ORIGINAL RESEARCH

Different Microcirculation Response Between Culprit and Non-Culprit Vessels in Patients With Acute Coronary Syndrome

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BACKGROUND: This study investigated whether the microvascular dysfunction differed between culprit and non-culprit vessels in patients with acute coronary syndrome who underwent percutaneous coronary intervention.

METHODS AND RESULTS: In 115 prospectively recruited patients, after successful percutaneous coronary intervention, culprit and non-culprit intracoronary hemodynamic measurements were performed and repeated at 6-month follow-up. ^{13}N-ammonia positron emission tomography was performed at 6-month follow-up visit to determine absolute myocardial blood flow. The resistance values of each vessel were calculated using the coronary pressure data and the myocardial blood flow values obtained from ^{13}N-ammonia positron emission tomography data. We compared the measurements between culprit and non-culprit vessels and assessed changes in microvascular dysfunction during the study period. In 334 vessels (115 culprit and 219 non-culprit), the culprit vessel group showed a lower fractional flow reserve and coronary flow reserve than the non-culprit vessel group at baseline and 6-month follow-up, respectively. The value of index of microcirculatory resistance was different between the 2 groups in the baseline but not at 6-month follow-up. The microvascular resistance at rest and hyperemic microvascular resistance were not different between the 2 groups, but resistance to stenosis was higher in the culprit vessel group, under both resting and hyperemic status (P=0.02 and P<0.01, respectively). In the culprit vessel analysis, the fractional flow reserve and index of microcirculatory resistance decreased whereas coronary flow reserve increased (P<0.01 for all) at 6-month follow-up. However, there was no change in index of microcirculatory resistance, coronary flow reserve, and fractional flow reserve from baseline to 6-month follow-up in the non-culprit vessel analysis.

CONCLUSIONS: The observed microvascular dysfunction in acute coronary syndrome is limited to the culprit vessel territory in the acute phase, which is relatively recovered in the chronic phase and there is no out-of-culprit territory involvement.

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Key Words: acute coronary syndrome ■ culprit vessel ■ index of microcirculatory resistance ■ microcirculation

C linical trials show that microvascular coronary disease is an independent predictor of poor prognosis in patients with or without significant epicardial coronary disease.[1–3] The treatment of coronary microvascular dysfunction may be different from the current approach to epicardial coronary artery disease.[4] Therefore, it is important for prognostic assessment and treatment plan to determine whether microvascular damage to culprit vessels in acute coronary syndrome (ACS) patients occurs only in the culprit territory or in the surrounding myocardium.

The extent of microvascular dysfunction in ACS patients is unclear. Some clinical studies showed that subendocardial ischemia induced significant microvascular dysfunction away from the ischemic territory.[5,6] In contrast, recent studies have reported that impaired microvascular function following ischemia does not affect other vascular regions.[7–9] However, these studies

CLINICAL PERSPECTIVE

What Is New?

- Index of microcirculatory resistance was different between culprit and non-culprit vessels in the acute phase but not in the chronic phase.
- Between the acute and chronic phases of acute coronary syndrome, culprit index of microcirculatory resistance, coronary flow reserve, and fractional flow reserve were changed, whereas non-culprit index of microcirculatory resistance, coronary flow reserve, and fractional flow reserve were not altered.

What Are the Clinical Implications?

- The priority in acute coronary syndrome should be a culprit vessel treatment for the recovery of microvascular dysfunction, as well as for the reduction of ischemia burden.
- Microvascular parameters of culprit-vessel may be inappropriate as a prognostic indicator since microvascular parameters of culprit vessel may not sufficiently reflect the patient's microvascular dysfunction.
- Our study also raises that there is a need for research on which of the acute and chronic assessments of microvascular function predict better prognosis for patients with acute coronary syndrome.

Nonstandard Abbreviations and Acronyms

ACC	American College of Cardiology
ACS	acute coronary syndrome
AHA	American Heart Association
CFR	coronary flow reserve
FFR	fractional flow reserve
IMR	index of microcirculatory resistance
MBF	myocardial blood flow
PCI	percutaneous coronary intervention
PET	positron emission tomography
STEMI	ST-segment–elevation myocardial infarction

were limited by the lack of long-term data[7–9] or small number of subjects.[5,6]

The goal of this study was to investigate using invasive and non-invasive physiologic measures whether the microvascular dysfunction varied between culprit and non-culprit vessels in the acute and chronic phases, respectively, in ACS patients who underwent percutaneous coronary intervention (PCI).

