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Investigation of Peripheral Arterial Tonometry as a Potential Surrogate Marker of Myocardial Blood Flow during Mental Stress

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Master of Public Health

Department of Epidemiology

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Faculty Thesis Advisor

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By

Mengxi Wang

B.S., University of Washington, 2014

Faculty Thesis Advisor: Amit Shah, MD, MSCR

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Abstract

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By Mengxi Wang

Background: Mental stress-induced myocardial ischemia (MSIMI) has been linked with increased adverse cardiovascular events in patients with CAD (coronary artery disease). The current best detection technique Positron emission tomography (PET) measuring myocardial blood flow is invasive and expensive. As peripheral arterial vasoconstriction measured by Peripheral Arterial Tonometry (PAT) has been found associated with the development of MSIMI, we aim to find the potential relationship of peripheral and coronary blood flow for possible noninvasive detection.

Methods and Results: 20 participants with CAD were recruited and randomized to biofeedback treatment and control group. Mental stress was induced by a standardized arithmetic test. PET were performed in stress and rest condition while PAT response was measured continuously every 30 seconds. Participants repeated the same tests after six weeks. Spearman correlation between the PAT and PET was not significant. Moderate correlations were found in African Americans ($r=0.5$, $p=0.07$), and females ($r=0.42$, $p=0.23$). Linear regression analysis shows biofeedback treatment did not predict any changes in the PAT ratio over time ($\beta=0.46$, $p=0.20$).Possible predictors of dissociation between PET and PAT include heart failure ($\beta=1.30$,$p=0.64$), hypertension ($\beta= 1.17$, $p=0.19$), antidepressant intake ($\beta= 0.64$, $p=0.62$), CABG($\beta=-0.90$, $p=0.42$) and gender ($\beta= 0.38$, $p=0.72$).

Conclusion: We did not find a statistically significant relationship between the peripheral and cardiac vasomotor responses to mental stress. A larger study is warranted to further investigate the potential relationship.

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Introduction

Myocardial ischemia, defined as an imbalance between myocardial oxygen demand and supply, has a high prevalence among patients with coronary artery disease (CAD) (1-4). It is often asymptomatic, but can be induced by both physical exercise and mental stress in laboratory setting (1, 3). Myocardial ischemia has been linked with increased higher risk of death and adverse cardiovascular events in patients with CAD (5). Therefore, detection of myocardial ischemia can improve the prognosis and treatment of the subsequent clinical events for CAD patients.

Mental stress-induced myocardial ischemia (MSIMI) has different pathophysiology from physical (exercise or pharmacologic) stress testing (PSIMI), and portends a worse prognosis (6). To date, the gold standard of myocardial ischemia assessment during mental stress is Positron emission tomography (PET), a sensitive and well-established technique that uses radionuclide imaging to quantify changes in myocardial blood flow (3, 7, 8). However, in addition to the high cost, PET exposes patients to radiation, is uncomfortable, and may have limited availability. Therefore, finding a non-invasive, inexpensive, and portable technique for approximating mental-stress induced changes in myocardial blood flow would be of great utility in risk-stratifying patients with CAD

Previous studies have reported an association of brachial endothelial function and coronary function (9), which suggests a common mechanism between cardiac and peripheral vascular function. Peripheral arterial tonometry (PAT) is a non-invasive, low-cost, portable solution for measuring peripheral vasomotor tone. Previous studies have found that peripheral

arterial response to stress, measured as PAT ratio, has moderate accuracy in predicting MSIMI among CAD patients (2, 10-12). This is likely because PAT reflect changes on coronary blood flow, and reductions in coronary blood flow lead to MSIMI. Nonetheless, the potential relationship of peripheral and coronary blood flow has never been proven with studies of real-time, absolute blood flow; this is important to prove because stress-induced coronary vasoconstriction may have adverse effects independently of MSIMI. Additional, the PAT test is less expensive, burdensome, and risky. In this study, we aim to evaluate the relationship of stress-induced peripheral blood flow changes, measured by peripheral arterial tonometry (PAT), and myocardial blood-flow, measured by positron emission tomography (PET), response during mental stress challenge in patients with CAD.

