Effect of Elective Percutaneous Coronary Intervention on Hyperemic Absolute Coronary Blood Flow Volume and Microvascular Resistance

Yoshihisa Kanaji, MD; Tadashi Murai, MD; Taishi Yonetsu, MD; Eisuke Usui, MD; Makoto Araki, MD; Junji Matsuda, MD; Masahiro Hoshino, MD; Masao Yamaguchi, MD; Takayuki Niida, MD; Masahiro Hada, MD; Sadamitsu Ichijyo, MD; Rikuta Hamaya, MD; Yoshinori Kanno, MD; Mitsuaki Isobe, MD, PhD; Tsunekazu Kakuta, MD, PhD

Background—The hemodynamics involved in the relationship between absolute coronary blood flow (ABF) volume and myocardial resistance (MR) are complex, and the effect of percutaneous coronary intervention (PCI) on their changes remains unclear. The aim of this study was to investigate the differences in hyperemic ABF and MR before and after elective PCI using a thermodilution method.

Methods and Results—We investigated 28 vessels (right coronary artery, 9; left anterior descending coronary artery, 18; left circumflex coronary artery, 1) from 28 patients with stable angina pectoris undergoing elective PCI. ABF was measured pre- and post-PCI using a pressure–temperature sensor-equipped wire, based on a thermodilution method with a continuous saline infusion of 20 mL/min through a proximally located microcatheter with an end-hole in the target vessel. MR equals distal coronary perfusion pressure divided by ABF at maximal hyperemia. Conventional fractional flow reserve was also measured pre- and post-PCI. Fractional flow reserve increased significantly after PCI (from 0.70 [0.65–0.75] to 0.88 [0.85–0.95]) in all examined territories. ABF also increased significantly (from 137.8 mL/min [86.3–180.8 mL/min] to 173.3 mL/min [137.9–234.3 mL/min] ; increase: 52.8 mL/min [9.7–80.8 mL/min]) while MR decreased in 11 vessels and increased in 17. No significant relationship was detected between these increases in fractional flow reserve and ABF. Both pre- and post-PCI MR distributed in a wide range, and there was a significant relationship between pre-PCI MR and the increase in ABF (r=0.44; P=0.02) although no significant change in MR was observed between pre- and post-PCI (P=0.37).

Conclusions—Direct measurement of ABF and MR using thermodilution method offers a feasible approach that could shed a light on previously unclear aspects of coronary hemodynamics. **(*Circ Cardiovasc Interv*. 2017;10:e005073. DOI: 10.1161/CIRCINTERVENTIONS.117.005073.)**

Key Words: absolute myocardial flow ■ angina, stable ■ coronary artery disease ■ hemodynamics ■ microvascular resistance ■ myocardium ■ percutaneous coronary intervention

The purpose of percutaneous coronary intervention (PCI) is to increase coronary flow by targeting epicardial coronary artery stenosis. Fractional flow reserve (FFR)–guided PCI results in better outcomes compared with angiographic guidance,[1,2] suggesting that FFR-guided PCI may benefit from the hyperemic increase in coronary flow. The most important factor in coronary heart disease is the existence and extent of ischemia.[3] PCI for epicardial lesions that brings no benefit in terms of coronary flow increase is of questionable merit or may even harm patients by exposing them to procedure-related and stent-related risk. The recent recognition of the significant association between myocardial blood flow and an adverse clinical outcome mandates a comprehensive approach to ischemic heart disease, incorporating the evaluation of coronary flow impairment and microvascular resistance (MR), as well as FFR.[4–8] Given that PCI is optimally performed without significant complications, post-PCI hyperemic coronary flow may increase with less effect from epicardial stenosis, provided that MR is minimized and constant during hyperemia before and after PCI.[9,10] However, few studies have documented changes in volumetric coronary blood flow and MR after elective PCI while quantitative measurement of absolute coronary blood flow (ABF) at the time

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From the Department of Cardiovascular Medicine, Tsuchiura Kyodo General Hospital, Japan (Y.K., T.M., T.Y., E.U., M.A., J.M., M.H., M.Y., T.N., M.H., S.I., R.H., Y.K., T.K.) and Department of Cardiovascular Medicine, Tokyo Medical and Dental University, Japan (M.I.).