METHODS

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population

This study was a prospective trial performed in a single center. We consecutively enrolled patients from Dong-A University Hospital who underwent PCI for ACS between December 2014 and December 2015. Individuals were eligible for inclusion if they underwent PCI for ACS, if the target lesion was found in the proximal or middle segments of a major epicardial coronary artery, if the lesion was successfully treated with a coronary stent, and if physiologic measurements were performed in both culprit and non-culprit vessels. Subjects with the following conditions were excluded: a previous infarction other than in the vessel of interest or a history of coronary artery bypass surgery, cardiogenic shock requiring inotropic support, chronic kidney disease requiring renal replacement therapy, or hypertrophic cardiomyopathy. In addition, this study excluded patients with collateral flow to the target vessel greater than angiographic grade 1, or statin or ticagrelor use within 1 year, which can affect physiological measurements.[10–12] The study protocol was approved by the institutional review board. The study was conducted in accordance with the *International Conference on Harmonization Guidelines* and the tenets of the Declaration of Helsinki (Version 2013 of December). Written informed consent was obtained before inclusion in the study.

Study Protocol

PCI was performed according to the latest standard guidelines.[13,14] Before PCI, all patients were pretreated with aspirin 300 mg and ticagrelor 180 mg followed by maintenance doses of aspirin 100 mg once a day and ticagrelor 90 mg twice a day for 12 months. At the beginning of the procedure, 5000 units of unfractionated heparin were administered intra-arterially and additional heparin was administered to maintain an activated clotting time of 250 to 300 seconds during the procedure. In the present study, the culprit vessel was defined as the coronary artery underlying atherosclerotic event based on the related electrocardiographic changes, echocardiographic left ventricular segment kinetics anomalies, and angiographic lesion morphology.[15] All culprit lesions were treated with a biodegradable polymer drug-eluting stent (Orsiro, Biotronik, Berlin, Germany). Physiologic measurements were obtained from the culprit and non-culprit artery during the acute and chronic phases. Microvascular dysfunction was compared between

the culprit and non-culprit vessels by defining the non-culprit vessels as a control group. All patients in this study were treated daily with rosuvastatin 5 mg (Crestor, AstraZeneca, Cambridge, UK) without substitution with other statin throughout the study period. The continuation of dual antiplatelet therapy following study completion was at the discretion of the treating physician.

Physiologic Measurements
Acute Phase

Physiological parameters of the culprit artery after PCI were determined with the restoration of thrombolysis in myocardial infarction 3 flow. To avoid variables affecting microvascular function in acute setting, physiologic measurements were performed in unstable angina immediately and in ST-segment–elevation myocardial infarction (STEMI) or non-STEMI at ≥3 days following PCI.[16,17] Invasive physiologic assessments for the culprit vessel were performed as previously described using an intracoronary pressure and temperature sensor-tipped guidewire (PressureWireCertus, ST. Jude Medical, MN, USA).[18] After equalization, the pressure wire was advanced across the stented segment and was located at the distal portion of the culprit vessel. Fractional flow reserve (FFR), coronary flow reserve (CFR) and index of microcirculatory resistance (IMR) were measured using a 0.014 coronary temperature and pressure-sensing guidewire. We did not integrate coronary wedge pressure to adjust IMR values. To adjust for the influence of collateral flow, IMR values were corrected using the Yong formula.[19] To induce maximal hyperemia, intravenous adenosine was administered via a femoral vein (140 μg/kg per minute). These parameters were then determined for non-culprit vessels. All 3 major epicardial vessels were measured if the vessels were not difficult for thermo-pressure wire to pass through.

