The relation between microalbuminuria and coronary collateral vessel development in patients with unstable coronary artery disease

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Microalbuminuria, considered a marker for systemic vascular disease, is a significant predictor of increased risk for cardiovascular morbidity and mortality in the general population. The relationship between microalbuminuria and cardiovascular disease is unknown. The aim of this study is to examine the association between microalbuminuria and coronary collateral vessel (CCV) development in nondiabetic and nonhypertensive patients with unstable coronary artery disease (USCAD). One hundred and six patients that had USCAD without hypertension and diabetes participated in the study. Microalbuminuria was assessed by radioimmunoassay in 24-h urine collections performed on the first day, and coronary angiography was performed 2–4 days after admissions. In total, 26 patients (mean age 56 ± 14 years) had the criteria of the microalbuminuria group and 80 patients with normoalbuminuria (mean age 59 ± 11 years), who had one or more diseased vessels with 80% or more stenosis, were included in the control group. The CCVs are graded according to the Rentrop scoring system and a Rentrop grade ≥ 1 was accepted as CCV development. CCV development was detected in eight (23%) of 26 patients in the microalbuminuria group and in 53 (74%) of 80 patients in the normoalbuminuria group. CCV development in the patients in the normoalbuminuria group was significantly different from that of the patients in the microalbuminuria group ($r = -0.15$, $P = 0.006$). In conclusion, these findings suggest that CCV development is poorer in the microalbuminuria group than the normoalbuminuria group. This study shows that in patients with USCAD, microalbuminuria, which is related to systemic vascular disease, affects CCV development negatively. *Coron Artery Dis* 20:431–434 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Albuminuria, considered a marker of both renal and systemic vascular disease, is a significant predictor of risk for cardiovascular disease in nondiabetic and diabetic patients [1]. Microalbuminuria is traditionally defined as a urinary albumin excretion rate of 20–200 μg/min or 30–300 mg/24 h [2]. Earlier studies show that high levels of albuminuria are associated with the increased incidence of cardiovascular mortality [3]. The link between albuminuria and atherosclerotic disease is suggested to be found in dysfunction of the endothelium. Coronary collateral vessels (CCVs) can provide a perfusion reserve in case of increased myocardial oxygen demand. Hypercholesterolemia also impairs endothelial function; therefore, it is possible that the extent of collateral vessel growth is poorer in hypercholesterolemia [4]. Patients with diabetes mellitus have a lesser ability to create CCVs. The authors speculated that endothelial dysfunction in diabetic patients may explain poorer collateral growth [5], as the endothelium is the most important element in the cascade of collateral growth [6]. In patients without diabetes mellitus and hypertension, the clinical relevance of microalbuminuria and cardiovascular disease is not clear, although several studies in the past few years show the increased risk of cardiovascular disease in nondiabetic individuals with microalbuminuria [7].

The pathogenic mechanisms leading to increased risk are still unknown, but microalbuminuria has been suggested as a marker of endothelial dysfunction and hyperpermeability of macromolecules [8,9], which occurs early in atherogenesis [10]. We hypothesized that in patients with unstable coronary artery disease (USCAD), microalbuminuria, which is related to systemic vascular disease, affects the CCV development negatively.

The aim of this study was to evaluate the relation between microalbuminuria and the development of CCVs.

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Methods

Study population

Two hundred and twelve consecutive and unselected patients admitted to intensive care units at the Erciyes University Heart Hospital with USCAD were studied. The exclusion criteria of the study were (i) diabetes mellitus, defined as a history of diabetes mellitus or the use antidiabetic drugs, fasting plasma glucose levels greater than 110 mg/dl, (ii) hypertension, defined as a history of hypertension or using antihypertensive drugs, blood pressure of 140/90 mmHg or more, (iii) a history of renal or urinary tract disease, (iv) a history of past coronary intervention or coronary artery bypass grafting, (v) a history of inflammatory rheumatic disease, (vi) chronic obstructive pulmonary disease, (vii) heart failure, and (viii) urine albumin excretion greater than 300 mg. The patients in whom coronary artery stenosis in the coronary angiography (had $< 80\%$ stenosis) was thought to be insufficient for the negative development of CCVs, were also excluded from the study. One hundred and six patients (26 patients with microalbuminuria, 80 patients with normoalbuminuria) were eligible for the study. The study was approved by the Erciyes University School of Medicine Ethics Committees, and was in accordance with the Helsinki Declaration. All participants gave written informed consent.

