

Acute Exercise Improves Forearm Blood Flow during Postprandial Hyperglycemia in Normotensive Offspring of Hypertensive Parents

Jutapakdeekul W, MSc¹, Kulaputana O, MD, PhD¹

¹ Sports Medicine Program, Department of Physiology, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Bangkok, Thailand

Background: Hyperglycemia can cause vascular impairment and exercise training improves it. It is unknown whether a single bout of high-intensity aerobic interval exercise (HIIE) can improve vasoactive impairment induced by high blood sugar in genetically predisposed hypertensive individuals.

Objective: To study the effects of HIIE on forearm blood flow (FBF) during postprandial hyperglycemia in healthy young men with a parental history of hypertension.

Materials and Methods: Ten normotensive young men (aged 21.3±1.4 year, BMI 21.3±2.1 kg/m²), with hypertensive parent(s), participated in two experimental conditions, oral glucose loading (OGL) without exercise and OGL with exercise, in a randomized crossover fashion on two separated visits. Glucose solution was ingested 10 minutes after treadmill exercise, which was performed for thirty-eight minutes. In both occasions, the area under curve of FBF (FBF_{AUC}) during reactive hyperemia using venous occlusion plethysmography was determined at baseline and thirty minutes after OGL.

Results: Differences in FBF response were found between the two conditions. FBF_{AUC} significantly decreased from 1,240.7±266.7 ml/100 ml/5 minute at baseline to 1,069.4±152.7 ml/100 ml/5 minute (p=0.011) after OGL without exercise. As for with exercise, FBF_{AUC} at 30 minutes after OGL tended to increase from baseline (baseline level 1,135.7±215.1 versus 1,253.3±193.7 ml/100 ml/5 minute at 30 minutes after OGL, p=0.104). The FBF_{AUC} in response to OGL with exercise was significantly higher when compared to without exercise (p=0.001).

Conclusion: HIIE can prevent a decline of blood flow due to high blood glucose in offspring of hypertensive parent(s). Such exercise may play an important role in preventing impaired vascular function and the development or progression of atherosclerosis in healthy young men at risk of hypertension.

Keywords: High-intensity aerobic interval exercise, Forearm blood flow, Postprandial hyperglycemia, Normotensive offspring of hypertensive parents

J Med Assoc Thai 2019;102(10):1053-9

Website: <http://www.jmatonline.com>

Received 29 Apr 2019 | Revised 5 Jul 2019 | Accepted 9 Jul 2019

Cardiovascular diseases, considered as non-communicable diseases, accounts for most global mortality⁽¹⁾. In addition to internal factors such as age, sex, genes, immunity, ethnicity, and stress, various external or environmental factors associated with daily

living behaviors such as smoking, high alcohol intake, high salt intake, and sedentary lifestyle appear to be involved in the development of non-communicable diseases^(2,3). Pathogenesis of cardiovascular disease has been linked to vascular dysfunction, which is defined as a decreased ability to induce vasodilation in response to specific stimuli and an imbalance between vasoconstrictor and vasodilator⁽⁴⁾. Moreover, diet with high sugar content causing high blood sugar level called postprandial hyperglycemia (PPH) has been implicated in the increased risk of not only diabetes⁽⁵⁾ but also hypertension⁽⁶⁾ and cardiovascular disease⁽⁷⁾. Furthermore, PPH has been

Correspondence to:

Kulaputana O.

Sports Medicine Program, Department of Physiology, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Bangkok 10330, Thailand.

Phone: +66-2-2564267

Email: onanong.k@chula.ac.th

How to cite this article: Jutapakdeekul W, Kulaputana O. Acute Exercise Improves Forearm Blood Flow during Postprandial Hyperglycemia in Normotensive Offspring of Hypertensive Parents. J Med Assoc Thai 2019;102:1053-9.

shown to rapidly suppress vasodilation function in individuals with abnormal glucose metabolism⁽⁸⁾ and healthy young subjects⁽⁹⁾. Such impairment has been related to vascular endothelial dysfunction induced by a reduction of nitric oxide bioavailability through over-generation of superoxide anion and associated oxidative stress⁽¹⁰⁾. Additionally, there is evidence that endothelial dysfunction occurs ahead of vascular atherosclerosis⁽¹¹⁾ and plays an important role in hypertension⁽¹²⁾. Thus, there is a possibility that repeated exposure to high sugar containing meals causing episodes of PPH over a long period of time enhances the risk of developing atherosclerosis and certain vascular abnormalities.

