Impairment of Endothelial Function—A Possible Mechanism for Atherosclerosis of a High-fat Meal Intake

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Abstract

***Introduction**: Endothelial dysfunction is known to occur in patients with coronary artery disease. Flow-mediated dilation of the brachial artery using Doppler ultrasound is a non-invasive technique for the assessment of endothelial function. The objective of the study was to use the above method to evaluate the pathophysiology of high-fat (HF) intake on endothelial function in a local population. A popular local dish "nasi-lemak", a source of high saturated fat content from coconut milk, was chosen to represent a local high-fat meal (LHF). In addition, the effects of a Western high-fat (WHF) ("McDonald's") meal and a low-fat (LF) meal control on endothelial function were studied. **Materials and Methods**: The study population consisted of 10 healthy male non-smoker (mean age 22 ± 2 years) with normal body mass index, normal fasting sugar and lipid profiles. Nitric oxide dependent flow-mediated dilation and nitric oxide independent (GTN) dilation was assessed by Doppler flow in the brachial artery before and 4 hours after each meal on separate occasions by 2 experienced sonographers blinded to the type of meals. **Results**: The baseline brachial artery size, baseline vessel flow and increase in flow after cuff deflation were similar for each of the six arterial studies. In response to reactive hyperaemia after cuff deflation, the endothelium-dependent dilation was significantly different between the meals. There was a marked decrease in endothelium-dependent dilation after the WHF meal compared to the LF meal (8.6 ± 2.2% vs. -0.8 ± 1.1%, P <0.006). There was also a marked decrease in endothelium-dependent dilation after the LHF meal compared to the LF meal (7.7 ± 2.1% vs. -0.8 ± 1.1%, P <0.001). When comparing between the two HF meals, the change in endothelium-dependent dilation was not significant (7.7 vs 8.6%, P = 0.678). GTN-induced dilation was not significantly different before and after the LF, WHF or LHF (0.1 ± 0.5% vs. 0.2 ± 0.9% vs. 1.3 ± 0.5%, P = 0.094). **Conclusion**: The results suggest that in a local population, impairment of endothelial function is a possible mechanism in the pathophysiology of atherosclerosis from HF intake, beyond just affecting lipid levels. This effect is observed after both a LHF and a WHF meal intake. This technique to study endothelial function may be a useful non-invasive screening tool in the study of other HF diet choices and provides further information for the education of the influence of dietary choices on atherosclerosis.*

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Key words: Coronary artery disease, Dietary intake, Endothelial dysfunction, Flow-mediated dilation, Risk factor

Introduction

The impairment of endothelial vasodilatory function has been considered an early event in atherogenesis.[1] This has been studied in association with various cardiovascular risk factors such as diabetes mellitus, hyperhomocystinuria, smoking, hypertension and hypercholesterolaemia.[2-7]

Endothelial function has been assessed invasively in the coronary circulation by measuring vascular reactivity to intracoronary infusion of endothelium-dependent agonists such as acetylcholine.[8,9] An accepted non-invasive method is to study vascular reactivity with ultrasonic assessment of brachial artery flow-mediated dilation (FMD).[10,11] The brachial artery is of a similar size to coronary arteries and brachial responses have been shown to correlate well with response in the coronary circulation.[12] Flow-related endothelial function has been shown to be mediated predominantly by nitric oxide (NO).[13] Endothelial dysfunction thus measured, appears to be representative of generalised endothelial dysfunction and offers a potentially useful measure of the propensity of vasculature for atherosclerosis.[14]

The objective of the study was to measure the effects of high-fat (HF) meals on endothelial function as a possible mechanism for the pathophysiology of HF intake for atherosclerosis. A local high-fat (LHF) and a Western high-fat (WHF) meal were selected to represent the HF food groups available in the local population. A low-fat (LF) meal challenge is used as a control.

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Materials and Methods

Ten healthy local Chinese, normocholesterolaemic medical students (10 men, mean age 22 ± 2 years) were studied. Table I shows the demographic characteristics of the study population. None of the subjects has a history of diabetes mellitus, hypertension, tobacco abuse or premature familial atherosclerosis.

All 10 subjects were not on any form of medications. Studies began in the morning after an overnight fast and after 10 min of rest. Written informed consent was obtained from all subjects and the Ethics Committee of the first author's hospital approved the protocol.

Fasting blood was drawn for serum total cholesterol, low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, triglycerides and glucose. Assays were performed in the hospital's clinical chemistry laboratory. Brachial artery vasoactivity, blood pressure and heart rate were then assessed. Following this, subjects consumed a LHF meal, a WHF meal or a LF meal in random order at 1 week apart.