Methods

Description of Recruitment Pool

We recruited participants with coronary artery disease from an existing cohort, the Mental Stress Ischemia Mechanisms and Prognosis Study (MIPS). A detailed description of the cohort has been published elsewhere.(13) MIPS is a longitudinal cohort study that enrolled 695 participants between July 2009 and July 2014. Eligibility criteria include age between 30 and 79 years and documented CAD from Emory University-affiliated hospitals or clinics.

Participants were excluded if they had an acute coronary syndrome or decompensated heart failure in the prior week, severe psychiatric conditions, uncontrolled high blood pressure (≥180/110 mmHg), or with contraindications for regadenoson administration(13). Participants with known mental stress ischemia were recruited with preference.

Study Design

We aimed to enroll 24 participants. After informed consent, participants were randomized 1:1 to HRV biofeedback therapy or waitlist control for 6 weeks with a baseline visit before, and a follow-up visit after. Each participant underwent a medical history and psychosocial/psychiatric assessments, blood draw, baseline vascular function testing and myocardial SPECT imaging at the first visit. After an overnight fast, participants were initially placed in a temperature controlled, quiet room for 30-min rest while heart rate and

blood pressure were measured at every 5 minutes. Then the obtained Rb^{82} PET image approximately 7.5 minutes prior and at 60 seconds into a 3 minutes standardized arithmetic mental stress test described by Soufer et al (14) . Peripheral arterial response was recorded continuously by pulsatile arterial tonometry (PAT, Itamar-Medical, Israel) during the rest, stress, and into the recovery period. They went for repeated testing after 6 weeks.

PET Imaging Protocol

The PET images were acquired using a Siemens Biograph-40 3D PET/CT scanner (Knoxville, TN) comprised of a lutetiun oxyorthosilicate (LSO) block detector ring of 162 mm field-of-view operating in 3D mode. First, a scout was done to define scan range. Then a CT attenuation scan was performed with the lowest pitch allowed by the scanner, covering the region of interest in 14 seconds during shallow breathing. A 7.5-minute rest emission scan in list mode was performed immediately. After the beginning of two rubidium infusions of 1295 – 2220 MBq (35-60 mCi), mental stress stimulation was then started, and the rubidium generator was started immediately after maximum mental stress at 1 minute. A 7.5-minute stress emission scan in list mode was started immediately after the beginning of rubidium infusion. Manufacturer-provided software was used to perform Manual rigid-body registration of the CT and PET images.

Digital blood flow measurement using finger plethysmography

Digital pulse wave amplitude was continuously measured during stress and rest period

using PAT devices (Itamar-Medical, Caesarea, Israel). The device was applied to the index finger, and then connected via thin flexible tubing to an isolated volume reservoir to buffer pressure changes within the probe. Venous stasis and unload arterial wall tension within the finger was eliminated by a constant pressure of 40–70 mm Hg. Another volume reservoir not connected to the probe served as a pressure reference. The distal compartment of the device was connected to a pressure transducer which sensed pulsatile fluctuations exerted by blood volume changes in the digital arteries (11). We examined the mean PAT ratio, which was calculated as the ratio of pulse wave amplitude during mental stress compared to rest. Decreased PAT ratio during mental stress period signifies stress-induced vasoconstriction (2).

Statistical analysis

We used Fisher's exact test for categorical variables and Wilcoxon tests for continuous variables to test the differences between baseline characteristics of biofeedback and control group. The mental stress PAT ratio was calculated as the ratio of pulse wave amplitude during mental stress divided by a baseline period of 3 minutes and 30 seconds immediately prior to stress onset. The ratio was calculated in sequential 30 second epochs from the start of stress until the end of a 7 minute period. Therefore, in 14 sequential time points, we calculated the PAT ratio. We then calculated several summary PAT statistics for analysis, including: the mean of the entire 7 minute period (most robust against noise/outliers); the last 2.5 minutes of the period (during which time the PET scan likely occurred); the minimum PAT ratio (measuring maximum vasoconstriction); and the maximum PAT ratio (measuring peak

mental stress-induced hyperemia). Each summary metric was evaluated as a possible predictor of myocardial blood flow changes with stress.

