

## Family history of hypertension is associated with exaggerated cardiovascular reactivity to mental, but not to physical test

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### Abstrak

**Tujuan** Membandingkan reaktivitas kardiovaskular terhadap tes mental dan fisik antara subjek normotensif dengan riwayat keluarga hipertensi dan subjek normotensif tanpa riwayat keluarga hipertensi.

**Metode** Mahasiswa normotensif dengan (n=40) dan tanpa (n=40) orangtua hipertensi melakukan tes aritmatika dan cold pressor. Kedua tes tersebut terdiri dari fase istirahat pra-tes, fase tes, dan fase istirahat pascates. Parameter kardiovaskular diukur pada tiap fase dengan menggunakan alat pengukur tekanan darah osilometrik otomatis. Data di analisis dengan tes t atau Mann-Whitney. Reaktivitas kardiovaskular diketahui berdasarkan selisih nilai fase tes dengan fase pra-tes.

**Hasil** Kedua kelompok tidak berbeda bermakna dalam usia, indeks masa tubuh, kadar gula darah puasa, dan kadar kreatinin plasma. Subjek normotensif dengan orangtua hipertensi menunjukkan tekanan darah sistolik istirahat (108,33±1,6 vs 103,00±1,6 mmHg) serta hipereaktivitas kardiovaskular (MABP 19,13±1,4 vs 15,5±1,0 mmHg, P= 0,04), yang lebih tinggi secara bermakna terhadap tes mental namun tidak terhadap tes fisik (MABP 24,26±1,7 vs 21,74±1,7 mmHg) dibandingkan dengan subjek normotensif tanpa orangtua hipertensi.

**Kesimpulan** Subjek normotensi dengan riwayat keluarga hipertensi mempunyai hipereaktivitas kardiovaskular terhadap tes mental namun tidak terhadap tes fisik dibandingkan dengan subjek normotensi tanpa riwayat keluarga hipertensi. Akan tetapi, belum jelas apakah riwayat keluarga hipertensi atau tekanan darah sistolik istirahat yang berhubungan dengan hipereaktivitas kardiovaskular terhadap tes mental. (*Med J Indones 2010; 19:118-23*)

### Abstract

**Aim** To investigate whether normotensive young adults with family history of hypertension demonstrate exaggerated cardiovascular responses to both mental and physical stimuli as compared to normotensive young adults without family history of hypertension.

**Methods** Normotensive undergraduate students of normotensive parents (n = 40) and of hypertensive father/ mother/ both (n = 40), aged 20 – 30 years, performed serial subtraction test in a sitting position for three minutes. After taking a rest, subjects performed cold pressor test in ninety seconds. In each test, blood pressure and pulse rate were recorded in pre-test, during test, and post-test using an automated oscillometric device. Changes score rather than absolute scores were analyzed using independent t-test or Mann-Whitney.

**Results** There were no significantly differences in age, body mass index, fasting blood sugar, and plasma creatinine between the two groups. Normotensives of hypertensive parents had significantly higher office systolic blood pressure (108.33±1.6 vs 103.00±1.6 mmHg) and delta change score of cardiovascular reactivity to serial subtraction test (MABP 19.13±1.4 vs 15.5±1.0 mmHg, P= 0.04), but not to cold pressor test (MABP 24.26±1.7 vs 21.74±1.7 mmHg) than those of normotensive parents.

**Conclusion** Normotensive young adults with family history of hypertension demonstrated exaggerated cardiovascular reactivity to mental test but not to physical test. As compared to normotensive young adults without family history of hypertension However, this familial difference in cardiovascular reactivity to mental test is confused with office blood pressure. (*Med J Indones 2010; 19:118-23*)

**Key words:** cardiovascular reactivity, cold pressor test, mental arithmetic test, of hypertension

Although still not popular in clinical setting, cardiovascular reactivity (CVR) can be used as a non-invasive method to identify pre-clinical state of cardiovascular disease, i.e the pathogenic changes in cardiovascular structure and function that if continued will later manifest as cardiovascular disease, such as hypertension, myocardial infarct, and stroke.<sup>1</sup> Thus, subjects who have exaggerated CVR as well