The WHF meal (900 calories, 50 g of fat, 14 g of saturated fat, and 255 mg of cholesterol) consisted of an Egg McMuffin®, Sausage McMuffin®, 2 hash brown patties and a non-caffeinated beverage (McDonald's Corporation). The LHF meal (900 calories, 50 g of fat, 40 g of saturated fat, and 255 mg cholesterol) consisted of a dish of rice cooked in coconut milk with the addition of anchovies and an egg (nasi-lemak). This meal was cooked with the guidance of the hospital's dietician to ensure integrity of taste and content. The isocaloric LF meal (0 g of fat) consisted of Frosted Flakes® (Kellogg Company), skimmed milk and carrot juice.

The scans were repeated at the 4-hour time-line after each meal.

The method of assessing endothelium-dependent and endothelium-independent dilation is as previously described by Celermajer et al.[10]

The measurements were done using a high-resolution machine (HDI 5000, ATL, Seattle, Washington) with a 5- to 12-MHz linear array transducer. Two independent investigators without knowledge of the scan sequence or test meal type measured the diameter of the vessel. Interobserver variability was determined by the Bland/Altman method.[15]

Group values are expressed as mean ± SD. Statistical change was analysed for repeated measurements using the repeat ANOVA test. A *P* value of less than 0.05 was considered significant.

Results

All 10 subjects had fasting serum cholesterol levels <5.2 mmol/L and LDL cholesterol levels <2.9 mmol/L. The mean body mass index was 19.2 ± 2.6 kg/m^2. The fasting glucose level was 4.8 ± 0.6 mmol/L. The 10 Chinese male subjects had ideal baseline characteristics as shown in Table I. Table II shows the baseline brachial artery size, baseline vessel flow and increase in flow after cuff deflation. They were not significantly different for each of the six arterial studies.

The glyceryl trinitrate (GTN)-induced response was not significantly different before and after the LF, WHF and LHF meals (0.1 ± 0.5% vs. 0.2 ± 0.9% vs. 1.3 ± 0.5%, *P* = 0.094).

In response to reactive hyperaemia after cuff deflation, the endothelium-dependent dilation was significantly different between the meals (Fig. 1).

TABLE I: BASELINE DEMOGRAPHICS CHARACTERISTICS

	Mean ± SD
BMI (kg/m^2)	19.2 ± 2.6
Total-Cholesterol (mmol/L)	4.5 ± 0.6
LDL-Cholesterol (mmol/L)	2.8 ± 0.4
HDL-Cholesterol (mmol/L)	1.3 ± 0.4
Triglycerides (mmol/L)	0.7 ± 0.2
Glucose (mmol/L)	4.8 ± 0.6

BMI: body mass index; HDL: high-density lipoprotein; LDL: low-density lipoprotein

TABLE II: ARTERIAL STUDY RESULTS IN 10 MALE SUBJECTS

	Low fat		Western high fat		Asian high fat		
	Pre-meal	Post-meal	Pre-meal	Post-meal	Pre-meal	Post-meal	*P**
Baseline vessel size (mm)	2.9 ± 0.5	2.9 ± 0.5	2.9 ± 0.7	3.1 ± 0.7	3.0 ± 0.5	3.1 ± 0.5	0.962
Baseline flow (mL/min)	174 ± 57	162 ± 68	178 ± 63	163 ± 87	179 ± 52	183 ± 54	0.697
Hyperaemia (%)	540 ± 136	538 ± 117	610 ± 72	571 ± 157	669 ± 97	611 ± 117	0.395
EDD (%)	4.0 ± 3.8	4.9 ± 3.3	5.7 ± 7.4	-2.8 ± 1.6	5.2 ± 2.6	-2.4 ± 2.9	<0.001
GTN-induced dilation (%)	18.9 ± 6.7	20.5 ± 4.2	18.0 ± 6.5	18.8 ± 6.7	19.7 ± 5.9	18.0 ± 5.9	0.094

EDD: endothelium-dependent dilation; GTN: glyceryl trinitrate

**P* values for the interaction between the effects of meal type by two-way repeated measure analysis of variance

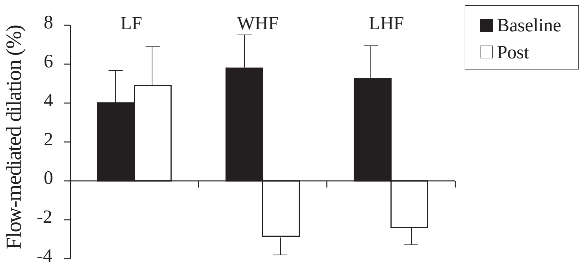

Fig. 1. Repeated measure analysis of variance showed that the flow-mediated dilation values were significantly lower post-meal for WHF and LHF compared with LF (P <0.001)
LF: low-fat meal; WHF: western high-fat meal; LHF: local high-fat meal

