TCD Cerebral Hemodynamic Changes During Moderate Intensity Exercise In Older Adults.

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TCD Hemodynamic Changes During Exercises in Older Adults.

BACKGROUND AND PURPOSE

Exercise plays an important role in supporting overall brain health. However, the mechanisms by which exercise supports brain health are imprecisely defined. Further, brain hemodynamic changes during exercise are not clearly understood, especially in older adults. The primary aim of this study was to compare cerebral blood flow velocity and pulsatility index (PI) during moderate-intensity exercise between older adults with normal pulsatile flow (normal PI) and older adults with elevated pulsatile flow (elevated PI). Secondary aims were to compare cardiovascular disease risk and cognitive function between individuals with elevated and non-elevated PI.

METHODS

Using transcranial Doppler ultrasound (TCD), middle cerebral artery blood velocity (MCAv) and PI were recorded during the rest and moderate intensity exercise. End tidal carbon dioxide ($P_{ET}CO_2$) and beat-to-beat mean arterial blood pressure (MAP) were also recorded.

RESULTS

We enrolled 104 older adults into the study. The change in PI was greater in normal PI group (35.5% vs. 21.3%, P=0.005). The change in MCAv was similar in both groups (11.6% for normal PI vs. 10.6% for elevated PI; P=0.22). There was no significant difference in cardiovascular disease risk between the two groups (P=0.77). Individuals with elevated PI performed significantly worse in WAIS-R Digit Symbol and Trail Making Test A (P=0.04 and P=0.01, respectively).

CONCLUSIONS

The percent increase in PI from rest to moderate intensity exercise was attenuated in the older adults with elevated resting PI. Higher resting PI may negatively affect brain health as evidenced by the slower processing speed scores.

Introduction

The brain comprises only about 2% of the human body mass, but it consumes about one-fifth of the cardiac output making the brain the most energetic organ in the body.[1] Unlike muscle cells or other organs, the brain has limited ability to store energy, requiring instead a constant supply of oxygen and energy substance. Because cerebral blood flow is necessary to deliver this continuous supply of oxygen and nutrition,[2] brain health depends both on healthy blood vessels and a healthy cardiovascular system.[3]

Compared with other organs, the brain's blood supply is high flow and low resistance.[4] During the aging process, the cerebrovascular network is subject to adaptive and perhaps maladaptive changes, including the narrowing and stiffening of a small cerebral vessel.[4] Pulsatility index (PI) is a measure of the downstream resistance in the cerebral arteries, and it is a measure of cerebrovascular health in the normal elderly population.[5,6] Transcranial Doppler (TCD) ultrasound is a non-invasive and cost-effective sensing modality that measures cerebral blood velocities (CBV) with high temporal resolution.[7] PI is calculated from the CBV envelope and characterizes the morphology of the pulsatile CBV waveform,[8] and has the potential to provide information regarding cerebrovascular health.[9]

Regular exercise is important for moderating age-related diseases,[10,11] and is considered an essential component for optimal brain health.[12] According to one study, a morning bout of moderate-intensity exercise led to an improvement in cerebral blood velocity for more than eight subsequent hours in older overweight adults.[13] Another study showed no significant change in PI in older adults (n = 10) after a 12-week aerobic exercise training program.[4] However, a significant decrease in PI was observed 30 minutes after an acute bout of exercise following the 12-week intervention, which may suggest a decrease in downstream resistance in the cerebral circulation and higher middle cerebral artery velocity (MCAv). It is important to note that these older adults all had normal PI values. Future directions should focus on whether PI decreases following an exercise intervention in those with elevated PI.

Numerous studies showed moderate-intensity exercise has a positive effect on cardiovascular health,[14] cognitive function,[15] and quality of life.[16] However, there is a lack of understanding of the fundamental mechanisms that regulate cerebral blood flow during an acute bout of exercise in older adults. Various TCD studies have shown an increase in MCAv and PI during moderate-intensity exercise in young healthy adults.[17–22] However, less is known about the change in MCAv and PI during moderate-intensity exercise in older adults – especially older adults with high pulsatile blood flow velocity (elevated PI). Since elevated PI is related to cardiovascular disease,[23] dementia,[24] white matter injury,[5] traumatic brain injury,[25] and intracranial pathology,[26] increasing our understanding about MCAv and PI and the potential influencing factors (cardiovascular disease) may help guide optimal therapeutic interventions aimed at brain health. Therefore, the main aim of the present study is to compare MCAv and PI during moderate-intensity exercise between older adults with normal PI and older adults with elevated PI. A secondary aim of this study is to compare cardiovascular disease (CVD) and cognitive function of the same groups: older adults with normal pulsatile blood flow velocity (normal PI) and older adults with high pulsatile blood flow (elevated PI).