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Correspondence to Tsunekazu Kakuta, MD, Department of Cardiovascular Medicine, Tsuchiura Kyodo General Hospital, 4-1-1, Otsuno, Tsuchiura, Ibaraki 300-0028, Japan. E-mail kaz@joy.email.ne.jp

WHAT IS KNOWN

- The hemodynamics involved in the relationship between absolute coronary blood flow volume and absolute hyperemic myocardial resistance are complex and may be influenced by percutaneous coronary intervention.
- Thermodilution method using a small specially designed infusion catheter in coronary arteries has been reported to be feasible for estimation of absolute coronary blood flow volume and absolute hyperemic myocardial resistance.

WHAT THE STUDY ADDS

- Thermodilution method by using an end-hole catheter with a pressure–temperature sensor-tipped wire allowed us to serially estimate the hyperemic blood flow volume and myocardial resistance before and after elective percutaneous coronary intervention.
- Hyperemic microvascular function may be involved in the determination of post–percutaneous coronary intervention coronary flow.
- Further studies using this method may shed a light on complex coronary hemodynamics in the context of coronary interventions at an individual lesion level.

of PCI is currently not possible. Furthermore, any increase in coronary flow after PCI may not only be determined solely by modification of the epicardial lesion but also by PCI-associated changes in MR, if any.[7,8] Whether PCI influences hyperemic MR is currently controversial.[11–14] Limitations in the methods available to measure or investigate the MR and coronary flow before and after PCI have been an obstacle to the evaluation of coronary hemodynamic changes caused by PCI.

A robust and operator-independent method to quantify volumetric coronary blood flow, based on the principle of thermodilution with continuous infusion of saline, has been reported and validated in animals and in humans.[15–17] Although this method may provide a technique for measuring ABF and absolute MR, it can have no clinical significance by itself as long as the myocardial distribution territory is unknown or undefined. It is also difficult to compare ABF or MR among different individuals. However, when this technique is used serially in the same coronary territory before and after PCI, we can evaluate the impact of PCI on ABF and the change in MR. Therefore, we hypothesized that the change in hyperemic ABF after PCI would be influenced by the change in MR and might decrease in individual cases after PCI. To test this hypothesis, we used the thermodilution-based technique to evaluate the serial changes in ABF and MR at hyperemia, before and after elective PCI, in patients with stable angina pectoris.

Methods

Study Population

This prospective study was conducted at Tsuchiura Kyodo General Hospital between July 2016 and September 2016. Thirty nonconsecutive patients with stable angina pectoris were prospectively enrolled. These patients were selectively and carefully chosen from our regular clinical population based on the following inclusion criteria: age at least 20 years; scheduled to undergo PCI for stable coronary disease, involving a single target lesion located in a proximal or mid coronary segment, with a >50% diameter reduction by visual assessment and a reference diameter >3 mm; and symptomatic ischemia or objective ischemia according to stress tests, including exercise tests, stress scintigraphy, cardiac magnetic resonance, and FFR measurements. Regarding the specific lesion location requirement for the present study, there had to be at least a 3-cm long coronary segment without major side branches (>2 mm in diameter) proximal to the index stenosis. Patients with pre-PCI cardiac troponin I elevation (institutional upper reference limit: >0.20 ng/mL) were excluded. Other exclusion criteria were significant left main disease, chronic total occlusion, congestive heart failure, significant valvular disease, previous coronary artery bypass graft, prior myocardial infarction in the target vessel territory, significant arrhythmias, or renal insufficiency with baseline serum creatinine level >1.5 mg/dL (132.6 μmol/L). In addition, patients with extremely tortuous vessels or heavy calcification were excluded because of anticipated difficulty in advancing the pressure wire (St. Jude Medical, St. Paul, MN) and the microcatheter for saline infusion as part of the thermodilution method. In this study, the distance required to guarantee the mixture of coronary blood and infused saline was at least 3 to 4 cm,[15] which further limited the eligible lesion anatomy. After PCI, we also excluded patients with periprocedural myocardial infarction as defined by the Third Universal Definition of Myocardial Infarction,[18] based on blood samples taken an average of 20 to 24 hours after PCI completion, because such events reportedly affect post-PCI MR and coronary flow.[19] Patients with minor cardiac troponin I elevation, without other manifestations required by the definition of periprocedural myocardial infarction, were included in the final analysis. The study protocol was approved by the institutional review board, and all patients provided written informed consent before catheterization.