Total PET ratio was calculated by the sum of LAD, LCX and RCA myocardial blood flow during stress divided by the sum of LAD, LCX and RCA myocardial blood flow during rest period. The ratio in each individual region was also evaluated separately as secondary analyses. Correlations between total PET ratio, LAD, LCX, RCA ratios and the PAT ratios (mean, last 2.5 min, minimum, and maximum) were assessed with Spearman correlation tests, as PAT ratio was not normally distributed. To evaluate potential effect modification due to demographic status, a secondary correlation of the mean PAT ratio and PET ratio was performed in race and sex stratified subgroups. To assess whether any particular health characteristics moderated the concordance between peripheral and cardiac vasomotor tone, we conducted a multivariable linear regression of baseline risk factors in modeling for the absolute normalized difference of PET and PAT ratio of the combined visit 1 and 2 data. A bland Altman plot between the 2 variables was created to visualize the agreement of PET and mean PAT ratios.

In addition to the analyses comparing the cardiac and peripheral blood flow, biofeedback treatment was also compared between groups. Because of imbalanace between the biofeedback arm and waitlist control group, multivariable linear regression analysis was conducted to account for differences. Baseline covariates used in the multivariable analysis performed for predictors of included age, gender, hypertension, diabetes mellitus, history of ever smoking, prior history of MSIMI and PSIMI, depression, BMI, race, heart failure history,

antidepressant intake, and CABG. Because of the small sample size, the most parsimonious model was selected using backwards elimination.

The difference in PAT ratio for each 30-second epoch between HRVB and waitlist controls was also calculated to examine whether the intervention influenced early or late mental stress-effects.

All statistical analysis and figures were conducted using SAS 9.4 and Microsoft Excel 2017.

Results

We recruited 27 participants in total, with 4 dropped out without making any appointments due to life changes, and 3 had imaging acquisition errors. The remaining 20 participants had participated in at least one of the visit, of which 10 from HRV biofeedback therapy and 10 waitlist control. We acquired data from 18 participants from visit 1, and 18 participants from visit 2; 13 participants had complete data from both visits for analyses comparing the change from visit 1 to visit 2.

Table1 summarizes the baseline characteristic of these participants stratified by biofeedback treatment groups. The average (standard deviation) age at enrollment in the treatment group was 60.6 (4.6) and 59.8(7.1) in the control group. The HRVB group had more African Americans (60%) than the waitlist control group (30%). PSIMI was present in 50% and 80% and MSIMI in 60% and 70% in treatment and control groups, respectively. A higher BMI was also noted in the HRVB arm (31.8 vs. 27.4) compared to waitlist controls.

For the first visit, PET ratio shows a weak negative correlation with average PAT ratio ($r=-0.11$). However, for the second visit, the correlation was much higher ($r=0.33$) (Table2). In subgroup analyses, African Americans and women demonstrated more consistent positive correlations in visits 1 and 2 than Caucasians and men, respectively (Table3).

Analysis of the complete data from both visits shows no significant change in average difference peripheral blood flow between visits and between treatment groups ($p=0.73$) (Table 4). Furthermore, no significant difference was found between treatment arms during each individual PAT epoch (Figure 2). In multivariable linear regression analysis examining

the effect of biofeedback treatment influence on difference of PAT between visits, biofeedback treatment has weak negative effect (B =-0.24) before adjustment and moderate positive effect (B =0.46) after adjustment for race and diabetes, which were the only 2 variables selected after backwards elimination (Table5). Multivariable linear regression analysis shows that heart failure (B =1.30, p=0.64), hypertension (B=1.17, p=0.19), antidepressant intake (B=0.64, p=0.62), CABG (B=-0.90, p=0.42) and gender (B=0.38, p=0.72) have no effects on PAT and PET difference (=-0.44, 0.39, -0.30) (Table 6).

Bland Altman test for visit 1 shows the difference between PET and average PAT first tends to narrow down and then increase as the average of the two methods increases. For visit 2, the difference between the PET and average PAT increased as the average of the two methods increases (Figure1).

Discussion

In this study, we examined the correlation of peripheral and myocardial vascular responses to mental stress in a randomized clinical trial of participants with CAD to biofeedback versus waitlist control. We did not find a statistically significant relationship between the peripheral and cardiac vasomotor responses to mental stress, regardless of cardiac region (LAD, LCX, or RCA) or methodology (mean vs. minimum, etc.) for measuring PAT. These findings suggest that different mechanisms may influence vasomotor tone as it relates to mental stress in the heart and periphery.