There are three principal presentations of unstable angina: (i) rest angina (angina occurring at rest and prolonged, usually greater than 20 min), (ii) new-onset angina (new-onset angina of at least Canadian Cardiovascular Society classification), (iii) increasing angina (angina diagnosed in the past that has become distinctly more frequent, longer in duration or lower in threshold) [11].

Serum cardiac enzymes and electrocardiogram were performed every 8 h during 48 h after admission. Subsequently, the tests were performed daily.

Baseline measures

Fasting blood samples were drawn for the measurement of blood glucose, plasma total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and plasma triglyceride (Thermo clinical lab system with Konelab 60 I kids, Helsinki, Finland).

Urinary albumin excretion was assessed in 24-h urinary collections, performed on the first day after admissions. Immediately after completion, volumes were measured and the samples sent to the laboratory. Here, urinary albumin was measured by radioimmunoassay, using a human albumin. Urinary albumin excretion was expressed as an albumin excretion rate of mg/24 h. Microalbuminuria was defined as a urinary albumin excretion rate of 30–300 mg/24 h.

Coronary angiography

Left and right coronary angiography was performed in multiple projections by the Judkins or Sones technique. Each angiogram was interpreted by two independent cardiologists. The degree of coronary artery diameter stenosis was estimated visually by two independent cardiologist. Coronary vessel disease was described as 80% or greater degree of diameter stenosis in only one coronary artery.

Collateral grading

Collateral circulation was graded according to the Rentrop classification. The collateral circulation was based on the injection that best opacified the occluded vessel: 0 = no visible filling of any collateral vessels, 1 = filling of side branches of the artery to be perfused by collateral vessels without visualization of the epicardial segment, 2 = partial filling of the epicardial segment by collateral vessels, and 3 = complete filling of the epicardial segment by collateral vessels [12].

Statistical analysis

Statistical analysis was performed with SPSS version 13.0 for Windows (SPSS Inc., Chicago, Illinois, USA). The differences between the continuous variables are expressed as mean ± SD. Comparisons between continuous variables were carried out with the unpaired Student's *t*-test, whereas the χ^2 test was performed for the comparison of the proportions of each categorical variable between the patients with and without microalbuminuria.

Results

The patients with microalbuminuria were characterized by an albumin excretion rate of 30–300 mg/24 h. Mean urine albumin excretion was 102 ± 71 (range, 30–257) in the group with microalbuminuria. The clinical characteristics of patients with and without microalbuminuria are presented in Table 1. Mean age, sex, smoking, weight, fasting blood glucose, blood pressure, body mass index,

Table 1 Clinical characteristic of the microalbuminuric and normoalbuminuric patients

	Micro-albuminuria ($n=26$)	Normo-albuminuria ($n=80$)	*P* value
Age (years)	56 ± 14	59 ± 11	0.09
Male, *n* (%)	25(96)	73(91)	0.41
Smoking, *n* (%)	23 (89)	59 (74)	0.12
BMI (kg/m^2)	27.7 ± 3.9	26.7 ± 3.6	0.16
Waist circumference (cm)	94.5 ± 10.1	90.4 ± 8.5	0.11
Hip circumference (cm)	102.3 ± 10.0	99.4 ± 8.7	0.30
Waist/hip ratio	0.9 ± 0.03	0.9 ± 0.03	0.86
Arterial blood pressure (mmHg)			
Systolic	112.6 ± 13.5	112.9 ± 12.4	0.93
Diastolic	71.4 ± 14.2	70.6 ± 10.7	0.92
Cholesterol (mg/dl)			
Total	184.5 ± 35.0	178.0 ± 40.1	0.17
Low-density lipoprotein	119.5 ± 25.3	121.1 ± 32.1	0.81
High-density lipoprotein	31.4 ± 7.3	34.7 ± 9.4	0.12
Triglycerides (mg/dl)	159.9 ± 117.5	114.7 ± 72.9	0.12
Troponin T (ng/ml)	0.71 ± 1.4	0.48 ± 0.87	0.38
CK-MB (U/l)	20.7 ± 10.5	19.7 ± 10.0	0.57

