Serum cystatin C levels in patients with stable angina and acute coronary syndrome

Cho, Yun-Hyeong

Department of Medicine
The Graduate School, Yonsei University

Serum cystatin C levels in patients with stable angina and acute coronary syndrome

Directed by Professor Hyuck Moon Kwon

The Master's Thesis Submitted to the
Department of Medicine,
the Graduate School of Yonsei University in partial
fulfillment of the requirements for the degree of
Master of Medical Science

Cho, Yun-Hyeong

December 2006

This certifies that the Master's Thesis
Cho, Yun-Hyeong is approved.

Thesis Supervisor : Hyuck Moon, Kwon

Bum-Kee Hong : Thesis Committee Member #1

Jeong-Ho Kim : Thesis Committee Member #2

The Graduate School
Yonsei University
December 2006

Acknowledgements

I would like to thank professor Hyuck Moon Kwon who gave me the opportunity to participate in such a great project and always provided me with good and thorough advices with deep sincerity. I am in debt to professor Bum-Kee Hong and Jeong-Ho Kim who gave me many great advices during this study. In addition, I especially thank Se-Jung Yoon who was an excellent helper about the statistical analysis. I express my greatest love to my wise and beautiful wife who always has been with me, prayed for me and supported for me with deep love and faith. Finally I dedicate this master's thesis to the Lord.

TABLE OF CONTENTS

LIST OF TABLES

ABSTRACT

Serum cystatin C levels in patients with stable angina and acute coronary syndrome

Cho, Yun-Hyeong

Department of Medicine
The Graduate School, Yonsei University

(Directed by Professor Hyuck Moon Kwon)

Atherosclerosis is an inflammatory disease characterized by extensive remodeling of the extracellular matrix architecture of the arterial wall. Atherosclerotic lesions have higher expression of cysteine protease cathepsins S and K, and lower expression of cystatin C, the endogenous inhibitor of these proteases. This study has examined the association between serum cystatin C and the severity of coronary artery disease (CAD), and also has measured serum cystatin C levels in patients with acute coronary syndrome (ACS). 265 consecutive patients with significant CAD (101 patients with ACS and 164 patients with stable CAD), and 159 consecutive patients without significant CAD as controls were enrolled. All patients underwent coronary angiography. The serum biochemical profile including serum cystatin C was measured before coronary angiography. Creatinine clearance was calculated with the Cockroft-Gault equation. Serum cystatin C levels were significantly higher in the stable angina patients with significant coronary artery disease and the ones with multivessel disease than controls. Serum cystatin C levels were correlated positively with hypertension, and negatively with creatinine clearance and HDL cholesterol. In multivariate analysis, serum cystatin C level was not an independent risk factor for significant CAD. In patients with ACS, serum levels of cystatin C were significantly lower than in patients with stable angina after adjustment of renal function using creatinine clearance. Serum hs-CRP levels were also higher in ACS patients. Serum cystatin C levels were correlated negatively with serum hs-CRP levels. Even though serum cystatin C was not an independent risk factor for CAD, serum cystatin C may reflect plaque instability in patients with ACS.

Keywords: cystatin C, coronary artery disease, stable angina, acute coronary syndrome

Clinical significance of serum cystatin C in patients with stable angina and acute coronary syndrome

Cho, Yun-Hyeong

Department of Medicine
The Graduate School, Yonsei University

(Directed by Professor Hyuck Moon Kwon)

I. BACKGROUNDS

Atherosclerosis is an inflammatory disease characterized by extensive remodeling of the extracellular matrix architecture of the arterial wall. Matrix metalloproteases and serine proteases have been implicated in these pathological processes.[1,2,3] Lysosomal cysteine proteases cathepsins S and K, the most potent mammalian elastases and also capable of collagenolysis, abound in human atherosclerotic lesions, in macrophages, smooth muscle cells (SMCs), and endothelial cells.[4] In contrast, atherosclerotic lesions have lower expression of cystatin C, the endogenous inhibitor of these proteases,[5] indicating an imbalance between protease and protease inhibitor that affects the integrity and homeostasis of the vasculature. In immunohistochemical studies, expression of cathepsins S and K mainly in macrophages in the shoulder regions of atheromata, in SMCs of the fibrous cap, and at sites of internal elastic laminae fragmentation, which may facilitate SMC migration, and destabilization of atherosclerotic plaque by degrading collagen of the fibrous caps,[6] which may cause acute coronary ischemic events.

