Coronary Artery Disease Severity and Cardiovascular Biomarkers in Patients with Peripheral Artery Disease

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Abstract

Keywords

- ▶ coronary artery
- ▶ cardiovascular disease
- ▶ peripheral artery disease
- ▶ claudication
- ▶ critical limb ischemia
- ▶ cardiac biomarkers
- ▶ cardiac catheterization

Cardiovascular mortality in peripheral artery disease (PAD) patients is higher in critical limb ischemia (CLI) than in intermittent claudication (IC). We sought to evaluate differential characteristics of coronary artery disease (CAD) severity and prognostic biomarkers for cardiovascular events between CLI and IC patients. Coronary angiography was performed on 242 PAD patients (age 73 ± 8 years) with either CLI or IC. High-sensitivity troponin T (hs-TnT), eicosapentaenoic acid–arachidonic acid ratio (EPA/AA), and lipoprotein(a), as biomarkers for prognostic factors, were measured from blood samples. The study patients were divided into a CLI-group ($n = 42$) and IC-group ($n = 200$). The Gensini score as an indicator of coronary angiographic severity was higher in the CLI-group than in the IC-group (39.1 ± 31.2 vs. 8.5 ± 8.3 , $p < 0.0001$). Hs-TnT and lipoprotein(a) values were higher in the CLI-group than in the IC-group (0.152 ± 0.186 ng/mL vs. 0.046 ± 0.091 , $p < 0.0001$, 45.9 ± 23.3 mg/dL vs. 26.2 ± 27.7 , $p = 0.0002$, respectively) and EPA/AA was lower in the CLI-group than in the IC-group (0.22 ± 0.11 vs. 0.38 ± 0.29 , $p = 0.0049$, respectively). Greater CAD severity, higher hs-TnT, and lipoprotein(a), and lower EPA/AA were observed in the CLI-group, which may explain higher cardiovascular events in patients with CLI.

Peripheral arterial disease (PAD), which is caused by atherosclerotic occlusion of the arteries to the lower extremities, is an important manifestation of systemic atherosclerosis. PAD impairs not only quality of life but also the long-term prognosis of patients with atherosclerosis due to coexisting coronary artery disease, which is a major cause of mortality and morbidity in patients with PAD.^{1,2} Symptomatic PAD is usually classified into intermittent claudication (IC) and critical limb ischemia (CLI). Cardiovascular mortality in patients with PAD is higher in CLI than in IC.² There are insufficient studies to indicate causes of higher cardiovascular morbidity and mortality in patients with CLI than in patients with IC.

The Gensini score is one of the coronary artery disease (CAD) scores determined by coronary angiogram.³ The coronary score was intended to take into account geometrically increasing severity of lesions, cumulative effect of multiple lesions, lesion location, and the influence of collaterals. The Gensini score is widely used for evaluation of coronary artery severity and has prognostic significance.⁴

Cardiac troponin T is a component of the contractile apparatus of cardiomyocytes and an established sensitive biomarker of myocardial cell injury. Cardiac troponin T measured by a highly sensitive assay predicts coronary heart disease, heart failure, and mortality.⁵ Elevated troponin T is reported to be associated with higher mortality and

amputation rates in patients with PAD.⁶ Lipoprotein(a) [Lp(a)] is a genetic variant of low-density lipoprotein in which apolipoprotein B100 is linked by a disulfide bond to apolipoprotein(a), with a high degree of structural homology with plasminogen.^{7,8} Lp(a) can exert the development, growth, and disruption of atherosclerotic plaques through its effects on lipid accumulation, inflammation, and thrombosis.^{9–14} Lp(a) is a strong predictor of acute myocardial infarction.^{15–17} Dietary essential fatty acids are classified into n-3 (e.g., eicosapentaenoic acid [EPA]) and n-6 (e.g., arachidonic acid [AA]) groups, and the metabolites of these fatty acids have opposing effects on coronary artery disease. Dietary intake of fish-derived polyunsaturated fatty acid shows favorable outcome in patients with coronary artery disease.^{18–20} The Japan EPA lipid intervention study showed for the first time that additive administration of purified EPA reduced coronary events by 19% in patients with statin therapy.²¹ EPA/AA ratio is reported to be a strong predictor of cardiovascular events.^{22–24}

The purpose of this study is to evaluate differential characteristics of coronary artery disease severity and prognostic biomarkers for cardiovascular events between CLI and IC patients and to assess causes of poorer outcomes in CLI patients than in IC patients.

Methods

Study Patients

The study included a total of 242 patients with symptomatic PAD who underwent endovascular therapy (EVT). The ankle-brachial index and duplex ultrasonography were routinely used to confirm the diagnosis of PAD. The study patients were divided into IC and CLI based on lower extremity conditions. IC was defined as Rutherford classification 2 to 3, while CLI was defined as Rutherford classification 4 to 6.²⁵

Study Protocols

All the study patients underwent coronary angiography and lower limb angiography before the day of EVT. Coronary angiography and lower limb angiography were performed with usual methods via a radial, brachial or femoral artery. Serum Lp(a), high-sensitivity troponin T, EPA, AA, low-density cholesterol, high-density cholesterol, triglyceride, and hemoglobin A_{1c} levels were measured in the fasting state before EVT. All the study patients underwent EVT based on the findings from a lower limb angiogram.