Regular aerobic exercise has been known to prevent vascular dysfunction in healthy persons^(9,13). Zhu et al⁽¹³⁾ found that moderate aerobic exercise prevents vascular dysfunction that occurs after eating high-density sugar. The vascular dilating function was assessed by measuring either blood flow or the size of the arteries at the time of enlargement. The high-sugar diet with no aerobic activity resulted in a decrease in flow-mediated dilation values of the brachial artery. After exercise, the decrease of flow-mediated dilation induced by high sugar concentration was not observed. Similarly, Endo et al⁽⁹⁾ found that aerobic exercise had a protective effect on vasodilation function in healthy young subjects. However, the effect of exercise being studied previously was based on continuously aerobic exercise at moderate intensity. The effect of high-intensity aerobic interval exercise (HIIE) on vasodilation function during PPH in healthy young men particularly those at high risk of vascular dysfunction due to genetic predisposition remains undetermined. The authors hypothesized that HIIE could help improvement of both PPH and PPH-induced impairment of forearm blood flow (FBF) in offspring of hypertensive parents (OHT). Thus, the purpose of the present study was to compare the responses of blood flow in the forearm after oral glucose loading (OGL) with and without a prior HIIE in normotensive young men with a family history of hypertension.

Materials and Methods

Subjects

Ten normotensive healthy young men aged between 18 and 30 years old participated in the present study. They were physically inactive, defined as involved in moderate-intensity exercise such as jogging, cycling, or recreational sport, lasting no longer than 30 minutes per session with a frequency

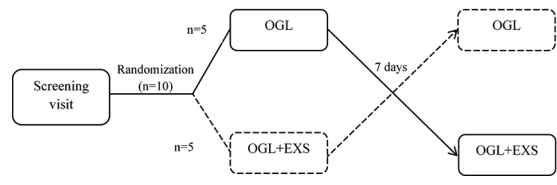


Figure 1. Crossover study design.

OGL, oral glucose load without exercise; OGL+EXS, oral glucose load with exercise

of less than two sessions per week for at least two years, non-smoking, and possessing a background of hypertension of either or both parents. Each subject had to participate in two experimental visits, oral glucose load with exercise (OGL+EXS) or oral glucose load without exercise (OGL). All participants were explained about the procedures and potential risks and benefits of the study. After that, the participants signed written informed consents. The present study was approved by the Ethics Committee of the Faculty of Medicine, Chulalongkorn University.

Experimental protocol

Each subject was scheduled for one screening visit and two experimental visits. The experimental visits were sequentially assigned in random order using a computer (Figure 1). At the first visit, the volunteers had blood testing to exclude individuals with abnormal fasting plasma glucose and lipid profiles. Blood samples were drawn by a certified medical technologist and sent to the accredited medical laboratory of King Chulalongkorn Memorial Hospital for lipid profiles and plasma glucose analyses. During this visit, all volunteers were screened for blood pressure. They had to have blood pressure less than 130/85 mmHg. They also had a maximal oxygen consumption test. The second visit (OGL visit) and third visit (OGL+EXS visit) were performed in a randomized crossover fashion, separated by at least one week. At the second visit, the participants reported to the lab at 7 am after an 8 to 10 hour overnight fast. After resting in a supine position for 30 minutes, they received an OGL in an upright position. Then the participants returned to a supine position soon after completing the OGL (within two minutes). At the third visit, the participants reported at 7 am after an overnight fast similarly to the second visit; however, after resting in a supine position for 30 minutes, they performed continuous HIIE (4 bouts of 4:3 work: active recovery). The participants received an OGL within 15 minutes after the exercise session. They

returned to a supine position just after completing the OGL (within two minutes). FBF, blood pressure, and blood glucose levels were measured at prior to OGL or OGL+EXS and 30 minutes after completing the OGL.

