Impaired coronary microvascular endothelial function in men with metabolic syndrome

Hiroki Teragawa, Naoya Mitsuba, Kenji Nishioka, Kentaro Ueda, Shingo Kono, Yukihito Higashi, Kazuaki Chayama, Yasuki Kihara

AIM: To assess coronary endothelial function of conduit and resistance vessels in patients with metabolic syndrome (MS).

METHODS: Seventy-eight men (mean age, 57 years) with chest pain and angiographically normal coronary arteries were included in the study. Patients with coronary spastic angina were excluded. Changes in coronary artery diameter and coronary blood flow (CBF) in response to acetylcholine (ACh) were determined using quantitative coronary angiography and Doppler velocity measurements. Coronary flow reserve was calculated as the ratio of coronary blood velocity after adenosine triphosphate infusion relative to baseline values. Patients were divided into two groups based on the presence or absence of MS.

RESULTS: There were 24 patients in the MS group (31%). The increase in CBF in response to ACh infusion was impaired in the MS group ($P < 0.0001$) compared to the non-MS group, whereas changes in coronary artery diameter in response to ACh infusion did not differ between the two groups. Multivariate regression analysis revealed that MS was a significant factor associated with the lesser change in CBF induced by ACh infusion at 30 μg/min ($P < 0.0001, r^2 = 0.46$).

CONCLUSION: Coronary endothelial dysfunction was present at the level of resistance vessels but not conduit vessels in the MS patients included in our study.

Key words: Endothelial dysfunction; Metabolic syndrome; Doppler flow; Conduit vessels; Resistance vessels

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Abstract

AIM: To assess coronary endothelial function of conduit and resistance vessels in patients with metabolic syndrome (MS).

INTRODUCTION

The metabolic syndrome (MS) is characterized by abdominal obesity, elevated blood pressure, hypertriglyceridemia,
Coronary angiography was performed under controlled conditions and at the end of each drug infusion. Coronary blood flow (CBF) velocity was monitored continuously using a 12-MHz pulsed Doppler velocimeter (FloMap; Volcano Therapeutics Inc. Rancho Cordova, CA). Arterial pressure, heart rate and ECG were monitored continuously and recorded using a multichannel recorder (Polygraph 1600; Nihon Electric Corporation, Tokyo, Japan).

**Quantitative coronary angiography**

The method for measuring coronary diameter has been previously described in detail[16,17]. The coronary segment 2 mm distal to the Doppler wire tip was selected for quantitative analysis. In each patient, luminal diameters of selected segments of the left anterior descending coronary artery were measured by a single investigator blinded to angiographic and clinical data in order to determine the effects of different drugs on epicardial coronary diameter. Luminal diameters were measured on an end-diastolic frame using a computer-assisted coronary angiographic analysis system (CAAS II/QUANTCOR; Siemens, Berlin and Munich, Germany). Means of triplicate measurements of luminal diameter were used for analysis. Changes in coronary diameter in response to ACh and nitroglycerin infusions are expressed as percent change from the baseline measurement on the angiogram obtained prior to infusion. Intra- and inter-observer variability have previously been reported to be excellent[18].

**Estimation of coronary blood flow and coronary flow reserve**

CBF was calculated as the product of CBF velocity and vessel diameter using the following formula: \( \pi \times \text{average peak velocity} \times \text{diameter}^2 \). For CBF calculations, the internal diameter of the vessel at the location of the flow measurements (2 mm distal to the wire tip) was measured using the method described above. CFR was calculated as the ratio of CBF velocity after an adenosine triphosphate infusion to the baseline velocity.

**The definition of metabolic syndrome**

The presence of MS was determined according to the final report of the National Cholesterol Education Program’s Adult Treatment Panel III criteria[5]. The above-mentioned criteria may not be suitable for determining abdominal obesity in Japanese patients; therefore, we adopted the Japanese criteria for abdominal obesity (waist circumference ≥ 85 cm in men) in the present study. Consequently, we defined MS as the presence of at least three of the following factors: (1) waist circumference ≥ 85 cm; (2) fasting triglycerides > 150 mg/dL; (3) HDL cholesterol < 40 mg/dL; (4) hypertension (systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg, or use of antihypertensive drug therapy); and (5) fasting glucose ≥ 110 mg/dL. The patients were divided into the following two groups based on the presence or absence of MS: the MS group comprising patients with MS and the non-MS group comprising patients without MS. In addition, the MS score was defined as the sum of the MS factors (0-5) that were present.
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RESULTS

Patients’ characteristics and biochemical parameters

The patients’ characteristics are indicated in Table 1. There were 24 patients with MS (31%). Body mass index, waist circumference and the frequency of having each MS factor were higher in the MS group than in the non-MS group. The average MS score was significantly higher in the MS group than in the non-MS group.

