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Endothelial Dysfunction in Healthy Passive Smoker

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Introduction. Passive smoking may have a deleterious effect to cardiovascular system and subsequent enormous public health implication. The sidestream cigarette smoke suggest impaired endothelial production of nitrit oxide. Since endothelial dysfunction is an early feature of atherogenesis, early detection on this become important and hopefully can prevents the subsequent atherosclerlotic events. There were only few studies have assessed the effects of passive smoking to human arterial wall. The objective of this study was to detect endothelial dysfunction in healthy passive smokers young adults.

Methods. We studied 80 healthy subjects 20 to 35 years old, which were divided into two groups, consist of 32 passive smokers and 48 subjects as controls. Passive smokers were defined as non-smokers who had been exposed to environmental tobacco smoke for at least one hour daily for three or more years. Endothelial function was measured by response of flow-mediated vasodilatation in brachial artery during reactive hyperemia.

Result. There are no significant differences in baseline characteristics (age, sex and baseline diameter) between two groups. Flow-mediated dilatation response was significantly impaired in the passive smokers 8.7 (2.9) percent compared with 12.8 (6.7) percent in control subject, $p = 0.006$.

Conclusion. Passive smoking is associated with impairment of endothelium-dependent dilatation, suggesting early event in atherosclerosis.

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Keywords: Passive smoking; endothelial dysfunction; flow-mediated vasodilatation brachial artery

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Penelitian Klinis

Disfungsi Endotel pada Perokok Pasif yang Sehat

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Latar belakang. Merokok pasifdapat mempunyai efek yang merugikan terhadap sistem kardiovaskular dan berdampak besar bagi kesehatan masyarakat secara luas. Asap rokok diduga mengganggu produksi nitrit oksida di endotel. Karena disfungsi endotel adalah ciri awal dari proses aterogenesis, deteksi dini sangat diperlukan sehingga dapat dilakukan upaya-upaya pencegahan kejadian kardiovaskular dikemudian hari. Hingga saat ini hanya sedikit saja penelitian yang membahas mengenai efek merokok pasif terhadap dinding pembuluh darah arteri. Tujuan dilakukan penelitian ini adalah untuk mendeteksi disfungsi endotel dini pada perokok-perokok pasif, dewasa muda dan sehat.

Metode. Kami meneliti pada sebanyak 80 subyek sehat berusia 20-35 tahun yang dibagi kedalam dua kelompok, terdiri dari 32 perokok pasif, dan 48 subyek sebagai kontrol. Perokok pasif didefinisikan sebagai orang yang tidak merokok, yang terkena paparan asap tembakau minimal satu jam setiap harinya, selama minimal tiga tahun. Fungsi endotel diukur dengan melihat respon vasodilatasi termediasi oleh aliran (*flow-mediated vasodilation*) selama hiperemia reaktif.

Hasil. Tidak ada perbedaan karakteristik dasar kelompok (usia, jenis kelamin dan diameter awal arteri brakhialis) yang signifikan diantara kedua kelompok. Respon dilatasi termediasi aliran secara signifikan menurun pada kelompok perokok pasif [8.7 (2.9) %] vs kelompok kontrol [12.8 (6.7) %] dengan p = 0.006.

Kesimpulan. Merokok pasif berhubungan dengan penurunan fungsi dilatasi – tergantung endotel (endothelium-dependent dilatation), menimbulkan dugaan adanya proses aterosklerosis dini.

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Kata kunci: Merokok pasif, disfungsi endotel, vasodilatasi arteri brakhialis termediasi aliran

Active cigarette smoking has long been known to predispose people to endothelial dysfunction that leads to atherosclerotic vascular disease. However it has recently became evident that passive smoking may also have a deleterious effect to cardiovascular system as well and subsequent enormous public health implication.[1]

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Passive smoking or often called as secondhand smoke (SHS) or environmental tobacco smoke (ETS) is the inhalation of smoke from tobacco products used by others, which includes exposure to both sidestream smoke from burning cigarettes and exhaled mainstream smoke.[2] Passive smoking increased the risk of heart disease by up to 30%, accounting for at least 35,000 deaths annually in the United States.[3]

Endothelial dysfunction is an early feature of atherogenesis in vitro,[4] in laboratory animals,[5] and in humans.[6] It represents an important marker of early vascular damage. Morphologic evidence of atherosclerosis can be detected as early as on second decade of life. Early detection on endothelial

dysfunction can hopefully prevents the subsequent atherosclerlotic events.

