

Cardiac autonomic modulation in healthy elderly after different intensities of dynamic exercise

Viviane Santos López
Droguett¹
Amilton da Cruz Santos²
Carlos Eduardo de
Medeiros²
Douglas Porto Marques²
Leone Severino do
Nascimento²
Maria do Socorro
Brasileiro-Santos²

¹Department of Pathology, Federal University of Pernambuco, Recife, Pernambuco, Brazil; ²Department of Physical Education, Federal University of Paraíba, João Pessoa, Paraíba, Brazil

Purpose: To investigate the heart rate (HR) and its autonomic modulation at baseline and during dynamic postexercise (P_{EX}) with intensities of 40% and 60% of the maximum HR in healthy elderly.

Methods: This cross-sectional study included ten apparently healthy people who had been submitted to a protocol on a cycle ergometer for 35 minutes. Autonomic modulation was evaluated by spectral analysis of HR variability (HRV).

Results: A relevant increase in HR response was observed at 15 minutes postexercise with intensities of 60% and 40% of the maximum HR (10 ± 2 bpm versus 5 ± 1 bpm, respectively; $P=0.005$), and a significant reduction in HRV was also noted with 40% and 60% intensities during the rest period, and significant reduction in HRV (RR variance) was also observed in 40% and 60% intensities when compared to the baseline, as well as between the post-exercise intensities (1032 ± 32 ms versus 905 ± 5 ms) ($P < 0.001$). In the HRV spectral analysis, a significant increase in the low frequency component HRV and autonomic balance at 40% of the maximum HR (68 ± 2 normalized units [nu] versus 55 ± 1 nu and 2.0 ± 0.1 versus 1.2 ± 0.1 ; $P < 0.001$) and at 60% of the maximum HR (77 ± 1 nu versus 55 ± 1 nu and 3.2 ± 0.1 versus 1.2 ± 0.1 [$P < 0.001$]) in relation to baseline was observed. A significant reduction of high frequency component at 40% and 60% intensities, however, was observed when compared to baseline (31 ± 2 nu and 23 ± 1 nu versus 45 ± 1 nu, respectively; $P < 0.001$). Moreover, significant differences were observed for the low frequency and high frequency components, as well as for the sympathovagal balance between participants who reached 40% and 60% of the maximum HR.

Conclusion: There was an increase in the HR, sympathetic modulation, and sympathovagal balance, as well as a reduction in vagal modulation in the elderly at both intensities of the P_{EX} .

Keywords: heart rate, autonomic nervous system, exercise

Introduction

The aging process reduces the parasympathetic activity of the heart and, consequently, decreases heart rate (HR) variability (HRV) indices.¹⁻⁶ Additionally, an increase in the prevalence of sympathetic activity over parasympathetic balance is also observed in older subjects at rest.³ Other results, however, suggest that the autonomic balance appears to be unaffected by aging due to the observed decrease in sympathovagal components.² These comments are relevant since the reduction of HRV with aging can be related to higher cardiovascular morbidity and mortality rates.^{7,8}

Parasympathetic activity has been shown to confer protection against arrhythmias in the setting of exercise-induced ischemia,^{9,10} while sympathetic activity has also been shown to provoke ventricular arrhythmias.¹¹ Many studies demonstrate that exercise has overall salutary effects. On the other hand, there is also evidence that the risk of sudden death is increased dramatically during and immediately after exercise.^{12,13} Although there are several possible mechanisms for this marked increase in the risk of sudden cardiac death,

Correspondence: Maria do Socorro Brasileiro-Santos
Universidade Federal da Paraíba,
Departamento de Educação Física,
Cidade Universitária, Código de
Endereçamento Postal 58051-900, João
Pessoa, Paraíba, Brasil
Tel +5583 3216 7212
Fax +5583 3216 7212
Email sbrasileiro@pq.cnpq.br

including the induction of myocardial ischemia, death may be related to acute changes in the autonomic tone that accompanies exercise. The prognostic significance of the abnormalities of autonomic tone has been established in multiple studies that have evaluated the autonomic control of HR, predominantly at rest or during activities. These studies have linked diminished parasympathetic control with increased mortality.¹⁴⁻¹⁸