There was a marked decrease in endothelium-dependent dilation after the WHF meal compared to the LF meal (8.6 ± 2.2% vs. -0.8 ± 1.1%, P <0.006). There was also a marked decrease in endothelium-dependent dilation after the LHF meal compared to the LF meal (7.7 ± 2.1% vs. -0.8 ± 1.1%, P <0.001). When comparing between the two HF meals, the change in endothelium-dependent dilation of the two HF meals was not significant (7.7 vs. 8.6%, P = 0.678).

The Bland Altman bias plot between observers A and B indicates that their agreement was closest for the LHF meal, with a bias of 0.001 (95% CI, -0.024-0.026). The 95% limits of agreement were found to be -0.068 to 0.070. For the WHF and LF meals, the biases were -0.021 (95% CI, -0.08-0.039) and 0.034 (95% CI, -0.024-0.092). Their corresponding limits of agreement were (-0.183-0.142) and (-0.125-0.193) respectively.

Discussion

The mortality rate for coronary artery disease in Singapore is similar to the United States of America and thrice as high as Japan.[16] Cross-country comparisons suggest that higher risk of coronary artery disease is generally observed with national diets rich in animal products.[16,17] Additionally, the dietary habits of the local population are influenced by a combination of cultural cooking methods and a Western dietary choice. Beyond affecting lipid levels, the effects of a HF diet on the pathophysiology of atherosclerosis in a local population remain largely unknown.

This pilot study was designed to assess the effects of the 3-meal types on endothelial function as measured non-invasively by the method described by Celermajer et al.[10] The subjects studied were healthy young men without obvious risk factors for coronary artery disease. They had ideal baseline demographic characteristics. Yet, endothelial function appeared to be impaired after a LHF and a WHF meal challenge. This information suggests that diets rich in animal and saturated fat content as experienced by the local population and even urbanised cities in the region may be a significant additional risk factor towards atherogenesis, particularly in the subclinical setting.

The LHF meal challenge showed impairment on endothelium-dependent dilation as much as the WHF meal. The two HF meals were matched for total calories and total fat. The difference was in the amount of saturated fat. This difference in saturated fat content did not, however, translate into a difference in effect on endothelium-dependent dilation. The specific components of digestion from fat intake resulting in this response require further biochemical studies; but the similar clinical effect suggests that more than one component of HF intake may be responsible.

Coconut milk is rich in saturated fat content.[18] It is a popular cooking ingredient locally. The results from this study provide additional information for the education and understanding of the influence of HF dietary intake on the pathophysiology of atherosclerosis, particularly in the subclinical setting. Additionally, the evolution in dietary patterns from globalisation has introduced increased consumption of higher fat foods with a shift from plant to animal protein. This pattern might be a factor for the similar mortality rates from cardiovascular causes between Singapore and North America, in addition to other environmental risk factors for atherosclerosis like tobacco abuse.[16] Interestingly, intervention of dietary habits, specifically in decreases of total fat, saturated fat and cholesterol has predicted a decline in mortality from coronary heart disease.[16,19]

This study is the first to show a direct impairment by meals rich in animal fat and coconut oil on endothelial function in a local population. The study suggests a possible subclinical mechanism in the pathophysiology of HF intake for atherosclerosis.

Limitations

This study was not designed to elucidate the biochemical components that might have caused a difference in endothelium-dependent dilation as proposed by many other investigators. There have been conflicting results on the influence of the various components.[20-24] Studies on animal models have shown a difference of the type of oil content affecting atherosclerosis.[25] This might provide an area for further interesting investigation.

The number of subjects investigated was small and were of the same ethnic group. Therefore, care must be taken in extrapolating these findings to other populations.

Clinical Implications

The results provide information on a possible mechanism in the pathophysiology of HF intakes on atherosclerosis in a local population, particularly in a subclinical setting. The influence of dietary intake as a risk factor might also take on more prominence in our multi-ethnic local population.

Assessment of flow-mediated dilation of the brachial artery as a measurement of endothelial function is a non-invasive technique. It might be a useful screening tool in the study of the mechanisms of the pathophysiology of various risk factors for atherosclerosis in our local population.

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