Title: POST-EXERCISE HYPOTENSION AND ITS HEMODYNAMIC DETERMINANTS DEPEND ON THE CALCULATION APPROACH

Running tittle: Post-exercise hypotension calculation approaches

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Abstract

Post-exercise hypotension (PEH) has been assessed by three calculation approaches: I= (post-exercise – pre-exercise); II = (post-exercise – post-control); and III = [(post-exercise – pre-exercise) – (post-control – pre-control)]. This study checked whether these calculation approaches influences PEH and its determinants. For that, 30 subjects underwent two exercise (cycling, 45min, 50%VO_2peak) and two control (seated rest, 45min) sessions. Systolic (SBP) and diastolic (DBP) blood pressures, cardiac output (CO), systemic vascular resistance (SVR), heart rate (HR) and stroke volume (SV) were measured pre and post-interventions in each session. The mean value for each moment in each type of session was calculated, and responses to exercise were analyzed with each approach (I, II and III) to evaluate the occurrence of PEH and its determinants. Systolic PEH was significant when calculated by all approaches (I = -5±1, II = -11±2 and III = -11±2 mmHg, $P<0.05$), while diastolic PEH was only significant when calculated by approaches II and III (-6±1 and -6±1 mmHg, respectively, $P<0.05$). CO decreased significantly after the exercise when calculated by approach I, but remained unchanged with approaches II and III; while SVR increased significantly with approach I, but decreased significantly with approaches II and III. HR was unchanged after the exercise with approach I, but increased significantly with approaches II and III, while SV decreased significantly with all approaches. Thus, PEH and its hemodynamic determinants are influenced by the calculation approach, which should be considered when designing, analyzing and comparing PEH studies.

Summary Table

What is know about topic • Post-exercise hypotension (PEH) is characterized by a reduction in blood pressure after a single session of exercise. • Previous studies have demonstrated diverse results regarding the occurrence, magnitude and subjacent hemodynamic determinants of PEH, which has been attributed to differences in populations studied and exercise protocols employed.
What this study adds • The diverse results obtained by previous studies can also be related to the different approaches used to calculate PEH and its determinants. • When designing studies, analyzing data and interpreting results about PEH and its determinants, it is essential to take into account the calculation approach employed.

INTRODUCTION

Post-exercise hypotension (PEH) is characterized by a reduction in systolic (SBP) and/or diastolic (DBP) blood pressure (BP) after a single session of exercise(1). PEH is accepted as clinically relevant due to its significant magnitude (mean decrease of 5/3 mmHg for SBP/DBP, respectively)(2) and long lasting duration (i.e. up to 16/12 hours for SBP/DBP, respectively)(3), which may benefit individuals with high BP(4). Moreover, PEH presents a strong and positive association with chronic BP reduction after exercise training(5,6), which suggests its use as a tool to predict BP responsiveness to training.

PEH has been reported after different aerobic exercise protocols and in diverse populations (normotensives, pre-hypertensives and hypertensives)(2); however its magnitude varies a lot among the studies(4). In addition, some studies did not report the occurrence of PEH(7,8). This large variation in PEH results is also observed regarding its hemodynamic determinants, since both a reduction in cardiac output (CO)(9–11) or in systemic vascular resistance (SVR)(7,12–15) have been reported in literature. Although this inconsistency has been attributed to differences in the characteristics of population and exercise protocols employed in the studies(16), the approach to calculate PEH may also influence such outcomes.

In many studies(5–7,9,17–21), PEH has been calculated simply by the difference between post- and pre-exercise BPs (I: post-exercise BP – pre-exercise BP). Other studies(8,10,13,14,22–24) have compared post-exercise BP with BP measured after a control session without exercise (II: post-exercise BP – post-control BP). Lastly, some studies(11,12,15) have employed a more complex approach, calculating the “net effect” of exercise as the difference between the BP response to an exercise session and the BP

response to a control session [III: (post-exercise BP – pre-exercise BP) – (post-control BP – pre-control BP)]. Nevertheless, to the best of our knowledge, no study has directly examined the influence of the calculation approach on the interpretation about the occurrence of PEH and its hemodynamic determinants. This possible influence is supported by the fact that approach I does not control for time changes in BP, and approach II does not consider day-to-day variations in BP.

