Normotensive Individuals with Exaggerated Exercise Blood Pressure Response Have Increased Cardiac Vagal Tone

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Abstract

Background: **Exaggerated systolic blood pressure (SBP) levels during a maximal cardiopulmonary exercise test (CPET) are classically considered as inappropriate and associated with a higher risk for the development of cardiovascular diseases. It is known that the autonomic nervous system modulates the BP during exercise. However, the behavior of the cardiac vagal tone (CVT) has not been fully established in healthy individuals with an exaggerated BP response to CPET.**

Objective: **To analyze the behavior of the CVT in healthy adult males presenting an exaggerated BP response to CPET.**

Methods: **Of the 2,505 cases evaluated between 2002-2009, 154 cases were thoroughly identified, consisting of healthy male normotensive subjects aged 20-50 years. The evaluation included clinical assessment, anthropometric measurements, 4-second exercise test (cardiac vagal tone) and cardiopulmonary exercise test (CPET) performed in a cycle-ergometer, with BP measurements being taken every minute through auscultation. Based on the maximum SBP value obtained at the CPET, the sample was divided in tertiles, comparing CVT, maximum workload and VO_2 max.**

Results: **The CVT results differed between individuals in the lower tertile and upper tertile for the SBP response to the CPET, respectively: 1.57 ± 0.03 and 1.65 ± 0.04 (mean ± standard error of mean) (p = 0.014). The two tertiles also differed regarding the VO_2 max (40.7 ± 1.3 *vs* 46.4 ± 1.3 ml/kg^{-1}.min^{-1}; p = 0.013) and the maximum workload (206 ± 6.3 *vs* 275 ± 8.7 watts; p < 0.001).**

Conclusion: **An increased BP response during the CPET in healthy adult males is accompanied by indicators of good clinical prognosis, including higher levels of aerobic fitness and cardiac vagal tone. (Arq Bras Cardiol 2010;95(1):85-90)**

Key words: **Blood pressure; autonomic nervous system; exercise; 4-s exercise test.**

Introduction

The hemodynamic responses during a maximal cardiopulmonary exercise test (CPET) can be used for the individualized prescription of exercises for diagnostic and prognostic purposes[1]. During the physical exercise, whether of submaximal[2] constant intensity or progressive and maximal, the blood pressure (BP) is regularly measured. The BP behavior is commonly assessed during the CPET and exaggerated systolic blood pressure (SBP) values - i.e., SBP > 220 mmHg[1] -, have been classically considered as inappropriate and associated with a higher future risk of the development of hypertension[3] and a higher cardiovascular mortality[4]. However, some recent evidence suggest that an increased pressure response to exercise can, as opposed to what was initially considered, mean a favorable prognosis[5,6].

The autonomic nervous system has an important role in BP modulation, both at rest[7] and during exercise[8,9]. It is common for hypertensive individuals to present, at rest, a predominance of sympathetic activity[10]. Eryonucu et al[8] verified that a greater BP variation between rest and standardized submaximal exercise reflected a higher sympathetic activity, both at rest and on exertion. On the other hand, there is evidence that individuals with a decreased cardiac vagal tone (CVT) tend to have higher rates of cardiovascular and all-cause mortality[11,12]. However, the CVT condition has not been clearly established in healthy and normotensive individuals that present an increased BP response during a CPET. One of the possibilities is that such response would be accompanied by a decrease in the CVT, thus associating two negative prognosis results. As opposed to that, it is possible that an increased BP response might be observed in individuals presenting better aerobic fitness and cardiac parasympathetic function integrity, being in these cases primarily the result of a physiologically increased maximum cardiac output. With the objective of clarifying these opposing possibilities, the present study analyzed the CVT in healthy adults that presented an increased BP response to a maximal CPET.