Exercise is characterized by activation of the sympathetic nervous system, as well as by an increase in serum catecholamine and parasympathetic withdrawal.¹⁹ Conversely, recovery has the opposite autonomic changes. The HR response after exercise has a prognostic and predictive role for cardiovascular events.^{20,21} Previous studies evaluating autonomic effects on recovery, however, have provided conflicting evidence,^{22,23} and it is unclear whether the intensity of exercise influences these effects. On the basis of these considerations, the purpose of the present study was to determine whether HR responses and cardiac autonomic regulation in elderly subjects following mild and moderate dynamic exercise (subacute effects) is associated with an increase in sympathetic hyperactivity and reduced vagal modulation.

Methods

Subjects

The study protocol was approved by the Human Ethical Subject Protection Committees of the Federal University of Paraiba. Written informed consent was obtained from all subjects. Measurements were obtained from a number of elderly subjects. The ten elderly subjects chosen were closely matched for age and body mass index, as well as for demographic, hemodynamic, clinical characteristics (Table 1).

Measurements and experimental protocol

All subjects were studied during the daytime (afternoon, 2 pm) in the Clinical Investigation Laboratory. Throughout the protocol, subjects were instrumented with a three-lead electrocardiograph (ECG) to determine HR, as well as with a respiratory belt (Pneumotrace II™; UFI, Morro Bay, CA, USA) to measure the respiratory rate. The ECG and respiratory signals were recorded on a Gould 2800S polygraph connected to a computer. After instrumentation and acclimation for at least 15 minutes, measurements were taken while the subjects were awake during 10 minutes of undisturbed supine rest. Subsequently, after the baseline condition had been established, the elderly subjects began a bicycle ergometer test set at a mild setting (model 740E ergometer; Siemens Healthcare USA, Inc., Malvern, PA, USA), corresponding to 40% of the working HR,²⁴ for 35 minutes. After completing the bicycle ergometer test, the subjects lay down again and rested for 15

Table 1 Population study characteristics

	Elderly subjects (n=10)
Age, years	66±2
Males/females	3/7
Height, cm	158±1
Weight, kg	58.4±4.4
Body mass index, kg/m ²	23.4±0.9
Heart rate, bpm	69.4±2.9
Systolic blood pressure, mmHg	120.4±2.5
Diastolic blood pressure, mmHg	71.8±1.9
Cholesterol, mg/dL	220.1±7.0
LDL cholesterol mg/dL	146.7±9.3
HDL cholesterol, mg/dL	52.6±3.7
Triglycerides, mg/dL	150.6±24.0
Glucose, mg/dL	89.2±3.7
T3, ng/dL	112.7±5.6
T4, µg/dL	5.9±1.6
Hemoglobin, g/dL	13.3±0.4

Note: Values are presented as the mean ± standard error.

Abbreviations: n, number; LDL, low-density lipoprotein; HDL, high-density lipoprotein; T3, triiodothyronine; T4, thyroxine.

minutes; then, the recording of ECG and respiratory signals began for a total of 10 minutes. After 5 days, the elderly subjects returned to the Clinical Investigation Laboratory and repeated the bicycle treadmill at 60% of the working HR.