Based on previous background, the current study aimed to investigate whether the occurrence and magnitude of PEH as well as its hemodynamic determinants are influenced by the calculation approach, employing the three above-mentioned approaches (I, II and III).

METHODS

Participants

Male and female subjects, aged between 20 and 60 years old were invited to participate in this study. The exclusion criteria were: 1) diagnosis of any cardiovascular disease, except for hypertension; 2) presence of electrocardiographic abnormalities that suggest cardiovascular disease; 3) resting SBP or DBP higher than 160 and 105 mmHg, respectively; 4) use of medication that directly affects the autonomic nervous system; and 5) presence of any health problem that restrains exercise execution.

The subjects who fulfilled the study criteria signed an informed written consent to participate. This study was approved by the local Ethics Committee (CAAE 43759215.3.0000.5391) and registered at the Brazilian Clinical Trials (www.ensaiosclinicos.gov.br-RBR-3nxn34).

Preliminary evaluation

To confirm the absence of any exclusion criteria, subjects underwent three visits to the laboratory in different days. In the first visit, they were interviewed, and anthropometric and resting BP measurements were performed. In the second visit, resting BP was measured again, and in the third visit, a maximal cardiopulmonary exercise test was conducted. The interview included questions regarding personal data, health condition, familiar health history, current medication treatment and physical activity practice. Anthropometric data consisted of body mass (kg) and height (m) measures (Filizola S.A, Personal, Campo Grande, Brazil), and the calculation of body mass index (BMI). Auscultatory BP was evaluated in triplicate in each visit. Measures were taken after 5 min of sitting rest with a mercury sphygmomanometer (Uniteq, São Paulo, Brazil). SBP and DBP were, respectively, determined by phases I and V of the Korotkoff sounds. The mean of the six measures was used to define the resting BP level of each subject(25). The maximal cardiopulmonary exercise test was performed on a cycle ergometer (Lode Medical Technology, Corival, Groningen, Netherlands) with an initial load of 30 W and increments of 30 W every 3 min until subjects were unable to proceed. A physician evaluated resting and exercise ECG as well as HR and BP responses. Peak oxygen uptake (VO_2peak) was defined as the highest value obtained during the test, in averages of 30 s

Experimental protocol

After the preliminary procedures, the experimental protocol was started. All subjects underwent two exercise and two control sessions, with an interval of at least two

days between them. The order of sessions' execution was randomized. For that, experimental sessions were divided in two blocks, each one being composed by one exercise and one control session. These blocks were performed successively and sessions were randomized within each block. Duplication of each session (exercise and control) was done to improve the precision of measures. Thus, the mean value of the two repeated sessions was considered for analyses.

Before all the experimental sessions, the subjects were instructed to keep similar and habitual routines in the previous 24h. They were also instructed to avoid: exercise execution for the previous 48h; alcoholic drinks for the previous 24h; and smoking and the ingestion of foods or drinks that might affect cardiovascular function on days of the sessions. In addition, they were instructed to have a light meal at least two hours before the sessions. The subjects in use of regular medications were instructed to take their medications as prescribed by the physician and at similar times before the experimental sessions.

Each subject performed all the experimental sessions in the same time of day. Laboratory temperature was controlled and kept between 20 and 22^{o}C. Each session was composed by pre-intervention, intervention (exercise or control) and post-intervention periods. Assessments were taken during the pre- and post-intervention periods with the subjects resting in sitting position. The pre-intervention assessment started after 20 min of rest, while the post-intervention assessment was taken 45 min after the end of the intervention. In each assessment, auscultatory BP, heart rate (HR) and CO were measured in this sequence. This sequence of measurements was repeated three times with an interval of 3 min between them. The average of the three measurements obtained in each

assessment period was calculated for each variable.

Exercise and control interventions

In the exercise sessions, during the intervention period, the subjects exercised on a cycle ergometer for 45 min at 50% of VO_2peak. The workload necessary to reach this intensity was calculated by the linear regression between workload and VO_2 obtained during the cardiopulmonary exercise test. In addition, exercise intensity was checked by the direct measurement of VO_2 from 15 to 35 min of the exercise. In the control sessions, the subjects remained seated on the cycle ergometer for the same amount of time of exercise sessions, but without performing any effort.