Data are presented as the mean value ± SD or percentage of patients.
BMI, body mass index; CK-MB, creatine kinase-MB.
$P<0.05$ statistically significant.

waist and hip circumferences, waist-to-hip ratio, plasma total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride, creatine kinase-MB, and troponin T levels did not differ significantly between the two groups. The coronary collateral presence was defined as the presence of minimal or well-developed collaterals (Rentrop 1, 2, 3) [12]. Grading was carried out independently by a trained research physician and cardiologist who were unaware of the clinical data. Coronary collaterals were present in 61 (58%) patients; 16 patients had grade 1 collaterals, 16 had grade 2 collaterals, and 29 had grade 3 collaterals (Fig. 1).

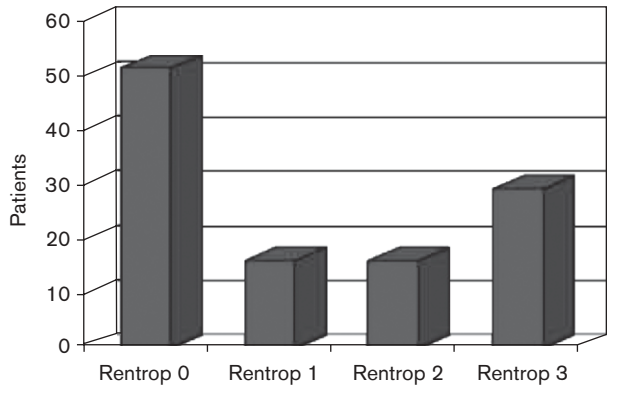
CCVs were present in eight patients (two patients had grade 1, two had grade 2, four had grade 3) in the microalbuminuria group and 53 patients (14 patients had grade 1, 14 had grade 2, 25 had grade 3) in the normoalbuminuria group. CCV development is significantly poorer in patients in the microalbuminuria group than that of patients in the normoalbuminuria group ($P = 0.006$) (Fig. 2).

Discussion

Our data indicated that CCV development is poorer in nondiabetic and nonhypertensive patients with microalbuminuria than patients with normoalbuminuria. To our knowledge, there are no data on the influence of microalbuminuria on collateral development in patients with USCAD.

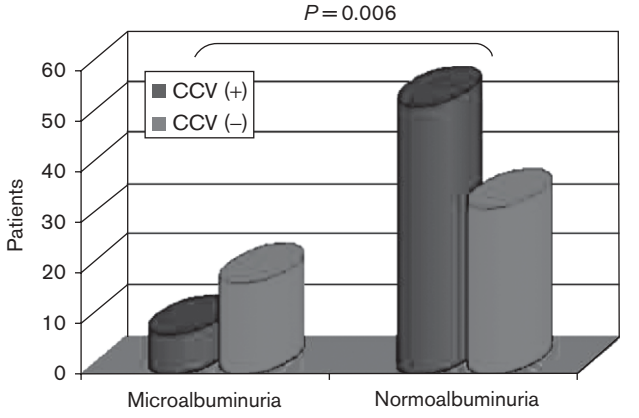
Microalbuminuria is a predictor of the development of ischemic heart disease, independent of other established atherosclerotic risk factors such as age, male sex, smoking, dyslipidemia, hypertension, and obesity. Microalbuminuria may represent an early marker of diffuse vascular endothelial dysfunction in patients with and without diabetes mellitus [8]. The prognostic significance of

Fig. 1



Coronary collateral vessel development in patients with unstable coronary artery disease.