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as family history of hypertension are in high risk to develop cardiovascular disease.<sup>2</sup> Numerous studies had investigated whether normotensive subjects with family history of hypertension have exaggerated CVR. However, those studies found conflicting results.<sup>3-4</sup> The controversial finding may be caused by several factors, such as the use of wide range of laboratory stimuli.<sup>4</sup> This study aimed to investigate whether normotensive young

adults with family history of hypertension demonstrate heightened cardiovascular responses to both mental and physical stimuli as compared to normotensive young adults without family history of hypertension.

## METHODS

### Participants

Participants were 80 undergraduate students of International Islamic University of Malaysia, Kuantan Campus. The inclusion criteria included subjects between 20-30 years old with systolic blood pressure (SBP) <140 mmHg and diastolic blood pressure (DBP) <90 mmHg.<sup>5</sup> The exclusion criteria were based on a self-reported questionnaire, anthropometric, and biochemistry measures. Based on a self-reported questionnaire, they were not having cardiovascular diseases, renal diseases, diabetes mellitus, psychiatric disorders, any medication affecting the cardiovascular system and not a smoker. By anthropometric measure, participants' body mass index was  $\leq 27.3$  kg/m<sup>2</sup> for female participants or  $\leq 27.8$  kg/m<sup>2</sup> for male participants. By biochemistry measures, participants' fasting blood sugar was <6.1 mmol/L and plasma creatinine was <133 mmol/L.

### Family history of hypertension

Participants were divided into two groups based on having or not family history of hypertension (FHoH), based on a self-reported questionnaire. Criteria for having FHoH were based on parental history of hypertension, in which either her/ his father or mother or both had one of the following criteria: a) high blood pressure (SBP >140 mmHg or DBP >90 mmHg), b) being diagnosed as hypertension, and c) being on medication for hypertension. Subjects were considered not having FHoH if her/ his father and mother did not have all the above criteria.

### Informed consent

The participants were given explanation on the purpose of the study, the laboratory tests required to do, the inconvenient consequences that might occur, and the data confidentiality. After the explanation, if the participants agreed to take part in this study, they were required to give their consent. The Ethical Committee of International Islamic University Malaysia, Kuantan Campus had approved the study protocol.

## Cardiovascular (CV) parameters

### Blood pressure

Office SBP and DBP were measured by using mercury column sphygmomanometer (W.A. Baum. Co. Inc., New York, USA) based on Korotkoff sounds, in a sitting position after taking a rest at least for five minutes.<sup>6</sup> During the test, SBP and DBP was measured using a non-invasive, automatic vital sign monitor device TM-2551 P (A & D Co. Ltd., Tokyo, Japan), from the brachial artery of the participants' dominant hand. The automatic vital sign monitor device TM-2551 P measures blood pressure by using oscillometric method, by which the blood pressure is derived from the oscillation of the pressure wave transmitted from peripheral artery during the cardiac cycle.<sup>7</sup> Blood pressure reading of the automatic, non-invasive, oscillometric method was generally in a good agreement with that of the invasive, intra-arterial method<sup>6</sup> and to remove observer bias.

### Pulse rate

Pulse rate (PR) rather than heart rate response was measured using a non-invasive, automatic vital sign monitor device TM-2551 P (A & D Co. Ltd., Tokyo, Japan).<sup>8</sup>

### Pulse pressure

Pulse pressure (PP) was calculated by subtracting SBP with DBP ( $PP = SBP - DBP$ ).<sup>8</sup>

### Mean arterial blood pressure

Mean arterial blood pressure (MABP) was calculated by the following formula:  $MABP = DBP + (PP/3)$ .<sup>8</sup>

### Rate pressure product

Rate pressure product (RPP) was calculated by using formula:  $RPP = (SBP \times PR)/100$ .<sup>8</sup>

### Laboratory tests

The laboratory tests consisted of mental arithmetic test and cold pressor test, which done in the order. Each test consisted of pre test, test, and post test.<sup>9</sup> Before the test, the participants must restrain from eating, drinking coffee and exercising at least one hour before the laboratory session.