Measurements

BP was measured by the auscultatory method on the dominant arm, using the technique described in the preliminary procedures, and with all measurements taken by the same trained evaluator. Mean BP (MBP) was calculated trough the following formula: (SBP + 2 × DBP) / 3. CO was estimated by the indirect method of Fick(26), through the maneuver of CO_2 rebreathing(27), using a gas analyzer (Medical Graphics Corporation CPX/Ultima, Minnesota, USA). HR was measured by radial pulse palpation. SVR was calculated by the quotient between MBP and CO, and stroke volume (SV) by the quotient between CO and HR.

Statistical analysis

Considering a statistical power of 90%, an alpha error of 5% and standard

deviations of 3 mmHg for SBP and 0.32 l/min for CO, the minimal sample size required was 10 subjects for SBP and 11 subjects for CO in order to detect worthwhile effects of 4 mmHg and 0.32 l/min, respectively(28).

Prior to data analyses, the mean value for each moment (pre and post) in each type of session (control and exercise) was calculated. Data normality was checked through Shapiro-Wilk test (SPSS, Illinois, USA).

First, to confirm similarity in pre-intervention values between the sessions, pre-exercise values were compared with pre-control values by paired t-tests. Then, the occurrence of PEH and its hemodynamic determinants were determined by each approach: Approach I - post-exercise values were compared with pre-exercise values; Approach II - post-exercise values were compared with post-control values; and Approach III, the net effects of exercise [(post-exercise values – pre-exercise values) – (post-control values – pre-control values)] were compared with zero. All these comparisons were done by paired *t* tests. Finally, the magnitudes of the responses obtained with each approach were compared using one-way ANOVA for repeated measures and Newman-Keuls post hoc test when necessary. Data was presented as mean ± SE and $p < 0.05$ was set as significant.

RESULTS

Thirty-eight subjects were assessed for eligibility, but 4 did not accept to participate in the study. From the remaining 34 subjects, one was excluded during the preliminary evaluation due to ECG abnormalities and another due to orthopedic limitation. Thus, 32 subjects started the experimental protocol, but two dropped out due to personal reasons. Therefore, the final sample was composed by 30 subjects (24 men and 6 women) whose

characteristics are shown in Table 1.

Pre-intervention SBP, DBP, CO, SVR, SV and HR were similar between the exercise and control sessions (Table 2).

PEH evaluated by the three calculation approaches are shown in Figure 1. Systolic PEH was significant when evaluated by approaches I (post-exercise: 115±2 vs. pre-exercise: 120±2 mmHg, $p<0.001$), II (post-exercise: 115±2 vs. post-control: 126±2 mmHg, $p<0.001$) and III (net effect: -11±2 mmHg vs. zero, $p<0.001$). Diastolic PEH was not significant with approach I (post-exercise: 82±2 vs. pre-exercise: 82±2 mmHg, $p=0.186$), but was significant when assessed by approaches II (post-exercise: 82±2 vs. post-control: 88±2 mmHg, $p<0.001$) and III (net effect: -6±1 mmHg vs. zero, $p<0.001$).

Hemodynamic determinants of PEH evaluated by the three methods of calculation are shown in Figure 2. CO decreased significantly after the exercise when analyzed by calculation approach I (post-exercise: 4.43±0.17 vs. pre-exercise: 5.05±0.21 l/min, $p<0.001$), while remained unchanged when analyzed by approaches II (post-exercise: 4.43±0.17 vs. post-control: 4.40±0.18 l/min, $p=0.808$) and III (net effect: -0.14±0.13 l/min vs. zero, $p=0.314$). SVR increased significantly after the exercise with approach I (post-exercise: 22.0±0.8 vs. pre-exercise: 19.7±0.7 U, $p<0.001$), but decreased significantly with approaches II (post-exercise: 22.0±0.8 vs. post-control: 24.2±1.1 U, $p=0.003$) and III (net effect: -1.5±0.7 U vs. zero, $p=0.033$). HR remained unchanged with approach I (post-exercise: 68±1 vs. pre-exercise: 66±1 bpm, $p=0.156$), but increased significantly when analyzed by approaches II (post-exercise: 68±1 vs. post-control: 61±2 bpm, $p<0.001$) and III (net effect: +7±1 bpm vs. zero, $p<0.001$). For SV, a significant decrease was found with all approaches (I = post-exercise: 66±3 vs. pre-exercise: 77±4 ml, $p<0.001$; II = post-

exercise: 66±3 vs. post-control: 73±3 ml, p=0.001; and III = net effect: -10±3 ml vs. zero, p<0.001).