Cardiac Catheterization

Each patient initially underwent standard selective coronary angiography for the assessment of coronary anatomy via the radial or the femoral artery, using a 6F or 7F system. Coronary angiograms were analyzed quantitatively using a CMS-MEDIS system (Medis Medical Imaging Systems, Leiden, the Netherlands) to measure lesion length, minimum lumen diameter, reference lumen diameter, and percent diameter stenosis at the target lesion. All patients received a bolus injection of heparin (5000 IU) before the procedure, and an additional bolus injection of 2000 IU was administered every hour as needed to maintain an activated clotting time >250 seconds. An intracoronary bolus injection of nitroglycerin (0.2 mg) was administered at the start of the procedure and repeated at least every 30 minutes. The minimum lumen diameter, reference diameter, and lesion length were measured in diastolic frames from orthogonal projections. FFR measurements and hyperemic ABF measurements were performed before and after PCI in the target vessels.

FFR Measurements

For FFR measurements, a RadiAnalyzer Xpress console with PressureWire Certus (St. Jude Medical, St. Paul, MN) was used to measure the distal coronary pressure. FFR was measured before and after PCI in the target vessels deemed to be culprit by angiography, with >50% diameter stenosis. After nitroglycerin administration, a pressure and temperature monitoring guidewire was advanced distal to the stenosis. Hyperemia was induced by intravenous infusion of adenosine at the rate of 140 $\mu g \cdot kg^{-1} \cdot min^{-1}$ via a central venous catheter. FFR was calculated by dividing the mean distal pressure by the mean aortic pressure during hyperemia.

Measurement of ABF and MR

After FFR measurement, hyperemic ABF was measured. A small infusion catheter with a distal end-hole (3.9F, KIWAMI, TERUMO,

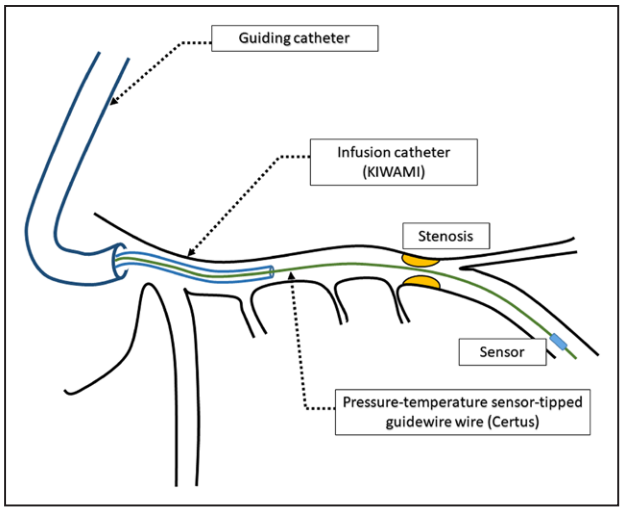

Figure 1. Schematic representation of setup and measurement. The tip of the infusion catheter was placed in the proximal portion of the coronary artery of interest, distal to the major branch. The pressure–temperature sensor-tipped wire was advanced and placed in the distal segment of the interrogated coronary artery, at a distance of at least 4 to 5 cm from the tip of the infusion catheter.

Japan) was advanced over the pressure–temperature sensor-tipped guidewire through a Y connector. This catheter was suitable for the present thermodilution method because (1) it has a relatively large saline infusion end-hole to guarantee infused saline volume and its complete mixing with the blood, and avoids jet infusion directed at the coronary wall; (2) positioning of the infusion catheter and instrumentation is easy, and the tip of the catheter is soft and nontraumatic; and (3) the outer diameter of the catheter is ≈1.3 mm, corresponding to an area stenosis of <19% in a coronary artery segment of 3 mm diameter, and <14% in a segment of 3.5 mm diameter. Therefore, it is not likely that its presence will significantly reduce ABF. The tip of the infusion catheter was placed in the proximal portion of the coronary artery of interest and distal to the major branch. The pressure–temperature sensor-tipped wire was advanced and placed in the distal segment of the interrogated coronary artery at a distance of at least 4 to 5 cm from the tip of the infusion catheter. The infusion catheter was then connected to an infusion pump via a second Y connector, enabling continuous saline infusion at a rate of 20 mL/min (Figure 1). This infusion rate was chosen on the basis of previous studies[15,16] reported by the inventors of this thermodilution method. The pressure–temperature sensor-tipped wire was then connected to the console (St. Jude Medical), and distal coronary pressure and temperature were simultaneously and continuously monitored and recorded. First, temperature zeroing was performed, and baseline coronary flow was measured by constant saline infusion. Distal temperature (T) at the sensor tip was documented, after which the wire was pulled back into the infusion catheter so that the temperature of the infused saline (Ti) could be measured. Complete mixing of blood and saline was confirmed by a steady temperature during the first 1- to 2-cm pull-back and forward maneuver (Figures 2–4; Movies in the Data Supplement). Subtle movement under fluoroscopic guidance close to and inside of the tip of the infusion catheter was required to find the location with the lowest temperature. Similarly, temperature zeroing was performed again after the induction of hyperemia, and a steady state was usually obtained within 30 to 40 seconds after starting constant saline infusion. Distal temperature (T) at the sensor tip was documented during maximal hyperemia under saline infusion on top of adenosine administration, and then the wire was pulled back into the infusion catheter so that the temperature of the infused saline (Ti) could be measured. Absolute blood flow (Q) and MR in maximum hyperemia were calculated as follows:

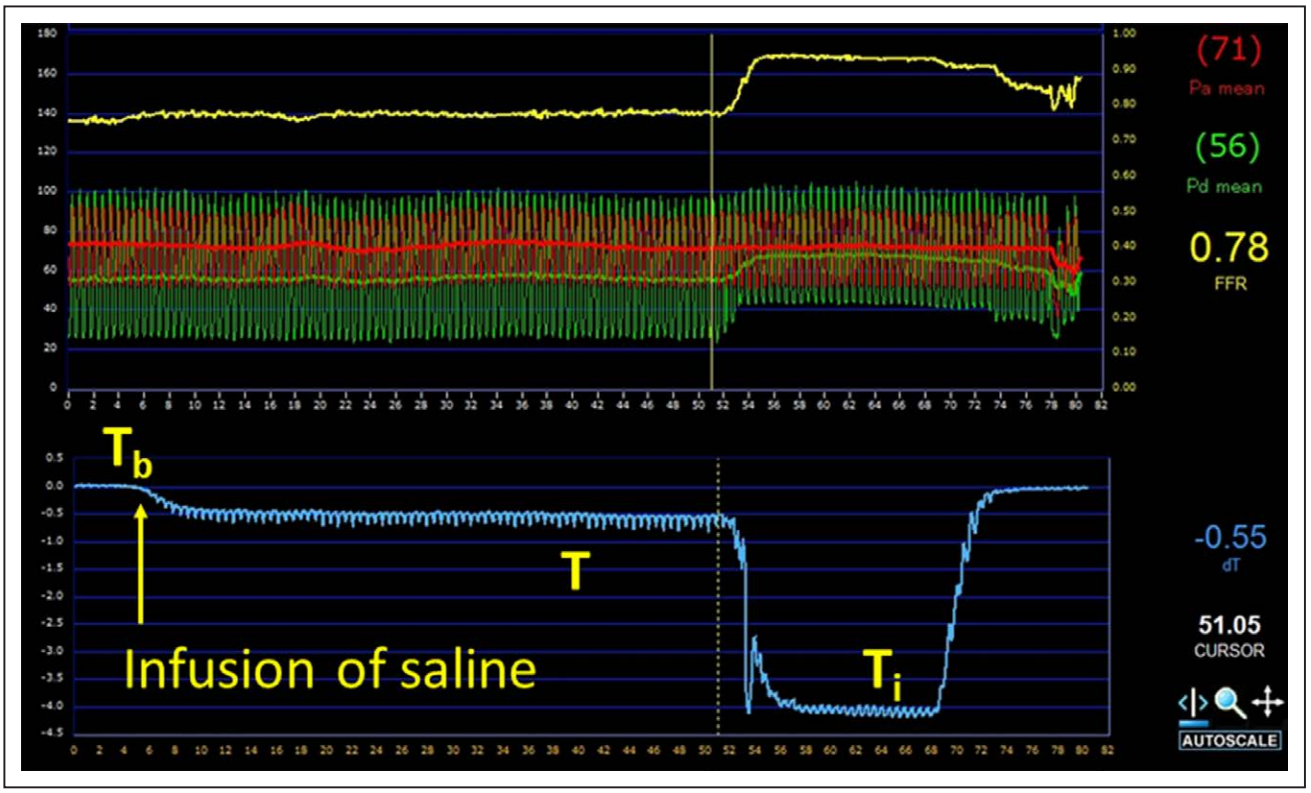

Figure 2. Example of a complete recording of intracoronary temperature and pressure measurement. Blood temperature at steady-state hyperemia is set to 0 at the beginning of the measurement (Tb). Thereafter, infusion of saline at room temperature is started (**arrow**), and temperature T in the distal coronary artery is recorded. The sensor wire is then pulled back into the infusion catheter to measure the temperature of the infused saline (Ti).