Chronic Phase

Physiologic measurements were repeated at both culprit and non-culprit arteries at 6-month follow-up. In this phase, physiologic measurements were performed on the same vessels and locations as those in the acute phase. ^{13}N-ammonia positron emission tomography (PET) was performed on the day of 6-month follow-up to determine the absolute myocardial blood flow (MBF) using a Biograph mCT Flow scanner (Siemens, Knoxville, TN, USA). A bolus of 370 MBq of ^{13}N-ammonia was injected via a peripheral vein in both rest and stress states. All ^{13}N-ammonia PET images were acquired at rest and in stress states by continuous intravenous infusion of adenosine (140 μg/kg per minute) started at 3 minutes, and were analyzed using Cedars-Sinai Cardiac Suite (Cedars-Sinai Medical Center, Los Angeles, CA, USA) for Syngo.Via (Siemens, Knoxville, TN, USA). Rest and stress MBF values were measured at each vessel region. MBF was expressed in milliliters per minute per gram of perfusable tissue. The resistance values of each vessel were calculated using the coronary pressure data and the MBF values obtained from the ^{13}N-ammonia PET data.[20] Rest stenotic resistance and hyperemic stenotic resistance were calculated by dividing the pressure gradient across a lesion by absolute MBF in the rest and hyperemia, respectively. Rest microvascular resistance and hyperemic microvascular resistance were measured as the ratio of distal coronary pressure to MBF during rest and hyperemia, respectively.

Statistical Analysis

Data are expressed as mean±SD for continuous variables and as n (%) for categorical variables. All physiologic data analyses were conducted on a per-vessel basis. Student t-test was used for comparing physiologic measurements in the acute and chronic phases between the culprit and non-culprit vessels. Their correlations were measured using the Pearson product-moment correlation coefficient, r. A paired-samples t test was performed for the changes in physiologic measurements between the acute and chronic phases. Since each patient provided both the culprit and non-culprit vessels, additional sensitivity analysis by using the paired t test was performed for comparing physiologic measurements between the culprit and non-culprit vessels. Univariate linear regression analyses were performed to assess the relationship between clinical variables and microcirculation improvement. Our study defined the microcirculation improvement as an improvement in IMR at 6 months. Multivariate linear and binary logistic regression analyses were performed to identify predictors independently associated with the microcirculation improvement. Variables associated with microcirculation improvement with a $P<0.1$ were entered into the multivariate analyses based on stepwise elimination. We evaluated the effect of risk factors including diabetes mellitus, hypertension, hypercholesterolemia, and current smoker on IMR in a linear regression model. In particular, interaction between clinical presentation and microcirculation improvement was evaluated in an analysis of covariance. All statistical analyses were performed using SPSS version 16 for Windows (IBM, Chicago, IL, USA). A 2-tailed value of $P<0.05$ was considered significant.

RESULTS
Baseline Characteristics

A total of 115 patients with ACS were included in our analyses. All patients were successfully treated with thrombolysis in myocardial infarction 3 flow established after PCI. None of the patients underwent previous coronary revascularization such as stenting or coronary bypass

Table1. General Characteristics of Study Population

Characteristic	n=115
Age, y	59.7±11.7
Male sex, n (%)	95 (82.6)
Height, cm	166.8±7.7
Weight, kg	68.7±12.0
Risk factors, n (%)	
Diabetes mellitus	41 (35.7)
Hypertension	50 (43.5)
Hypercholesterolemia	35 (30.4)
Current smoker	59 (51.3)
Ejection fraction, %	51.9±8.8
Biomarker	
Serum hemoglobin, g/dL	14.2±1.6
Platelet count, ×10^9/L	23.4±6.4
Serum creatinine, mg/dL	1.0±0.27
Lipid profile, mg/dL	
Total cholesterol	190.4±46.1
Low-density lipoprotein cholesterol	118.1±34.5
High-density lipoprotein cholesterol	42.8±10.8
Triglycerides	159.9±121.9
Cardiac troponin-I, ng/mL	45.4±65.9
Brain natriuretic peptide, pg/mL	150.7±401.8
Clinical diagnosis, n (%)	
ST-segment–elevation myocardial infarction	37 (32.2)
Non–ST-segment–elevation myocardial infarction	50 (43.5)
Unstable angina	28 (24.3)
Culprit-vessel, n (%)	
Left anterior descending artery	59 (51.3)
Left circumflex artery	24 (20.9)
Right coronary artery	32 (27.8)
Number of vessels diseased, n (%)	
1-vessel disease	58 (50.4)
2-vessel disease	46 (40.0)
3-vessel disease	11 (9.6)
ACC/AHA lesion type of culprit vessel, n (%)*	
A	8 (7.0)
B1	27 (23.5)
B2	56 (48.7)
C	24 (20.9)
Stents, n	1.0±0.2
Stent diameter, mm	2.9±0.4
Stent length, mm	24.2±9.8

Data were expressed as means±SD or n (%). ACC/AHA indicates American College of Cardiology/American Heart Association.