Methods

Participants

All subjects were recruited from a registry of individuals at the University of Kansas Alzheimer's Disease Center (KU ADC). Inclusion criteria for the study were: (1) 65–90 years of age; (2) sedentary or underactive lifestyle; (3) the absence of major orthopedic disability; (4) the ability to perform moderate physical exercise; (5) cognitively normal/nondemented based on neuropsychological testing and a Clinical Dementia Rating (CDR) =0.[27] Exclusion criteria included (1) Diagnostic and Statistical Manual of Mental Disorders-IV defined drug or alcohol abuse within the previous 2 years; (2) clinically significant depression or anxiety; (3) insulin-dependent diabetes; (4) myocardial infarction or symptoms of coronary artery disease within the previous 2 years; (5) acute decompensated congestive heart failure or class IV heart failure. All participants were consented according to a protocol approved by the Institutional Review Board at the University of Kansas Medical Center.

Protocol

Before the study visit, participants abstained from caffeine for 12 hours, physical activity for 24 hours, and eating a large meal for two hours. All participants began study procedures between 7:30 and 9:00 AM. After consent, participants underwent a physical exam including height, weight and heart rate. Cardiovascular disease (CVD) risk (defined as the atherosclerotic cardiovascular disease, ASCVD risk score) and was calculated for each participant. The ASCVD algorithm uses sex, age, race, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure (SBP), as well as smoking, diabetes, and hypertension treatment status to calculate 10-year risk of heart disease or stroke.[28] For the ASCVD risk score calculation, SBP was assessed after 20 minutes of supine rest.

Participants were well-characterized as having normal cognition (CDR=0) at a clinical evaluation at the KU ADC prior to the TCD evaluation. During the clinic visit, all participants completed a standard battery of neuropsychological tests,[29] that included the Mini-Mental State Examination,[30] the Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit Symbol,[31] Trail Making Test A, Trail Making Test B,[32] and category naming (animals).[33]

TCD Evaluation

The laboratory room for the experimental session was dimly lit, the temperature was maintained between 22 and 24°C, and external stimuli were kept to a minimum during testing. All participants sat quietly on the recumbent stepper (NuStep, T5XR) and rested for 15 min. During the last 8 min of rest, we measured MCAv, beat-to-beat mean arterial pressure (MAP), end tidal carbon dioxide ($P_{ET}CO_2$), and heart rate (HR).

MCAv was assessed using a 2-MHz probe (RobotoC2MD, Multigon Industries) and TCD ultrasound (TOC2MD Neurovision, Multigon Industries). The TCD transducer, equipped with auto-tracking to find the optimal signal was fixed on the left temporal window. If the left acoustic window did not yield a signal, then the right side was used. MAP was collected using (Finometer Pro, Finapres Medical Systems), which uses a finger plethysmography to continuously measure beat to beat MAP. $P_{ET}CO_2$ was assessed using a nasal cannula and capnograph (BCI Capnocheck Sleep 9004 Smiths Medical) and ECG waveform was measured using a 5-lead electrocardiogram (Cardiocard, Nasiff Associates).

After 8 minutes of data collection at rest, the participant performed a single bout of moderate intensity exercise on the recumbent stepper. Moderate intensity was defined as 40% to 60% of age-predicted HR reserve.[34] All participants began the exercise at 40 W and a step rate of 90 steps per minute. The resistance was increased until the HR reached the desired exercise intensity.[35,36] Once participants were in steady-state for one minute, the 8-minute exercise recording for MCAv, MAP, $P_{ET}CO_2$ and HR commenced.