Some factors had been associated with endothelial dysfunction severity on passive smokers, such as the number of hours of the exposure per day, the proximity to the active smokers, the number of active smokers at home of workplace, and the room ventilation size where inhalation takes place.[1] We try to study one factor that may associates to the severity of endothelial dysfunction in passive smoking, which is the dose of exposure. In relation to dose-dependent, some previous studies found there were inverse relationships, while other studies found the contrary result. This might be due to the many parameters used, such as hours/day, or just the number of years of exposure. Dose of environmental tobacco smoke exposure using hour-years parameter which means the number of hours/day multiply by the number or years of exposure has never been used before, and we assumed that this parameter will be more accurate to measure the dose of exposure.

There's been only a few studies assessed the effects of passive smoking to arterial wall in human.[2] Therefore, to gain data of the environmental tobacco smoke effects on healthy young adults, we assessed endothelial dysfunction in arteries of healthy young adults (mean age 25 years old) who had no known risk factors for atherosclerosis other than exposure to environmental tobacco smoke using hour-years parameter.

Methods

Subjects

We studied the subjects, who were eligible if they were 20 to 35 years of age, had normal blood pressure, did not have diabetes, and had no history of hyperlipidemia or family history of premature vascular diseases. They were clinically well and taking no regular cardiovascular medications. The subjects were chosen by a consecutive sampling, bordered by some period of time, and were matched in age and gender. Subjects were recruited from friends, families, hospital staff and other community volunteers. Subjects had to meet one of two groups criteria, control group or passive smoker group. Subjects in control group were nonsmokers who had never been regularly exposed to environmental tobacco smoke at home or workplace, while passive smokers group were nonsmokers with self-reported history of exposure to environmental tobacco smoke at least one hour per day for at least three years. All subjects gave informed consent, and the study was approved by the institutional committees on ethical practice.

Study Design

This was a cross-sectional study. Each subject made one visit to the study hospital, which was also the time for medical history anamnesis, measurement of supine resting blood pressure, and the assessment of vascular reactivity of the brachial artery.

Measurements and data analysis

The ultrasound method for measuring endothelium-dependent arterial dilatation was measured in brachial artery, usingVivid 7® with 7.0 MHz linear array transducer. In this study, scans were obtained with the subject at rest, 1 minute and 2 minutes during reactive hyperemia. The brachial artery was scanned in cross-sectional section, 5 cm above the elbow, and the center of the artery was identified when the clearest picture of the anterior and posterior intimal layer was obtained.When a satisfactory transducer position was found, the skin was marked and the arm remained in the same position throughout the study.Increased flow was then induced by the inflation of a pneumatic torniquet placed around the forearm (distal to the scanned part of the artery) to a pressure 50 mmHg above subject's systolic pressure, for 4 minutes and 30 seconds. A second scan was performed at 60 seconds after deflation of the cuff, and the third was performed at 90 seconds.

The diameter of the vessel and flow-mediated vasodilatation responsewas measured by one observer, who was unaware of the subject status in groups. Then the cross-sectional boundaries of the artery were traced manually. This vasodilatation response was calculated as a percentage of change between maximum diameter of brachial artery reached before and after hyperemia reactive.

Statistical Analysis

Descriptive data for age and baseline brachial artery diameter were expressed as means ± SD, and gender was expressed in percentage. An analysis for mean differences

between two groups, based on important base-line characteristics, which were known could influence the FMD examination such as age, sex and baseline brachial artery diameter, were analyzed in Mannn-whitney test and chi-square. Then the differences of vasodilation response within two group was analyzed by Mann-whitney test. Among the passive smokers, the relation between the dose of tobacco smoke's exposure to vasodilatation response was assessed by Spearman correlation analysis. The determinant of vasodilatation response were then assessed by multipar linear regression analysis, with the vasodilatation response as the dependent variable, and age, sex, baseline diameter of brachial artery and duration on tobacco smoke's exposure as the independent variables. Statistical significance was inferred at a two-tailed p value or less than 0,05. All statistical analyses were performed using SPSS version 14.