### Mental arithmetic test (MAT)

In pre-test, participant took a rest in a sitting position for at least five minutes. At the end of this period, CV

parameters were measured for at least three times. The two closest measurements were being averaged. During test, participant performed serial-subtraction test by subtracting seven continuously from the number 99 in the first thirty seconds, 300 in the proceeding one minute, and 2816 for the last one and half minutes in a sitting position. The participant had to calculate as quickly and accurately as possible (being harassed by the observer) and stated loudly the answers. If a wrong answer was given, she/ he had to repeat from the last right answer. Cardiovascular parameters were measured at the twentieth seconds of the 2<sup>nd</sup> minutes. After completing the measurement, the participant ended the calculation. The total duration of the test was 3 minutes. In post-test, the participant took a rest in a sitting position for another 1½ half minutes. At the end of this, CV parameters were measured for at least three times. The two closest measurements were being averaged.

### Cold Pressor Test (CPT)

The pre test and post test of CPT were similar with MAT. During test, the participant performed hand immersion test by immersing her/ his left hand up to the wrist into the 5°C iced-water placed in an icebox. Cardiovascular parameters were measured at the 5<sup>th</sup> seconds. After completing the measurement, the hand was dried with a dry-towel. The total duration of the test period was 1½ minutes.

### Data reduction

A delta change score of cardiovascular reactivity (CVR) was calculated by subtracting the CV parameters measured in the pre-test from the CV parameters measured during the test. A delta change score of cardiovascular recovery (CVRec) was calculated by subtracting the CV parameters measured in the pre-test from the CV parameters measured in the post-test.<sup>9</sup> Delta change score was used rather than absolute value in order to control the baseline level.<sup>9</sup> Moreover, delta change score yields reliable measures of blood pressure and heart rate reactivity to laboratory stimulus.

### Data handling and analysis

Microsoft Office Excel 2003 was used for data entry and reduction. Statistical Package for Social Sciences version 14.0 (SPSS Inc., Chicago, USA) was used for data summarize and analysis. Normality of data was tested by one sample Kolmogorov-Smirnov test. Mean ± standard error of the mean (SEM) or median with

inter-quartile range was used to summarize the data that normally or not normally distributed, respectively. To determine whether any differences of CVR and CVRec existed between the group with and without FHoH, independent t-test or Mann-Whitney U test was performed for data that normally or not normally distributed, respectively. *p* value < 0.05 was considered as the statistical significance level.

## RESULTS

### Characteristics of subjects

Eighty subjects who met the inclusion and exclusion criteria joined this study. They were students from International Islamic University Malaysia, Kuantan Campus. All subjects were Malay, except 1 male and 2 female subjects who were Indian. We had 40 subjects without FHoH and another 40 subjects with FHoH, which comprises of 17 subjects with hypertensive father, 15 subjects with hypertensive mother, and 8 subjects with both hypertensive father and mother. Gender was distributed equally: 20 female and 20 male subjects in each group, thus making the gender ratio 1:1 in each group. There were no significant differences in age, body mass index, fasting blood sugar, and plasma creatinine between normotensive young adults with and without FHoH (Table 1).

Table 1. Characteristics of subjects stratified by family history of hypertension

Characteristics	Without FHoH <sup>a</sup>	With FHoH <sup>a</sup>
Age (years)	22 (21.5 – 23) <sup>b</sup>	22 (21 – 22) <sup>b</sup>
BMI (kg/m <sup>2</sup> )	21.19 ± 0.4	21.59 ± 0.4
FBS (mmol/L)	4.43 ± 0.05	4.46 ± 0.06
Plasma creatinine (mmol/L)	80.55 ± 2.7	84.65 ± 2.7

Note. FHoH = family history of hypertension; BMI = body mass index; FBS = fasting blood sugar. Data are summarized as mean ± standard error of the mean (SEM), except for the data that are not normally distributed.

<sup>a</sup> N = 40 subjects. <sup>b</sup> Median (lower quartile – upper quartile) for data that are not normally distributed.