Data Processing

Blood flow MCAv, MAP, $P_{ET}CO_2$ data, and HR were sampled at 500 Hz (NI-USB-6212, National Instruments) and then exported for further analysis in MATLAB (R2019 b v. 9.6.0, Mathworks). Before analysis, a lowpass-filter with a passband frequency of < 5 Hz was used to remove high-frequency components of the raw TCD data. ECG R-wave was used to identify cardiac cycles. The customized MATLAB program detected the systolic velocity (Vs), diastolic velocity (Vd), systolic blood pressure (SBP) and diastolic blood pressure (DBP) in each cardiac cycle. Numerical integration via the trapezoidal method was used to calculate MCAv, MAP, $P_{ET}CO_2$ for each cardiac cycle.

PI was calculated using Gosling's pulsatility index equation as PI=(Vs-Vd)/MFV.[37] Then two grand averages of MCAv, MAP, $P_{ET}CO_2$ and PI were calculated for each participant during the eight minutes of rest and the eight minutes of exercise. Based on the measured PI value, the study population was divided into two groups: 1) individuals with normal PI and 2) individuals with elevated PI. Since PI increases with age (per year 0.01),[7,38] the distinction between normal PI and elevated PI was made by a formula (the equation of the linear regression) implemented from a large population study:[38]

$$PI(cal)=(0.01*Participant\ age+0.32) \qquad (1)$$

PI (cal) is the calculated age-appropriate expected PI. If the measured PI is higher than the PI (cal) by 1.5 standard deviations, then the participant was classified as elevated PI. This equation is only valid for individuals above 64 years old.

Statistical Analysis

Means and standard deviations were calculated for all quantitative variables. Frequencies and proportions were calculated for all categorical variables. The Lilliefors test was used to check the normality assumption of the data.

Between-group (elevated PI vs normal PI) differences of quantitative normally distributed variables were assessed using Welch's t-test. Wilcoxon rank-sum test was used for non-normally distributed quantitative variables. Large-sample categorical data were evaluated using Chi-squared and small-sample categorical data were evaluated using Fisher’s exact test.

Percentage change between rest and exercise were calculated and between-group percentage change (Δ%) comparisons were made with Welch's t-test. All statistics were computed using the MATLAB Statistics and Machine Learning Toolbox and $P < 0.05$ was considered statistically significant.

Results

Participant Characteristics

One hundred and four participants enrolled in this study. The demographic data is presented in Table 1. Using the equation to calculate PI, we found 77 participants demonstrated a normal PI and 27 were considered to have an elevated PI. There were no statistical differences between groups in age or the distribution by gender or education ($p > 0.05$). Additionally, there were no significant differences in resting HR or body mass index (BMI). All participants reached the target HR range using the appropriate estimated HR equations. There were no significant differences in ASCVD risk score between participants with elevated PI and those with normal PI. Moreover, none of the variables used in the ASCVD prediction equation were significantly different between elevated and non-elevated PI. Individuals with elevated PI performed significantly worse in WAIS-R Digit Symbol and Trail Making Test A. No significant differences were found for the MMSE, Animal Naming or Trail Making Test B.

Absolute TCD Parameters and Blood Pressure

TCD parameters during rest and exercise are summarized in Table 2. In addition to the inherent significant differences in PI at rest, PI remained significantly higher during exercise in subjects with elevated PI. Vs was significantly higher at rest and during exercise in participants with elevated PI. However, no significant group differences were found for MCAv, Vd, MAP, SBP or $P_{ET}CO_2$ at rest and during exercise. MAP and SBP were not significantly different between elevated and non-elevated PI at rest and during exercise. Participants with elevated PI showed a significantly lower DBP at rest but not during exercise.

Relative TCD Parameters and Blood Pressure

Between-group percent change from rest to exercise are summarized in Figure 1. In those with elevated PI, the percent change from rest to exercise (ΔPI) was significantly lower than subjects with normal PI ($P=0.005$). However, there were no significant difference with the other variables of interest.

Discussion

This experiment provided novel insight into the ΔPI and ΔMCAv in older adults at rest and during exercise. The major findings of the study are twofold. First, during moderate intensity exercise, cerebral perfusion was similar between the groups. Second, the ΔPI% in the group with elevated PI was 14.2% lower than in the group with normal PI (Figure 1).