Fig. 2



Relation between microalbuminuria and coronary collateral vessels (CCVs).

microalbuminuria in patients with myocardial infarction in unselected general coronary-care patients has been observed earlier [13]. Randomized placebo-controlled trials such as The Heart Outcomes Prevention Evaluation Study have revealed that treatment of persons with baseline cardiovascular disease or persons with important absolute risk of cardiovascular disease, based on a constellation of risk factors including microalbuminuria, offers significant primary and secondary prevention against cardiovascular disease [14]. Albuminuria, even in low levels within the normal range, is an independent predictor of cardiovascular and all-cause mortality in patients with stable coronary artery disease [15].

The underlying mechanism of the association between microalbuminuria and cardiovascular disease risk is unclear. A pathophysiologic link between microalbuminuria and atherosclerosis may be mediated through an increased generalized transvascular leakage of albumin. It is hypothesized that the systemic transvascular leakiness may also include lipoproteins, thus allowing for increased lipid penetration into the vessel walls. The leakiness might be because of hemodynamic factors or structural or functional perturbations of the endothelium or intracellular matrix beneath [9]. Microalbuminuria has been described as the strongest independent predictor of 11-year cardiovascular mortality in the Casale Monferrato Study [16]. As there is no plausible mechanism directly linking atherothrombotic disease to the urinary albumin loss, endothelial dysfunction has been suggested to be, at least partly, the pathophysiological process that causes both increased renal albumin loss and coronary artery disease endothelial dysfunction, which occurs early in the atherosclerotic process [17]. Coronary endothelial dysfunction has been recently reported to predict cardiovascular events in diabetic patients with angiographically normal coronary arteries and in the nondiabetic population [18,19].

Coronary collaterals may help in the protection of myocardium in patients with coronary artery disease, as they limit myocardial ischemia during coronary occlusion [20]. Fukai *et al.* [21] found that well-developed coronary collaterals may minimize the infarct area and predict the presence of viable myocardium in patients with a history of myocardial infarction. Sabia *et al.* [22] showed that the myocardium may remain viable for a prolonged period in patients with a recent acute myocardial infarction and an occluded infarct-related coronary artery in the presence of collaterals.

Our findings suggest that the prevalence of coronary collateral development in patients with microalbuminuria group is much lower than in patients with normoalbuminuria group. This may be explained by the effect of endothelial dysfunction and systemic vascular disease on patients with microalbuminuria in USCAD.

Study limitations

There are three limitations to our study. (i) Current equipment and angiographic technique enable us to demonstrate only vessels of which the luminal diameter is 100 μm or larger; in addition, angiography delineates epicardial collateral vessels, whereas the majority of human collaterals are subendocardial, but the effect of this consideration on collateral vessels must be the same in the two groups and thus should not change the analysis of our results. (ii) Regular physical exercise encourages the development of coronary collateralization [23]. In our study, there are no data about physical activity patients. (iii) Coronary collateral vessels could not have been developed in early period in patients with USCAD.

Clinical Implications

To our knowledge, this study is the first investigation in microalbuminuria patients with USCAD that shows the relation between microalbuminuria and CCV development. It shows that collateral vessels development is poorer in patients with microalbuminuria than in patients with normoalbuminuria.

References

1 Gerstein HC, Mann JF, Yi Q, Zinman B, Dinneen SF, Hoogwerf B, *et al.* Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA* 2001; **286**:421–426.

2 Hillege HL, Fidler V, Diercks GF, van Gilst WH, de Zeeuw D, van Veldhuisen DJ, *et al.* Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. *Circulation* 2002; **106**:1777–1782.

3 Jager A, Kostense PJ, Ruhé HG, Heine RJ, Nijpels G, Dekker JM, *et al.* Microalbuminuria and peripheral arterial disease are independent predictors of cardiovascular and all-cause mortality, especially among hypertensive subjects: five-year follow-up of the Hoorn Study. *Arterioscler Thromb Vasc Biol* 1999; **19**:617–624.

4 Van Belle E, Rivard A, Chen D, Silver M, Bunting S, Ferrara N, *et al.* Hypercholesterolemia attenuates angiogenesis but does not preclude augmentation by angiogenic cytokines. *Circulation* 1997; **96**:2667–2674.

5 Abaci A, Oğuzhan A, Kahraman S, Eryol NK, Unal S, Arinç H, Ergin A. Effect of diabetes mellitus on formation of coronary collateral vessels. *Circulation* 1999; **99**:2239–2242.