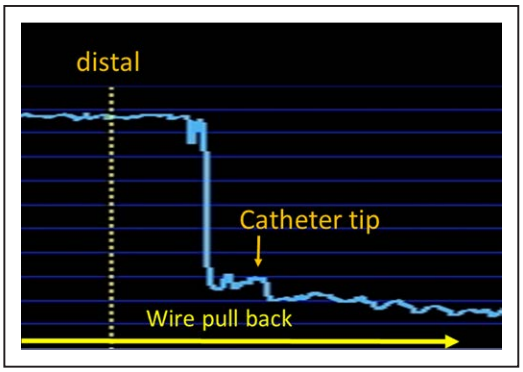

Figure 3. Magnified captured image of temperature measurement curve during the pull-back of wire. The temperature is not changed at the beginning of the pull-back, and the temperature curve seems a plateau while the sensor was being pulled back in the vessels where mixture was sufficient.

ABF (Q)=1.08×Ti/T×Qi (mL/min)[16] (Qi=infusion rate of saline, 20 mL/h)

Absolute MR=distal coronary pressure/Q (dyne·s·cm^{-5})

ABF in the present study was calculated by the simplified equation on the assumptions as follows; constant of 1.08 relates to the difference between the specific heats and densities of blood and saline, and when saline is infused in blood, this constant equals 1.08.[15] Furthermore, blood temperature is supposed to be ≈37°C, and the part of the equation can be neglected in practice when infused saline is 20 mL/min. FFR, ABF, and MR were measured pre- and post-PCI. Post-PCI FFR was measured ≈10 minutes after the completion of PCI. Another 5 minutes later, hyperemic post-PCI ABF was measured according to exactly the same protocol as pre-PCI. The exact position of the pressure–temperature sensor-tipped guidewire during the pre-PCI measurement was documented on angiograms to make sure that the wire was located at the same site as in the pre-PCI measurement.

PCI Procedure

All patients underwent coronary drug-eluting stent implantation with predilatation as indicated by the protocol. The stent type was selected at the operator's discretion, and the strategy was determined by the interventionist. To avoid aggressive stent expansion, online quantitative coronary angiography and intravascular ultrasound were used to help determine the proper stent size. Successful PCI was defined as <20% residual stenosis with Thrombolysis in Myocardial Infarction Trial grade 3 flow. After the angiographic end point was achieved, an intravascular ultrasound examination was performed to confirm optimal stent deployment, and additional PCI was performed in cases of suboptimal results.

Statistical Analysis

Statistical analysis was performed using SPSS version 23.0 (SPSS, Inc, Chicago, IL). Patient demographics are presented as n (%) where appropriate. Categorical data are expressed as absolute frequencies and percentages and were compared using the χ^2 or Fisher exact tests, as appropriate. Continuous variables are expressed as mean±SD for normally distributed variables or as median (25th–75th percentile: interquartile range) for non-normally distributed variables and compared using the Student *t* test and the Mann–Whitney *U* test, respectively. Correlations between 2 parameters were evaluated using linear regression analysis. Comparisons between multiple groups were performed by ANOVA test followed by post hoc tests for pairwise comparison of variables according to Bonferroni correction. $P<0.05$ indicated statistical significance.

Results

Patient Characteristics

In 2 patients, pressure tracing and temperature measurements were not optimal, and these patients were excluded from the

Figure 4. Experimental equipment for simulating the mixture of room temperature saline (red colored, 20 mL/min, 25°C) infused from the end-hole catheter and pulsatile flow of body temperature saline (pulsation flow auxiliary circulation system, 150 mL/min, 37°C) within a model composed of silicon tube, infusion pump, and dialysis machine. The sensor of a pressure–temperature sensor-tipped wire was placed 5 to 6 cm distal to the end-hole catheter (**bottom right**).

analysis. Seven patients showed minor troponin elevation (mean, 2.31±0.35 ng/mL), but because none of them presented ECG abnormalities, chest pain, or echocardiographic abnormalities, they were included in the analysis. There was no significant relationship between the post-PCI cardiac troponin I increase and the change in MR (P=0.14). One patient presented transient atrioventricular block but completed ABF measurement. Therefore, we evaluated data from 28 patients for the final analysis. The patients' baseline characteristics are summarized in Table 1. Angiographic and physiological data are shown in Table 2. Pre-PCI and post-PCI FFR values were 0.70 (0.65–0.75) and 0.88 (0.85–0.95), respectively. Stenting was performed successfully in all these patients. No significant complications were observed during the physiological examinations, and ABF and MR were determined successfully.