Pulsatility index

PI has traditionally been interpreted as a descriptor of distal cerebrovascular resistance. The driving force in PI between elevated and normal PI values in our study can be explained by Vs. We suspect that the reason for the high PI value at rest in the elevated PI group is a significant increase in Vs. Also, we observed that the ΔPI from rest to moderate intensity exercise in people with elevated PI is lower than those with normal PI. This result suggests that individuals with elevated cerebral pulsatility may have a protective mechanism to prevent a further increase in PI during exercise. This result is an essential first step to understand the hemodynamic response to moderate intensity exercise in those with elevated PI. This could have significant implications for those with impaired cerebral autoregulation such as AD[39] and traumatic brain injury.[40]

Middle Cerebral Blood Flow Velocity

Both groups increased the MCAv to the brain during exercise by 11.6% for individuals with normal PI and 10.6% for those with elevated PI. In contrast to the breadth of research gathered from healthy young individuals, few studies have examined ΔMCAv% and ΔPI% in older individuals from rest to moderate intensity exercise. Prior work showed an increase of 7% (n=9) and 24% (n=14) during moderate intensity exercise in older adults.[41,42] Therefore, to our knowledge, we are the first to present a larger dataset of well characterized older adults and show the ΔMCAv% from rest to moderate exercise in older individuals with normal and elevated PI. Other TCD studies have shown an attenuation in cerebral perfusion at rest with age.[7] This age-related reduction in cerebral perfusion is independent of other physiological factors such as BP, MAP, or BMI[22] and is postulated to reflect global brain atrophy or reduced neuronal activity.[43] In addition to low resting MCAv, our study showed a lower ΔMCAv% from resting levels to moderate intensity exercise levels when compared to young healthy adults (~20% in MCAv).[22]

Blood Pressure

Figure 1 shows an increase in MAP, SBP and DBP with exercise for both groups (elevated and normal PI). This increase in arterial blood pressure is necessary to supply blood to the vital organs and the working muscle during moderate intensity exercise. However, studies in young healthy individuals showed an increase in MAP and SBP with moderate intensity exercise, while DBP remained unchanged.[20,44] Therefore, in healthy young individuals, only MCAv and Vs, and not Vd, increase with moderate intensity exercise. To our surprise, Vd did not increase in our study, while DBP increased by 27.5% in the normal PI group and 33.7% in the elevated PI group. These findings suggest that dynamic cerebral autoregulation in older adults is intact and was able to maintain unchanged Vd despite an increase in DBP.

Cardiovascular Disease Risk and Cognitive Function

Current evidence suggests that high pulsatile blood velocity is associated with CVD.[45] However, our results did not support this hypothesis and showed no significant difference in ASCVD score between the elevated and normal PI group in our sample of relatively healthy older adults. However, SBP tended be higher in subjects with elevated PI. This is not surprising since prior studies have shown that increased pulse wave (SBP-DBP) is associated with increased resting PI.[46]

Our results suggest that elevated PI may be associated with cognitive changes in the brain. Individuals with elevated PI display lower processing speed and psychomotor speed by scoring worse in WAIS-R Digit Symbol and Trail Making Test A. Our results agree with a previously published study showing the association between high PI and slower processing speed.[47] Therefore, microvascular damage measured by PI may contributes to the cognitive changes in cognitively normal older individuals.

Experimental considerations

The present study has several strengths including inclusion of both male and female participants. It included a sample size of one hundred and four well characterized, cognitively normal older adults who underwent a cardiovascular risk assessment and cognitive screening. We believe a strength of our study is the addition of other MCA data such as PI, Vs and Vd. Examination of all indices provides more perception to understand the complexity of the overlapping regulatory mechanism of blood velocity during exercise. TCD measures of MCAv as an index of cerebral blood flow are challenged by the assumption of constant MCA diameter (Ainslie and Hoiland, 2014),[48] and the error in velocity estimate caused by the angle of insonation.[49] However, in our study, the increase in $P_{ET}CO_2$ in our study was less than +7.5, which is the amount needed to see a change in MCA diameter.[50] Therefore, the implications of MCA diameter changes in our study is unlikely.

In conclusion, older adults with elevated PI present with an attenuated ΔPI% between rest to exercise and slower cognitive processing speed. SBP increases during moderate-intensity exercise in older individuals. However, autoregulation appears intact and able to retain (Vs) from increasing in the phase of SBP.