*Lesion complexity was classified according to the American College of Cardiology/American Heart Association classification; class A indicates a simple lesion, B1 and B2 a moderately complex lesion, and C a complex lesion.

surgery. The baseline characteristics of the patients are presented in Table 1. The mean age was 57.7±11.7 years, and 95 (82.6%) patients were men. Patients with STEMI represented 32.2% of the study population. All culprit lesions were treated with a biodegradable polymer drug-eluting stent (Orsiro, Biotronik, Berlin, Germany). The mean left ventricular ejection fraction was 51.9±8.8%. Medical therapy included dual anti-platelet agents (100%), beta blockers (94%), angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (87%) and statins (100%) on discharge.

Comparison of Physiologic Measures Between Culprit and Non-Culprit Vessels in the Acute Phase

After PCI for ACS, physiological parameters were successfully obtained in all patients. In these patients, 115 culprit vessels and 219 non-culprit vessels were evaluated. Many (151 out of 219 vessels) of the non-culprit vessels were angiographically inconspicuous. Coronary physiological data are outlined in Table 2. The culprit-vessel group showed lower CFR (2.66±0.78 versus 3.66±1.59, *P*<0.01) and FFR (0.89±0.09 versus 0.92±0.11, *P*<0.01), compared with non-culprit vessel group. Our analyses showed that major coexisting risk factors such as diabetes mellitus and current smoker have an effect on IMR of non-culprit vessel group. The IMR values in the culprit vessels were higher than in non-culprit vessels (27.10±10.88 versus 22.76±17.25, *P*<0.01), which remained significant after adjustment for diabetes mellitus and current smoker (*P*<0.01 for all). These results did not change substantially after additional sensitivity analysis by using the paired t test.

Comparison of Physiologic Measures Between Culprit and Non-Culprit Vessels in the Chronic Phase

The invasive physiologic data at 6-month follow-up were obtained in 105 patients (91.3%). We analyzed 297 vessels of registered patients as culprit (105) and non-culprit (192) vessels based on physiological parameters determined during the chronic phase. ^{13}N-ammonia

Table 2. Comparison of Physiologic Parameters Between the Culprit and Non-Culprit Vessels in the Acute Phase

Study Outcomes	n=115 Patients		P Value
	Culprit Vessel (n=115)	Non-Culprit Vessel (n=219)	
Invasive measurement			
Index of microcirculatory resistance	27.10±10.88	22.76±17.25	<0.01
Coronary flow reserve	2.66±0.78	3.66±1.59	<0.01
Fractional flow reserve	0.89±0.09	0.92±0.11	<0.01

Data were expressed as means±SD.

PET imaging was performed in 92 (85.7%) of 105 patients. Complete ^{13}N-ammonia PET images of 2 patients were not available for analysis because of technical reasons and the patients were excluded.

Six-month follow-up data showed that CFR (3.61±0.78 versus 3.83±1.19, P=0.04) and FFR (0.87±0.10 versus 0.91±0.09, P<0.01) were significantly lower in the culprit-vessel group than the non-culprit-vessel group. However, IMR was not different (18.34±7.64 versus 20.45±15.12, P=0.11) between the 2 groups (Table 3), which remained insignificant after adjustment for risk factors. In PET data analysis, both rest (0.70±0.21 mL/min per g versus 0.78±0.22 mL/min per g, P=0.01) and hyperemic MBF (1.64±0.54 mL/min per g versus 1.84±0.62 mL/min per g, P=0.02) were lower in the culprit-vessel group. Stenotic resistance was higher in the culprit-vessel group, under both resting (3.41±3.55 versus 2.11±3.33, P=0.02) and hyperemic status (6.40±4.97 versus 3.87±5.03, P<0.01), whereas rest microvascular resistance and hyperemic microvascular resistance were not different between the culprit and non-culprit vessels. Sensitivity analysis using the paired t test did not alter these results substantially.

Temporal Changes in Physiologic Data of Culprit and Non-Culprit Vessels

Between the acute and chronic phases, culprit (but not non-culprit) IMR, CFR, and FFR values were

significantly altered (Figure 1). In the culprit-vessel group, IMR declined from 27.10±10.88 in the acute phase to 18.34±7.64 (P<0.01) in the chronic phase. A significant increase in CFR (2.66±0.78 versus 3.61±0.78, P<0.01) and a decrease in FFR (0.89±0.09 versus 0.87±0.10, P<0.01) were also observed in culprit vessels. However, FFR, CFR, and IMR remained unchanged between acute and chronic phases of non-culprit vessels as shown in Table 2. The temporal change of IMR, CFR, and FFR mean values in both groups are detailed in Figure 2.