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Methods

Sample

Through a detailed review of 2,505 medical-functional evaluations performed at our laboratory between 2002 and 2009, we identified 154 individuals that met, concomitantly, the following inclusion criteria: a) male gender; b) aged between 20 and 50 years; c) no known clinical diseases (i.e. healthy individuals) d) normotensive at rest - SBP $\leq$ 140 mmHg and diastolic BP $\leq$ 90 mmHg; e) no regular use of any medication, except for vitamins and similar supplements; f) CPET performed in lower limbs cycle-ergometer and g) completion of a true maximal CPET, without the need for early interruption due to clinical criterion or based on heart rate and/or BP thresholds and no electrocardiographic alterations compatible with significant myocardial ischemia.

The assessment included a clinical examination, which consisted of a detailed anamnesis and physical examination. At the anamnesis, the emphasis was put on the categorization of the physical activity pattern during childhood/adolescence, throughout adult life and in the last year, customary ingestion of alcohol, the past and present habit of smoking, known lipid profile abnormalities and family history of arterial hypertension. This was followed by anthropometric measurements and the 4-second exercise test (4sET) (cardiac vagal tone) and maximal CPET. The assessments were carried out by individual request, but usually after referral of the assistant physician. All individuals read and signed a specific Free and Informed Consent Form before undergoing the procedures and the study protocol was previously approved by the Research Ethics Committee of the institution.

Assessment of the cardiac vagal tone (CVT)

The cardiac vagal tone (CVT) was assessed by observing the rapid initial heart rate transient (rest-exercise transition) obtained through the 4sET and represented by the CVT. Briefly, the 4sET consists in pedaling as fast as possible from the 5th to the 8th second of a 12-second maximal inspiratory apnea in an unloaded lower limbs cycle-ergometer. Four verbal commands are given during the 4sET regarding the actions to be performed successively every four seconds: 1) fast maximal inspiration, primarily through the mouth; 2) pedaling as fast as possible; 3) sudden cessation of pedaling; and 4) expiration.

The assessment of the CVT by the 4sET is based on the reflex physiological response of vagal withdrawal, induced by rapid limb movement and cortical irradiation. The assessment of the CVT by the 4sET is reproducible[13] and was pharmacologically validated for the isolated assessment of the parasympathetic component[14], having been previously used in several physiological autonomic[15-18] and clinical studies by our group[19-22] and by other authors[23,24]. For the CVI measurement, two specific R-R intervals were identified and measured from digital electrocardiographic records (Elite PC, Micromed, Brazil), obtained from a single lead (CC_5 or CM_5) with 10-ms resolution, as follows: a) the RR interval obtained immediately before or the first one after the start of exercise, whichever is the longest and b) the shortest R-R interval (RRC) during the 4-s exercise (usually, the last one)[20,25]. The ratio between the duration of these two RR intervals generates an adimensional variable called Cardiac Vagal Index (CVI), which expresses the 4sET result and the higher the magnitude of the exercise-induced vagal withdrawal, the higher the CVI. Usually, two 4sET maneuvers are performed in order to obtain that with the highest ratio between these two intervals as representative of the CVI.

Cardiopulmonary exercise test (CPET)

Immediately after the 4sET, the individuals were submitted to a maximal CPET in a lower limbs cycle-ergometer, with collection and analysis of the expired gases (VO2000, MedGraphics, USA), following an individualized ramp protocol. The individuals were stimulated to reach their degree of exhaustion, objectively defined as the incapacity to maintain an adequate and constant rhythm of pedaling, in spite of strong verbal encouragement. None of the CPET was interrupted early due to clinical abnormalities or because the individuals had exceeded defined maximal heart rate or systolic/diastolic blood pressure values. The present study included only the CPET of which results indicated voluntary exhaustion as the reason for interruption, as reported by the physician who supervise it.

During the CPET, the electrocardiogram was continuously monitored from rest until at least 5 minutes after the maximal exertion, considering the same lead and digital electrocardiography system used for the 4sET [19,20].