Oral glucose load

The participants ingested 75 grams of glucose powder dissolved in 225 ml of drinking water. This intake was the same standard amount used for the oral glucose tolerance test⁽⁹⁾. The drinking process finished within 10 minutes.

Blood pressure

Blood pressure measurement was performed by bedside monitor (Life Scope TR; BSM-6501) on the right side, while supine. The measurement was repeatedly recorded at baseline and 30 minutes after the high concentration of sugar loading.

Forearm blood flow

All participants had a 10-minute rest prior to the measurements of FBF during reactive hyperemia. The measured arm was positioned at least 30° above heart level when the strain gauge was placed at the widest diameter of the forearm. The size of the mercury strain gauge was selected by its length of 2 to 3 centimeters less than the circumference of the arm⁽¹⁴⁾. To measure blood flow at the forearm, a venous cuff was placed on the upper arm and an arterial cuff on the wrist to exclude hand circulation. Then, the wrist cuff was pumped to meet the cuff pressure at the subject's suprasystolic pressure (systolic pressure+30 mmHg) and venous cuff at 50 mmHg. Blood flow data was collected using NIVP3 software (D.E. Hokanson, Inc., USA). After five minutes of arterial occlusion in the upper arm, serial measurements of FBF were recorded every 15 seconds during five minutes of reactive hyperemia. FBF_{AUC} was determined as the area under the curve of blood flow rate serially recorded over the period of five minutes of reactive hyperemia.

Maximal oxygen consumption test (VO_{2max} test)

After electrocardiogram (EKG) screening to exclude individuals with any cardiac abnormalities, each participant had a maximal oxygen uptake test on a motor-driven treadmill (Nautilus TM model; T518) with a continuous breath by breath gas analysis (Oxycon™ Mobile, Cardinal Health, Germany). The participants had a muscle-stretch warm up for three to five minutes on a treadmill followed by walking or running at speed and slope adjusted to

meet 70% of their age-predicted maximal heart rate [(220-age)×70%]. The slope was then increased by 2% and maintained for two minutes as stage 1, and increased to 6% for two minutes for stage 2. This was followed by incremental slope adjustment of 2% every two minutes until volitional exhaustion. The maximal oxygen uptake (VO_{2max}) was obtained as a plateau in oxygen uptake with additional work rate. The respiratory exchanged ratio (RER) of greater than 1.15, the heart rate reaching an age-predicted maximal heart rate of ±5% and the RPE Borg Scale of 19 or 20 were the criteria of VO_{2max} in the present study.

High-intensity interval exercise

The participant's maximal heart rate (HR_{max}) obtained during VO_{2max} test was used for exercise intensity prescription. The exercise protocol was comprised of treadmill running at 85% to 95% HR_{max} for four minutes, alternating with three minutes of jogging at 70% HR_{max}. The subjects performed four sets of such alternating intensities. A 5-minute warm up and 5-minute cool down were also included in the exercise protocol, resulting in 38 minutes of exercise.

Statistical analysis

Statistical analyses were performed using SPSS 22.0 software. Data was presented as mean with standard deviation (SD). The effect of OGL, with and without exercise, on FBF_{AUC}, blood glucose, mean arterial pressure, and heart rate were analyzed by repeated measurements ANOVA. For analyses of within and between experiments, pairwise comparisons were employed. A significant level was set at p-value less than 0.05 for all analyses.

Results

Basic characteristics of the participants are shown in Table 1. The participants' occupations were students (n=8), coffee seller (n=1), and physical therapist (n=1). Most subjects (n=9) had a single parent with hypertension. All subjects were normotensive as shown in Table 1.