Result

Baseline characteristics

There are 80 subjects, consist of 44 males and 36 females, which had an average age of 25.0 (4.0) years (range, 20-35). Passive smoking groups consist of 32 subjects, 17 males (53.1%) and 15 females, with an average age 25.8 (4.6) years. In the 48 subjects as control group, 27 males (56.3 %) and 21 females, the average age was 24.4 (3.4) years old.This data shows that age and sex was similar in both groups (Table 1). Other important base-line characteristics – such as sex and vessel size at rest – were also similar in both groups. Baseline brachial artery diameter was not different between passive smokers 3.5 (0.5) mm and in control subjects 3.3 (0.5) mm.

Vascular-Study Results

In response to reactive hyperemia, the average of vasodilatation response is 12,8 (6,7) percent in the control group. In the passive smokers group, the average ofvasodilatation responseis 8,7 (2,9) percent;which is significantly lower ($p<0,006$) for the comparison with the control group.

The range distribution of the vasodilatation response datain control group, is wider than the data in passive groups. The 95% CI for vasodilatation response in control groups are between 3-24%, whila in passive smoker groups are 5-15%. Then we can see the details in the box plot graph for analyze the descriptivecomparison between two groups, clearly, as in figure 1 below.

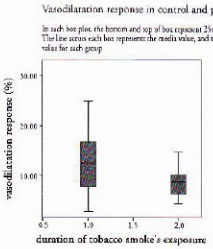

Figure 1. Data distribution of endothelium-dependent vasodilatation response (%)

Table 1. Baseline Characteristics of Subjects

Characteristic	Control	Passive smokers	Total	P value
Subjects	48	32	80	
Age (yr)	25,8 (4,6)	24,4 (3,4)	25,0 (4,0)	0,125
Sex	27 male (56,3%)	17 male (53,1%)	44 male (55 %)	0,481
	21 female (43,4%)	15 female (46,9%)	36 female (45 %)	
Brachialartery diameter at rest (mm)	3,3 (0,5)	3,5 (0,5)	3,4 (0,5)	0,200

Table 2. Vasodilatation response

Characteristic	Control	Passive smokers	P value
Average of vasodilatation response (%)	12,8 (6,7)	8,7 (2,9)	0,006

Among the 32 subjects in passive smoker group, although statistically insignificant, the dose of tobacco smoke's exposure had a trendto inversely correlatedwith severity of endothelial dysfunction,which means that the higher the dose of tobacco smoke's exposure, the lower vasodilatation response, as seen in the figure 2 below.

Factors which influence the vasodilatation response among the passive smokers were then assessed by multiple variable linear regression analysis, with the vasodilatation response as dependent variable and age, sex, baseline diameter and dose of tobacco smoke's exposure as independent variables.

The analysis shows that the dose of tobacco smoke's exposure is not an independent factor for the severity of endothelial dysfunction. The baseline brachial

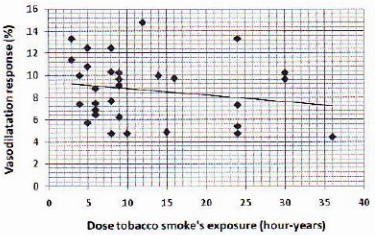

Figure 2. Relation between vasodilatation response of the brachial artery induced and the dose of tobacco smoke's exposure

Table 3. Multiple variable linear regression analysis to vasodilatation response among the passive smoker group