6 Fujita M, Ikemoto M, Kishishita M, Otani H, Nohara R, Tanaka T, *et al.* Elevated basic fibroblast growth factor in pericardial fluid of patients with unstable angina. *Circulation* 1996; **94**:610–613.

7 Ljungman S, Wikstrand J, Hartford M, Berglund G. Urinary albumin excretion – a predictor of risk of cardiovascular disease. A prospective 10-year follow-up of middle-aged nondiabetic normal and hypertensive men. *Am J Hypertens* 1996; **9**:770–778.

8 Deckert T, Feldt-Rasmussen B, Borch-Johnsen K, Jensen T, Kofoed-Enevoldsen A. Albuminuria reflects widespread vascular damage. The Steno hypothesis. *Diabetologia* 1989; **32**:219–226.

9 Jensen JS. Renal and systemic transvascular albumin leakage in severe atherosclerosis. *Arterioscler Thromb Vasc Biol* 1995; **15**:1324–1329.

10 Kuusisto J, Mykkänen L, Pyörälä K, Laakso M. Hyperinsulinemic microalbuminuria. A new risk indicator for coronary heart disease. *Circulation* 1995; **91**:831–837.

11 Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE Jr, *et al.* ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-Elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2007; **50**:e1–e157.

12 Rentrop KP, Cohen M, Blanke H, Phillips RA. Changes in collateral channel filling immediately after controlled coronary artery occlusion by an angioplasty balloon in human subjects. *J Am Coll Cardiol* 1985; **5**:587–592.

13 Berton G, Cordiano R, Palmieri R, Cucchini F, De Toni R, Palatini P. Microalbuminuria during acute myocardial infarction; a strong predictor for 1-year mortality. *Eur Heart J* 2001; **22**:1466–1475.

14 Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000; **342**:145–153.

15 Solomon SD, Lin J, Solomon CG, Jablonski KA, Rice MM, Steffes M, *et al.* Prevention of Events With ACE Inhibition (PEACE) Investigators. Influence of albuminuria on cardiovascular risk in patients with stable coronary artery disease. *Circulation* 2007; **116**:2687–2693.

16 Bruno G, Merletti F, Biggeri A, Bargero G, Ferrero S, Pagano G, Cavallo-Perin P. Casale Monferrato Study. Fibrinogen and AER are major independent predictors of 11-year cardiovascular mortality in type 2 diabetes: the Casale Monferrato Study. *Diabetologia* 2005; **48**:427–434.

17 Schächinger V, Britten MB, Zeiher AM. Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease. *Circulation* 2000; **101**:1899–1906.

18 Nitenberg A, Valensi P, Sachs R, Cosson E, Attali JR, Antony I. Prognostic value of epicardial coronary artery constriction to the cold pressor test in type 2 diabetic patients with angiographically normal coronary arteries and no other major coronary risk factors. *Diabetes Care* 2004; **27**:208–215.

19 Lerman A, Zeiher AM. Endothelial function: cardiac events. *Circulation* 2005; **111**:363–368.

20 Cohen M, Rentrop KP. Limitation of myocardial ischemia by collateral circulation during sudden controlled coronary artery occlusion in human subjects: a prospective study. *Circulation* 1986; **74**:469–476.

21 Fukai M, Ii M, Nakakoji T, Kawakatsu M, Nariyama J, Yokota N, *et al.* Angiographically demonstrated coronary collaterals predict residual viable myocardium in patients with chronic myocardial infarction: a regional metabolic study. *J Cardiol* 2000; **35**:103–111.

22 Sabia PJ, Powers ER, Ragosta M, Sarembock IJ, Burwell LR, Kaul S. An association between collateral blood flow and myocardial viability in patients with recent myocardial infarction. *N Engl J Med* 1992; **327**:1825–1831.

23 Niebauer J, Hambrecht R, Marburger C, Hauer K, Velich T, von Hodenberg E, *et al.* Impact of intensive physical exercise and low-fat diet on collateral vessel formation in stable angina pectoris and angiographically confirmed coronary artery disease. *Am J Cardiol* 1995; **76**:771–775.