Predictors of Microcirculation Improvement

There was no significant correlation between any of the clinical variables and physiologic measurements. The univariate and multivariate factors associated with microcirculation improvement are shown in Table 4. In univariate binary logistic regression analysis, serum hemoglobin (odds ratio [OR], 2.12; 95% CI, 1.02–5.33; P=0.04), cardiac troponin-I (OR, 0.65; 95% CI, 0.30–0.97; P<0.01), and stent length (OR, 0.76; 95% CI, 0.35–0.88; P=0.03) were related to microcirculation improvement. In a multivariate regression model, the strongest predictor for an improvement in the microcirculation was the troponin-I level (OR, 0.76; 95% CI, 0.35–0.92; P=0.02). There was no interaction between clinical presentation and microcirculation improvement among those patients enrolled to the study (P for interaction 0.53).

DISCUSSION

There have been studies on the physiological response of coronary vessels because of ischemic injury in ACS. However, it is unclear whether the microvascular damage after ischemic events occurs locally in the involved vessel or throughout the myocardium. A recent study reported frequent microvascular dysfunction in the non-culprit artery of patients with STEMI.[21] In contrast, other studies have also reported that impaired microvascular function following ischemia does not affect other vascular regions.[7,9] There is a lack of data on extent and duration of microvascular dysfunction in patients with ACS. In the present study, we compared culprit and non-culprit vessels based on physiologic data obtained during 6-month follow-up. The key findings suggest differences in baseline IMR between the culprit and non-culprit vessels, whereas the 6-month IMR and microvascular resistance in both resting and hyperemic states did not differ between the 2 groups. In addition, the microcirculation of culprit vessels was impaired in the acute

Table 3. Comparison of Physiologic Parameters Between the Culprit and Non-Culprit Vessels in the Chronic Phase

Study Outcomes	105 Patients		P Value
	Culprit Vessel (n=105)	Non-Culprit Vessel (n=192)	
Invasive measurement			
Index of microcirculatory resistance	18.34±7.64	20.45±15.12	0.11
Coronary flow reserve	3.61±0.78	3.83±1.19	0.04
Fractional flow reserve	0.87±0.10	0.91±0.09	<0.01
Positron emission tomography–derived measurement			
Rest MBF, mL/min per g	0.70±0.21	0.78±0.22	0.01
Stress MBF, mL/min per g	1.64±0.54	1.84±0.62	0.02
Stenosis resistance, mm Hg·min·g/mL			
Rest	3.41±3.55	2.11±3.33	0.02
Hyperemic	6.40±4.97	3.87±5.03	<0.01
Microvascular resistance, mm Hg·min·g/mL			
Rest	99.06±39.58	88.66±32.82	0.10
Hyperemic	42.28±20.35	37.81±14.51	0.12