Although the small sample size limits statistical inferences, subgroup analyses showed trends that merit further exploration. We found moderate correlations in certain groups such as African Americans (r=0.5, p=0.07), and females (r=0.42, p=0.23). Previous studies have also found sex differences in the sympathetic nervous system response to mental stress(15), which may provide additional support for these findings (10). Our linear regression analysis also indicated that heart failure(β=1.30,p=0.64), hypertension (β= 1.17, p=0.19), antidepressant intake (β= 0.64, p=0.62), CABG(β=-0.90, p=0.42) and gender (β= 0.38, p=0.72) may predict a larger dissociation between peripheral and cardiac mental stress responses, although because none of the results were statistically significant, no conclusions can be made until a larger study is performed.

In Bland Altman Analysis for the first visit, the difference between the PET and PAT first tends to narrow down and then increase as the average increases, indicating possible proportional bias. For the second visit, most differences lie close to the mean difference but

grow large at extreme values. This might suggest that PAT has higher accuracy of prediction of PET when peripheral vasoconstriction is low.

Biofeedback treatment did not predict any changes in the PAT ratio over time. However, the effect of biofeedback changed from weak negative to positive after multivariable adjustment. Although the confidence intervals were wide for both models, it might indicate that diabetes and race have the potential influence on the effect of biofeedback treatments.

Despite the negative findings from this study, more research in larger sample sizes is indicated. Mental stress may have significant effects on systemic vascular resistance (12). Several previous studies have identified that peripheral arterial response to mental stress measured as PAT ratio has modest accuracy in predicting MSIMI (10, 11), with a higher likelihood of MSIMI in those with lower PAT ratio (2). Patients with CAD, compared to normal controls, have also been found to experience reduced myocardial blood flow response to mental stress (16). Therefore, it is reasonable to continue investigating the relationship between myocardial and peripheral response to stress despite these initial negative findings.

This study was subject to several limitations. A major limitation of this paper is small sample size. As a result, the analysis was subject to large influences from outliers, and a moderate to high correlation was necessary in order to have adequate power for statistical significance. We also cannot rule out the possible effects from unmeasured confounders. For example, peripheral blood flow can be influenced by several environmental, local, and systemic factors unrelated to mental stress (17). Although we attempted to control for some of these factors, like performing the study in a temperature controlled environment, there could be other factors that influenced our results. Also, the stress PET was performed right after the

mental stress test rather than during the mental stress test, likely resulted in misclassification and bias towards the null. Besides measurement errors, the pathophysiological mechanisms may vary among different individuals or subgroups in ways that cannot be measured.

In conclusion, this is the first study to compare cardiac and peripheral arterial vasomotor changes during mental stress. We found mild correlations for visit 2 only, and neither visit was statistically significant. We also did not find any relationship with HRV biofeedback and changes over time. A larger study is warranted to further investigate the potential relationship and whether any particular subgroups (gender, race, etc.) moderate this finding.

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Tables

Table 1. Selected baseline characteristics[1] of the study participants (n=20) by treatment group in the study

	HRVB(n = 10)	Controls (n = 10)
Demographic factors		
Age at enrollment, years (SD)	60.6 (4.6)	59.8 (7.1)
Race/ethnicity		
Caucasian	40%	70%
African American	60%	30%
Female	30%	30%
Cardiovascular risk factors		
BMI, kg/m^2 (SD)	31.8(4.3)	27.4(4.6)
Diabetes	30%	40%
Depression	20%	10%
Ever smoke	70%	30%
Hypertension	80%	60%
Cardiac disease history		
Heart failure	10%	10%
PSIMI	50%	80%
MSIMI	60%	70%
CABG	0%	40%
Gensini score, mean (SD)	32.3 (30.0)	42.9 (45.0)
Medications		
Antidepressant	10%	30%
Beta blocker	70%	70%
Hemodynamics		
SBP, mmHg (SD)	139.8(22.5)	128.7(16.5)
DBP, mmHg (SD)	80.7(8.4)	71.4(8.4)
HR, beats/min(SD)	65.2(11.9)	59.1(11.1)

Abbreviations: HRVB, Heart rate variability biofeedback; BMI, body mass index; PSIMI, physical stress-induced myocardial ischemia; MSIMI, metal stress-induced myocardial ischemia; Gensini, total amount of cardiac diseases; CABG, Coronary artery bypass grafting; SBP, Systolic blood pressure; DBP, Diastolic blood Pressure. HR, heart rate.