Blood pressure (BP) assessment

Resting BP was measured after the individual remained in dorsal decubitus for at least five minutes, using a conventional sphygmomanometer or a digital professional Omron sphygmomanometer model XML-907 (Omron, USA) on the right upper limb. During the CPET, the systolic (SBP) and diastolic (DBP) arterial pressures were measured at the end of each minute by a properly trained and skilled physician, using the auscultation method on the brachial artery of the right upper limb, which was kept extended and supported by the physician or on the physician's shoulder, aiming at minimizing any effort on the part of the assessed individual. The individuals were advised to keep the trunk in the erect posture throughout the CPET, refraining from leaning the trunk forward at the final phase of the test. The measurements were obtained using a mercury column sphygmomanometer (American Diagnostic Corporation, USA) using a scale between 0 and 300 mmHg and employing a measurement resolution of 2 mmHg. For the analysis purpose, the highest SBP value obtained during the CPET was considered the maximum SBP, almost always the one obtained in the last minute of test.

Statistical analysis

The sample was described by means and standard deviations, whereas the inferential procedures were described as means and standard error of mean. Based on the maximum SBP value obtained at the CPET, the sample was divided in tertiles for the comparison of the CVI, maximum workload and VO_2 max through one-way ANOVA (Analysis of Variance), followed by Bonferroni test, when appropriate. Considering that the study inclusion criterion limited the levels of SBP and DBP, potentially compromising the parametric nature of the distribution, we chose to use Kruskal-Wallis ANOVA for the comparison of these measurements among the three tertiles, and the results were presented as median, minimum and maximum values. Pearson's correlation was used to evaluate the association between variables. The frequencies of the clinical variables of the individuals of each tertile were compared using the Chi-square test. The statistical analyses were carried out using the SPSS statistical program (release 17, *SPSS*, USA) and the level of significance was set at 5%.

Results

All CPET were performed without immediate or late clinical complications, although they were not interrupted, even when the maximal HR or the SBP and DBP levels considered to be elevated were reached. Of the 154 individuals included in the study, 31.8% (49 individuals) presented increased SBP (maximal SBP > 220 mmHg) at the CPET. The sample demographic characteristics divided in tertiles are shown in Table 1.

There was no difference regarding BMI, age, maximal HR and DBP at rest between individuals allocated in the three tertiles. However, the tertile that presented the lowest maximal SBP during the CPET, presented the lowest SBP at rest, when compared to the 3rd tertile of the highest BP response at the CPET ($p < 0.001$). Moreover, there was no difference regarding the clinical variables collected at the anamnesis, including alcohol consumption ($p = 0.641$), smoking status ($p = 0.548$), dyslipidemia ($p = 0.123$) and family history of arterial hypertension ($p = 0.311$) among the three tertiles (Table 1), except for the regular pattern of physical exercises at the three phases of life ($p < 0.001$; $p = 0.003$ and $p = 0.015$), i.e., childhood, adolescence and current, respectively.

The individuals at the upper tertile for SBP (SBP> 220 mmHg, maximal of 260 mmHg) during the CPET presented a higher CVI when compared to those at the first tertile (SBP < 205 mmHg) (1.65 ± 0.04 *vs* 1.57 ± 0.03; $p = 0.014$). The same occurred with VO_2 max (46.4 ± 1.3 *vs* 40.7 ± 1.3 ml/kg^{-1}.min^{-1}; $p = 0.013$) and for the maximum workload (275 ± 8.7 *vs* 206 ± 6.3 watts; $p < 0.001$) reached at the CPET (Figure 1). The individuals at the two tertiles with lower maximal SBP at the exercise did not differ regarding any of the three measurements above. There was a slight association between the CVI and the VO_2 max at the CPET, with a coefficient of correlation $r = 0.302$ ($p < 0.001$).