ABF Measurements and MR Before and After PCI

The mean distance between the tip of the infusion catheter and the sensor tip was 5.3 cm (4.5–6.1 cm). No significant relationship between this distance and temperature drop caused by saline infusion was observed (P=0.32). At baseline of the present protocol, saline infusion induced submaximal hyperemia (Table2; Figure 5), and adenosine infusion significantly increased coronary flow above the hemodynamic status by saline infusion only. ABF at maximum hyperemia was measured by saline infusion (20 mL/min) through a distal end-hole microcatheter on top of adenosine infusion (Figure 5). Saline infusion further induced a numerically minor increase of pressure gradient over adenosine induced hyperemia. Data on ABF and MR before and after PCI are presented in Table 3. In the total cohort, ABF increased significantly (P<0.01; Figure 6) although 6 territories showed a decrease in ABF despite successful PCI and FFR improvement. The median increase in ABF was 52.8 mL/min (interquartile range, 9.7–80.8 mL/min). Figure 7 shows the MR before and after PCI. Seventeen territories showed an increase in MR and 11 showed a decrease. The difference between the MR values before and after PCI was not significant (P=0.37). Table 4 shows the baseline clinical, angiographic, and physiological characteristics according to the increase or decrease in ABF after PCI. There was no significant difference between the 2 groups in baseline clinical characteristics or troponin elevation, but significant differences were observed in pre-PCI ABF, pre-PCI MR, and post-PCI distal coronary pressure. Change in ABF by PCI (post-PCI ABF–pre-PCI ABF) was correlated with the change in MR (Figure 8). There was no significant relationship between the change in FFR and an increase in ABF (r=0.27; P=0.16). There was no significant difference in pre-PCI FFR between territories that showed increased ABF after PCI and territories that showed decreased ABF after PCI (P=0.82).

Table 1. Baseline Characteristics of Patients

Age, y	67.6±11.8
Male, n (%)	25 (89.3)
Mean body mass index, kg/m^2	24.6±3.3
Hypertension, n (%)	22 (78.6)
Hyperlipidemia, n (%)	20 (71.4)
Diabetes mellitus, n (%)	7 (25.0)
History of smoking, n (%)	20 (71.4)
Lesion location RCA/LAD/LCx, n (%)	9 (32.1)/18 (64.3)/1 (3.6)
Left ventricular ejection fraction (%)	63.0 (56.8–68.0)
Laboratory date	
WBC/μL	6565 (5793–7489)
LDL-chol, mg/dL	98 (75–139)
HDL-chol, mg/dL	46 (40–49)
TG, mg/dL	149 (94–239)
Creatinine, mg/dL	0.88 (0.72–1.09)
eGFR, mL·min^{-1}·1.73 m^{-2}	70.0 (51.5–81.6)
HbA1c, %	5.9 (5.6–6.2)
NT-proBNP, pg/mL	101 (63.5–222)
Medication, n (%)	
ACE-I or ARB	17 (60.7)
β-Blocker	12 (42.9)
Calcium antagonist	16 (57.1)
Statin	26 (92.9)

ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL-chol, high density lipoprotein cholesterol; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; LDL-chol, low density lipoprotein cholesterol; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RCA, right coronary artery; TG, triglyceride; and WBC, white blood cells.

Discussion

The main findings of the present study were as follows: (1) ABF and MR were measured by thermodilution method with the use of an end-hole catheter and pressure–temperature sensor-tipped wire without significant complication in a series of 28 patients at pre- and post-PCI; (2) an increase in ABF after PCI was observed in 22 territories (78.6%), whereas 6 (21.4%) territories presented a decrease; and (3) no significant difference was detected between pre- and post-PCI MR in a total cohort, whereas MR of individual territories distributed in a wide range both pre- and post-PCI and not constant.