1. Continuous variables are presented as means (standard deviation), categorical variables are presented percentages.

Table 2. Spearman Correlation between Mental Stress Ratios of Cardiac and Peripheral Blood Flow, Stratified by Visit

	Mean		Last 2.5 min		Minimum		Maximum	
	r	P-value	r	P-value	r	P-value	r	P-value
Visit 1(n=16)								
Total Pet Ratio	-0.11	0.68	-0.14	0.60	0.03	0.94	-0.17	0.53
LAD	0.06	0.83	0.04	0.88	0.08	0.77	0.06	0.83
LCX	-0.19	0.48	-0.23	0.39	-0.02	0.94	-0.24	0.35
RCA	-0.16	0.56	-0.17	0.53	-0.03	0.92	-0.20	0.46
Visit 2(n=15)								
Total Pet Ratio	0.33	0.23	0.28	0.32	0.35	0.20	0.06	0.82
LAD	0.24	0.40	0.19	0.50	0.31	0.26	0.00	0.99
LCX	0.37	0.18	0.21	0.44	0.30	0.28	0.10	0.71
RCA	0.29	0.30	0.24	0.38	0.30	0.28	0.10	0.71
Total(n=31)								
Total Pet Ratio	0.07	0.72	0.06	0.73	0.03	0.85	0.05	0.80
LAD	0.12	0.51	0.14	0.45	0.07	0.69	0.12	0.51
LCX	0.07	0.70	0.02	0.92	0.02	0.90	0.03	0.86
RCA	0.02	0.91	0.05	0.77	-0.02	0.92	0.03	0.88

Abbreviation: LAD, left anterior descending artery; LCX, left circumflex; RCA, right coronary artery.

Table 3. Spearman Correlation between Mental Stress Ratios of Cardiac and Peripheral Blood Flow-Subgroup Analysis

	Caucasian		African American		Male		Female	
	r	P-value	r	P-value	r	P-value	r	P-value
Visit 1(n=16)	-0.72	0.02	0.37	0.47	-0.24	0.46	0.2	0.8
Visit 2(n=16)	0.33	0.42	0.29	0.49	0.35	0.33	0.31	0.54
Total(n=32)	-0.18	0.48	0.5	0.07	0.04	0.87	0.42	0.23

Table 4. Changes from Visit 1 to Visit 2 in Mental Stress PAT Ratio[1] in Biofeedback vs. Control Groups, Stratified by Treatment group in the study

Pat ratio, mean(SD)	HRVB(n=6)	Control(n=7)	P value[2]
Visit1	1.06 (0.33)	0.88 (0.21)	0.18
Visit2	1.14 (0.27)	0.99 (0.47)	0.23
Visit2-Visit1	0.08 (0.27)	0.11 (0.45)	0.73

Abbreviation: HRVB, Heart rate variability biofeedback.

1: Average peripheral blood flow measured by PAT of 14 time points in 7 minutes experiment period of operational and control arms.

2: P values calculated by Wilcoxon-Mann Whitney test.

Table 5. Linear Regression Predicting difference between Visit 2 and Visit 1 for PAT Ratio

