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Transcardiac adiponectin gradient is independently related to endothelial vasomotor function in large and resistance coronary arteries in humans

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coronary circulation; coronary artery spasm; microvascular angina; acetylcholine; endothelium

ADIPONECTIN, THE MOST ABUNDANT protein secreted from adipose tissue, possesses vasculoprotective effects (1, 15, 17–19, 21). It is known that adiponectin stimulates production of nitric oxide in vascular endothelial cells (4) and that hypoadiponectinemia is associated with an impaired endothelium-dependent vasodilatation (20), a predictor of coronary events. Furthermore, adiponectin levels are reduced in patients with coronary artery disease, and low adiponectin levels are an independent predictor of future coronary events (21). These findings suggest that adiponectin has antiatherogenic properties and that adiponectin levels in the peripheral circulation play an important role in the pathogenesis of coronary artery disease. However, it remains unknown whether adiponectin levels in the coronary circulation may also be related to the pathogenesis of coronary artery disease.

Coronary spasm has been shown to play an important role in the pathogenesis of not only variant angina but also ischemic heart disease in general (13, 22). We have shown that coronary endothelial vasomotor dysfunction as well as a hypercontractile response of smooth muscle in epicardial coronary arteries may play an important role in the genesis of coronary spastic angina (13, 22). However, the precise mechanism by which coronary vasomotor dysfunction occurs in epicardial coronary arteries of patients with coronary spastic angina remains unclear. Microvascular angina, characterized by angina pectoris, a positive exercise stress test, and a normal coronary angiogram, has been shown to exhibit an impairment of coronary flow reserve (3, 5, 11, 12).

Recently, Furuhashi et al. (8) showed that a low transcardiac gradient of adiponectin in the coronary circulation was associated with extensive coronary artery disease in patients with Type 2 diabetes. Although low adiponectin levels in the peripheral circulation have been reported to be associated with vasomotor dysfunction in systemic arteries (20), it remains unknown whether adiponectin levels in the coronary circulation are also related to coronary artery spasm or microvascular angina that have abnormal vasomotor functions in large and resistance coronary arteries, respectively.

In this study, we examined a possible relation of vasomotor response of the left anterior descending coronary artery with transcardiac gradient of adiponectin levels in the myocardial region supplied by the left anterior descending coronary artery. We found that the transcardiac gradient of adiponectin was importantly related to the regulation of coronary vasomotor function in the epicardial and resistance coronary arteries. Moreover, no transcardiac gradient of adiponectin was observed in patients with coronary spastic angina or in patients with microvascular angina.

METHODS

Study subjects and patients. This study included three groups, control subjects, patients with coronary spastic angina, and patients with microvascular angina, who were admitted to Yamanashi Univer-

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sity Hospital. All three groups of subjects and patients fulfilled the following inclusion criteria: *1*) angiographically normal coronary arteries (<25% narrowing after nitrate admission); *2*) normal left ventriculography; *3*) no left ventricular hypertrophy, verified by both electrocardiogram (ECG) and echocardiography; and *4*) no history of myocardial infarction, congestive heart failure, valvular heart disease, secondary hypertension, stroke, renal dysfunction (serum creatinine concentration >2.0 mg/dl), or other serious diseases. The control subjects consisted of a consecutive series of 108 subjects who were examined for a correlation between adiponectin levels and coronary vasomotor tone. They underwent diagnostic coronary angiography for atypical chest pain at rest. The control subjects also fulfilled all of the following inclusion criteria: *1*) no significant ST segment changes during the chest pain on 12-lead ECG and ambulatory ECG; *2*) neither chest pain nor ST segment changes during the treadmill test; and *3*) no coronary artery spasm during the ACh provocation test, as previously reported (11, 13). The group of patients with coronary spastic angina consisted of a consecutive series of 41 patients who were examined for a possible relationship between adiponectin levels and coronary spastic angina. The enrolled patients with coronary spastic angina had the following characteristics: *1*) spontaneous attacks of chest pain associated with ST segment elevation or depression on the 12-lead ECG or ambulatory ECG at rest, usually in the middle of the night or early morning; or *2*) coronary artery spasm (total or subtotal occlusion) in the left anterior descending coronary artery, demonstrated angiographically during the anginal attack with ST segment changes during the intracoronary infusion of 100 μg/min of ACh. The group of patients with microvascular angina consisted of 32 consecutive patients who were examined for a possible relationship between adiponectin levels and microvascular angina. These patients had predominantly effort-induced angina and had either chest pain or horizontal or downsloping ST segment depression ≥1 mm in the precordial leads during exercise stress testing. None of the enrolled patients with microvascular angina had spasm in the large coronary arteries during the ACh provocation test. All lipid-lowering drugs and other medications that could have affected coronary vasomotor reactivity were withdrawn more than 5 days before the study. Written informed consent was obtained from all study subjects before the study. The study, which was in accordance with the Declaration of Helsinki, was approved by the Ethics Committee at Yamanashi University Hospital.