Sufficient mixture of saline and blood is essential for the present methodology for absolute flow measurement. Before PCI, conceivably, infused saline and blood flow are likely to be sufficiently mixed because of convergence, friction, and turbulence caused by coronary significant stenosis of the lesion. In postprocedural measurement where a significant stenosis was canceled, we confirmed that the temperature was not changed at the beginning of pull-back of the wire, which indicated that the original sensor position was sufficiently far distal to the mixing point, and the temperature curve appeared a plateau until the mixing point at the proximal portion (Figure 3). The simulation study of ABF measurement in the present study was performed to ensure the mixture of the infused indicator and coronary flow as shown by the Figure and Movies in the Data Supplement. In the simulated experiment with the room temperature saline (red colored, 20 mL/min, 25°C) infused from an end-hole catheter used in the present study and pulsatile flow of body temperature saline

Table 2. Angiographic and Physiological Data

			Pre-PCI		Post-PCI	
QCA analyses						
MLD, mm			0.89 (0.71–1.17)		2.98 (2.89–3.15)	
RD, mm			3.09 (2.75–3.39)		3.29 (3.17–3.48)	
%stenosis, %			70.4 (60.4–77.4)		9.4 (8.3–12.2)	
Lesion length, mm			13.4 (8.2–15.5)			
Physiological indices						
		Baseline	Infusion of saline	Infusion of adenosine	Infusion of adenosine+saline	*P* Value
Pre-PCI	HR, bpm	68±8	65±7	74±7*	74±8*	<0.01
	Pa, mm Hg	94±16	96±14	84±15*	87±13*	<0.01
	Pd, mm Hg	77±19	74±18	57±11*	54±11*	<0.01
	Pd/Pa	0.86 (0.80–0.91)	0.83 (0.72–0.86)	0.69 (0.66–0.75)*	0.64 (0.57–0.70)*	<0.01
Post-PCI	HR, bpm	68±9	67±10	76±11*	75±9*	<0.01
	Pa, mm Hg	101±12	103±12	87±14*	90±13*	<0.01
	Pd, mm Hg	96±13	96±15	77±12*	77±15*	<0.01
	Pd/Pa	0.96 (0.92–0.98)	0.95 (0.90–0.98)	0.87 (0.85–0.94)*	0.87 (0.83–0.90)*	<0.01

HR indicates heart rate; MLD, minimal lumen diameter; Pa, aortic pressure; PCI, percutaneous coronary intervention; Pd, coronary distal pressure; QCA, quantitative coronary angiography; and RD, reference diameter.

*P<0.01 vs infusion of saline.

(pulsation flow auxiliary circulation system, 150 mL/min, 37°C) inside a silicon tube with a diameter of 3 mm, acceptable mixture was confirmed showing a small temperature variation within 0.08°C (Movies in the Data Supplement).

Our study demonstrated a significant relationship between a change in MR and an increase in ABF after PCI (Figure 8). Notably, at the cohort level, no significant difference was observed between MR values before and after PCI (Figure