Outcomes in response to PPH without exercise (OGL)

At 30 minutes after OGL, the mean arterial pressure did not change from precondition (Table 2). Heart rate slightly increased at 30 minutes after OGL (p=0.009). Glucose load significantly decreased FBF_{AUC} by 13.8% (p=0.011) (Figure 2). Blood glucose significantly increased by 82% after 30 minutes of glucose load (p<0.001) (Figure 3).

Outcomes in response to PPH with exercise (OGL+EXS)

At 30 minutes after OGL, heart rate remained significantly elevated ($p<0.001$) when glucose solution was consumed after exercise. However, the mean arterial pressure was elevated non-significantly (Table 2). FBF_{AUC} showed a non-significantly increase by 10.4% with OGL+EXS ($p=0.104$) (Figure 2). There was a 58% increase of blood glucose levels

at 30 minutes after OGL+EXS ($p<0.001$) (Figure 3).

Comparison of PPH and FBF between OGL and OGL+EXS

Baseline values of blood glucose and FBF_{AUC} measured prior to OGL were not different between the two experiments ($p=0.724$). The value of FBF_{AUC} in response to OGL+EXS was significantly greater than in response to OGL ($1,253.3\pm 266.7$ mL/100 mL of tissue/minute versus $1,069.4\pm 152.7$ mL/100 mL of tissue/minute, $p=0.001$). The increase of blood glucose with OGL was significantly lower in OGL+EXS compared to OGL alone (152.6 ± 19.0 mg/dL versus 134.0 ± 17.4 mg/dL, $p=0.005$).

Table 1. Participant characteristics (n=10)

Participant characteristics	Mean±SD
Age (year)	21.3±1.4
Height (cm)	170.2±5.9
Weight (kg)	61.9±6.5
BMI (kg/m ²)	21.3±2.1
Resting SBP (mmHg)	109.9±11.0
Resting DBP (mmHg)	60.3±9.8
Resting heart rate (beats/minute)	71.0±9.6
VO ₂ max (ml kg ⁻¹ min ⁻¹)	34.7±5.0
Total cholesterol (mg/dl)	159.7±27.3
HDL-C (mg/dl)	48.3±7.4
LDL-C (mg/dl)	100.7±19.8
Triglyceride (mg/dl)	53.6±19.4
Fasting plasma glucose (mg/dl)	82.4±4.8
History of hypertensive parents, n	
Father	5
Mother	4
Both parents	1

BMI=body mass index; SBP=systolic blood pressure; DBP=diastolic blood pressure; HDL-C=high-density lipoprotein-cholesterol; LDL-C=low-density lipoprotein-cholesterol; SD=standard deviation

Discussion

The present study aimed to assess the effects of HIIE on FBF during hyperglycemia induced by OGL of healthy young men with a family history of hypertension. The present study findings were that FBF_{AUC} during PPH tended to increase in response to aerobic exercise performed prior to OGL while FBF_{AUC} was decreased in response to OGL without exercise. This may indicate that high intensity interval exercise prevented a decline in vasodilating function induced by oral glucose consumption. In addition, hyperglycemia induced by OGL was attenuated when a high intensity exercise bout was performed. These data may implicate an important role of HIIE in preventing impaired vascular function and potentially the development and progression of atherosclerosis in OHT.

PPH has been reported to be involved in impaired vascular function and physical changes in blood vessels⁽⁴⁾. The blood vessels must continuously maintain balance in homeostasis when exposed to altered vascular environment such as high blood sugar

Table 2. Blood glucose, peak forearm blood flow, mean arterial pressure, and heart rate during postprandial hyperglycemia with and without exercise (n=10)

Variables	OGL, Mean±SD		OGL+EXS, Mean±SD		p-value (ANOVA)
	Pre	Post 30	Pre	Post 30	
Blood glucose (mg/dl)	83.8±4.4	152.6±19.0***	84.8±6.3	134.0±17.4***,###	<0.001
FBF_{AUC} (ml/100 ml of tissue)	1,240.7±266.7	1,069.4±152.7*	1,135.7±215.1	1,253.3±193.7**	0.036
MAP (mmHg)	70.5±6.3	70.0±6.3	70.5±5.3	72.8±4.0	0.181
Heart rate (beats/minutes)	64.7±6.0	68.1±6.5**	65.3±7.9	88.2±6.9***,###	<0.001