TABLES & FIGURES

Table 1. Demographic and neuropsychological data

Characteristics	Overall N=104	Elevated PI N=27	Normal PI N=77	P Value
Age(y)	70.39 ± 4.78	70.22 ± 3.97	70.45 ± 5.0	0.78
Gender (F:M)	75:39	17:10	58:19	0.29
Education (y)	16.78± 2.59	16.78 ± 2.9	16.83 ± 2.4	0.81
BMI (kg/m2)	26.8± 4.45	27.39 ± 5.5	26.68 ± 4.01	0.62
Resting HR	64.8± 8.2	62.22± 10.13	65.66± 7.2	0.11
MMSE	28.01± 1.52	28.74± 1.7	28.8± 1.50	0.95
WAIS-R Digit Symbol	49.85± 9.5	46.33± 8.4	51.18± 9.7	0.04*
Trail Making Test A	31.44± 10.8	35.70± 11.7	29.83± 10.2	0.01*
Trail Making Test B	79.22± 37.6	79.74± 30.6	79.32± 39.7	0.6
Animal Naming	21.99± 5.1	21.70± 4.6	22.05± 5.4	0.85
ASCVD score	14.8± 9.0	14.78± 8.2	14.78± 9.3	0.77
Resting Systolic blood pressure	130.54± 14.34	134.77± 16.42	128.89± 13.33	0.09
Total cholesterol (mmol/L)	186.30± 36.10	186.30± 37.30	187.30± 37.30	0.86
HDL cholesterol (mmol/L)	60.72± 17.7	61.07± 18.06	60.38± 17.71	0.64
Blood pressure treatment %	46.48	58.82	42.6	0.47
Diabetes %	4	0	5.48	0.57
Smoking status %	1.96	3.85	1.3	0.43

N=number of subjects; PI=pulsatility index; F=female; M=male; Y=years; BMI= body mass index; HR=heart rate; MMSE=The Mini-Mental State Exam; ASCVD = atherosclerotic cardiovascular disease; HDL=High-density lipoprotein. Values are presented as mean ± standard deviation (range) or number (percentage). *P < 0.05 for Welch's t-test or Wilcoxon rank sum test or Chi-square test or Fisher's exact test

Table 2. TCD parameters of subjects with high resting PI and subjects with low resting PI at rest.

	Overall N=104	Elevated PI N=27	Normal PI N=77	P Value
Rest PI	1.02 ± 0.2	1.26 ± 0.1	0.95 ± 0.1	<0.001*
Exercise PI	1.33 ± 0.2	1.52 ± 0.3	1.26 ± 0.2	<0.001*
Rest MCAv (cm/s)	47.01± 11.15	47.90± 11.9	46.62± 11.0	0.62
Exercise MCAv (cm/s)	51.93± 12.6	52.30± 12.4	51.81± 12.9	0.86
Rest Vs (cm/s)	80.08± 19.8	90.45± 22.4	76.43± 17.5	0.005*
Exercise Vs (cm/s)	94.32± 22.5	103.10± 23.6	91.4± 21.5	0.03*
Rest Vd (cm/s)	31.96 ± 7.0	30.13 ± 6.6	32.61 ± 7.07	0.11
Exercise Vd (cm/s)	31.18 ± 7.4	29.5 ± 6.7	31.7 ± 7.6	0.2
Rest $P_{ET}CO_2$ (mmHg)	33.97± 4.7	33.9± 4.01	33.5± 5.2	0.96
Exercise $P_{ET}CO_2$ (mmHg)	38.33± 4.2	38.1± 4.1	38.4± 3.9	0.66
Rest MAP (mmHg)	81.33± 12.1	79.37± 13.0	83.06± 13.0	0.212
Exercise MAP (mmHg)	112.54± 19.4	113.59± 21.5	112.0± 21.9	0.75
Rest SBP (mmHg)	131.76± 20.7	136.33± 22.8	130.13± 19.8	0.22
Exercise SBP (mmHg)	187.62± 34.9	192.70± 39.7	185.82± 33.2	0.44
Rest DBP (mmHg)	70.80± 11.2	66.58± 11.8	72.25± 10.61	0.03*
Exercise DBP (mmHg)	91.14± 18.03	89.2± 17.2	91.8± 18.44	0.71

N=number of subjects; PI= pulsatility index; MCAv=mean middle cerebral artery velocity; Vs= systolic velocity; Vd= diastolic velocity; $P_{ET}CO_2$ = end-tidal carbon dioxide; SBP=systolic blood pressure; DBP= diastolic blood pressure. Values are presented as mean ± standard deviation.