Data analysis

Analog-to-digital conversion was performed in 1,000 samples/second/channel and stored on a computer for offline signal processing and subsequent analysis (WinDaq DI-200 Acquisition; DATAQ Instruments, Inc., Akron, USA) with a personal computer. R-R intervals were calculated from the time difference of successive R-wave peaks. The software for data acquisition and spectral analysis has been described elsewhere²⁵ and consist of the use of WinDaq for the identification of R-R intervals in the ECG wave and in the wave of the respiratory rate. Visual inspection was carried out to identify some incorrect markings. Following this, the time series of the cardiac interval (tachogram) and respiration (respirogram) were generated. The power spectral density was integrated into two frequency bands of interest through the normalized data: high frequency (HF) between 0.15 Hz and 0.40 Hz; and low frequency (LF) between 0.03 Hz and 0.15 Hz. The sympathovagal balance, or autonomic balance, was also calculated, which is determined by the ratio between the components and assess the proportion (ratio) between the spectral power of low frequency component and high frequency component. All variability series were analyzed by means of autoregressive parametric spectral algorithms that automatically provided the number, center frequency, and power of each oscillatory component.^{2,25}

The LF and HF spectral components of the R-R interval were expressed in normalized units (nu).^{2,26}

Statistical analysis

The results are expressed as the mean and standard error. HR responses were analyzed using Student's paired *t*-test. To determine the effect of exercise intensity on cardiac variability, a one-way analysis of variance was performed, followed by Scheffé's test for multiple comparisons, in order to allow pairwise testing for significant differences between the stages. $P < 0.05$ was considered significant.

Results

HR responses were significantly lower after mild-intensity exercise (dynamic postexercise [P_{EX}]40%: 5 ± 1 bpm) when compared with moderate-intensity exercise (P_{EX} 60%: 10 ± 2 bpm) in elderly subjects (Figure 1). The R-R interval was significantly decreased in elderly subjects after mild and moderate intensive exercises ($1,032 \pm 23$ ms and 905 ± 8 ms, respectively), as opposed to the baseline conditions ($1,240 \pm 32$ ms). Similar to the ratio between the different intensities, the R-R at P_{EX} 60% was significantly lower than that at P_{EX} 40% (905 ± 8 ms versus $1,032 \pm 23$ ms) (Figure 2A). R-R interval variance was significantly reduced at both intensities of the exercise (P_{EX} 40%: $1,535 \pm 73$ ms; P_{EX} 60%: $1,213 \pm 35$ ms) when compared to baseline conditions ($3,154 \pm 110$ ms) (Figure 2B). Elderly subjects had a considerably increased normalized LF variability in the R-R interval after mild- (P_{EX} 40%: 68 ± 2 nu) and moderate- (P_{EX} 60%: 77 ± 1 nu) intensity exercises when compared with baseline conditions (55 ± 1 nu; $P < 0.001$, all comparisons). When both components of LF (low frequency) (nu) with 40% and 60% of the maximum HR were compared, a significant statistical difference (68 ± 1 nu and 77 ± 1 nu;

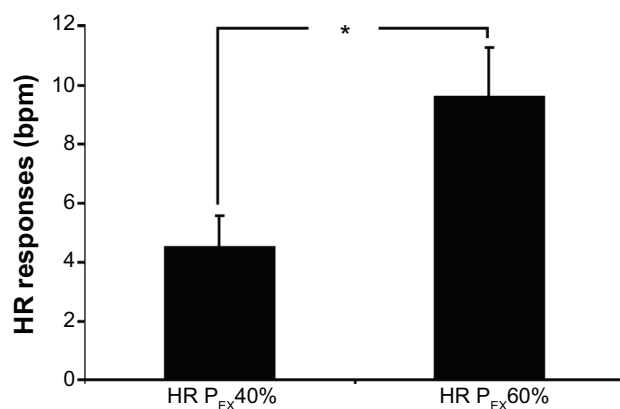


Figure 1 HR responses at mild (P_{EX} 40%) and moderate (P_{EX} 60%) dynamic exercise in elderly subjects ($n=10$).

Notes: * $P < 0.001$ P_{EX} 40% versus P_{EX} 60%. Values are presented as the mean \pm standard error.

Abbreviations: HR, heart rate; P_{EX} , postexercise; n, number.