Eriksson et al[7] recently demonstrated that a human cystatin C promoter polymorphism mutation, associated with reduced plasma cystatin C, correlated with a higher than average number of angiographically evident stenosis per coronary artery segment in survivors of myocardial infarction. Lindholt et al[8] and Shi et al[5] independently showed a significant reduction of cystatin C level in the serum of patients with dilated abdominal aortas, highlighting the potential function of cystatin C not only in the local vascular microenvironment but systemically as well. Furthermore, Noto et al[9] found lower levels of cystatin C only in the AMI group in a

sample of patients with unstable angina and acute myocardial infarction.
On the other hand, a recent series of publications from the Cardiovascular Health Study[10,11,12,13,14] showed that mild elevations in cystatin C serum concentration at baseline in elderly patients was a good predictor of cardiovascular events as well as of cardiovascular, non-cardiovascular and all-cause mortality during a follow-up of 9 years. In adjusted analysis, the subgroup with the highest serum cystatin C values was at significantly increased risk for myocardial infarction.
Until now, there have been these above conflicting data from epidemiological and molecular genetic studies on the association of cystatin C with cardiovascular disease. This study has examined the association between serum cystatin C and the presence, severity of coronary artery disease (CAD), reflecting systemic atherosclerosis, and also examined the association between serum cystatin C and acute coronary ischemic events. To investigate these associations, we measured serum levels of cystatin C and evaluated coronary angiographic findings in patients with CAD.

II. METHODS

1. Study population.

Those eligible for entry in this study were the patients who underwent coronary angiography at Yongdong Severance Hospital, Yonsei University, from January 2005 through June 2006 because of an abnormal electrocardiogram or angina-like chest symptoms. Patients with a previous history of coronary intervention or coronary artery bypass graft surgery were excluded to avoid artificial bias from such procedures. We also excluded patients with malignant disease, infectious disease, inflammatory disease such as collagen disease, advanced liver disease, and advanced renal disease (serum creatinine>1.3 mg/dl).

According to these criteria, this study enrolled 287 consecutive patients with significant CAD (123 patients with ACS and 164 patients with stable CAD), and 159 consecutive patients without significant CAD as controls. AMI patients were enrolled if they matched the Joint European Society of Cardiology/American College of Cardiology Committee 2000 criteria[15], if elevated levels of enzymes (including CK–MB or troponin I or T) together with clinical symptoms or ECG changes suggestive of ischemia were detected. Unstable angina (UA) was assessed according to the American College of Cardiology/American Heart Association (ACC/AHA) 2000 criteria[16] in patients with typical symptoms of prolonged chest pain without specific enzymes elevation and coronary lesions detected by coronary angiography. Confirmation of UA required a 70% epicardial coronary stenosis or true positive abnormal stress test performed during the index hospitalization or subsequent 6- to 8-week follow-up period. ACS was prospectively defined to satisfy guidelines established by the ACC/AHA[17] with the following modifications. Possible or probable ACS required resting chest pain compatible with myocardial ischemia of ≥30 min duration within 12 hours of emergency department presentation (an entry criterion that excludes chronic SA). For this study, ACS combines AMI and UA unless specifically noted.

Stable CAD was defined as no episodes of angina at rest but angiographically documented organic stenosis of ≥50% in at least one of the major coronary arteries and no previous MIs. Written informed consent was obtained from each patient before study participation. The study was conducted in accordance with guidelines approved by the ethics committee of our institution.