Blood sampling and measurements of adiponectin and insulin levels. Cardiac catheterization and blood sampling were performed in the morning when the patients were fasting, in the same manner as described in our previous report (23). Before coronary angiography, a 5-Fr coronary sinus catheter (multipurpose type) (Goodman, Nagoya, Japan) was placed in the coronary sinus via a brachial vein. The catheter was then advanced into the anterior interventricular vein (AIV) under fluoroscopy by a guide wire. The position of the catheter tip in the AIV was confirmed by injection of contrast dye medium. A Judkins catheter was placed at the root of the aorta by way of a femoral artery. Blood was then sampled within 2 min at the aortic root (Ao), AIV, and from a peripheral vein. Care was taken to draw the blood samples slowly. Initial parts of the sample, including those forcibly drawn, were discarded. The blood samples, anticoagulated with EDTA, were immediately centrifuged at 3,000 rpm for 10 min at 4°C, and the EDTA plasma was aliquoted and stored at −80°C until analyzed. A monomer form of adiponectin in the plasma from all blood samples was measured by solid-phase ELISA with a commercially available kit (Otsuka Pharmaceutical) after the samples were boiled for 5 min. Plasma insulin levels in the vein were measured by a radioimmunoassay method (Insulin RIA bead; Dainabot, Tokyo, Japan). Plasma glucose was determined by the glucose oxidase method. A homeostasis model assessment of insulin resistance (HOMA-IR) was calculated by fasting plasma insulin (in mU/l) × fasting plasma glucose (in mmol/l)/22.5 (16).

Protocol for coronary angiography. After the blood sampling, a quantitative coronary angiographic study was performed in all of the study subjects with the Judkins technique as in our previous reports (10, 13). After baseline angiography, incremental doses of ACh (5, 10, and 50 μg/min) were infused directly into the left coronary artery through the Judkins catheter for 2 min with a 5-min interval between each dose. Hemodynamic measurements and coronary angiography were reported before and during each of the ACh infusions. After an additional 15 min, intracoronary injection of sodium nitroprusside (SNP, 10 μg/min) was done in the same manner as the infusion of ACh. After another 15 min, intracoronary injection of isosorbide dinitrate (1 mg) was performed; 2 min after that, coronary angiography was performed in multiple projections in all study subjects and patients.

Quantitative coronary angiography and the measurement of coronary blood flow. Measurement of luminal diameter of the left anterior descending coronary artery at the midsegment was performed quantitatively by use of a computer-assisted coronary angiographic analysis system (Cardio 500, Kontron Instruments, Munich, Germany), and the results were analyzed by two observers (T. Nakamura and Y. Kodama) blinded to the study protocol (10, 13). Responses of the coronary artery diameter to infusions of ACh and nitrates were expressed as percent changes from baseline diameter measured on angiograms taken just before each infusion.

Blood flow velocity was measured with the use of a 0.014-in. wire equipped with a Doppler crystal at its tip (Flow Wire, Cardiometrics, Mountain View, CA) (10). The wire was advanced through the Judkins catheter and carefully positioned in a straight proximal segment of the left anterior descending coronary artery to obtain a stable flow velocity signal. The stable peak flow velocity signals at baseline and during a 2-min infusion of each dose of ACh and SNP were used for the analysis (Flow Map, Cardiometrics). Coronary blood flow (in ml/min) was estimated from coronary blood flow velocity and arterial diameter by the following formula: average peak velocity (in cm/min) × cross-sectional area (in cm^2). The responses of coronary blood flow to intracoronary infusions of each dose of ACh and SNP were expressed as a percent change from the baseline blood flow just before each infusion.

Measurements of the percent changes in coronary diameter and blood flow in response to ACh (10 μg/min) from the respective baseline values by the two independent observers were highly reproducible (%change in coronary diameter response: $r = 0.99$, mean difference 0.81 ± 0.04%; %change in coronary flow response: $r = 0.99$, mean difference 2.4 ± 0.3%).