Table 1 - **Clinical and demographic characteristics of the sample**

Variable	Maximum systolic blood pressure at the CPET		
	1st tertile (n = 53)	2nd tertile (n = 52)	3rd tertile (n = 49)
	SBP < 205 mmHg	SBP 205 – 220 mmHg	SBP > 220 mmHg
Age (yrs)	36 ± 8.2	37 ± 7.0	38 ± 8.3
Dyslipidemia	18 (33%)	13 (25%)	8 (16%)
Smoking	14 (26%)	10 (18%)	9 (18%)
Alcohol consumption	11 (20%)	12 (23%)	14 (28%)
Family history of hipertension	6 (11%)	10 (19%)	11 (22%)
Weight (kg)	77.1 ± 14.2 *	80.9 ± 11. 5	83.3 ± 7.5
Height (m)	1.75 ± 0.07 *	1.76 ± 0.06	1.78 ± 0.06
BMI (kg/m^2)	25.0 ± 3.5	25.9 ± 3.1	26.2 ± 2.3
RHR (bpm)	66 ± 13.6 *	61 ± 8.4	68 ± 10.6
MHR (bpm)	185 ± 12.2	182 ± 14.4	180 ± 11.1
rSBP (mmHg)	120 (96 - 137)*	123 (108 - 140)	126 (112 - 140)
rDBP (mmHg)	72 (46 - 86)	74 (64 -92)	78 (53 - 90)
ΔSBP (mmHg)	72 ± 11.0 * †	88 ± 11.4 ‡	100 ± 11.4
Duration CPET (min)	10 ± 1.8 *	11 ± 2.2 ‡	13 ± 2.3

**p < 0.05 vs 3rd tertile; † p < 0.05 vs 2º tertile; ‡ p < 0.05 vs 3º tertile. SBP - systolic blood pressure; ECG - Electrocardiogram; BMI - body mass index; RHR - resting heart rate; MHR - maximum heart rate at the CPET; rSBP - resting systolic blood pressure; rDBP - resting diastolic blood pressure; ΔSBP - maximum SBP during CPET minus rSBP; CPET - cardiopulmonary exercise test.*

Discussion

Our study contributes with original data to the available body of knowledge on the assessment of the BP response to the exercise test. From a methodological point of view, the study presents a quite adequate control of many of the intervenient variables. All data obtained throughout the 7 years of study, including the anthropometric variables, the 4sET and the truly maximal CPET, were carried out and supervised by only 5 physicians, using identical criteria for the anthropometric measurements and for the clinical interruption of the CPET, as well as the same equipment for BP measurement, which was carefully verified, with a 2-mmHg resolution at every minute of the CPET.

The classification of the individuals as healthy was based on several criteria that had to be concomitantly met, including specifically never have been diagnosed or treated for cardiovascular disease, being normotensive, not be using relevant medications and not presenting exertion-induced electrocardiographic alterations. Even the regular ingestion of alcoholic beverages, which was recently studied[26] and shown to be associated with the incidence of arterial hypertension, was analyzed and did not show any difference among the three tertiles.

In spite of these methodological details, some limitations must be mentioned, including the exclusion of women and the limitation of the age range - between 20 and 50 years of age - which can interfere with the external validity of the study. It was not possible to obtain objective data of ambulatory monitoring of BP and of the endothelial function of the assessed individuals or of a simultaneous and standardized laboratory assessment of the lipid profile. Additionally, the present results cannot be extrapolated to individuals with a clinical diagnosis of arterial hypertension.