When the magnitudes of changes were compared among the three calculation approaches significant differences were observed for all variables (p≤0.05), except for SV, with approach I providing results significant different from approaches II and III that in turn produced similar results (Table 3).

DISCUSSION

The main finding of this study is that the interpretation of results about the occurrence of PEH as well as its subjacent hemodynamic determinants varied according to the calculation approach employed.

In the current study, systolic PEH occurred regardless of the approach (I, II and III), but the magnitudes of SBP decrease were different among the approaches, with calculations II and III revealing greater PEH than I. Along this line, diastolic PEH was significant when calculated by approaches II and III, but not by approach I. These divergences may have occurred due to BP changes in the control session. Actually, SBP and DBP increased from pre to post-intervention in the control sessions (SBP: 119±2 vs 126±2 mmHg, P=<0.001; and DBP: 82±2 vs 88±2, p<0.001; data not shown). The increase in BP after a control condition has been already reported(11,12), and has been attributed to the circadian variation of BP when experiments were conducted in the morning(29) and/or to a response to the orthostatic stress imposed by the sitting position(30). Without considering the responses to a control session, the effect of exercise blunting the increase in SBP and DBP would not be taken into account. It is also important to consider that under different

experimental conditions, BP might change in a different ways after a control period. For example, BP might decrease during a control session performed in evening(11). In that case, a decrease in BP observed with approach I (post-pre-exercise) could reflect the effect of the exercise, the circadian behavior or the additive effect of both.

The current study also showed that the calculation approach may influence the interpretation of the systemic hemodynamic determinant of PEH. In the present study, using approach I, BP decrease after the exercise would be attributed to a decrease in CO, while with approaches II and III, a decrease of SVR would be the underlying determinant. Actually, CO decreased after exercise in comparison with pre-exercise, but it was similar to post-control values because CO also decreased in the control session (4.89±0.20 vs 4.40±0.18 ml/min, $p<0.001$, data not shown). Similarly, post-exercise SVR increased when compared to pre-exercise values, but it was lower than post-control values, because SVR increased more in the control session from pre-control to post-control (20±5 vs 24±6, $p<0.001$; data not shown). In accordance with the present data, previous studies(11,12,31) have also reported a decrease in CO and an increase in SVR during a control session performed in the sitting position, which might be explained by the orthostatic stress promoted by this position that decreases venous return and deactivates the cardiopulmonary reflex(30). Consequently, in the present study, when time effects were considered (i.e. employing a control situation), previous exercise promoted PEH by a SVR decrease.

The current results support that different approaches to evaluated PEH may lead to conflicting results, demonstrating the importance of choosing an adequate method for calculating PEH in accordance to the study objectives and, specially, to interpret study´s results in accordance with the approach employed. The assessment of PEH through

approach I has limitations related to the absence of controlling the time influence, which has been emphasized in the Consolidated Standards of Reporting Trials (CONSORT)(32). Thus, when calculation approach I is employed the real effect of the previous exercise on post-exercise response might be inadequately assessed. This approach might be useful to compare the post-effect of different exercise protocols, but it is not adequate to stablish the occurrence, magnitude and determinants of PEH. Time influence is controlled with approaches II and III.

Interestingly, in the current study, approaches II and III provided similar results which can be explained by the fact that pre-intervention values were similar in the exercise and control sessions (Table 2). However, it is important to mention that a difference in pre-intervention values can happen due to day-to-day BP variability(33) or to an effect of a previous intervention (e.g. comparing PEH before and after a period of training that changed baseline BP). Differences in pre-intervention values would introduce an important bias to approach II, preventing to attribute post-exercise responses to exercise per se, since they can just reflect the pre-intervention differences. Approach III overcame this limitation.