Statistical analysis. Results are expressed as means ± SE or percentage. The mean values of continuous variables were compared between the three groups by using one-way ANOVA, and frequencies between the two groups were compared by χ^2-analysis. Linear regression analysis was used to determine the relationship between the coronary responses and all continuous variables. Multivariate linear regression analyses were also used to determine the relationship between coronary responses and adiponectin plasma levels; independent covariates included any continuous variable that was significantly correlated with the coronary responses in the univariate analysis. In addition, the multivariate analysis also included any categorical risk factors that led to a significant difference in coronary responses when patients with and without traditional risk factors were compared with the use of an unpaired *t*-test. The categorical variables were coded by using the following dummy variables: 0 for the absence of the risk factor or 1 for the presence of the risk factor. A confidence level of $P < 0.05$ was considered statistically significant. Analyses were partially assessed by using StatView 5.0 (SAS Institute, Cary, NC).

Table 1. *Comparisons of clinical characteristics and adiponectin levels among control subjects, patients with coronary spastic angina, and those with microvascular angina*

	Control	Coronary Spastic Angina	Microvascular Angina
n	108	41	32
Age, yr	62±1.8	64±1.0	61±1.2
Male, %	59	45	44
Body mass index, kg/m^2	24±0.8	23±0.6	24±0.5
Smoking, %	28	41	32
Total cholesterol, mg/dl	203±37	206±39	198±38
Diabetes mellitus, %	28	25	28
Hypertension, %	43	42	38
HOMA-IR	1.39±0.09	1.72±0.11*	1.55±0.06
Baseline LAD diameter, mm	2.7±0.1	2.5±0.6	2.7±0.7
Baseline CBF, ml/min	38±2.2	36±2.4	35±2.8
Adiponectin levels, μg/ml			
Vein	10.5±0.2	7.5±0.3*	7.4±0.4*
Ao	10.6±0.1	7.6±0.2*	7.5±0.3*
AIV	9.3±0.2†	7.2±0.3*	7.1±0.3*
Ao − AIV	1.7±0.1	0.5±0.3*	0.2±0.3*

Data are expressed as means ± SE or percentage. HOMA-IR, homeostasis model assessment of insulin resistance; LAD, left anterior descending coronary artery; CBF, coronary blood flow; Ao, aorta; AIV, anterior interventricular vein; Ao − AIV, aortic levels minus anterior interventricular vein levels of adiponectin. *$P < 0.01$ vs. respective values in control subjects; †$P < 0.01$ vs. Ao adiponectin levels in control subjects.

Table 2. *Relationships of clinical parameters (continuous variables) and adiponectin levels with %changes in coronary diameter and blood flow response to ACh using univariate linear regression analysis in control subjects*

	%Change in Epicardial Diameter			
	ACh (5 μg/min)	ACh (10 μg/min)	ACh (50 μg/min)	Nitrate
Age (yr)	−0.35	−0.37*	−0.43*	0.13
BMI (kg/m^2)	0.02	−0.06	−0.07	0.09
Total cholesterol (mg/dl)	0.12	0.14	0.08	0.11
Adiponectin (μg/ml)				
Vein	−0.13	−0.19	−0.21	0.13
Ao	−0.12	−0.19	−0.23	0.23
AIV	−0.39*	−0.41*	−0.43*	0.17
Ao − AIV	0.45*	0.44*	0.61†	0.21
	%Change in CBF			
	ACh (5 μg/min)	ACh (10 μg/min)	ACh (50 μg/min)	SNP
Age (yr)	−0.38*	−0.36	−0.34	−0.18
BMI (kg/m^2)	−0.09	−0.05	−0.07	0.09
Total cholesterol (mg/dl)	0.08	−0.21	−0.24	−0.16
Adiponectin (μg/ml)				
Vein	−0.22	−0.19	−0.21	0.14
Ao	−0.24	−0.22	−0.21	0.21
AIV	−0.44*	−0.39*	−0.36	0.17
Ao − AIV	0.67†	0.56*	0.49*	0.11

Data are expressed as regression coefficient. SNP, sodium nitroprusside; BMI, body mass index. *$P < 0.05$; †$P < 0.01$.