### Office blood pressure

Normotensive young adults with FHoH had significantly higher office SBP than normotensive young adults without FHoH (*t* = -2.34, *p* = 0.02). However, normotensive young adults with and without FHoH did not differ significantly in office DBP (Table 2).

Table 2. Office blood pressure stratified by family history of hypertension

Office blood pressure	Without FHoH <sup>a</sup>	With FHoH <sup>a</sup>
SBP (mmHg)	103 ± 1.6	108.33 ± 1.6*
DBP (mmHg)	60 (56.5 – 70) <sup>b</sup>	67.5 (60 – 70) <sup>b</sup>

Note. FHoH = family history of hypertension; SBP = systolic blood pressure; DBP = Diastolic blood pressure. Data are summarized as mean ± standard error of the mean (SEM), except for the data that are not normally distributed.

<sup>a</sup> N = 40 subjects. <sup>b</sup> Median (lower quartile – upper quartile) for data that are not normally distributed.

\* p < 0.05 vs. control group.

### Cardiovascular reactivity to MAT

This study found that normotensive young adults with FHoH exerted greater CVR to MAT as compared to normotensive young adults without FHoH. Normotensive young adults with FHoH showed greater DBP ( $Z = -2.05$ ,  $p = 0.05$ ), MABP ( $t = -2.04$ ,  $p = 0.04$ ) and RPP reactivity ( $t = -2.06$ ,  $p = 0.04$ ) to MAT than those without FHoH. However, both groups did not differ significantly in SBP, PR, and PP reactivity to MAT (Table 3). In terms of CVRec from MAT, both groups did not differ significantly.

Table 3. Delta change score of cardiovascular reactivity to mental arithmetic test stratified by family history of hypertension

Cardiovascular reactivity	Without FHoH <sup>a</sup>	With FHoH <sup>a</sup>
SBP (mmHg)	17.46 ± 1.4	20.7 ± 1.6
DBP (mmHg)	13.5 (9.13 – 19.25) <sup>b</sup>	16.75 (11.63 – 24.38) <sup>b</sup>
PR (beats/min)	8.75 (5.5 – 13) <sup>b</sup>	9.25 (4.5 – 14.88) <sup>b</sup>
PP (mmHg)	2.94 ± 1.4	2.36 ± 1.3
MABP (mmHg)	15.5 ± 1.0	19.13 ± 1.4*
RPP (mmHg . beats/min)	22.92 ± 1.4	29.84 ± 2.8*

Note. FHoH = family history of hypertension; SBP = systolic blood pressure; DBP = diastolic blood pressure; PR = pulse rate; PP = pulse pressure; MABP = mean arterial blood pressure; RPP = rate pressure product. Data are summarized as mean ± standard error of the mean (SEM), except for the data that are not normally distributed.

<sup>a</sup> N = 40 subjects. <sup>b</sup> Median (lower quartile – upper quartile) for data that are not normally distributed.

\* p < 0.05 vs. control group.

### Cardiovascular reactivity to CPT

There were no significant differences in SBP, DBP, PR, PP, MABP, and RPP reactivity to CPT between normotensive young adults with and without FHoH (Table 4). Both groups did not differ significantly in terms of CVRec from CPT.

Table 4. Delta change score of cardiovascular reactivity to cold pressor test stratified by family history of hypertension

Cardiovascular reactivity	Without FHoH <sup>a</sup>	With FHoH <sup>a</sup>
SBP (mmHg)	23.84 ± 1.9	26.68 ± 1.8
DBP (mmHg)	20.69 ± 1.8	23.05 ± 1.8
PR (beats/min)	1.25 (-4.75 – 6.25) <sup>b</sup>	3.25 (-0.38 – 8.63) <sup>b</sup>
PP (mmHg)	2.5 (-1.25 – 5.88) <sup>b</sup>	3.25 (-1.88 – 9.75) <sup>b</sup>
MABP (mmHg)	21.74 ± 1.8	24.26 ± 1.7
RPP (mmHg . beats/min)	18.73 ± 2.4	24.80 ± 1.8

Note. FHoH = family history of hypertension; SBP = systolic blood pressure; DBP = diastolic blood pressure; PR = pulse rate; PP = pulse pressure; MABP = mean arterial blood pressure; RPP = rate pressure product. Data are summarized as mean ± standard error of the mean (SEM), except for the data that are not normally distributed.

