Relation of heart rate recovery after exercise testing to coronary artery calcification. *Ann Med* 2017;49:404-10.
37. Mohlenkamp S, Lehmann N, Schmermund A, Roggenbuck U, Moebus S, Dragano N, et al. Association of exercise capacity and the heart rate profile during exercise stress testing with subclinical coronary atherosclerosis: Data from the heinz nixdorf recall study. *Clin Res Cardiol* 2009;98:665-76.
38. Kuo HK, Gore JM. Relation of heart rate recovery after exercise to insulin resistance and chronic inflammation in otherwise healthy adolescents and adults: Results from the national health and nutrition examination survey (nhanes) 1999-2004. *Clin Res Cardiol* 2015;104:764-72.
39. Maddox TM, Ross C, Ho PM, Magid D, Rumsfeld JS. Impaired heart rate recovery is associated with new-onset atrial fibrillation: A prospective cohort study. *BMC Cardiovasc Disord* 2009;9:11.
40. Georgoulas P, Valotassiou V, Tsougos I. Heart-rate recovery as a clinical marker of cardiovascular autonomic dysfunction in diabetic patients. *Eur J Nucl Med Mol Imaging* 2009;36:320-1.
41. Hai JJ, Siu CW, Ho HH, Li SW, Lee S, Tse HF. Relationship between changes in heart rate recovery after cardiac rehabilitation on cardiovascular mortality in patients with myocardial infarction. *Heart Rhythm* 2010;7:929-36.

42. Maddox TM, Ross C, Ho PM, Masoudi FA, Magid D, Daugherty SL, et al. The prognostic importance of abnormal heart rate recovery and chronotropic response among exercise treadmill test patients. *Am Heart J* 2008;156:736-44.
43. Hage FG, Heo J, Franks B, Belardinelli L, Blackburn B, Wang W, et al. Differences in heart rate response to adenosine and regadenoson in patients with and without diabetes mellitus. *Am Heart J* 2009;157:771-6.
44. Hage FG, Perry G, Heo J, Iskandrian AE. Blunting of the heart rate response to adenosine and regadenoson in relation to hyperglycemia and the metabolic syndrome. *Am J Cardiol* 2010;105:839-43.
45. Hage FG, Wackers FJ, Bansal S, Chyun DA, Young LH, Inzucchi SE, et al. The heart rate response to adenosine: A simple predictor of adverse cardiac outcomes in asymptomatic patients with type 2 diabetes. *Int J Cardiol* 2013;167:2952-7.
46. Hage FG, Dean P, Iqbal F, Heo J, Iskandrian AE. A blunted heart rate response to regadenoson is an independent prognostic indicator in patients undergoing myocardial perfusion imaging. *J Nucl Cardiol* 2011;18:1086-94.
47. AlJaroudi W, Anokwute C, Fughhi I, Campagnoli T, Wassouf M, Vij A, et al. The prognostic value of heart rate response during vasodilator stress myocardial perfusion imaging in patients with end-stage renal disease undergoing renal transplantation. *J Nucl Cardiol* 2017.
48. Andrikopoulou E, AlJaroudi WA, Farag A, Lester D, Patel H, Iskandrian AE, et al. The reproducibility and prognostic value of serial measurements of heart rate response to regadenoson during myocardial perfusion imaging. *Eur J Nucl Med Mol Imaging* 2016;43:1493-502.
49. AlJaroudi W, Campagnoli T, Fughhi I, Wassouf M, Ali A, Doukky R. Prognostic value of heart rate response during regadenoson stress myocardial perfusion imaging in patients with end stage renal disease. *J Nucl Cardiol* 2016;23:560-9.
50. Chrapko BE, Jaroszynski AJ, Glowinski A, Bednarek-Skubiewska A, Zaluska W, Ksiazek A. Iodine-123 metaiodobenzylguanidine myocardial imaging in haemodialysed patients asymptomatic for coronary artery disease: A preliminary report. *Nucl Med Commun* 2011;32:515-21.
51. Anastasiou-Nana MI, Terrovitis JV, Athanasoulis T, Karaloizos L, Geramoutsos A, Pappa L, et al. Prognostic value of iodine-123-metaiodobenzylguanidine myocardial uptake and heart rate variability in chronic congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol* 2005;96:427-31.
52. Nakayama N, Negi K, Watanabe K, Hirai M. Life activities improve heart rate variability in patients with mild hypertension and/or the initial stage of heart failure. *J Clin Nurs* 2014;23:367-73.
53. Gladwell VF, Kuoppa P, Tarvainen MP, Rogerson M. A lunchtime walk in nature enhances restoration of autonomic control during night-time sleep: Results from a preliminary study. *Int J Environ Res Public Health* 2016;13.
54. Jolly MA, Brennan DM, Cho L. Impact of exercise on heart rate recovery. *Circulation* 2011;124:1520-6.