Data for other conventional risk factors, including biochemical parameters and medications taken, are also indicated in Table 2. The triglyceride, fasting blood sugar, hemoglobin A1C, and HOMA-IR levels were higher in the MS group and the level of HDL cholesterol was lower in the MS group compared with the non-MS group. The frequency of medication intake was similar in the two groups.

Factors responsible for coronary microvascular endothelial dysfunction

Analysis of individual MS factors indicated that elevated triglycerides ($P = 0.0246$), low HDL cholesterol ($0.0409$), elevated blood pressure ($0.0032$), and hyperglycemia ($P = 0.0309$) were associated with a lower change in CBF in response to ACh infusion at 30 μg/min. Univariate analysis revealed that the presence of MS ($P < 0.0001$), reduced CFR ($P = 0.0003$) and an elevated CRP level ($P = 0.0027$) were associated with a lower CBF response induced by ACh infusion at 30 μg/min; a high heart rate at baseline also tended to be associated with the reduced response. Multivariate regression analysis using these parameters demonstrated that the presence of MS ($P < 0.0001$) and reduced CFR ($P = 0.0005$) and elevated CRP ($P = 0.0234$) were significant.
DISCUSSION

The present study revealed that coronary endothelial function at the level of resistance vessels is impaired in MS patients while that at the level of conduit vessels is similar among both MS and non-MS patients. Multivariate regression analysis demonstrated that the presence of MS was a significant factor associated with impaired coronary endothelial function at the level of resistance vessels. Many reported studies have used several modalities to investigate the relationship between MS and coronary microvascular circulation. PET analysis has revealed that the increase in myocardial blood flow in response to a cold pressor test is impaired in MS patients,[7], indicating the presence of coronary microvascular endothelial dysfunction; this is in accordance with the results obtained in the present study. On the other hand, Pirat et al[9], using UCG, have reported an impaired CFR in the LAD of coronary arteries in patients with MS. Furthermore, Turhan et al[8] reported an impaired CBF using the Thrombolysis in Myocardial Infarction frame count method in MS patients with angiographically normal coronary arteries. The purpose of the present study was to assess ACh-induced coronary vasomotion and circulation, and thus our study protocol excluded patients with several conditions, such as severely reduced CFR (< 2.0) or LVH, which are frequently observed in MS patients. Therefore, differences in patient selection and other patient characteristics may contribute to the discrepancy in the results. In all the above-mentioned studies, the presence of coronary endothelial dysfunction at the level of the resistance vessels was shown in MS patients; however, no studies have investigated coronary endothelial function at the level of the conduit vessels. The patients in our study exhibited chest symptoms, even in the non-MS group, and it was not clarified whether coronary endothelial function, especially at the level of the conduit vessels, was preserved in such patients. Nonetheless, the finding that coronary
microvascular endothelial dysfunction was severely impaired in the MS group is certain and clarifies the impact of MS on pathogenesis of the coronary artery vasculature. If the degree of MS is severe and its duration is longer, coronary endothelial dysfunction at the level of conduit vessels may be evident after the establishment of coronary microvascular endothelial dysfunction. There are several possible mechanisms responsible for MS-induced coronary endothelial dysfunction. Several studies have revealed that insulin resistance may induce endothelial dysfunction mediated by oxidative stress[21,22] and decreases in insulin-dependent activation of endothelial nitric oxide synthase (eNOS)[23]. Furthermore, it has been reported that adiponectin may play a role in the phosphorylation of eNOS[24] and reduced adiponectin, which is often recognized in MS patients, may lead to endothelial dysfunction. In addition, it has been reported that pericardial fat tissue, which is increased in MS patients, may lead to endothelial dysfunction. In conclusion, these findings suggest that coronary microvascular endothelial dysfunction at the level of resistance vessels was more prominent than that at the level of conduit vessels in MS patients. Until now, there has been no data available indicating which is the stronger factor; i.e. coronary endothelial dysfunction at the level of conduit vessels or that of resistance vessels, affecting future cardiovascular events. However, Halcox et al[13] have reported that if coronary endothelial dysfunction is present either at the level of conduit or resistance vessels, future cardiovascular events occur more frequently. Thus, the finding that coronary microvascular endothelial dysfunction is more prominent in MS patients may provide important information clarifying the pathogenesis of MS-induced cardiovascular events. The present study also demonstrated that coronary microvascular endothelial function declined in association with increased total MS score, even in non-MS patients with a moderate MS score such as 2; careful follow-up may be needed for such subjects.