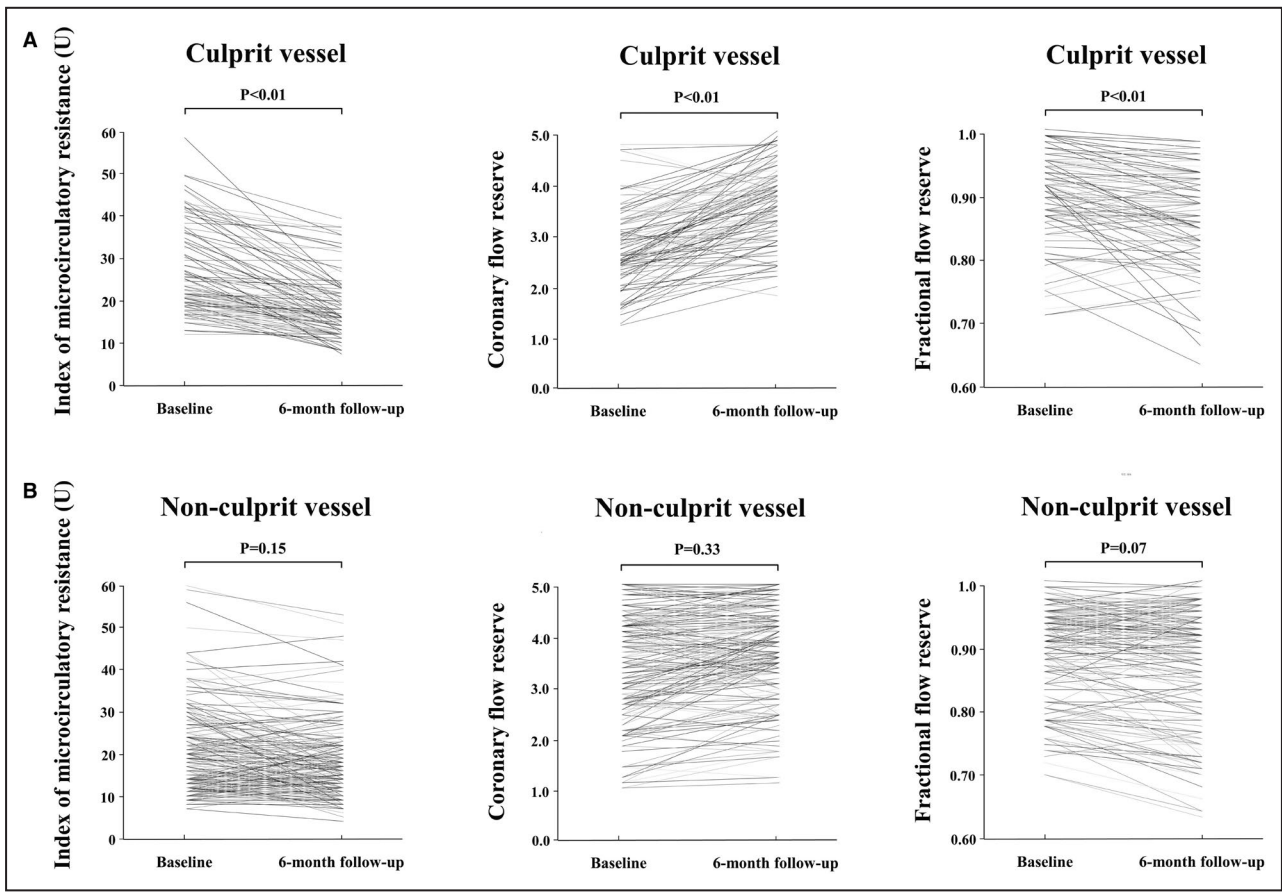Data were expressed as means±SD. MBF indicates myocardial blood flow.

Figure 1.   Temporal changes of index of microcirculatory resistance, coronary flow reserve, and fractional flow reserve from baseline to 6 months according to whether or not there were culprit vessels.
Plot illustrates the individual physiologic data from baseline to 6 months in the culprit (**A**) and non-culprit vessels groups (**B**).

phase but recovered in the chronic phase after PCI. However, microcirculation remained constant under acute and chronic phases in the non-culprit vessels.

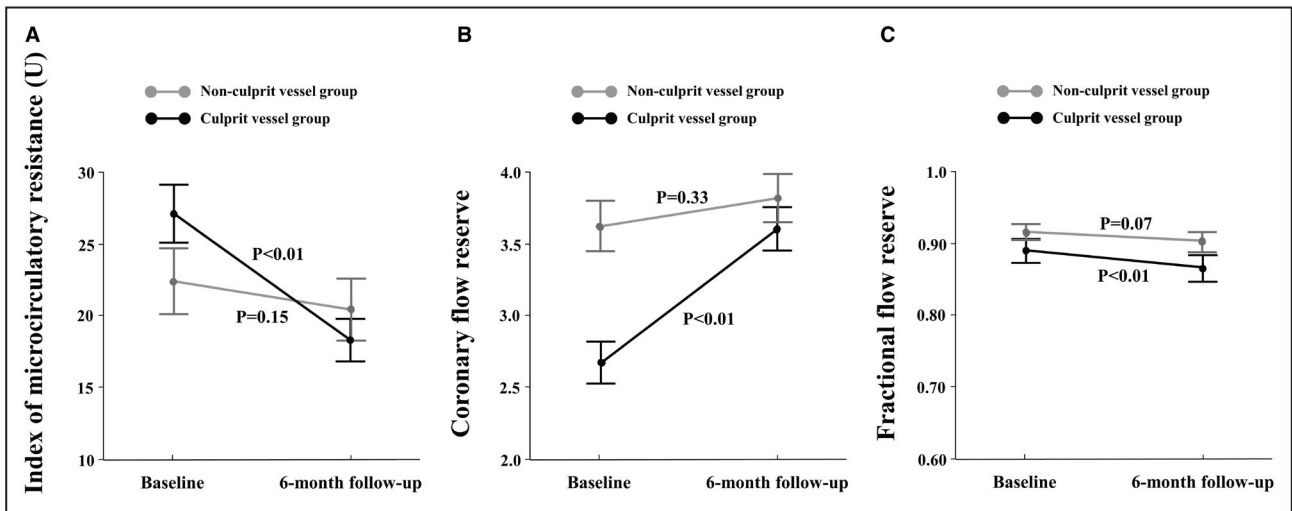The improvement of microcirculation after ischemic injury in ACS patients was highly associated with troponin-I level.