2. Coronary angiography

All patients underwent routine coronary angiography using the Judkins technique

on digitized coronary angiography equipment (Integris, Phillips). All coronary angiograms were visually assessed by at least 3 experienced angiographers (case load >5000 angiograms each), and a consensus was reached. The reviewers were blinded to the results of serum cystatin C. For this study, we defined significant CAD as at least 50% or greater diameter stenosis in at least 1 coronary vessel or prior percutaneous or surgical coronary revascularization. The extent of CAD was defined as 1-, 2-, and 3-vessel disease. Multivessel CAD was defined as angiographically more than 1-vessel disease. The absence of CAD was defined as completely smooth epicardial coronary arteries without any narrowings visible on coronary angiogram.

3. Blood sampling and laboratory procedures

Venous blood samples were obtained just before the emergency coronary angiography in patients with ACS and were obtained in the early morning after a 12-h fast in patients with stable CAD. The serum profile, including fasting blood glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglyceride, creatinine, high-sensitivity C-reactive protein (hs-CRP), and cystatin C levels, was measured in the hospital laboratory. Total cholesterol, triglycerides, HDL cholesterol, and creatinine plasma levels were measured using standard enzymatic–colorimetric procedures[18] on a Hitachi 7600-110 (Hitachi, Tokyo, Japan). Cystatin C plasma levels were assessed by immunonephelometry on a Berhing Nephelometer using a certified assay kit (Dade Berhing, Newark, DE, USA).[19] Creatinine clearance was calculated with Cockcroft-Gault equation.[20]

4. Statistical analysis

Results of normally distributed continuous variables are expressed as the mean value ± SD, and those for continuous variables with skewed distribution are expressed as the median value (interquartile range). Comparisons of continuous variables were analyzed with the unpaired *t* test and the Mann-Whitney *U* test, as appropriate. Categorical variables are presented by frequency counts, and intergroup comparisons were analyzed by the chi-square test. Associations between the presence of significant coronary artery disease and all other parameters were first analyzed by simple logistic regression analysis and then by multivariate analysis. We performed multiple logistic regression analysis to calculate the odds ratios (ORs) and 95% confidence intervals (CIs) for single and multiple CAD, as compared with simple lesions, in relation to all parameters. In this analysis, factors that were associated with the dependent variable

at $p < 0.20$ in the univariate analysis were entered into the multivariate model and eliminated using a backward procedure. Statistical significance was defined as $p < 0.05$. All analyses were performed using SPSS 13.0K for Windows (SPSS Inc., Seoul, Korea).

III. RESULTS

1. Comparisons between SA CAD patients and controls

The demographic and metabolic characteristics of all patients are shown in Table 1. No difference was seen between SA with significant CAD group and control group in body mass index (BMI), creatinine, total cholesterol, triglyceride, HDL cholesterol, LDL cholesterol, or hs-CRP levels. A significant difference between the two groups was seen in age, sex, hypertension, and diabetes. The SA patients with angiographically proven significant CAD had a higher serum cystatin C levels and creatinine clearance by Cockcroft-Gault formula[20] than the control group. After renal function adjustment using cystatin C dividing by creatinine clearance, Cys C/CCR ratio was significantly higher in the SA group than the control group.

Table 2 shows the correlation of cystatin C levels with the investigated parameters. At univariate analyses (Table 2, column A), cystatin C levels were positively correlated with age, hypertension and hs-CRP, and were negatively correlated with creatinine clearance (all patients with creatinine above 1.3 mg/dl were excluded from calculation) and HDL cholesterol. The same variables but age and hs-CRP were also independently correlated with cystatin C levels in a multiple-regression analysis (Table 2, column B) with a multiple R = 0.557.

A multiple logistic regression analysis revealed serum cystatin C level not to be an independent risk factor for significant CAD. (Table 3)

Table 1. Comparisons of the Baseline Demographic and Metabolic Characteristics between SA CAD Patients and Controls (creatinine<1.3 mg/dL)