Coronary Angiography and Lower Limb Angiography

All coronary angiograms were scored for luminal narrowing using a modified American Heart Association/American College of Cardiology classification.²⁶ Patients were designated as having angiographically smooth normal coronary arteries, nonsignificant CAD (visible plaque resulting in < 50% luminal stenosis), or significant CAD (at least one major epicardial vessel with ≥50% stenosis). The severity of their CAD was calculated based on angiographic disease of their native vessels before revascularization. Quantitative angiographic scoring was performed using the Gensini score that

quantifies CAD severity by a nonlinear points system for degree of luminal narrowing.³ Lower limb angiography showed culprit lesions for symptomatic PAD.

Blood Sampling

Venous blood was drawn from all patients in the fasting state. Levels of low-density lipoprotein cholesterol, high-density cholesterol, triglyceride, and hemoglobin A_{1c} were measured. Serum levels of Lp(a) were measured using a latex agglutination turbidimetric immunoassay (Sekisui Medical Co., Tokyo, Japan). Serum high-sensitivity troponin T levels were measured using high-sensitivity assay with electrochemiluminescence detection (Roche Diagnostics Co., Tokyo, Japan), the normal range was less than 0.014 ng/mL (cut off value for acute myocardial infarction of 0.1 ng/mL). Plasma levels of EPA and AA were measured using gas chromatography (SRL Co., Tokyo, Japan). The values of EPA/AA ratio were calculated for analysis.

Statistical Analysis

Data were expressed as mean ± SD. Continuous variables were compared using the Student *t*-test. Chi-square analysis was used to test the differences between proportions. Fisher exact test was used when the expected value for a cell was < 5. Lp(a) values were logarithmically transformed to statistically analyze Lp(a) as a continuous variable. All statistical analyses were performed using JMP version 10 (SAS Inc., Chicago, IL). Statistical significance was defined as a *p*-value less than 0.05 (two tailed).

Results

Patient clinical characteristics are shown in ►Table 1. Laboratory findings are indicated in ►Table 2. Values of high-sensitivity troponin T, Lp(a) were higher in the CLI group than in the IC group, while EPA/AA ratio was lower in the CLI group than in the IC group. Coronary angiographic findings showed a higher incidence of significant coronary artery stenosis in at least one major coronary artery and greater values of Gensini score in the CLI group than in the IC group (►Table 3). Lower limb angiographic findings are shown in ►Table 4.

Discussion

This study showed that the CLI group had a higher incidence of diabetes mellitus, significant coronary artery stenosis in at least one major coronary artery, higher values of high-sensitivity troponin T and Lp(a), and lower ratio of EPA/AA than the IC group. Those findings may explain higher incidences of major adverse coronary and cerebral events in CLI patients.

CLI is defined as limb pain that occurs at rest or impending limb loss that is caused by severe compromise of blood flow to the affected extremity. CLI patients showed extremely poorer prognosis than IC patients due to higher rates of cardiovascular events.² Evaluation of the mechanisms of higher rates of cardiovascular events are needed for improvement of prognosis in CLI patients.

There are few studies to assess differences of CAD severity between IC and CLI patients. Although it is unclear why CLI

Table 1 Patients' clinical characteristics

Clinical characteristics	IC	CLI	p-Value
Men/women	156/44	30/12	0.3679
Age (y)	72 ± 8	74 ± 11	0.2965
Body mass index (kg/m ²)	22.1 ± 4.2	22.1 ± 7.9	0.9856
Hypertension	163 (82%)	32 (76%)	0.4020
Diabetes mellitus	102 (51%)	32 (76%)	0.0024
Hypercholesterolemia	84 (42%)	10 (24%)	0.0224
Smoking (current or ex-smoker)	107 (54%)	16 (38%)	0.0685
CKD	143 (72%)	32 (76%)	0.5629
Hemodialysis	77 (39%)	18 (43%)	0.6005
Rutherford class			
2	98 (49%)		
3	101 (51%)		
4		12 (29%)	
5		28 (67%)	
6		2 (4%)	
Statin use	136 (68%)	25 (60%)	0.2899
Aspirin use	184 (92%)	38 (90%)	0.7444
Clopidogrel use	180 (90%)	36 (86%)	0.4149
Cilostazol use	22 (52%)	129 (65%)	0.1405

Abbreviations: CLI, critical limb ischemia; CKD, chronic kidney disease; IC, intermittent claudication.