OGL=oral glucose load without exercise; OGL+EXS=oral glucose load with exercise; Pre=precondition; Post 30=at 30 minutes after OGL; FBF_{AUC} =area under curve of forearm blood flow; MAP=mean arterial pressure; SD=standard deviation

* $p<0.05$ compared with the precondition in the same experimental condition; ** $p<0.01$ compared with the precondition in the same experimental condition; *** $p<0.001$ compared with the precondition in the same experimental condition; ### $p<0.01$ compared with post 30 minutes of OGL; #### $p<0.001$ compared with post 30 minutes of OGL

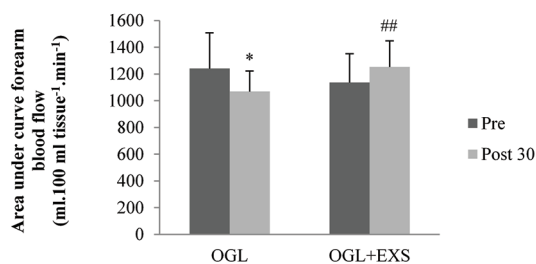


Figure 2. Comparison of area under curve of forearm blood flow of two experimental conditions: OGL with (OGL+EXS) and without exercise (OGL), both at pre-condition (Pre) and at 30 minutes after OGL (Post 30).

* $p < 0.05$ compared with the precondition in the same experimental condition; ## $p < 0.01$ compared with post 30 minutes of OGL

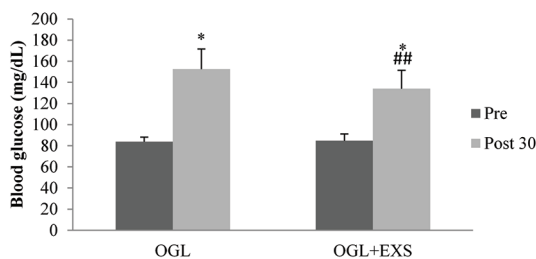


Figure 3. Comparison of blood glucose of two experimental conditions: OGL with exercise (OGL+EXS) and without exercise (OGL) precondition (Pre) and post 30 minutes after OGL (Post 30).

* $p < 0.001$ compared with the precondition in the same experimental condition; ## $p < 0.01$ compared with post 30 minutes of OGL

level, which may lead to further vascular disorders in the long term⁽¹⁵⁾. This notion agreed with the proposed vascular remodeling in people with PPH that increases the risk of developing hypertension⁽⁶⁾ and cardiovascular disease⁽⁷⁾.

Hypertension has a link between genetic factors and environmental factors, which are called hypertensinogenic factors. Hypertensinogenic factors associated with higher blood pressure, include obesity, insulin resistance, high alcohol intake, high salt intake, aging, and sedentary lifestyle⁽¹⁶⁾. In addition, PPH has been implicated in a decreased level of competent endothelium-dependent vasodilation due to reactive oxygen species (ROS)^(8,17). It was suggested that when increased, ROS decreases the response of bioavailable nitric oxide, a principal vasodilator molecule produced by vascular endothelium⁽¹⁰⁾. Thus, the interestingly proposed idea was that having

repeated bouts of PPH or occurring over an extended period may play an important role in the process of atherosclerosis development⁽⁸⁾. This leads to the present research question of how blood vessels in healthy young individuals who may be at high risk of developing hypertension, despite being normotensive, would respond to hyperglycemia. In addition, the authors proposed a question if HIIE would be of benefit to vascular function in this group of subjects who may have subclinical vascular abnormality. The present study findings indicated that hyperglycemia induced by OGL impaired vasodilation function in normotensive individuals with a high risk of hypertension due to parental history of hypertension. This suggested that dysfunction of blood vessels occurred transiently in this population and maybe even worse with repeated dysfunction due to several episodes of PPH in daily living.