	Control (n=164)	SA CAD (n=159)	*p* value
Age (yrs)	58.2±9.68	63.1±8.89	<0.001*
Sex (M/F)	89/70	70/94	0.019*
BMI (kg/m^2)	25.4±3.16	25.1±2.87	0.483
Hypertension (%)	57.9%	68.9%	0.049*
DM (%)	12.6%	33.5%	<0.001*
Current smoker (%)	24.5%	34.8%	0.052
hs-CRP (mg/dL)	2.98±6.825	3.51±11.139	0.610
Creatinine (mg/dL)	0.91±0.175	0.93±0.166	0.269
CCR (ml/min)	61.9±14.57	57.7±12.65	0.007*
Cystatin C (mg/dL)	0.84±0.126	0.87±0.154	0.049*
Cys C/CCR (g·min/L^2)	1.16±0.392	1.27±0.424	0.014*
T. chol (mg/dL)	160.8±32.68	158.5±39.21	0.561
TG (mg/dL)	137.8±82.82	139.4±114.26	0.887
HDL chol (mg/dL)	44.4±10.21	42.8±11.24	0.167
LDL chol (mg/dL)	98.8±28.39	97.1±34.83	0.636

Data are expressed as Mean ± SD.

*, significant if $p < 0.05$

Control, normal or minimal coronary control group; SA CAD, stable angina group with significant CAD; BMI, body mass index; DM, diabetes mellitus; CCR, creatinine clearance by Cockcroft-Gault formula; hs-CRP, high sensitivity C-reactive protein; T. chol, total cholesterol; TG, triglyceride; HDL chol, high-density lipoprotein cholesterol; LDL chol, low-density lipoprotein cholesterol

Table 2. Univariate Correlation and Multiple Regression Analysis of Serum Cystatin C with the Investigated Parameters (Creatinine<1.3mg/dL)

	Pearson's *R* (*p*)	Multiple beta (*p*)
Age (years)	0.401 (<0.001*)	NS
Sex	NS	NS
BMI (kg/m^2)	NS	NS
Hypertension	0.147 (0.008*)	0.104 (0.032*)
DM	NS	NS
Current Smoker	NS	NS
hs-CRP (mg/dL)	0.144 (0.01*)	NS
CCR (ml/min)	-0.504 (<0.001*)	-0.509 (<0.001*)
T. chol (mg/dL)	NS	NS
TG (mg/dL)	NS	NS
HDL chol (mg/dL)	-0.180 (0.001*)	-0.205 (<0.001*)
LDL chol (mg/dL)	NS	NS

*, significant if $p < 0.05$; NS, nonsignificant

Table 3. Multiple Logistic Regression Analysis for Significant CAD

	OR	95% CI	*p* value
Age (years)	1.073	1.029 ~ 1.118	<0.001*
Sex	1.962	1.082 ~ 3.560	0.027*
Hypertension	1.317	0.785 ~ 2.208	NS
DM	2.436	1.322 ~ 4.488	0.004*
Current Smoker	1.629	0.860 ~ 3.083	NS
hs-CRP (mg/dL)	0.999	0.973 ~ 1.026	NS
CCR (ml/min)	1.001	0.972 ~ 1.031	NS
Cystatin C (mg/dL)	0.520	0.064 ~ 4.261	NS
HDL chol (mg/dL)	0.996	0.972~ 1.021	NS

*, significant if $p < 0.05$

OR, odds ratio; CI, confidence interval; NS, nonsignificant

2. Correlation between cystatin C levels between the severities of CAD in SA patients

There was a significant difference in serum cystatin C and creatinine between the groups according to the degree of CAD in SA patients. There was no difference in serum creatinine. The serum cystatin C was negatively correlated with creatinine clearance.

Table 4. Comparison of Cystatin C, Creatinine, Creatinine Clearance According to the Degree of CAD in SA Patients

	Control (n=159)	1-VD (n=66)	Multi-VD (n=98)	*p* value
Cystatin C (mg/dL)	0.84±0.126	0.85±0.141	0.89±0.162	0.047*
Creatinine (mg/dL)	0.91±0.175	0.92±0.172	0.94±0.163	0.314
CCR (ml/min)	61.9±14.57	58.2±11.49	57.3±13.38	0.021*

*, significant if $p < 0.05$; 1-VD, 1-vessel disease; Multi-VD, multi-vessel disease

3. Comparisons between ACS, SA CAD and control group

The demographic and biochemical parameters between ACS patients, SA patients with significant CAD, and control group are shown in Table 5. No difference was seen between ACS group, SA with significant CAD group and control group in body mass index (BMI), hs-CRP, total cholesterol, triglyceride, HDL cholesterol and cystatin C. A significant difference between the three groups was seen in age, sex, hypertension, diabetes, current smoking, creatinine, creatinine clearance, LDL cholesterol, and cystatin C/CCR ratio. Between SA and ACS group, serum cystatin C levels and cystatin C/CCR ratio were significantly lower in ACS group. Between SA and control group, there was no significant difference in serum cystatin C and cystatin C/CCR ratio.