$P < 0.001$) was observed (Figure 2C). The normalized HF variability of the R-R interval was significantly decreased after mild (P_{EX} 40%: 23 ± 1 nu) and moderate (P_{EX} 60%: 31 ± 2 nu) intensities of dynamic exercises when compared to baseline conditions (45 ± 1 nu). In terms of the different intensities of the dynamic exercises, we observed that high frequency in P_{EX} 60% was significantly lower than P_{EX} 40% (31 ± 2 high nu versus 23 ± 1 nu) (Figure 2D). Consequently, the LF-to-HF ratio of R-R variability was increased in mild (P_{EX} 40%: 2.0 ± 0.1) and moderate (P_{EX} 60%: 3.2 ± 0.1) dynamic exercise intensities when compared to baseline conditions (1.2 ± 0.1) in elderly subjects. In addition, when mild and moderate exercise intensities were compared, we observed that the sympathovagal balance was significantly lower in P_{EX} 40% compared to P_{EX} 60% (2.0 ± 0.1 versus 3.2 ± 0.1) (Figure 2E) ($P < 0.001$, for all comparisons).

Discussion

Our results indicate that elderly subjects at baseline conditions showed a predominance of sympathetic activity, and after mild and moderate dynamic exercise, this activity increased while vagal modulation decreased.

The role of aging on markers of autonomic modulation at rest or during exercise is well established.^{6,27,28} In the present study, moderate exercise imposed additional sympathetic overactivity (an increased LF nu and LF/HF ratio) and greater parasympathetic withdrawal (HF nu, R-R variance) when compared to baseline and postexercise at mild intensity (P_{EX} 40%). These effects might be due to a recurrent combination of adrenergic modulation with the increased residual effect of exercise (muscle and systemic metabolic effects) that promoted increased vascular reactivity.^{23,29}

Many studies have investigated chronic adaptations to exercise training and the acute effects of exercise, but little is known about the subacute effects on HR responses of a single round of exercise, and their cardiac autonomic regulation in healthy elderly people. In the present study, different exercise intensities showed responses of significantly different magnitudes when compared to the baseline condition. Acute exercise reduces triglyceride levels, increases high-density lipoprotein cholesterol levels,³⁰ insulin sensitivity, and the ability to resynthesize the glycogen of skeletal muscle.³¹ It also produces an acute blood pressure reduction,³² increases vascular conductance and vasodilatory reactivity,²⁹ alters the HR,^{33,34} decreases baroreflex sensitivity and HRV, and augments the LF component of systolic blood pressure.³⁴

Several studies have shown that healthy subjects and athletes, in periods after high-intensity exercise, exhibit a suppression of or slow parasympathetic reactivation,