Regular exercise has been shown to prevent vascular dysfunction⁽¹⁸⁾. Aerobic exercise can increase FBF_{AUC} by 22% in the OHT group and 11% in the group of individuals without a parental history of hypertension, and reduce peak forearm vascular resistance by 17% in the OHT group and 11% in the individuals without a parental history of hypertension⁽¹⁴⁾. Zhu et al⁽¹³⁾ found that aerobic exercise prevented the vascular dysfunction that occurred after eating high-density sugar. However, the present study employed moderate and steady exercise at 60% VO_{2max} , which was commonly prescribed for health benefits in individuals. Such exercise often results in boredom and loss of interest for young individuals to keep up with exercise for health⁽¹⁹⁾. Interestingly, previous studies have shown high HIIE having a greater improvement on vascular function than moderate intensity exercise^(20,21). The authors proposed HIIE as an additional alternative to conventional aerobic exercise at the constant intensity for young population to keep their interest to gain health with exercise. Another objective of the present study was to investigate how vasodilation function of a blood vessel in the presence of hyperglycemia would respond to an acute episode of HIIE in OHT. From the present study results, the authors were able to demonstrate that HIIE prevented the attenuation of FBF_{AUC} induced by OGL.

The present study encountered some limitations. In the family history of hypertension, the participants may have either a history of a father or a mother or both parents with high blood pressure. Hence, the participants could be somewhat heterogeneous, and they might be different in risk of hypertension

inherited from their one or both parents⁽²²⁾. Regarding the sample size, the small number of subjects may be an imperfect representative of the population with parents who are hypertensive. One important reason was that hypertension is well accepted as a condition with polygenic inheritance and multifactorial influences. A larger number of subjects would provide more confidence in the findings. However, to ensure that the number of participants was enough to answer the research question, the pilot study was conducted to determine the sample size with the alpha value of 0.05 and the power of 0.9. Using the FBF as the variable, the sample size of at least 10 participants per group was required to complete the study. Additionally, the study has a self-control repeated measure with crossed over design, which should help enhance the strength of the outcomes. From the present study results, the authors would recommend that HIIE may be performed when high sugar containing meal is consumed to reduce hyperglycemia postprandially and the detrimental effect of hyperglycemia. However, postprandial blood sugar elevation may last several hours; therefore, further studies are required to investigate the effect of meal-induced hyperglycemia in longer monitoring periods such as 2, 4, and 24 hours after exercise.

Conclusion

In conclusion, high intensity interval exercise was effective in protecting impaired vasodilation capacity induced by PPH in offspring parental history of hypertension. The study implication is that a single bout of such exercise when performed prior to sugar consumption could reduce PPH and help preventing an impairment of vasodilation function. In addition, in young individuals with genetic predisposition of impaired vascular function, such exercise may play a role in decreasing future risk of vascular abnormality that may develop when sugar consumption is hardly avoided in daily living.

What is already known on this topic?

Vascular impairment has been shown to improve with moderate-intensity, aerobic exercise in various populations.

It is unknown whether a more challenging HIIE can improve hyperglycemia-induced impairment of vasodilation in young individuals having genetic risk of developing hypertension.

What this study adds?

Impaired vasodilation induced by acute

hyperglycemia was restored with an acute HIIE in young men having a genetic risk of developing hypertension.

Acute hyperglycemia after eating a meal with high sugar content should be avoided in daily life. A bout of continuous aerobic exercise or a high intensity interval exercise may be recommended to prevent vascular impairment induced by PPH in genetically predisposed hypertensive population.

Acknowledgement

The authors would like to thank Wasan Punyasang for assisting with statistical analyses. The authors would like to thank all volunteers who participated in the study. This work was supported by the Ratchadaphiseksomphot Endowment Fund (Grant No.2560-106), Faculty of Medicine, Chulalongkorn University, Thailand. All authors read and approved the final manuscript.

Conflicts of interest

The authors declare no conflict of interest.

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