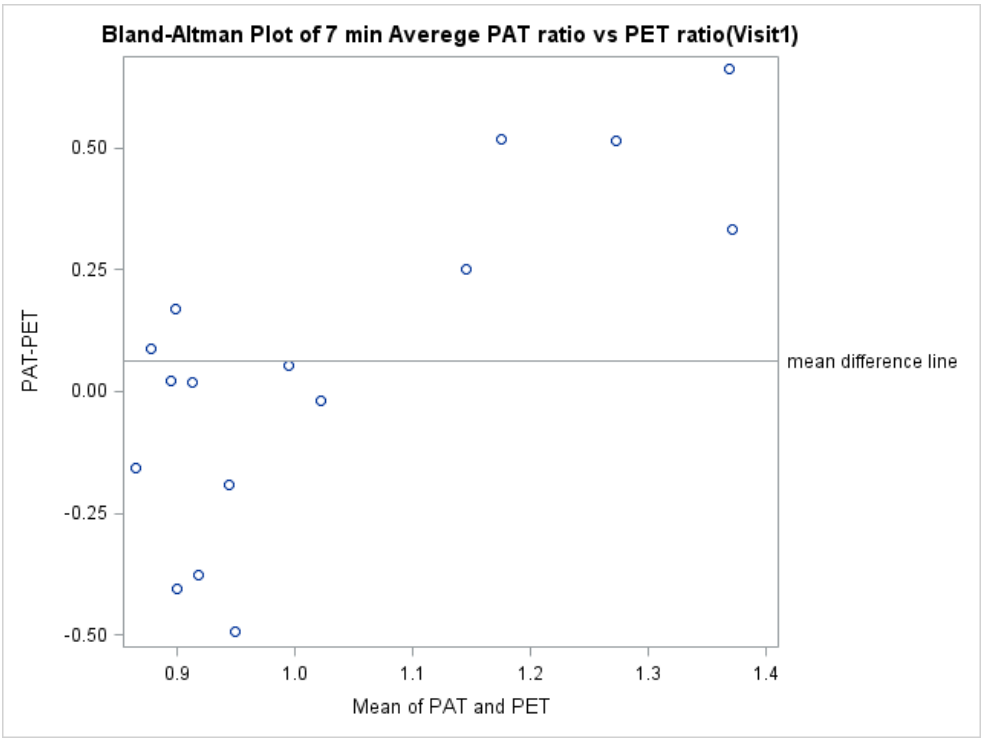
	Model	Parameter estimate for HRVB arm	P value	95% Confidence Limits	
Unadjusted model	Unadjusted	-0.24	0.69	-1.55	1.06
Adjusted model	Adjusted for diabetes and African American race	0.46	0.20	-0.29	1.20

Table 6. Linear Regression Analysis of Predictive Variables for Difference between PET and PAT Ratio

Variable	Parameter Estimate	P value	95% Confidence Limits	
Treatment Group	0.23	0.68	-0.96	1.43
Visit time	0.13	0.74	-0.66	0.92
Diabetes	0.10	0.92	-1.95	2.15
Depression	-1.34	0.48	-5.24	2.56
Hypertension	1.17	0.19	-0.65	2.99
Smoke History	-0.58	0.35	-1.86	0.69
Enrolled Age	0.04	0.72	-0.21	0.30
BMI	-0.16	0.26	-0.46	0.13
Gender	0.38	0.72	-1.88	2.65
Caucasian	0.23	0.81	-1.79	2.25
Heart Failure	1.30	0.64	-4.53	7.13
PSIMI	-1.22	0.23	-3.28	0.84
MSIMI	-0.18	0.75	-1.42	1.05
Antidepressant	0.64	0.62	-2.07	3.35
CABG	-0.90	0.42	-3.20	1.40

Abbreviations: BMI, body mass index; CABG, Coronary artery bypass grafting; MSIMI, metal stress-induced myocardial ischemia; PSIMI, physical stress-induced myocardial ischemia.