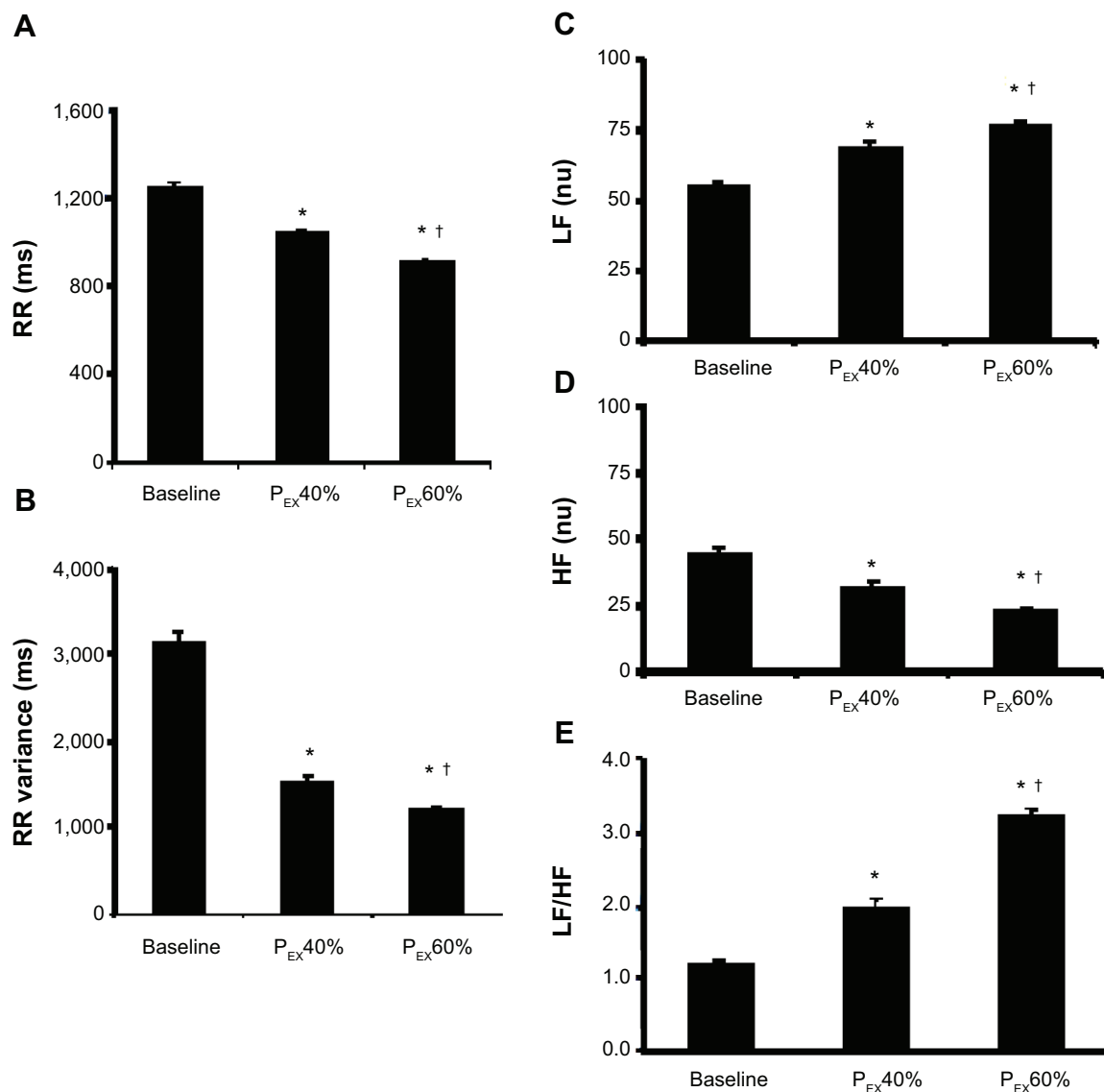


Figure 2 R-R intervals, R-R variance, normalized LF spectral component, normalized HF spectral component, and LF-to-HF ratio of the R-R interval in elderly subjects (n=10).

Notes: (A) R-R intervals; (B) R-R variance; (C) normalized LF spectral component (LF nu); (D) normalized HF spectral component (HF nu); and (E) LF-to-HF ratio of the R-R interval (LF/HF). The R-R intervals, R-R variance, and HF nu were significantly reduced in P_{EX}40% and P_{EX}60% when compared to the baseline condition. In addition, the parameters in the P_{EX}60% condition were significantly lower than those in the P_{EX}40% condition. *P<0.001 versus the baseline condition. †P<0.001 versus P_{EX}40%. Values are presented as the mean ± standard error.

Abbreviations: P_{EX}, postexercise; LF, low frequency; HF, high frequency; n, number; nu, normalized units.

sometimes followed by sympathetic suppression.^{35–38} Our results, however, show that in the elderly, sympathetic hyperactivation occurs in the moments after exercise. In fact, the very process of aging promotes modifications in HR and its HRV,^{4–6,39,40} and it also leads to impairments in baroreflex sensibility,^{41–44} a reduction in synthesis nitric oxide,^{45–47} and increases in sympathetic activity³ with concomitant reduced vagal activity.^{4–6,39} A combination of these disturbances adding the hard exercise and considering the age can be capable of causing autonomic cardiac disturbance in the elderly and exposes them to cardiac danger.