Despite approaches II and III are more robust to assess PEH than approach I, important aspects involving the application of PEH should be mentioned. The use of PEH to identify individuals with greater responsiveness to training has been only explored with approach I(5,6). However, it is possible that employing approaches II and III would improve this prediction, which needs to be investigated. Other aspect that deserves further elucidation is which approach provides results with greater clinical relevance. It is not clear the clinical difference of decreasing BP after exercise in relation to pre-exercise (approach I) or to a control condition (approaches II and III).

The current study is not without limitations. The sample was composed by subjects with different characteristics (different BP status, taking or not-taking anti-hypertensive medications, a wide age range and both genders) to generate a comprehensive sample that produces results not restrained to a specific population. The study demonstrated that calculation approach can influence the interpretation about PEH occurrence, magnitude and determinants. However, the specific influence in specific populations and study conditions should be addressed by future research.

In conclusion, the current study empirically demonstrated that different approaches to calculate PEH may lead to conflicting interpretations regarding its occurrence, magnitude and hemodynamic determinants. Therefore, study design, data analyses and interpretation of results about PEH and its determinants must take into account the calculation approach employed. Future studies should explore the clinical impact of the results obtained with each one of these different calculation approaches, since they provide different outcomes.

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Conflict of interest

The authors declare no conflict of interest.

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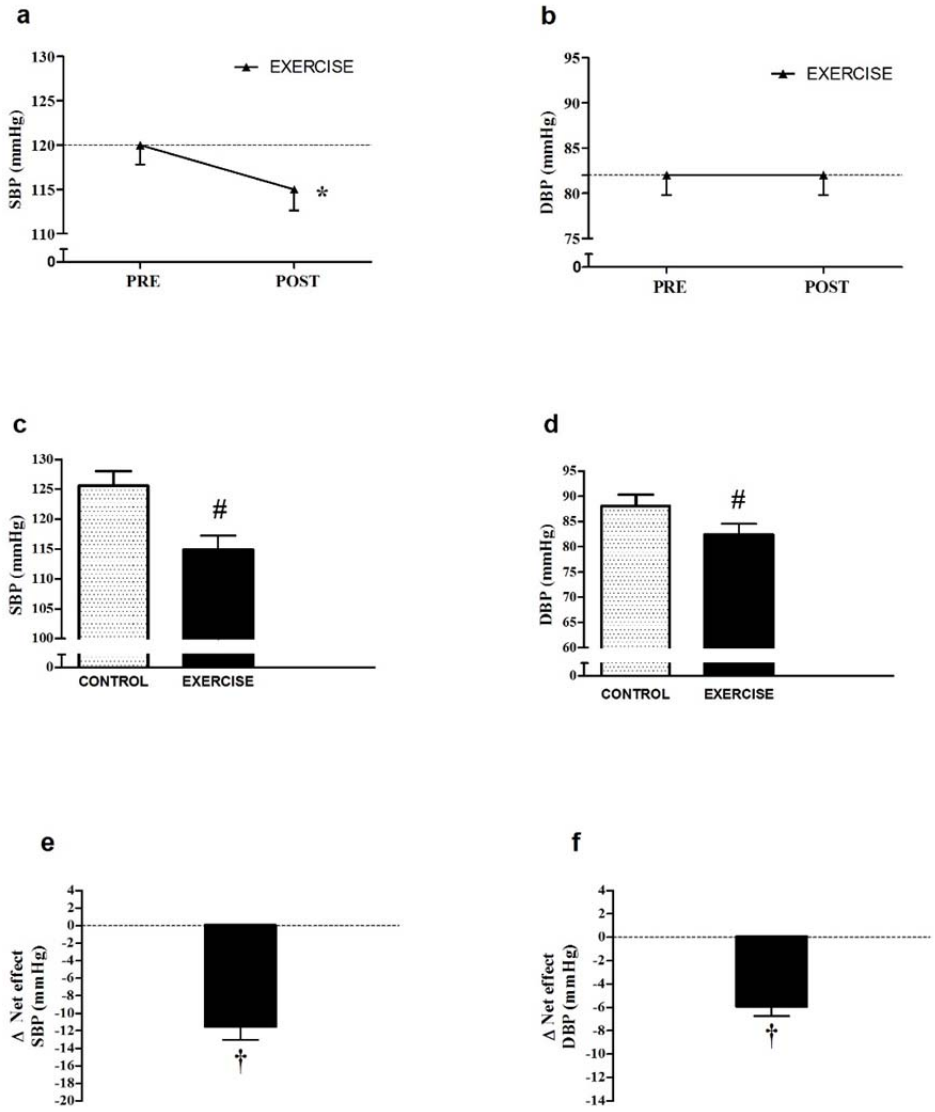
Figure legends