Figure 2.   Temporal changes in physiologic measure levels.
Shown are mean (±SE) measure levels of index of microcirculatory resistance (**A**), are mean (±SE) measure levels of coronary flow reserve (**B**), are mean (±SE) measure levels of fractional flow reserve (**C**) from baseline to 6 months in the 2 study groups.

Table 4.   Multivariate Regression Model to Microcirculation Improvement

Variables	Univariate Logistic Regression			Multivariate Logistic Regression		
	OR	95% CI	P Value	OR	95% CI	P Value
Age	0.99	0.94–1.05	0.83			
Sex	0.46	0.08–2.52	0.37			
Risk factors						
Diabetes mellitus	0.90	0.29–2.75	0.40			
Hypertension	0.83	0.39–3.35	0.65			
Hypercholesterolemia	0.69	0.21–2.26	0.54			
Current smoker	0.54	0.29–2.92	0.21			
Ejection fraction	0.81	0.68–1.94	0.18			
Biomarker						
Serum hemoglobin	2.12	1.02–5.33	0.04	1.78	1.02–3.19	0.09
Platelet count	0.94	0.76–2.04	0.89			
Serum creatinine	0.83	0.76–1.11	0.42			
Cardiac troponin-I	0.65	0.30–0.97	<0.01	0.76	0.35–0.92	0.02
Brain natriuretic peptide	0.36	0.96–8.58	0.67			
Clinical diagnosis	2.56	0.59–6.62	0.18			
Location of culprit-vessel	1.24	0.53–2.34	0.75			
ACC/AHA lesion type	4.20	0.32–7.29	0.59			
Stents number	0.46	0.35–5.37	0.48			
Stent diameter	0.57	0.44–3.25	0.65			
Stent length	0.76	0.35–0.88	0.03	0.68	0.45–1.17	0.32

ACC/AHA indicates American College of Cardiology/American Heart Association; and OR, odds ratio.

Different Response Between Culprit and Non-Culprit Vessels After Ischemic Injury in ACS

In the acute setting of ACS, the culprit IMR increased and the CFR and FFR declined, whereas non-culprit IMR, CFR, and FFR were unaffected in acute setting relative to chronic setting.[22] These findings suggest that microvascular dysfunction of culprit vessels may be a localized phenomenon attributed to differences in microvascular resistance to ischemic injury between culprit and non-culprit vessel territories in the acute phase. To support this mechanism, data of the microvascular resistance in the acute phase may be helpful. However, in our study, we could not measure the microvascular resistance because the PET test was not performed in the acute phase. The possibility of differences in microvascular resistance to ischemic injury may be considered based on differences in IMR, which is a highly reproducible tool and the indirect indicator of microvascular resistance,[22] between the culprit and non-culprit groups during the acute phase. CFR, although it has a variability that limits its reproducibility,[22] also differed between culprit and non-culprit vessels in the acute phase. Previous studies have suggested that mechanisms contributing to increased microvascular resistance are likely to be multifactorial in the culprit vessel. Atherothrombotic embolization from a culprit lesion is one of the leading mechanisms contributing to microvascular impairment after PCI.[23] Embolized particles during PCI can trigger mechanical obstruction because of their mass effect and also activate pathways that result in situ coagulation and inflammatory response in the downstream microcirculation.[24] Leukocyte and platelet plugging and red-cell aggregation also contribute to intraluminal microvascular obstruction.[25,26]

In addition, localization of microvascular dysfunction may be explained by the localized microvascular degeneration in the target vessel during the early intervention of the ischemic vessel. In our study, the door-to-balloon time was <60 minutes when the STEMI patients were analyzed separately. Considering the longer door-to-balloon time in studies where microvascular dysfunction has also been observed in the surrounding area,[6] it is important to perform coronary revascularization of ischemic vessels promptly, which is consistent with recommendations for early treatment of culprit vessels.