Model	Variables	Coefficients B	Std. Error	R	Adjusted R square	p value
1	Constant	25.840	14.940	0.550	0.099	
	Age	0,067	0.384			0.864
	Baseline diameter	-4.064	4.374			0.362
	Dose of exposure	-0.186	0.196			0.353
	Sex*age	-0.010	0.268			0.972
	Sex*dose	0.135	0.128			0.305
	Sex*diameter	0.520	3.086			0.868
	Sex	-4.820	9.902			0.631
2	Constant	26.000	13.963	0.550	0.135	
	Age	0.054	0.125			0.672
	Baseline diameter	-4.019	4.103			0.337
	Dose of ecxposure	-0.184	0.188			0.335
	Sex*dose	0.133	0.120			0.279
	Sex* diameter	0.485	2.867			0.867
	Sex	-4.932	9.207			0.597
3	Constant	23.877	6.023	0.549	0.167	
	Age	0.054	0.123			0.661
	Baseline diameter	-3.368	1.401			0.024
	Dose of ecxposure	-0.196	0.172			0.264
	Sex*dose	0.140	0.112			0.221
	Sex	-3.401	1.669			0.054
4	Constant	24.682	5.657	0.544	0.192	
	Baseline diameter	-3.184	1.318			0.023
	Dose of ecxposure	-0.198	0.169			0.252
	Sex*dose	-0.146	0.109			0.193
	Sex	-3.477	1.655			0.045
5	Constant	24.835	5.693	0.511	0.182	
	Baseline diameter	-3.768	1.228			0.005
	Sex*dose	-0.025	0.037			0.500
	Sex	-2.243	1.397			0.094
6	Constant	23.682	5.387	0.498	0.197	
	Baseline diameter	-3.489	1.148			0.005
	Sex	-1.996	1.239			0.018
7	Constant	16.440	3.049	0.426	0.154	
	Baseline diameter	-2.243	0.871			0.015

Table 4. Analysis of Variance for the predictor of baseline brachial artery diameter to vasodilatation response

Model		Sum of Squares	df	Mean Square	F	Sig.
7	Regression	46.692	1	46.692	6.636	.015(g)
	Residual	211.081	30	7.036		
	Total	257.774	31			

Predictors: (Constant), baseline diameter

Dependent Variable: vasodilatation response

artery diameter becomes the only determinant factor for the vasodilatation response in passive smoker (p = 0,015), which means that the higher baseline brachial artery diameter, the lower vasodilatation response. Multiple linear regression equation for this data is : vasodilatation response = 16,440 – 2,243xbaseline brachial artery diameter (Table 3).

That equation is a valid model for predictor of vasodilatation response (F value = 6,636; p = 0,015) that can be seen in table 4. From the model summary, only 15,4% (adjusted R^2 square = 0,154) of vasodilatation response (table 3) can be explained by this equation, and the rest are explained by other variables which not included in this study.

Discussion

Active cigarette smoking has long been known to predispose people to atherosclerotic vascular disease, but it has recently become evident that exposure to environmental tobacco smoke/passive smoking may also have deleterious cardiovascular effects, with enormous public health implications. This study shows that endothelial dysfunction, an important early feature of the atherogenic process, may occur in the systemic arteries of healthy young adults due to environmental tobacco smoke exposure. In this study we have shown that passive smokers have significantly impaired arterial endothelial function (p= 0.006). The mean vasodilatation response in passive smoker group was 8.7 (2.9) %, compared to 12.9 (6.7) % in control groups. This result wassimilar with previous study by Celermajer, which was 8.2 (3.1) % in control groups compared to 3.1 (2.7) % in passive smoker group.[1] Woo et al also found the differences in the subjects of passive smokers who were exposed to environmental tobacco smoke for over 8hours/day for at least two years to control group. The difference of mean and SD of diameter was 6.6 (3.4)% compared to 10.6 (2.3) % in control group.[7] Endothelium-dependent dilatation was significantly better in passive smoker groups 2.3 (2.1) % compared to control group 8.9 (3.2) % in Raitakari studies, which had exposure to environmental tobacco smoke for 1 hours/day for > 2 years as criteria for the passive smoker group.[8] In study by Holay et al, FMD% was significantly higher in non-smokers than passive smokers 8.9 (4.8) compared to 5.0 (2.3) in control group.[9]However there was different results from study by Woo that showed36 active or passive Chinese young adults smokers have less evidence of arterial dysfunction (7.3%) than the nonsmokers (7.9%) p>0.2.[10] All of this data brought the fact that passive smoking have contribution to endothelial dysfunction formation. However, Woo et al was not exactly studied passive smoker group but His study compared young Chinese active and passive smokers who were matched in direct or indirect exposure with young Caucasians (England and Aussie), so the results were not as specific as other studies.