Figure 1. Systolic (SBP) and diastolic blood pressures (DBP) responses to exercise calculated by the following three approaches: I: post-exercise vs. pre-exercise **(panel a and b)**; II: post-exercise vs. post-control **(panel c and d)**; and III: [(post-exercise – pre-exercise) – (post-control – pre-control)] vs. zero **(panel e and f)**. *Post-exercise significantly different from pre-exercise ($p<0.05$). #Post-exercise significantly different from post-control ($p<0.05$). †Net effect significantly different from zero ($p<0.05$). Values are mean ± SE.

Figure 2. Cardiac output (CO), systemic vascular resistance (SVR), heart rate (HR) and stroke volume (SV) responses to exercise calculated by the following three approaches: I: post-exercise vs. pre-exercise **(panel a and b)**; II: post-exercise vs. post-control **(panel c and d)**; and III: [(post-exercise – pre-exercise) – (post-control – pre-control)] vs. zero **(panel e and f)**. *Post-exercise significantly different from pre-exercise ($p<0.05$). #Post-exercise significantly different from post-control ($p<0.05$). †Net effect significantly different from zero ($p<0.05$). Values are mean ± SE.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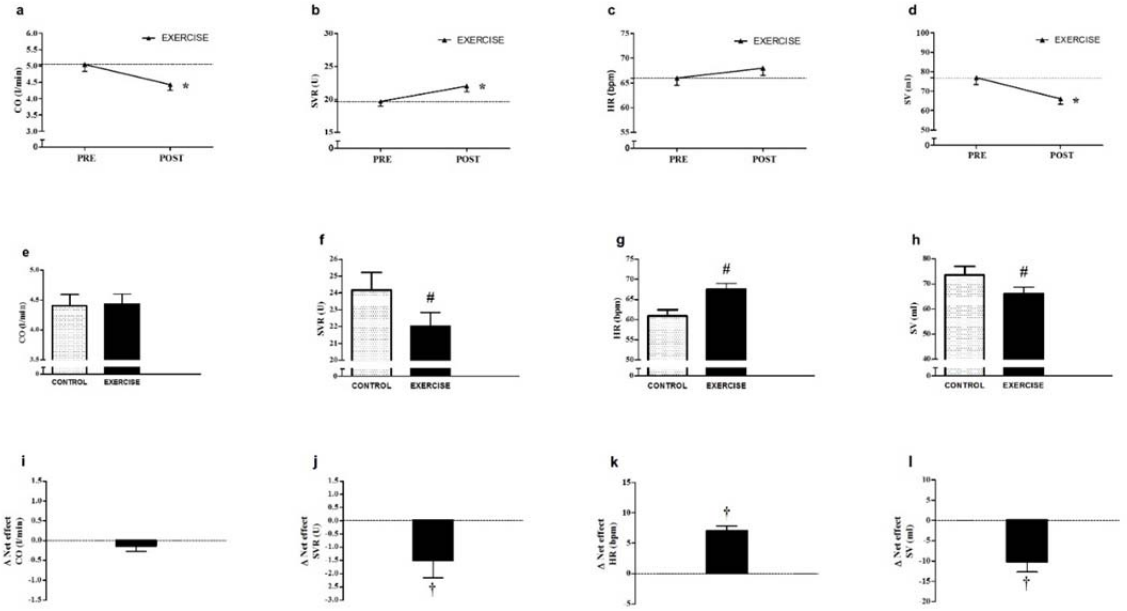
a
EXERCISE
CO (l/min)
PRE
POST
*
b
EXERCISE
SVR (U)
PRE
POST
*
c
EXERCISE
HR (bpm)
PRE
POST
d
EXERCISE
SV (ml)
PRE
POST
*
e
CO (l/min)
CONTROL
EXERCISE
f
SVR (U)
#
CONTROL
EXERCISE
g
HR (bpm)
#
CONTROL
EXERCISE
h
SV (ml)
#
CONTROL
EXERCISE
i
Δ Net effect
CO (l/min)
j
Δ Net effect
SVR (U)
†
k
Δ Net effect
HR (bpm)
†
l
Δ Net effect
SV (ml)
†