Although the results found in this study showed different magnitudes of HR recovery that are dependent upon exercise intensity and differences in indicators of cardiac autonomic modulation, it is worth highlighting that the current literature does not clearly show a correlation between HR recovery and HRV during rest and postexercise.^{6,48,49} In the present study, we evaluated the cardiac autonomic modulation by spectral analysis of HRV. However, other methods of investigation for efferent autonomic control are important, such as spontaneous baroreflex sensitivity, HR turbulence, and a symbolic analysis of HR. Nevertheless, these analyses were

precluded because of the absence of stress maneuvers that promote turbulence in HR; in addition, we did not simultaneously collect the blood pressure signal, preventing analysis of spontaneous baroreflex sensitivity. Additionally, we opted not to carry out analyses using nonlinear methods of cardiac autonomic control.

Considering the risk of cardiovascular events during and after exercise,^{12,13} our results call attention to the moments after exercise, especially following exercises of moderate intensity. For future research, it is important to monitor the elderly across different durations of exercise, to include tests of high intensity, and to monitor these variables.

Conclusion

In conclusion, an increase in HR, sympathetic modulation, sympathovagal balance, and a reduction in vagal modulation was observed in the elderly at both levels of intensity following dynamic postexercise; however, moderate exercise elevated these effects.

Acknowledgments

Grant support: This study was supported by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), and by the Brazilian National Research Council (Conselho Nacional de Pesquisa [CNPq]).

Disclosure

The authors report no conflicts of interest in this work.