Previous studies have demonstrated that the increased BP response during a maximal CPET might be associated with unfavorable outcomes, such as the future onset of

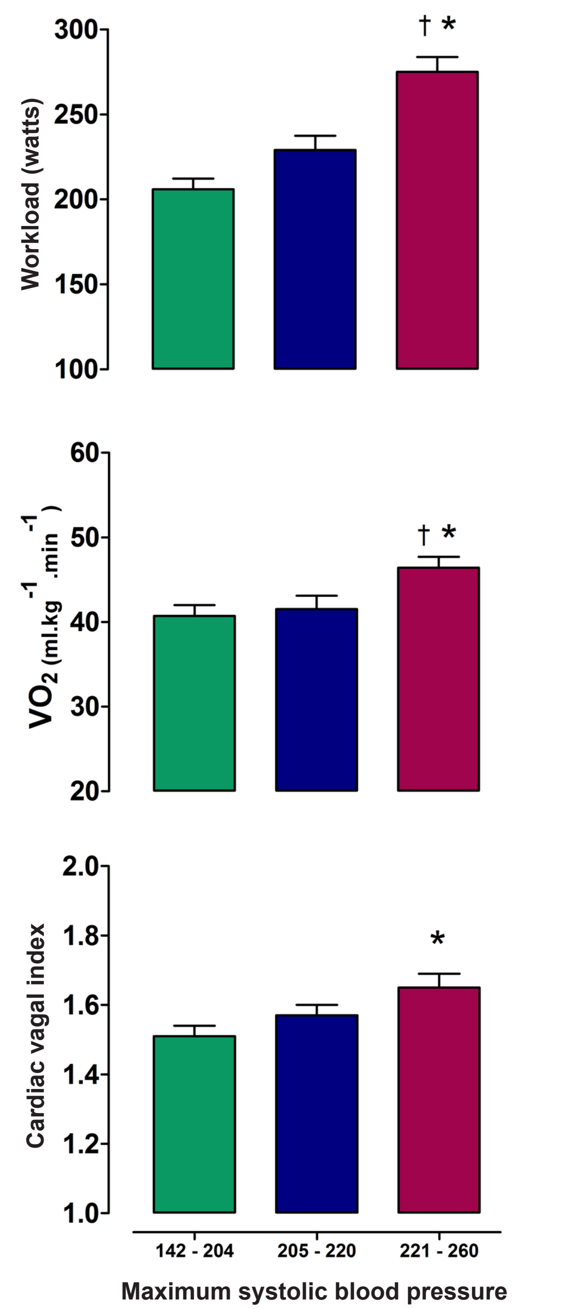

*Figure 1 - Comparison of the cardiac vagal index, VO_2 max and maximum workload attained at the CPET between the maximum SBP tertiles at the CPET (*p < 0.05 vs 1st tertile; † p < 0.05 vs 2nd tertile).*

systemic arterial hypertension[3] and a higher mortality due to cardiovascular diseases[4].

An increased SBP value during the CPET might be related to an increase in the sympathetic activity and endothelial dysfunction in hypertensive individuals[27]. On the other hand, some authors have pointed out that individuals that present increased SBP during a CPET present lower rates of cardiovascular mortality[28] and all-cause[5] mortality. Analyzing patients with other characteristics, Hedberg et al[6] recently demonstrated that elderly individuals that presented a higher pressure response (Δ SBP > 55 mmHg) at the CPET lived longer. In fact, increased SBP values during the CEPT, when accompanied by a physiological chronotropic response, will yield a higher double-product and, very probably, a higher myocardial oxygen consumption, which is only possible in healthy hearts[29].

While the participation of the autonomic nervous system in the BP modulation at rest is well known, its role in the genesis of the increased BP response during exercise has not been clearly established. Our results indicate that healthy adult men, that is, those who do not present any relevant clinical diagnosis and do not use any type of regular medication, but present an increased BP response (SBP > 220 mmHg) during a maximal CPET, present a physiological behavior of CVT, attaining higher values than those observed in individuals with maximum SBP values < 220 mmHg. These findings are very likely associated with a good prognosis, as it is known that the decrease in CVT is associated with the development of cardiovascular diseases and premature mortality[12].