<sup>a</sup> N = 40 subjects. <sup>b</sup> Median (lower quartile – upper quartile) for data that are not normally distributed.

## DISCUSSION

This study found normotensive young adults with FHoH have exaggerated CV reactivity to MAT but not CPT. These results are in accordance to previous studies.<sup>10-12</sup> Based on the reactivity hypotheses<sup>13</sup>, there are at least three levels that might account for individual differences in cardiovascular responses, namely cortical (such as temperament), subcortical (autonomic outflow and endocrine regulation from the brain stem and hypothalamus), and peripheral (such as differences in sensitivity of adrenergic receptors in blood vessels). MAT and CPT differ in the mechanism to stimulate CV response. MAT is an active task; it is a cardiac stimulator because the mental load promotes a rise in plasma epinephrine and elicits a rise in blood pressure through an increase in cardiac output (CO).<sup>14-15</sup> The reason of CO increases in response to an active task had been explained by Obrist, in nearly 30 years ago.<sup>9</sup> Meanwhile, CPT is a passive coping task; it is a vascular stimulator since it causes a rise in plasma norepinephrine<sup>8</sup> and promotes a pressor response through an increase in total peripheral resistance.<sup>16</sup> Therefore, MAT and CPT can be used to assess either cortical, subcortical, or peripheral tissues differences of the cardiovascular responses in the background of the influence of familial history of hypertension.

The results of the study seem to support a view that normotensive young adults with FHoH already have structural changes in CV system.<sup>1, 17</sup> Among CV parameters measured in this study, exaggerated response in DBP and RPP reach borderline significant and significant difference, respectively. However,

the exaggeration of DBP in response to MAT among normotensive young adults with FHoH is not in line with the fact that MAT is a cardiac stimulator. If CO increases, SBP should be affected first than DBP. Consequently, as Obrist had explained, an inappropriate increased CO will disturb vascular autoregulation.<sup>9</sup> Actually, autonomic or sympathoadrenal dysfunction for long time had been suspected to contribute to the development of hypertension, although conflicting results were also still observed.<sup>18-19</sup> Baroreflex dysfunction<sup>4</sup> may contribute the disturbance of vascular autoregulation, serving as another explanation for the exaggerated DBP reactivity in normotensive young adults with family history of hypertension.

In this study, normotensive subjects with FHoH have significantly greater office SBP than the controls. Thus, it opens to debate whether FHoH or office SBP that correlates to exaggerated CV response to MAT. A line of evidences shows that normotensive offspring of hypertensive parents have slightly higher office<sup>20</sup>, home<sup>21</sup>, and 24-hour-SBP<sup>22</sup> as compared to normotensive offspring of normotensive parents. Recently, Flaa *et al.*<sup>23</sup> has examined CVR in normotensive men, who were divided into different level office BP (low, normal, and high). They found that normotensive subjects with high level of office BP exerted greater CV reactivity to MAT, but not to CPT, as compared to normotensive subjects with lower level of office BP. What Flaa *et al.* have reported supports the possibility that office BP does contribute to the development of exaggerated CVR. It may provide additional explanatory variable to explain conflicting results in this area.

This study was not conducted to verify causal relationship between exaggeration of CVR to mental stressor/ stimulus and the development of hypertension.<sup>24</sup> However, in the study of family history of hypertension, the question of having hypertensive or normotensive parents should be validated as there may be potential for misclassification which otherwise would obscure relationships of the status of FHoH and cardiovascular hyperactivity.

As conclusion, normotensive young adults with family history of hypertension had exaggerated cardiovascular reactivity to mental but not to physical test. However, we are not sure whether familial history of hypertension or office blood pressure that relates to cardiovascular hyperactivity.

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