References

- Gautschi B, Weidmann P, Gnädinger MP. Autonomic function tests as related to age and gender in normal man. *Klin Wochenschr.* 1986;64(11):499–505.
- Pagani M, Lombardi F, Guzzetti S, et al. Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. *Circ Res.* 1986;59(2):178–193.
- Lipsitz LA, Mietus J, Moody GB, Goldberger AL. Spectral characteristics of heart rate variability before and during postural tilt. Relations to aging and risk of syncope. *Circulation.* 1990;81(6):1803–1810.
- Lakatta EG, Levy D. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: Part II: the aging heart in health: links to heart disease. *Circulation.* 2003;107(2):346–354.
- Jensen-Urstad K, Storck N, Bouvier F, Ericson M, Lindblad LE, Jensen-Urstad M. Heart rate variability in healthy subjects is related to age and gender. *Acta Physiol Scand.* 1997;160(3):235–241.
- Antelmi I, de Paula RS, Shinzato AR, Peres CA, Mansur AJ, Grupi CJ. Influence of age, gender, body mass index, and functional capacity on heart rate variability in a cohort of subjects without heart disease. *Am J Cardiol.* 2004;93(3):381–385.
- Bigger JT Jr, Fleiss JL, Steinman RC, Rolnitzky LM, Kleiger RE, Rottman JN. Frequency domain measures of heart period variability and mortality after myocardial infarction. *Circulation.* 1992;85(1):164–171.
- Semrád B, Fiser B, Honzíkóvá N. Ageing and cardiac autonomic status. In: Malik M, editor. *Clinical Guide to Cardiac Autonomic Tests.* Dordrecht, Boston, London: Kluwer Academic Publishers; 1998:285–300.
- Billman GE, Hoskins RS. Time-series analysis of heart rate variability during submaximal exercise. Evidence for reduced cardiac vagal tone in animals susceptible to ventricular fibrillation. *Circulation.* 1989;80(1):146–157.
- Vanoli E, De Ferrari GM, Stramba-Badiale M, Hull SS, Foreman RD, Schwartz PJ. Vagal stimulation and prevention of sudden death in conscious dogs with a healed myocardial infarction. *Circ Res.* 1991;68(5):1471–1481.
- Miyazaki T, Zipes DP. Pericardial prostaglandin biosynthesis prevents the increased incidence of reperfusion-induced ventricular fibrillation produced by efferent sympathetic stimulation in dogs. *Circulation.* 1990;82(3):1008–1019.
- Albert CM, Mittleman MA, Chae CU, Lee IM, Hennekens CH, Manson JE. Triggering of sudden death from cardiac causes by vigorous exertion. *N Engl J Med.* 2000;343(19):1355–1361.
- Mittleman MA, Siscovick DS. Physical exertion as a trigger of myocardial infarction and sudden cardiac death. *Cardiol Clin.* 1996;14(2):263–270.
- Bigger JT Jr, Fleiss JL, Rolnitzky LM, Steinman RC. Frequency domain measures of heart period variability to assess risk late after myocardial infarction. *J Am Coll Cardiol.* 1993;21(3):729–736.
- Kleiger RE, Miller JP, Bigger JT Jr, Moss AJ. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol.* 1987;59(4):256–262.
- La Rovere MT, Bigger JT, 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(9101):478–484.
- Lanza GA, Guido V, Galeazzi MM, et al. Prognostic role of heart rate variability in patients with a recent acute myocardial infarction. *Am J Cardiol.* 1998;82(11):1323–1328.
- Ponikowski P, Anker SD, Chua TP, et al. Depressed heart rate variability as an independent predictor of death in chronic congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol.* 1997;79(12):1645–1650.
- Rowell LB. *Human Circulation: Regulation during Physical Stress.* New York, NY: Oxford University Press; 1986.
- 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(18):1351–1357.
- Yanagisawa S, Miki K, Yasuda N, Hirai T, Suzuki N, Tanaka T. The prognostic value of treadmill exercise testing in very elderly patients: heart rate recovery as a predictor of mortality in octogenarians. *Europace.* 2011;13(1):114–120.
- Savin WM, Davidson DM, Haskell WL. Autonomic contribution to heart rate recovery from exercise in humans. *J Appl Physiol Respir Environ Exerc Physiol.* 1982;53(6):1572–1575.
- 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(6):1529–1535.
- Karvonen MJ, Kentala E, Mustala O. The effects of training on heart rate; a longitudinal study. *Ann Med Exp Biol Fenn.* 1957;35(3):307–315.
- Pagani M, Montano N, Porta A, et al. Relationship between spectral components of cardiovascular variabilities and direct measures of muscle sympathetic nerve activity in humans. *Circulation.* 1997;95(6):1441–1448.
- 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(3):354–381.
- Trevizani GA, Benchimol-Barbosa PR, Nadal J. Effects of age and aerobic fitness on heart rate recovery in adult men. *Arq Bras Cardiol.* 2012;99(3):802–810.
- Zhang J. Effect of age and sex on heart rate variability in healthy subjects. *J Manipulative Physiol Ther.* 2007;30(5):374–379.