There are several limitations to the present study. First, all the patients in our study had chest symptoms and had undergone coronary angiography; thus, they may represent a specific group. In addition, MS patients met the minimal criteria for MS and several non-MS patients also had a moderate MS score. Therefore, the results of the present study may not always represent endothelial function in all MS patients. Second, our data showed that CFR was not different in the two groups. However, we excluded patients with a CFR < 2.0 and/or LVH in order to accurately measure ACh-induced coronary circulation. However, in general, many such patients may be regarded as MS patients. If we had added them in the MS group in the present study, CFR in the MS group might have been lower than that in the non-MS group. There have been many studies showing impaired CFR in patients with MS[19,27] and we do not mean to imply that CFR is preserved in MS patients. Finally, we did not measure biochemical parameters associated with MS, such as adiponectin, interleukin-6 and tumor necrotizing factor-α. Therefore, we cannot report on the precise mechanisms of MS-induced coronary microvascular endothelial dysfunction in the present study.

In conclusion, these findings suggest that coronary microvascular endothelial dysfunction is present in MS patients who have chest pain but angiographically normal coronary arteries. Such coronary microvascular endothelial dysfunction may be involved in the pathogenesis of MS-induced cardiovascular events.

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COMMENTS

Background
Metabolic syndrome (MS) is a major cause of future cardiovascular events. Endothelial dysfunction is thought to be involved in the pathogenesis of MS-induced cardiovascular events. However, coronary endothelial function in patients with MS remains to be elucidated.

Table 4  Multivariate analysis of variables influencing % change in coronary blood flow induced by acetylcholine at 30 μg/min

| Variables                  | % change in coronary blood flow induced by ACh 30 μg/min |
|----------------------------|--------------------------------------------------------|
| Presence of MS             | -5.07                                                  |
| Coronary flow reserve      | 3.62                                                   |
| C-reactive protein         | -2.76                                                  |
| Baseline heart rate        | -1.13                                                  |

ACh: Acetylcholine; MS: Metabolic syndrome.
Coronary endothelial dysfunction in metabolic syndrome

**Research frontiers**
The purpose of the present study was to assess the coronary endothelial function of the conduit and resistance vessels in patients with MS and angiographically normal coronary arteries.

**Innovations and breakthroughs**
Several studies investigating coronary endothelial function in patients with MS have been reported and their results have identified coronary endothelial dysfunction at the level of the resistance vessels. However, no study has investigated coronary endothelial function at the level of the conduit vessels. Quantitative coronary angiography and Doppler velocity measurements, which we adopted in the present study, can assess coronary endothelial function at the levels of the conduit and resistance vessels simultaneously. Our study demonstrates that the increase in coronary blood flow in response to acetylcholine (ACH) infusion was impaired in MS patients compared with non-MS patients, whereas changes in coronary artery diameter in response to ACH infusion did not differ between the two groups. These findings suggest that coronary endothelial function at the level of the resistance vessels is impaired earlier and is more prominent than that at the level of the conduit vessels.

**Applications**
These findings suggest that coronary microvascular endothelial dysfunction is present in MS patients who have chest pain but angiographically normal coronary arteries. Such coronary microvascular endothelial dysfunction may provide a vital evidence for the pathogenesis of MS-induced cardiovascular events.

**Peer review**
This is an interesting study confirming previous findings on how MS affects coronary function.

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