Table 5. Comparisons of Demographic and Biochemical Parameters between ACS, SA CAD, and Control Group

	ACS (n=101)	SA CAD (n=164)	Control (n=159)	p^a (p^b)
Age (years)	57.9±11.88	63.1±8.89	58.2±9.68	< 0.001* (< 0.001*)
Sex(M/F)	90/26	94/70	70/89	< 0.001*
BMI (kg/m^2)	24.9±4.27	25.1±2.87	25.4±3.16	0.590
Hypertension (%)	53.6%	68.9%	57.9%	0.023*
DM (%)	20.5%	33.5%	12.6%	< 0.001*
Current smoker (%)	44.6%	34.8%	24.5%	0.002*
hs-CRP (mg/dL)	5.29±9.730	3.51±11.139	2.98±6.825	0.144(0.173)
Cystatin C (mg/dL)	0.84±0.145	0.87±0.154	0.84±0.126	0.059 (0.046*)
Creatinine (mg/dL)	0.97±0.153	0.93±0.166	0.91±0.175	0.011* (0.039*)
CCR (ml/min)	79.7±22.35	73.0±18.57	78.1±21.36	0.017* (0.009*)
Cys C/CCR (g·min/L^2)	1.14±0.437	1.27±0.424	1.16±0.392	0.014* (0.015*)
T. Chol. (mg/dL)	163.2±34.12	158.5±39.21	160.8±32.68	0.552
TG (mg/dL)	119.0±62.28	139.4±114.26	137.8±82.82	0.142
HDL Chol (mg/dL)	42.3±10.45	42.8±11.24	44.4±10.21	0.198
LDL Chol (mg/dL)	109.2±30.83	97.1±34.83	98.8±28.39	0.005* (0.003*)

*, significant if $p < 0.05$;

[a], ANOVA test;

[b], *t* test between ACS and SA group;

AMI, acute myocardial infarction; SA CAD, stable angina patients with significant coronary artery disease; CCR, creatinine clearance by Cockcroft-Gault formula; Cys C, cystatin C

IV. DISCUSSION

The extracellular matrix (ECM) of the vascular wall, largely elastin and collagen, subserves many functions essential for vessel homeostasis. Normal tissues exhibit strict regulation of the expression and turnover of ECM.[21] In addition to matrix metalloproteases and serine proteases, lysosomal cysteine proteases have recently been recognized to participate in the pathogenesis of atherosclerosis.[22] Atherosclerotic lesions in humans[4,5] and in the apolipoprotein E-deficient
mouse (ApoE -/-), an established animal model for atherosclerosis, over-express the elastolytic and collagenolytic cathepsins S and K and show relatively reduced expression of cystatin C, their endogenous inhibitor.[22] Cystatin C, a potent protease inhibitor able to inhibit different cathepsins, is believed to play a role in the balance of the proteolytic/antiproteolytic activities in the arterial wall.[23] Lower plasma levels, as well as low intralesion cystatin C expression, have been found in patients with established aortic aneurysm,[5] and acute myocardial infarction.[9] Recently, the determination of renal function, either by estimating creatinine clearance with the Cockroft-Gault equation or by measuring serum creatinine, has been shown to be a prognostic value in the population of suspected or confirmed ACS patients.[24,25] In the present paper, we investigated the role of cystatin C levels in patients with angiographically-proven coronary artery disease. Our population was composed of patients with acute coronary syndrome and stable angina with significant coronary artery disease, and patients without angiographically-proven significant coronary artery disease. Because cystatin C levels were strongly correlated with creatinine levels in previous studies,[9] all patients with creatinine levels above 1.3 mg/dl were excluded. Under these conditions, serum cystatin C levels were compared between stable angina patients with significant coronary artery disease and control patients without significant coronary artery disease. Cystatin C levels were higher in SA group with significant CAD than control group. Serum creatinine levels were not different between the two groups. But, creatinine clearance was significantly lower in stable angina patients with significant CAD than controls. Serum cystatin C levels were also higher in multivessel disease group than control. Analyzing the correlation between cystatin C serum levels and the investigated parameters, we found that cystatin C increases with age and decreases with creatinine clearance even in subjects with normal serum creatinine levels (creatinine below 1.3 mg/dl). We also found that cystatin C level showed a negative, independent correlation with the HDL cholesterol, and a positive, independent correlation with the hs-CRP. In multivariate analysis, serum cystatin C was no longer independent risk factor for the presence and degree of coronary artery disease in stable angina patients. These above findings might be paradoxical. In previous reports,[5,22] local cystatin C deficiency has been demonstrated