Possible Recovery of Microvascular Dysfunction After Successful PCI in ACS

Many studies have reported that microvascular dysfunction is related to prognosis.[1–3] Therefore, the degree of recovery of microvascular function may be an

important prognostic factor. Based on our findings, the observed microvascular dysfunction was limited to the culprit vessel territory in the acute phase, which was relatively recovered in the chronic phase and there was no out-of-culprit territory involvement. Consistent with the 6-month IMR data, no differences were found in the microvascular resistance at rest and hyperemia based on ^{13}N-ammonia PET data. These findings suggest that microvascular resistance in the culprit vessel was improved and microvascular resistance of non-culprit vessels was stable at 6 months post-PCI.

It may have 2 clinical implications. One is that the first priority in ACS should be a culprit vessel treatment for recovery of microvascular dysfunction, which may lead to an increase in MBF. Microvascular resistance may affect epicardial blood flow. The pressure gradient at rest in patients with microvascular dysfunction is not different from that of patients without microvascular dysfunction at rest if the extent of epicardial stenosis is identical.[27] However, in patients with microvascular dysfunction, the flow cannot increase sufficiently during maximal hyperemia, causing a reduced pressure gradient across the stenotic lesion.[28] As shown in our study, there was no difference in IMR and FFR between acute and chronic phases in non-culprit vessels, indicating that there was little change in the epicardial pressure gradient because of no change in microvascular resistance. After all, MBF might not have differed between acute and chronic phases. However, in the culprit vessels, IMR and FFR were significantly decreased in the chronic phase compared with the acute phase. The results suggested that the restoration of the microvascular function may have influenced the increase of epicardial pressure gradient that might led to an increase in MBF, and microvascular damage determined the FFR value in the acute phase, as shown in other studies.[29,30] The other is that microvascular parameters of single vessel of acute phase may be inappropriate as prognostic indicators, since there are regional differences in microvascular function between culprit and non-culprit vessels.

There have been studies of risk factors for microvascular abnormalities, but there are few reports of microcirculation improvement.[31,32] Our multivariate model showed that the most clinically useful predictor for a microcirculatory improvement was troponin-I level. We subsequently evaluated the association between clinical presentations and microcirculation improvement and found that there was no interaction between clinical presentation and the recovery of microvascular dysfunction. This observation may mean that the microvascular function is improved if early intervention led to less myocardial necrosis during the ischemic event. Full control of risk factors and medical therapy may improve microvascular dysfunction. Clinical studies suggest that medications, such as angiotensin-converting enzyme inhibitors and statin, improve the microcirculation.[33,34] The detailed information and compliance for the medication used during the study period were not recorded because this study was not designed to find predictors on microcirculation improvement. Thus, we cannot exclude the contribution of other drug therapy to improving microvascular function since we adjusted only antiplatelet agents and statin in this study. Thus, further studies are required to directly examine factors on the microcirculation improvement.

Besides, culprit FFR was lower than non-culprit FFR in both the acute and chronic phases. The corresponding PET-derived data also revealed differences in the stenotic resistance at rest and hyperemic status. These differences in FFR and stenotic resistance at rest and hyperemia indicate differences in severity of epicardial lesions between culprit and non-culprit vessels in the present study. Furthermore, these results may suggest that the diseases of the epicardial vessel and the microvessels do not coincide with each other, based on the eventual decrease in differences of microvascular dysfunction between the initial culprit and non-culprit vessels.

Study Limitations

There are several limitations of this study that should be addressed. First, the relatively small sample size of the study population is a concern although the number of registered patients in this study was higher than in previous studies. Second, there was the high variability of IMR measurements, which may be attributable to the heterogeneous clinical diagnosis of population or coexisting risk factors. For adjustment of the high variability of IMR, statistical analyses were used for controlling risk factors and assessing the interaction of clinical presentation. IMR values corrected by using the Yong formula were used to minimize the influence of collateral flow. Third, the study had a single-center design and was not powered to detect clinical outcomes, which limited further interpretation of efficacy.

CONCLUSIONS

The observed microvascular dysfunction in ACS is limited to the culprit vessel territory in the acute phase, which is relatively recovered in the chronic phase and there is no out-of-culprit territory involvement. Microvascular injury after ischemic insult in culprit vessels may occur locally in the myocardium.

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