29. Bousquet-Santos K, Soares PP, Nóbrega AC. Subacute effects of a maximal exercise bout on endothelium-mediated vasodilation in healthy subjects. *Braz J Med Biol Res.* 2005;38(4):621–627.
30. Carlson LA, Mossfeldt F. Acute effects of prolonged, heavy exercise on the concentration of plasma lipids and lipoproteins in man. *Acta Physiol Scand.* 1964;62:51–59.
31. Perseghin G, Price TB, Petersen KF, et al. Increased glucose transport-phosphorylation and muscle glycogen synthesis after exercise training in insulin-resistant subjects. *N Engl J Med.* 1996;335(18):1357–1362.
32. Kenney MJ, Seals DR. Postexercise hypotension. Key features, mechanisms, and clinical significance. *Hypertension.* 1993;22(5):653–664.
33. Forjaz CL, Matsudaira Y, Rodrigues FB, Nunes N, Negrão CE. Post-exercise changes in blood pressure, heart rate and rate pressure product at different exercise intensities in normotensive humans. *Braz J Med Biol Res.* 1998;31(10):1247–1255.
34. Piepoli M, Coats AJ, Adamopoulos S, et al. Persistent peripheral vasodilation and sympathetic activity in hypotension after maximal exercise. *J Appl Physiol (1985).* 1993;75(4):1807–1814.
35. Peçanha T, Prodel E, Bartels R, et al. 24-h cardiac autonomic profile after exercise in sedentary subjects. *Int J Sports Med.* 2014;35(3):245–252.
36. Stewart GM, Kavanagh JJ, Koerbin G, Simmonds MJ, Sabapathy S. Cardiac electrical conduction, autonomic activity and biomarker release during recovery from prolonged strenuous exercise in trained male cyclists. *Eur J Appl Physiol.* 2014;114(1):1–10.
37. de Oliveira TP, de Alvarenga Mattos R, da Silva RB, Rezende RA, de Lima JR. Absence of parasympathetic reactivation after maximal exercise. *Clin Physiol Funct Imaging.* 2013;33(2):143–149.
38. Ostojic SM, Stojanovic MD, Calleja-Gonzalez J. Ultra short-term heart rate recovery after maximal exercise: relations to aerobic power in sportsmen. *Chin J Physiol.* 2011;54(2):105–110.
39. Craft N, Schwartz JB. Effects of age on intrinsic heart rate, heart rate variability, and AV conduction in healthy humans. *Am J Physiol.* 1995;268(4 Pt 2):H1441–H1452.
40. Irigoyen MC, Moreira ED, Werner A, et al. Aging and baroreflex control of RSNA and heart rate in rats. *Am J Physiol Regul Integr Comp Physiol.* 2000;279(5):R1865–R1871.
41. Ebert TJ, Morgan BJ, Barney JA, Denahan T, Smith JJ. Effects of aging on baroreflex regulation of sympathetic activity in humans. *Am J Physiol.* 1992;263(3 Pt 2):H798–H803.
42. Gribbin B, Pickering TG, Sleight P, Peto R. Effect of age and high blood pressure on baroreflex sensitivity in man. *Circ Res.* 1971;29(4):424–431.
43. Matsukawa T, Sugiyama Y, Mano T. Age-related changes in baroreflex control of heart rate and sympathetic nerve activity in healthy humans. *J Auton Nerv Syst.* 1996;60(3):209–212.
44. Parati G, Frattola A, Di Rienzo M, Castiglioni P, Pedotti A, Mancia G. Effects of aging on 24-h dynamic baroreceptor control of heart rate in ambulant subjects. *Am J Physiol.* 1995;268(4 Pt 2):H1606–H1612.
45. Al-Shaer MH, Choueiri NE, Correia ML, Sinkey CA, Barenz TA, Haynes WG. Effects of aging and atherosclerosis on endothelial and vascular smooth muscle function in humans. *Int J Cardiol.* 2006;109(2):201–206.
46. Singh N, Prasad S, Singer DR, MacAllister RJ. Ageing is associated with impairment of nitric oxide and prostanoid dilator pathways in the human forearm. *Clin Sci (Lond).* 2002;102(5):595–600.
47. Mingorance C, Herrera MD, Alvarez De Sotomayor M. [Mechanism involved in aged-related endothelial dysfunction]. *Med Clin (Barc).* 2009;132(2):62–69. Spanish.
48. Antelmi I, Chuang EY, Grupi CJ, Latorre MRDO, Mansur AJ. [Heart rate recovery after treadmill electrocardiographic exercise stress test and 24-hour heart rate variability in healthy individuals]. *Arq Bras Cardiol.* 2008;90(6):413–418. Portuguese.
49. Esco MR, Olson MS, Williford HN, Blessing DL, Shannon D, Grandjean P. The relationship between resting heart rate variability and heart rate recovery. *Clin Auton Res.* 2010;20(1):33–38.

Clinical Interventions in Aging

Publish your work in this journal

Clinical Interventions in Aging is an international, peer-reviewed journal focusing on evidence-based reports on the value or lack thereof of treatments intended to prevent or delay the onset of maladaptive correlates of aging in human beings. This journal is indexed on PubMed Central, MedLine,

CAS, Scopus and the Elsevier Bibliographic databases. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <http://www.dovepress.com/clinical-interventions-in-aging-journal>

Dovepress