in atherosclerotic and aneurismal lesions, suggesting a protective role of cystatin C in the vessel wall.

Since cystatin C is produced by all nucleated cells, it is unlikely that local variations in cystatin C synthesis in diseased arteries –rather than global cystatin C production and renal elimination– should determine its serum concentration. In line with this reasoning, the association between serum cystatin C and the presence and degree of coronary artery disease may indeed reflect incipient renal failure – which does not exclude local cystatin C deficiency in diseased arteries. Serum cystatin C was a better estimator of renal function than serum creatinine in our study. We think we can use serum cystatin C as a measurement of renal function before coronary angiography to prevent contrast-induced nephropathy.

In patients with acute coronary syndrome, plasma levels of cystatin C were lower than in SA patients. There was no difference in serum cystatin C between ACS group and control group. Cystatin C was lower in ACS patients than in SA patients. Between ACS patients and control group, there was no difference. When cystatin C/creatinine clearance ratio was considered, significantly lower values were found in ACS patients. This difference of cystatin C among the two study groups might be due to a negative acute phase response during acute myocardial infarction. Higher hs-CRP levels, but not significantly, in ACS patients also might support this hypothesis. However, other hypothesis could be possible. The lower serum levels of cystatin C in ACS patients might be due to the consumption of antiproteolytic factors during acute plaque rupture.

In order to solve the paradox between the local insufficiency of cystatin C in atherosclerotic lesion and higher serum levels of cystatin C in patients with coronary artery, it will be necessary to include a gold-standard measurement of kidney function and a broad range of both traditional and nontraditional cardiovascular risk factors[26] in future studies. Also, pharmacological interventions aimed at modifying cystatin C serum concentrations (e.g. by the induction of hyperthyroidism, which is associated with an increase in both serum cystatin C and creatinine clearance[27]) in animal models prone to develop atherosclerosis could be used to study whether there is a direct atherogenic effect of systemically elevated cystatin C.

In summary, serum cystatin C levels were higher in stable angina patients with significant coronary artery disease and multivessel disease, and correlated with creatinine clearance even in subjects with normal serum creatinine levels (creatinine below 1.3 mg/dl). Serum cystatin C levels were also lower in patients with acute coronary syndrome than stable angina patients after adjustment of renal function using creatinine clearance. Serum cystatin C was negatively correlated with hs-CRP.

V. CONCLUSION

Even through serum cystatin C was not an independent risk factor for CAD and may reflect incipient renal dysfunction, serum cystatin C may reflect immunoinflammation and plaque instability in patients with ACS, suggesting its role in acute plaque rupture.