*P < 0.05 for Welch's t-test or Wilcoxon rank sum test between elevated and normal PI percentage absolute values. *P< 0.05 Welch's t-test or Wilcoxon rank sum test between elevated and normal PI percentage change from rest to exercise.

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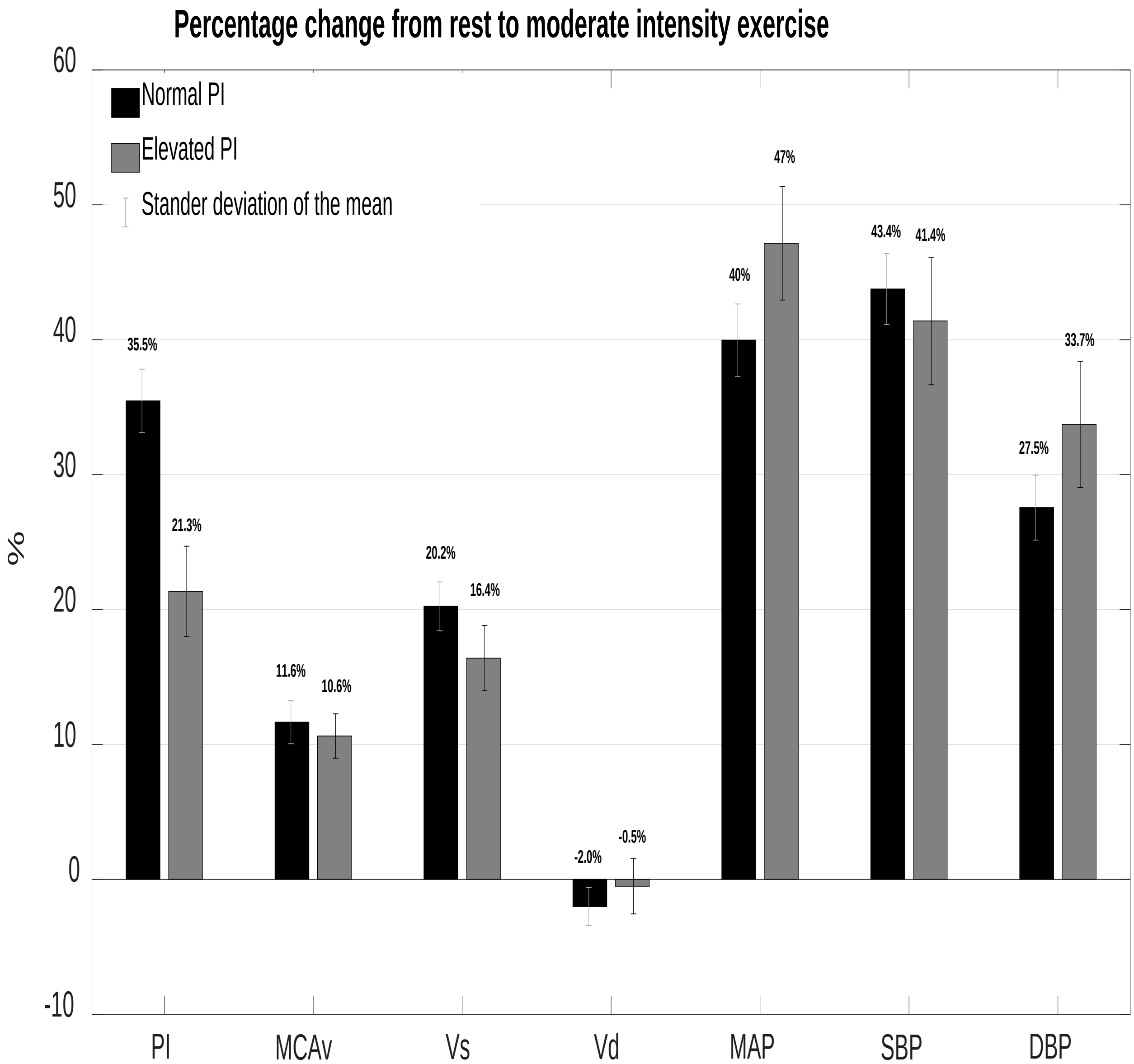

Figure 1. PI= pulsatility index; MCAv=middle cerebral artery velocity; Vs= systolic velocity; Vd= diastolic velocity; MAP=mean arterial pressure; SBP=systolic blood pressure; DBP= diastolic blood pressure

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