Figures and Figure Legends



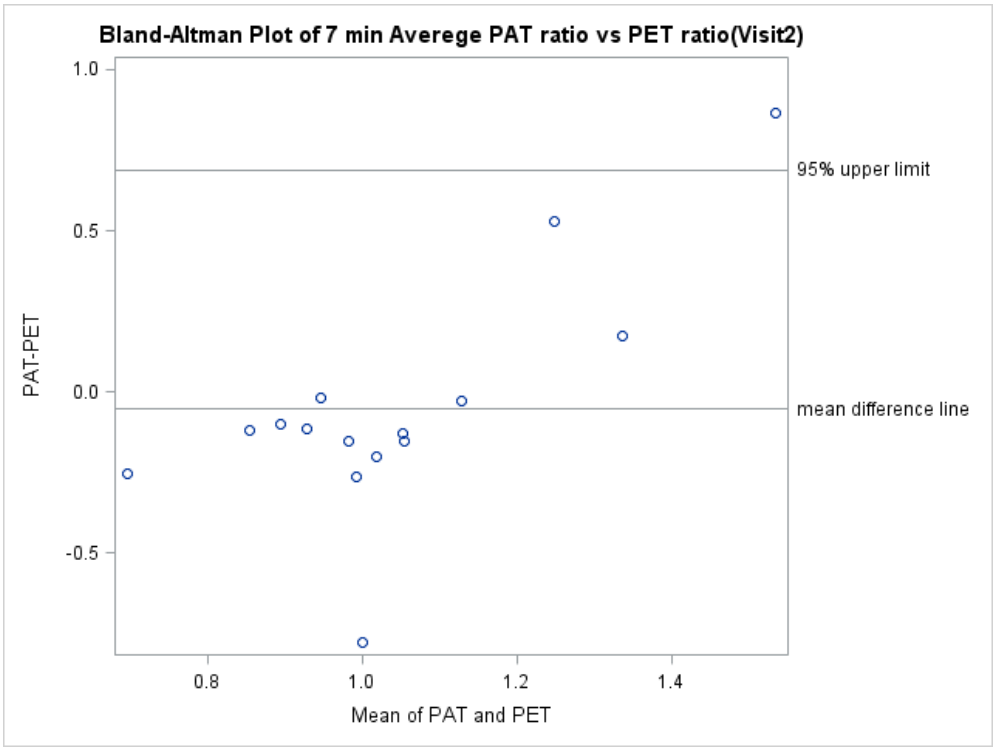


Figure 1. Bland-Altman plot showing agreement between cardiac blood flow by PET and average peripheral blood flow measured by PAT by visit.

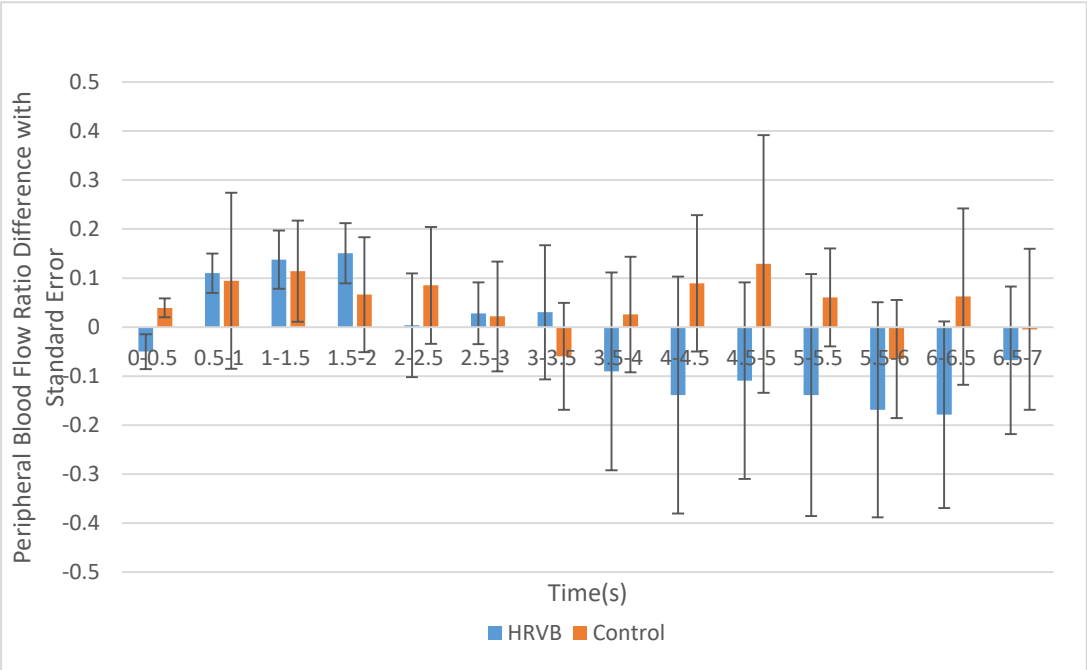


Figure 2. Change of peripheral blood flow ratio overtime between HRVB treatment group and control group in Visit2. Peripheral Blood flow measured per 30 seconds epoch over 7 minutes after the beginning of the mental stress challenging