REFERENCES

1. Libby P. Vascular biology of atherosclerosis: overview and state of the art. Am J Cardiol 2003;91:3A–6A.
2. Galis ZS, Khatri JJ. Matrix metalloproteinases in vascular remodeling and atherogenesis: the good, the bad, and the ugly. Circ Res 2002;90:251–262.
3. Lijnen HR. Extracellular proteolysis in the development and progression of atherosclerosis. Biochem Soc Trans 2002;30:163–167.
4. Sukhova GK, Shi GP, Simon DI, Chapman HA, Libby P. Expression of the elastolytic cathepsins S and K in human atheroma and regulation of their production in smooth muscle cells. J Clin Invest 1998;102:576–583.
5. Shi GP, Sukhova GK, Grubb A, Ducharm A, Rhode LH, Lee RT et al. Cystatin C deficiency in human atherosclerosis and aortic aneurysms. J Clin Invest 1999;104:1191–1197.
6. Shah PK, Falk E, Badimon JJ, Fernandez-Ortiz A, Mailhac A, Villareal-Levy G et al. Human monocytederived macrophages induce collagen breakdown in fibrous caps of atherosclerotic plaques: potential role of matrix-degrading metalloproteinases and implications for plaque rupture. Circulation. 1995;92:1565–1569.
7. Eriksson P, Deguchi H, Samnegard A, Lundman P, Boquist S, Tornvall P et al. Human evidence that the cystatin C gene is implicated in focal progression of coronary artery disease. Arterioscler Thromb Vasc Biol. 2004;24: 551–557.
8. Lindholt JS, Erlandsen EJ, Henneberg EW. Cystatin C deficiency is associated with the progression of small abdominal aortic aneurysms. Br J Surg. 2001;88:1472–1475.
9. Noto D, Cefalu' AB, Barbagallo CM, Pace A, Rizzo M, Marino G et al. Cystatin C levels are decreased in acute myocardial infarction Effect of cystatin C G73A gene polymorphism on plasma levels. International Journal of Cardiology. 2005;101: 213–217.
10. Shlipak MG, Sarnak MJ, Katz R, Fried LF, Seliger SL, Newman AB et al. Cystatin C and the risk of death and cardiovascular events among elderly persons. N Engl J Med 2005;352:2049–2060
11. Shlipak MG, Katz R, Fried LF, Jenny NS, Stehman-Breen CO, Newman AB et al. Cystatin-C and mortality in elderly persons with heart failure. J Am Coll Cardiol 2005;45:268–271
12. Sarnak MJ, Katz R, Stehman-Breen CO, Fried LF, Jenny NS, Psaty BM, et al. Cystatin C concentration as a risk factor for heart failure in older adults. Ann Intern Med 2005;142:497–505
13. Fried LF, Katz R, Sarnak MJ, Shlipak MG, Chaves PH, Jenny NS et al. Kidney

function as a predictor of noncardiovascular mortality. J Am Soc Nephrol 2005;16:3728–3735
14. O'Hare AM, Newman AB, Katz R, Fried LF, Stehman-Breen CO, Seliger SL et al. Cystatin C and incident peripheral arterial disease events in the elderly: results from the Cardiovascular Health Study. Arch Intern Med 2005;165:2666–2670
15. The Joint European Society of Cardiology/American College of Cardiology Committee. Myocardial infarction redefined a consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. Eur Heart J 2000;21:1502–1513.
16. Braunwald E, Antman EM, Beasley JW, Califf RM, Cheitlin MD, Hochman JS et al. ACC/AHA guidelines for the management of patients with unstable angina and non-STsegment elevation myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients with Unstable Angina). J Am Coll Cardiol 2000 ep.;36(3):970– 1062.
17. Braunwald E, Antman EM, Beasley JW, Califf RM, Cheitlin MD, Hochman JS et al. ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction: executive summary and recommendations: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (committee on the management of patients with unstable angina). Circulation. 2000;102:1193–1209.
18. Noto D, Barbagallo CM, Cefalu' AB, Cavera G, Sapienza M, Notarbartolo A et al. Factor VII activity is an independent predictor of cardiovascular mortality in elderly women of a Sicilian population: results of an 11-year follow-up. Thromb Haemost 2002 Feb.;87(2):206–210.
19. Uhlmann EJ, Hock KG, Issitt C, Sneeringer MR, Cervelli DR, Gorman RT et al. Reference intervals for plasma cystatin C in healthy volunteers and renal patients, as measured by the Dade Behring BN II system, and correlation with creatinine. Clin Chem 2001 Nov.;47(11):2031–2033.
20. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41
21. Libby P, Lee RT. Matrix matters. Circulation. 2000;102:1874–1876.
22. Liu J, Sukhova GK, Sun JS, Xu WH, Libby P, Shi GP. Lysosomal cysteine proteases in atherosclerosis. Arterioscler Thromb Vasc Biol 2004;24:1359–1366.
23. Parks WC. Who are the proteolytic culprits in vascular disease? J Clin Invest 1999;104(9):1167– 1168.