RESULTS

Clinical characteristics in the control subjects. Clinical characteristics, baseline coronary diameters and coronary blood flow, and adiponectin levels of the control subjects are shown in Table 1. Plasma adiponectin levels in the AIV were significantly lower than those in the Ao and in a peripheral vein, as shown in Table 1. There was significant correlation between the Ao and Ao − AIV levels of adiponectin ($r = 0.37$, $P < 0.05$), the Ao and AIV levels of adiponectin ($r = 0.93$, $P < 0.01$), and the Ao − AIV and AIV levels of adiponectin ($r = 0.38$, $P < 0.05$).

Correlation of epicardial coronary diameter response to ACh with clinical characteristics and adiponectin levels in the control subjects. Baseline coronary diameter had no significant correlation with the Ao, AIV, and Ao − AIV levels of adiponectin ($r = 0.02$, 0.05, and 0.01, respectively; all P = not significant). Intracoronary infusion of ACh dilated the coronary arteries in a majority of subjects and constricted the arteries in a small number of subjects, resulting in an overall dilator response. With the use of univariate linear regression analysis, the dilator response of epicardial coronary arteries to ACh had a significant positive correlation with the transcardiac gradient of adiponectin (Ao − AIV levels of adiponectin) (at all doses of ACh), as shown in Table 2 and Fig. 1. Furthermore, the dilator response to ACh had an inverse correlation with the AIV levels of adiponectin (at all doses of ACh) and age (at doses of 10 and 50 μg/min of ACh), as shown in Table 2. Smokers had an impaired dilation of epicardial coronary arteries to ACh compared with nonsmokers (at a dose of 50 μg/min of ACh) (3.6 ± 0.9% vs. 7.8 ± 0.5%, respectively; $P < 0.05$). With the use of multivariate linear regression analysis, the Ao − AIV levels of adiponectin remained significantly and positively correlated with the coronary diameter response, after adjustment for age, smoking status, and AIV levels of adiponectin as covariates (these covariates were significantly related to the diameter response in the univariate linear regres-

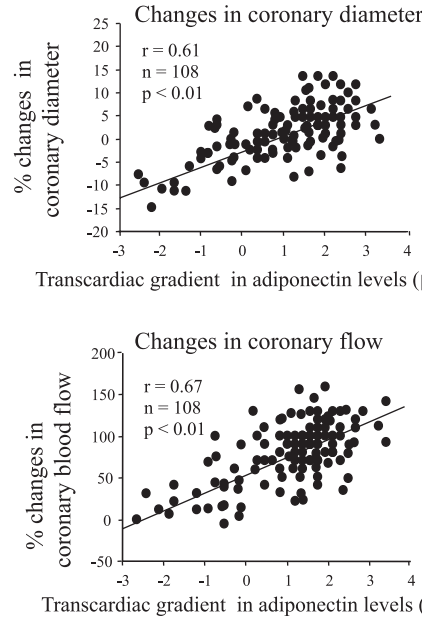

Fig. 1. Correlations between the aortic (Ao) minus the anterior interventricular vein (AIV) levels of adiponectin and the percent changes in coronary arterial diameter (*top*) and in coronary blood flow (*bottom*) in response to intracoronary infusion of ACh (at 50 and 5 μg/min of ACh, respectively); *n*, no. of control subjects.

Table 3. *Multiple linear regression analysis for the association of risk factors with relative changes in coronary diameter and flow response to ACh*

	%Change in Coronary Diameter		
	ACh (5 μg/min)	ACh (10 μg/min)	ACh (50 μg/min)
Age (yr)		−0.12	−0.20
Smoking			−0.28*
Adiponectin (AIV)	0.15	0.11	0.09
Adiponectin (Ao − AIV)	0.45*	0.47*	0.51†
	%Change in CBF		
	ACh (5 μg/min)	ACh (10 μg/min)	ACh (50 μg/min)
Age (yr)	−0.12		−0.12
Smoking			−0.23
Diabetes	−0.28*	−0.12	0.08
Adiponectin (AIV)	0.12	0.09	0.08
Adiponectin (Ao − AIV)	0.61†	0.54†	0.51†

Data are expressed as standardized regression coefficient. *$P < 0.05$; †$P < 0.01$.

sion or the unpaired *t*-test) (Table 3). The dilator response to nitrate was not significantly correlated with the Ao, AIV, or Ao − AIV levels of adiponectin (Table 2).