Table 1. Characteristics of the subjects (n=24 males and 6 females).

Characteristic	Value
Age (ys)	42 ± 2
Height (m)	1.73 ± 0.01
Weight (kg)	90.5 ± 3.4
Body Mass Index (kg/m^2)	30.1 ± 0.9
Systolic BP (mmHg)	123 ± 2
Diastolic BP (mmHg)	83 ± 2
Blood pressure diagnosis	
Normotensive, n (%)	9 (30)
Pre-hypertensive, n (%)	8 (27)
Hypertensive, n (%)	13 (43)
Anti-hypertensive Drug therapy	
No medication, n (%)	22 (73)
AT1 Receptor blocker, n (%)	5 (17)
Angiotensin-converting enzyme inhibitor, n (%)	2 (7)
Diuretic, n (%)	2 (7)
Dihydropyridine calcium channel blocker, n (%)	1 (3)
Treatment Strategy	
Not using anti-hypertensive medication	5 (17)
Monotherapy	7 (23)
Polytherapy	1 (3)

Continuous values are expressed as mean ± SE. BP = blood pressure. Normotension was defined as systolic and diastolic blood pressure < 130 and 85 mmHg, respectively. Pre-hypertension was defined as systolic and/or diastolic blood pressure between 130-139 and/or 85-89 mmHg, respectively. Hypertension was defined as systolic and/or diastolic blood pressure ≥ 140 and/or 90 mmHg or the use of anti-hypertensive medications.

Table 2 Blood pressure and its hemodynamic determinants measured in the pre-intervention periods of the exercise and control sessions (mean value of the two sessions of the same type – exercise or control).

	Exercise	**Control**	**P value**
SBP (mmHg)	120 ± 2	119 ± 2	0.469
DBP (mmHg)	82 ± 2	82 ± 2	0.751
CO (l/min)	5.05 ± 0.21	4.89 ± 0.20	0.219
SVR (U)	19.7 ± 0.7	20.3± 0.9	0.198
HR (bpm)	66 ± 1	67 ± 2	0.671
SV (ml)	77 ± 4	74 ± 3	0.222

Values are mean ± SE; P value = significance levels in paired t-test; SBP = systolic blood pressure; DBP = diastolic blood pressure; CO = cardiac output; SVR = systemic vascular resistance; HR = heart rate; SV = stroke volume.

Table 3. Magnitudes of changes of blood pressure and its hemodynamic determinants after the exercise calculated by three different calculation approaches: I = post-exercise – pre-exercise; II = post-exercise – post-control; and III = (post-exercise – pre-exercise) – (post-control – pre-control).

Variable	I	II	III	P-value
SBP (mmHg)	-5 ± 1	-11 ± 2†	-11 ± 2†	< 0.01
DBP (mmHg)	1 ± 0	-6 ± 1†	-6 ± 1†	< 0.01
CO (l/min)	-0.62 ± 0.12	0.03 ± 0.11†	-0.14 ± 0.13†	< 0.01
SVR (U)	2.3 ± 0.6	-2.2 ± 0.7†	-1.5 ± 0.7†	< 0.01
HR (bpm)	1 ± 1	7 ± 1†	7 ± 1†	< 0.01
SV (ml)	-11 ± 2	-7 ± 2	-10 ± 3	0.180

Values are mean ± SE. P value = significance levels in one-way ANOVA. SBP = systolic blood pressure; DBP = diastolic blood pressure; CO = cardiac output; SVR = systemic vascular resistance; HR = heart rate; SV = stroke volume. †Significantly different ($p < 0.05$) from approach I.