24. Al Suwaidi J, Reddan DN, Williams K, Pieper KS, Harrington RA, Califf RM et al. Prognostic implications of abnormalities in renal function in patients with acute coronary syndromes. Circulation. 2002;106:974-980.
25. Januzzi JL, Cannon CP, DiBattiste PM, Murphy S, Weintraub W, Braunwald E. Effects of renal insufficiency on early invasive management in patients with acute coronary syndromes (The TACTICS-TIMI 18 Trial). Am J Cardio. 2002;90:1246-1249.
26. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in cardiovascular disease, high blood pressure research, clinical cardiology, and epidemiology and prevention. Hypertension 2003;42:1050–1065.
27. Fricker M, Wiesli P, Brandle M, Schwegler B, Schmid C. Impact of thyroid dysfunction on serum cystatin C. Kidney Int 2003;63:1944–1947

ABSTRACT (IN KOREAN)

급성관동맥증후군 및 안정형 협심증 환자에서 혈청 시스타틴 C의 임상적 중요성

<지도교수 권혁문>

연세대학교 대학원 의학과

조윤형

죽상경화증은 동맥벽의 세포외간질의 광범위한 재형성을 특징으로 하는 염증성 질환이다. 죽상경화병변 내에서 시스테인 단백분해효소인 카텝신 S와 K가 과표현되어 있으며, 이 단백효소의 억제자인 시스타틴 C는 감소되어 있다. 본 연구에서는 혈청 시스타틴 C와 관상동맥 질환의 유무 및 정도와의 연관성 및 급성 심근경색증에서의 혈청 시스타틴 C 치에 대한 검사를 시행하였다. 유의한 관상동맥질환을 가진 265명의 환자군(급성 심근경색증 환자 101명, 안정형 협심증 환자 164명) 및 유의한 관상동맥 질환이 없는 대조군 159명이 연구대상에 포함되었다. 모든 환자들은 관상동맥조영술을 시행받았으며, 조영술 시행 전 시스타틴 C를 포함한 생화학적 검사가 시행되었으며, 크레아티닌 청소율은 Cockcroft-Gault 공식에 의해 계산되었다. 혈청 시스타틴 C 치는 관상동맥질환을 가진 안정형 협심증 환자군에서 대조군에 비해 유의하게 높았으며, 다혈관질환군에서 대조군에 비해 유의하게 높았다. 또한 혈청 시스타틴 C는 고혈압과 양의 상관관계를 보였으며, 크레아티닌 청소율 및 고밀도 지단백과는 음의 상관관계를 나타내었다. 다변량분석에서 시스타틴 C는 관상동맥질환의 유무 및 다혈관질환 유무에 대한 독립적 예측인자는 아니었다. 급성관동맥증후군 환자군에서 혈청 시스타틴 C 치가 안정협심증 환자군에 비해 유의하게 낮았다. 고민감도 C-반응 단백은 급성관동맥증훈군 환자군에서 안정협심증, 통계적으로 유의하지는 않지만, 높은 경향을 보였다. 혈청 시스타틴 C 치는 혈청 고민감도 C-반응 단백치와 음의 상관관계를 나타내었다. 비록 혈청 시스타틴 C가 관상동맥질환에 대한 독립적인 위험인자가 아닐지라도, 혈청 시스타틴 C가 급성관동맥 증후군 환자에서 경화반의 불안정성을 반영할 수도 있다.

핵심 단어 : 시스타틴 C, 관상동맥질환, 안정형 협심증, 급성 관동맥 증후군