Individuals that presented an increased BP response during a CPET are the ones that present higher workload and VO_2 max values. Considering that the aerobic fitness alone, measured or estimated, is an excellent predictor of the risk of cardiovascular or all-cause mortality[30], the individuals at the 3rd tertile (SBP > 220 mmHg) that present higher values of VO_2 max and CVT have two prognostic markers favorable to cardiovascular protection and survival. It is appropriate to emphasize that, due to the slight association between the VO_2 max and CVT, only 10% of the variability (r^2) of one of the variables is explained by the other, thus characterizing the isolated importance of each of these findings and indicating that they are not intrinsically dependent for individuals with the characteristics presented by the ones assessed in this study.

There is a certain clinical consensus in the interpretation of the pressure response, considering certain levels - more frequently 220 mmHg - as a cutoff to define a response as normal or abnormal. Conceptually, one could argue that the higher the absolute intensity of the performed exercise, there should be a tendency toward higher values. In other words, it is very logical to think that, when comparing two adult males of the same weight (and muscular mass) and age, with VO_2 max of 8 and 16 MET, both will tend to present similar decreases in peripheral vascular resistance on maximal exertion (muscular mass involved in similar exercise). The one with the double aerobic fitness, and probably also maximal cardiac output, when compared to the other, will probably generate a higher maximum SBP. One way to contemplate this question would be to express the behavior of the maximum SBP in relation to the aerobic fitness, as for instance, with a measurement of the ΔSBP (maximum SBP - SBP at rest) divided by ΔMET (VO_2 max - VO_2 at rest). Unfortunately, our experimental design does not allow us to confirm such hypothesis, which shall be addressed in further studies.

The measurement of SBP during the CPET is rarely obtained in athletes who present high aerobic performance. The two main reasons are very probably the lack of clinical interest regarding this information in individuals presumably healthy and the technical difficulty inherent to this measurement, especially when an individual is running on a treadmill at 18 or 20 km/h. With the growing interest in aerobic activities, including road cycling by adult and middle-aged men, there has been an increase in the number of healthy and normotensive individuals with an aerobic condition > 120% of that predicted for the age, thus attaining, according to Fick's equation, higher levels of maximum cardiac output.

Considering these aspects, it is very possible that a higher maximum SBP level at exercise is a physiological response and reflects then, in theory, just a high maximum oxygen consumption, and therefore, of the cardiac output for a normally - but not exceptionally - decreased peripheral vascular resistance in aerobically well-trained individuals and that have a normal or increased CVT.

Data that corroborate this impression can be deduced from the study by Nazar et al[31], who demonstrated an important increase in cardiac output in healthy individuals with hypertensive response to exercise, but no difference in the peripheral vascular resistance, when compared to individuals with normal SBP values during a CPET. Therefore, the increased maximum SBP values during the CPET in healthy individuals can, at least in part, be justified by the need to supply the demand caused by the exertion, not necessarily characterizing a pathological response, but representing, at least in normotensive adult men, a physiological response.

Gupta and cols.[5] have reported that a ΔSBP during the CPET > 44 mmHg is associated with a 23% improvement in survival, regardless of the age and aerobic fitness of the study participants. However, future studies are necessary to evaluate the outcome and confirm whether the healthy adult men with increased maximum SBP during a CPET, but who present higher CVT values, represented by the CVI, will develop systemic arterial hypertension or if they will present a higher rate of unfavorable cardiovascular outcomes or, on the contrary, if they will present an increased survival and a better quality of life.

Conclusion

The present study was the first to demonstrate that normotensive healthy male adults, with a BP response considered clinically increased, i.e., SBP > 220 mmHg (in some cases as high as 260 mmHg), present some indicators of good clinical prognostic at exercise, including higher aerobic fitness and cardiac vagal tone. In this sense, at least for a maximal CPET carried out in a lower limbs cycle-ergometer, it is suggested that the type of assessment recommended in the guidelines[1] for the evaluation of BP response to exertion should be reviewed. Future studies will identify the late implications of these findings.

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Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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