But because our study examined the effects of passive smoking cessation on arterial reactivity in a cross sectional setting, the result should interpreted with caution. A more ideal approach would be serial prospective study of persons.

Self-reporting of exposure to environmental tobacco smoke by questionnaire was used because no methods are available to objectively quantify previous exposure to tobacco smoke.

The actual mechanism responsible for this arterial damage is not known, but might be related to the effects of tobacco smoke by interactions between platelets and vessel wall or by alteration of oxidation products or lipid components due to long-term environmental tobacco smoke exposure.[11]

Environmental tobacco smoke consists of approximately 85 percent sidestream smoke (from the burning ends of cigarettes) and 15 percent exhaled mainstream

smoke.[12] Since cigarettes burn at higher temperatures during inhalation, combustion is more complete, and some toxic components, such as carbon monoxide and benzopyrene, are found in higher concentrations in sidestream than in inhaled smoke.[13] Moreover, there are as many as 4000 chemicals are contained in environmental tobacco smoke.[12]

Environmental tobacco smoke in both low and high dose, increases the percentage of the aorta covered by atheroma in cholesterol-fed rabbits.[14] It also expose cockerels to levels of environmental tobacco smoke routinely encountered by people in smoke-filled environments is associated with the increasing size of aortic atheroma plaques.[15] Sun et alhave shown that dietary supplementation with L-arginine (the precursor of nitrit oxide, or endothelium-derived relaxing factor) protects cholesterol-fed rabbits from the endothelial dysfunction associated with exposure to environmental tobacco smoke. This finding suggests impaired endothelial production of nitrit oxide might be pathogenetically important in environmental tobacco smoke-related atherosclerosis of this animal model.[16]

Impaired bioavailability of nitrit oxide as endothelium-derived relaxing factor, may be particularly important, since nitrit oxide acts to inhibit platelet aggregation, adhesion of monocytes to the arterial wall, and proliferation of smooth-muscle cells. Dilatation mediated by brachial-artery flow is endothelium-dependent and is mediated in large part by the release of nitrit oxide. Therefore, our result suggest that the activity of endothelial nitrit oxide may be impaired in young passive smokers as well as in active smokers.[17] Passive smoking-related arterial damage may also be the consequence of enhanced degradation of nitrit oxide secondary to formation of oxygen-derived free radicals.[18]

Because we studied healthy young adults without known atherogenic risk factors, such as diabetes or hypertension, which have been shown to cause impaired vascular reactivity, we were able to investigate the effects of passive smoking alone on endothelial physiology.[19] Although only superficial systemic arteries can be studied with this ultrasound-based method, endothelial dysfunction in the brachial artery appears to be well correlated with both coronary endothelial physiology[20] and coronary atherosclerosis.[21]

This data could support individual and public health policy initiatives to allow nonsmokers to avoid smoke-filled environments at home or in the workplace.All the passive smokers in this study were exposed to environmental tobacco smoke for at least one hour per day. Unexpectedly, the result of this study shows that there are no significant dose-dependent relationship between exposure to tobacco smoke to the severity of endothelial dysfunction ($r = -0.239$. $p=0.187$). Contrary to Celermajer study that showed FMD was inversely related to the intensity of exposure ($r = -0.39$, $p=0.04$).[1]The study use exposure in hours/day on subjects that were divided into three groups, light (exposure 1-3 hrs/day), moderate (4-6 hrs/day) an heavy (more than 6 hrs/day).[1]