Correlation of coronary flow response to ACh with clinical characteristics and adiponectin levels in the control subjects. Baseline coronary blood flow had no significant correlation with the Ao, AIV, and Ao − AIV levels of adiponectin (r = 0.1, 0.01, and 0.05, respectively; all P = not significant). Coronary blood flow was increased in response to ACh infusion in all control subjects, but there was a considerable variation in the magnitude of the coronary blood flow response to ACh among the control subjects, as shown in Fig. 1. With the use of univariate linear regression analysis, the percent increase in coronary blood flow response to ACh had a significant positive correlation with the Ao − AIV levels of adiponectin (at all doses of ACh) and inversely with age (at 5 μg/min of ACh) and AIV levels of adiponectin (at 5 and 10 μg/min of ACh), as shown in Fig. 1 and Table 2. The percent increase in coronary blood flow from baseline in response to ACh was less in patients with diabetes than those without diabetes (at all doses of ACh) (66 ± 10% vs. 84 ± 15% at 5 μg/min of ACh, respectively; $P < 0.05$), and it was also less in patients with a history of smoking than those without smoking (at 50 μg/min of ACh) (136 ± 21% vs. 166 ± 19%, respectively; $P < 0.05$). With the use of multivariate linear regression analysis, the Ao − AIV levels of adiponectin remained significantly and positively correlated with the coronary blood flow response to ACh after adjustment for age, smoking and diabetes status, and the AIV levels of adiponectin as covariates (these covariates were significantly related to the coronary blood flow response to ACh in the univariate linear regression analysis or the unpaired *t*-test) (Table 3). The increase in coronary blood flow response to SNP was not significantly correlated with the Ao, AIV, and Ao − AIV levels of adiponectin (Table 2).

Comparison of adiponectin levels among controls, coronary spastic angina, and microvascular angina. The clinical characteristics were compared among these three groups in Table 1.

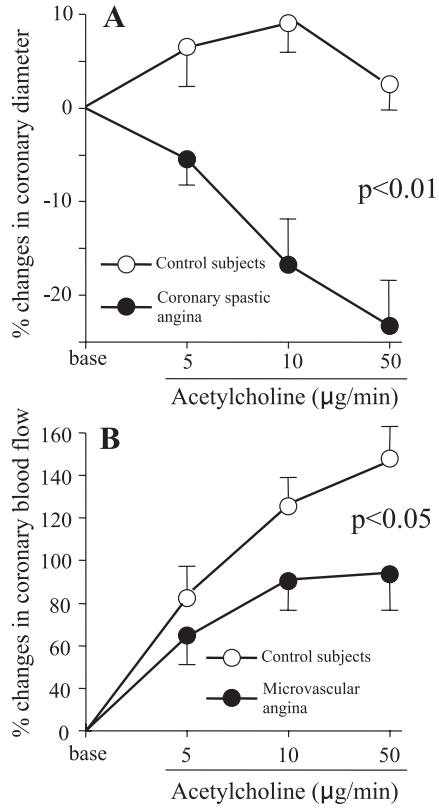

Fig. 2. *A*: comparisons of the percent changes in coronary arterial diameter in response to ACh between control subjects (n = 108) and patients with coronary spastic angina (n = 41). *B*: comparisons of the percent changes in coronary blood flow in response to ACh between control subjects (n = 108) and patients with microvascular angina (n = 32).

The risk factor profiles were similar among the three groups. HOMA-IR, an index of insulin resistance, was significantly higher in patients with coronary spastic angina than control subjects. HOMA-IR tended to increase in those with microvascular angina as compared with control subjects, but the

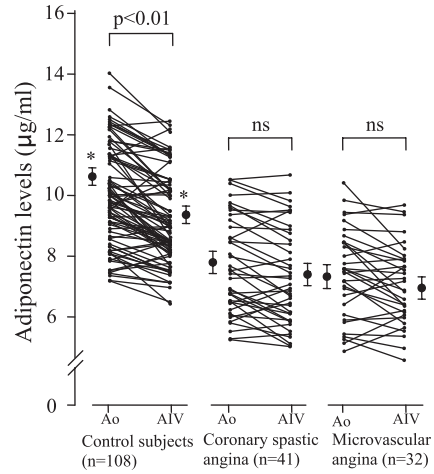

Fig. 3. Comparisons of adiponectin levels in the Ao and the AIV in control subjects (n = 108), patients with coronary spastic angina (n = 41), and patients with microvascular angina (n = 32). NS, not significant. *$P < 0.01$ vs. respective values in patients with coronary spastic angina and those with microvascular angina.