Note: Mean ± SD.

patients have higher coronary artery severity than IC patients, higher incidence of diabetes mellitus, higher Lp(a) values, and lower EPA/AA may be related with coronary artery disease progression. Greater coronary artery lesion severity may be related with greater values of serum high-sensitivity troponin T in CLI patients, compared with IC patients. Lp(a) values are increased in an inflammatory condition.²⁷ Although Lp(a) is usually genetically determined, CLI with inflammatory condition may elevate Lp(a) level. There are few studies to assess

Lp(a) values between CLI and IC patients. Lp(a) level is a reliable biochemical marker for survival in patients with critical limb ischemia.²⁸ An elevated Lp(a) level of > 24 mg/dL incurred a 107 and 45% increase in mortality at 3 and 5 years, respectively.²⁸ A lower serum EPA/AA ratio is associated with a greater risk of cardiovascular disease, especially coronary heart disease.²⁹ Linnemann et al have reported that high-sensitivity troponin T is frequently elevated in PAD and is associated with higher rates of not only mortality but also limb amputation.⁶ In

Table 2 Laboratory findings

Findings	IC	CLI	p-Value
HbA1c (%)	6.4 ± 1.5	6.5 ± 1.6	0.1511
LDL cholesterol (mg/dL)	83.3 ± 25.4	88.2 ± 33.5	0.2932
HDL cholesterol (mg/dL)	45.3 ± 13.1	38.1 ± 12.3	0.0015
Triglyceride (mg/dL)	143.5 ± 94.5	113.0 ± 37.1	0.0456
High-sensitivity Troponin T (ng/mL)	0.046 ± 0.091	0.152 ± 0.186	< 0.0001
Lp(a) (mg/dL)	26.2 ± 27.7	45.9 ± 23.3	0.0002
EPA/AA	0.38 ± 0.29	0.22 ± 0.11	0.0049
ABI	0.67 ± 0.28	0.48 ± 0.29	0.0004

Abbreviations: AA, arachidonic acid; ABI, ankle brachial index; CLI, critical limb ischemia; EPA, eicosapentaenoic acid; HDL, high-density lipoprotein; IC, intermittent claudication; LDL, low-density lipoprotein; Lp(a), lipoprotein (a).

Note: Mean ± SD.

Table 3 Findings of coronary angiography

Findings	IC	CLI	p-Value
Significant coronary stenosis in at least one major coronary artery	44 (22%)	25 (60%)	< 0.0001
Gensini score	8.5 ± 8.3	39.1 ± 31.2	< 0.0001

Abbreviations: CLI, critical limb ischemia; IC, intermittent claudication.
Note: Mean ± SD.

Table 4 Findings of lower limb angiography

Findings	IC	CLI	p-Value
Locations of culprit lesions			
Iliac artery	70	15	< 0.0001
SFA	135	18	
BTK	3	13	
CTO	57 (38%)	21 (54%)	0.1813

Abbreviations: BTK, below the knee; CLI, critical limb ischemia; CTO, chronic total occlusion; IC, intermittent claudication; SFA, superficial femoral artery.
Note: Mean ± SD.

their study, a prevalence of elevated high-sensitivity troponin T (> 0.01 ng/mL) was higher in CLI patients (Rutherford categories 4 and 5) than in IC patients (Rutherford categories 2 and 3). These results support our study results in terms of high-sensitivity troponin T. Elevated high-sensitivity troponin T concentration is also associated with an impaired renal function.⁶ However, there were no significant differences of incidences of chronic renal disease and hemodialysis in our study.

Our study demonstrated that CLI patients had greater severity of coronary artery lesions, higher values of high-sensitivity troponin T and Lp(a), and lower values of EPA/AA. These findings may support higher rates of mortality, cardiovascular events in CLI patients. The diagnosis of CLI thus predicts a poor prognosis for life and limb. Patients with CLI should undergo aggressive assessment of coronary artery conditions and biomarkers for future prediction of cardiovascular events in addition to limb evaluation. Furthermore, patients should have aggressive modification of their cardiovascular risk factors and coronary revascularization if necessary.

The high rate of patients on hemodialysis and suffering from diabetes mellitus was shown in our study. Our hospital has a large hemodialysis center which sees almost all patients with hemodialysis in our medical care zone. The leading cause of hemodialysis was diabetes mellitus in our hemodialysis center. PAD patients with hemodialysis in the hemodialysis center were referred to our cardiovascular center. That was the reason why our study indicated high rate of patients with hemodialysis and diabetes mellitus.

Our study has several limitations. First, the sample size was relatively small. Second, patient enrollment for this study was selective because the only patients who underwent EVT were included for the study. Third, prognosis of our study patients was not evaluated in this study. Therefore, we were not able to

evaluate which factors predicted cardiovascular mortality in our study. Long follow-up data are needed to determine the prognostic factors for cardiovascular mortality in our study population.

Conclusion

Greater severity of coronary artery disease, higher high-sensitivity troponin T and Lp(a) values, and lower EPA/AA were observed in the CLI patients, which may explain higher cardiovascular events in patients with CLI than with IC.

Conflict of Interest

The authors declare no potential conflicts of interests with respect to the authorship and/or publication of this article.

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