In He et al[22] meta-analytic studies, the relative risk of coronary heart disease increased significantly with exposure to a higher level or a longer duration of passive smoking. Compared to non-smokers who were not exposed to smoke, non smokers who were exposed to 1 to 19 cigarettes per day and to 20 or more cigarettes per day had relative risks of coronary heart disease of 1.23 (95% CI, 1.13-1.34) and 1.31 (95% CI, 1.21-1.42), respectively ($p = 0.006$). Likewise, as compared with nonsmokers who were not exposed to cigarette smoke, non smokers who were exposed to the spouse's smoke for 1 to 9 years, 10 to 19 years, and 20 or more years had relative risks of coronary heart disease of 1.18 (95% CI 0.98-1.42), 1.31 (95% CI 1.11-1.55) and 1.29 (95% CI 1.16-1.43), respectively ($p=0.01$ for linear trend). This study showed a significant result when compared to non-smokers, but the relative risk shows smaller trends after some degree of exposure. Negative trends also found in groups with the exposure > 20 years.[22]

This study uses a new parameter, hours-years, of which hours/day of exposure multiplies with years of exposure. With this new parameter, we expect to get more accurate result on the relation between the doseof tobacco smoke's exposure with the severity of endothelial dysfunction. This study showed there was an inverse trend, that the bigger and the longer amount of exposure, the lower vasodilatation response with FMD in brachial artery. However this finding was not significant. This might happened due to the homogenity of the passive smokersubjects that distribute in "low dose" passive smoking, or maybe it is true that there is no dose dependent in this relationship.

It leads to an interesting question of what can act as a cause. The alteration of gene transcription in nitrit oxide synthetase or alteration related to endothelial progenitor cells are assumed as the underlying

mechanism. However, further study is required to intensively learn about the dose dependent which related to the severity. The study should also control confounding factors, such as proximity to the smokers, ventilationof the room where the exposure takes place, the number of cigarettes, etc. Further study also required to find at what level of the exposure does endothelial dysfunction begins to develop, and the reversibility.

In the determination of flow-mediated dilatation among passive smokers assessed by multivariable regression analysis, baseline brachial artery diameter becomes the only independent variables as predictor for the vasodilatation response. This is similar to study by Ryliskite,that found FMD in low cardiovascular risk patient inversely correlates with age as well as brachial artery diameter.Age was not an independent factor in the study, which might be due to the narrow range of the age.[23]

Limitation

In this study, there were some uncontrolled factors that can impede the result of FMD examination such as menstrual phase from female subjects, homocysteine blood level and birth weight. However, the menstrual phase should not confound the study because the two groups were gender matches. Differential analysis according to gender are probably not worthwhile considering small numbers of subjects studied.Data on traditional cardiovascular risk factors were not objective as they were only based on subject's history and physical examination. But then again since all subjects were young and clinically healthy, this also should not be considered as a confounding factor.

In the present study, passive smoking was identified and assessed by self-reporting data using structured questionnaire, which we have previously shown to be reliable. Ideally, the concentrations of nicotine/cotinine in the body should be measured since there were positive associations between self-reported and/or objective measures of secondhand tobacco smoke exposure.[24]But study by Steenland, stated that serum cotinine only reflects recent ETS exposure, and also showed that there will only be a low heart disease risk factors when ETS exposure is determined by self-reported data.[25]

There has been difficulty in quantifying the "dose" of passive smoking with certainty, as the intensity of exposure depends on a large number of variables, such as hours of exposure per day, the proximity to active smokers, the number of active smokers in the room, and the size and ventilation of the rooms where passive smoking takes place.[1] But because that was not the main objective of this study, the data was not obtained. But for further study ahead, those data should be collected to sharpen the result and the study should also be analyzed using multivariate analysis to find which variableis more likely related to the severity of endothelial dysfunction in passive smoker.

Conclusion

Passive smoking is associated with significant impairment of endothelial function in healthy young adults, independent of age, gender and baseline brachial artery diameter, and traditional risk parameters. There was no dose-dependent relationship between hours-years of exposure parameters to severity of endothelial dysfunction. This means, even short term and regularly exposure of smoking can impact to a damaged in arterial wall. This result hopefully can strengthen government effort on campaignsof smoking ban in public area. To achieve a significant reduction of society burden on coronary heart disease, both passive and active cigarette smoking must be considered. Clinicians should inform their patients about all risks associated with passive smoking and also suggestion to give all support to enforcement of smoking bans in all public areas.

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