difference did not reach statistical significance. Most of the patients with coronary spastic angina showed a constrictor response of the epicardial coronary arteries to ACh, as shown in Fig. 2*A*. The percent increase in the coronary blood flow response to ACh was significantly less in patients with microvascular angina than control subjects, as shown in Fig. 2*B*. Both adiponectin levels in the Ao and AIV were significantly lower in patients with coronary spastic angina and microvascular angina than the respective levels in control subjects (Fig. 3). The AIV levels of adiponectin were significantly lower than the Ao levels in control subjects, whereas the AIV levels of adiponectin were similar to the Ao levels in patients with coronary spastic angina and in patients with microvascular angina (Fig. 3).

DISCUSSION

The present study showed that the Ao − AIV gradient of plasma adiponectin, reflecting adiponectin uptake and/or accumulation in the vascular bed of the left anterior descending coronary artery, was positively and independently correlated with increases in epicardial diameter and blood flow response of the left anterior descending coronary artery to ACh. However, systemic circulating adiponectin levels (the Ao levels) were not correlated with these vasomotor responses to ACh. Furthermore, the Ao − AIV gradient of adiponectin was not significantly correlated with coronary vasomotor responses to nitrate and SNP, both endothelium-independent dilators. Thus the Ao − AIV adiponectin gradient is intimately related to endothelium-dependent dilation of large and resistance coronary arteries. The results suggest that adiponectin utilization and/or accumulation in the coronary vascular bed may importantly regulate nitric oxide-dependent vasomotor function in large and resistance coronary arteries. These results are compatible with previous reports (4, 15, 17–19) that adiponectin stimulates endothelial nitric oxide synthesis and that adiponectin uptake and accumulation in the arterial intima exert vasculoprotective actions. Furthermore, the present study showed that patients with coronary spastic angina and microvascular angina had no significant difference in adiponectin levels between the Ao and AIV, indicating little uptake or accumulation of adiponectin into the coronary vascular bed in these patients. The close relationship between the transcardiac adiponectin gradient and vasomotor function of epicardial and resistance coronary arteries in the present study suggests that the lack of coronary uptake of adiponectin may play a role in the pathogenesis of coronary artery spasm and microvascular angina.

The present study showed that patients with coronary spastic angina and microvascular angina had lower adiponectin levels in both the Ao and AIV compared with their respective levels in the control subjects. Although various factors determine adiponectin levels in the peripheral circulation (14, 15), insulin sensitivity is an important determinant (14). We and others (2, 9) have previously shown that insulin resistance is related to the pathogenesis of coronary artery spasm and microvascular angina. In fact, HOMA-IR, an index of insulin resistance, was significantly higher in the present patients with coronary spastic angina than control subjects. HOMA-IR tended to increase but was not significantly higher in the present patients with microvascular angina than control subjects. However, more precise determinations of insulin resistance using the euglycemic hyperinsulinemic clamp technique or the steady-state plasma glucose method may possibly reveal insulin resistance in the present patients with microvascular angina. Therefore, insulin resistance may account for lower adiponectin levels in the Ao and AIV in patients with coronary spastic angina and microvascular angina.

The transcardiac gradient of adiponectin is determined by the net balance between uptake and production of adiponectin in the coronary circulation. Recently, we have shown that cardiomyocytes produce adiponectin (7). However, myocardial expression of adiponectin is extremely low compared with adipose tissue; therefore, the myocardial production of adiponectin may not largely contribute to levels in the coronary circulation.

A recent report (6) showed that adiponectin levels stepped up from the Ao to the great cardiac vein and that the transcardiac difference of adiponectin levels from the Ao to the great cardiac vein was weakly correlated with coronary flow reserve in response to papaverine, an endothelium-independent dilator, in a heterogeneous group of patients. That study included a small number of patients and did not analyze the effects of other confounding factors on the relationship between adiponectin levels and coronary blood flow. Furthermore, adiponectin derived from epicardial adipose tissue may be included in the blood from the great cardiac vein, accounting for the discrepant results between that report and the present study.

In conclusion, a low transcardiac uptake of adiponectin is an independent risk factor for the impairment of endothelium-dependent vasomotor function in large and resistance coronary arteries. The lower transcardiac uptake of adiponectin may play a possible role in the pathogenesis of coronary spastic angina and microvascular angina, two conditions with impaired coronary vasomotor responses.

GRANTS

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