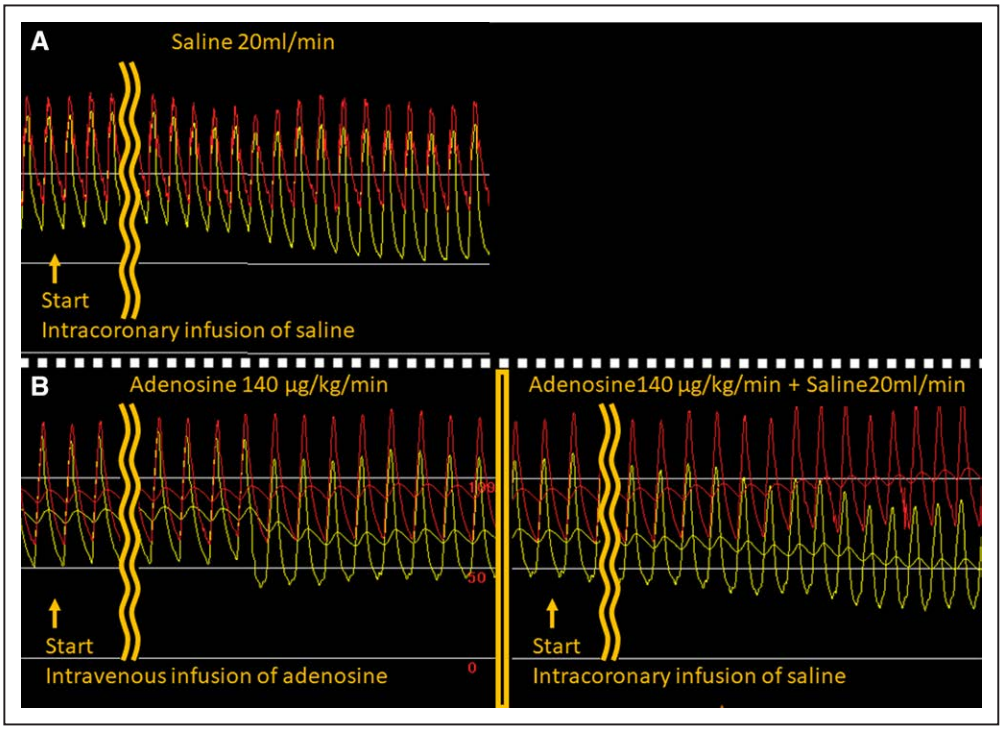

Figure 5. Screenshots of coronary flow pressure tracings during infusion of saline at room temperature at the rate of 20 mL/min through the end hole of the catheter advanced over the pressure–temperature sensor-tipped wire. **A**, At baseline, submaximal hyperemia was induced by saline infusion. **B**, Adenosine infusion significantly increased coronary flow above the hemodynamic status by saline infusion only. Then, saline infusion further induced a minor increase of pressure gradient.

Table 3. Absolute Coronary Flow Volume and Microvascular Resistance Before and After PCI

	Pre-PCI	Post-PCI	*P* Value
Pa, mm Hg	87±13	90±13	0.26
Pd, mm Hg	54±11	77±15	<0.01
Absolute hyperemic coronary blood flow (ABF), mL/min	137.8 (86.3–180.8)	173.3 (137.9–234.3)	<0.01
Microvascular resistance (MR), dyne s cm−5	31 997 (24 398–44 796)	36 797 (27 998–43 596)	0.37

Pa indicates aortic pressure; PCI, percutaneous coronary intervention; and Pd, coronary distal pressure.

7). However, at the individual patient or territory level, a serial change in hyperemic MR significantly influenced the increase or decrease in ABF after elective PCI. The 3 possible mechanisms to explain the change in MR after PCI have been reported as follows: (1) an increase in coronary pressure after PCI leading to an increase in diameter in target vessels and to a decrease in MR; (2) long-term reduction in perfusion pressure causing inward remodeling and impaired capacity for autoregulatory control, which consequently make the MR stay high after PCI at least for a certain period of time; and (3) coronary microembolization considered as a cause for increased MR. It is conceivable that the combination of these mechanisms regulates the change of coronary flow and MR after PCI. An ABF increase with an acute decrease in hyperemic MR could be explained by the dilatation of the microvasculature after PCI after the distal pressure restoration. Namely, a higher pre-PCI MR might reflect not only various chronic microvascular alterations and remodeling but also the reduced passive distension of the microvasculature because of a loss of perfusion pressure. In some of these cases with preserved microvascular responsiveness to increased pressure, coronary flow increased immediately after PCI because of the microvascular distension resulting from the acute

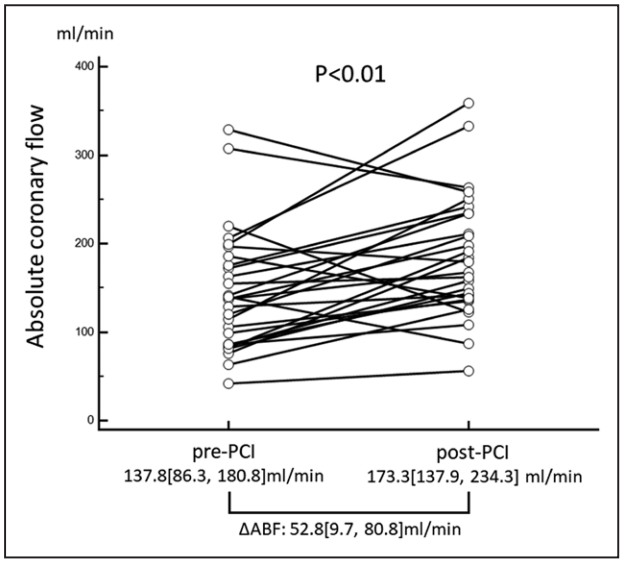

Figure 6. Serial changes in absolute coronary flow (ABF) after percutaneous coronary intervention (PCI).

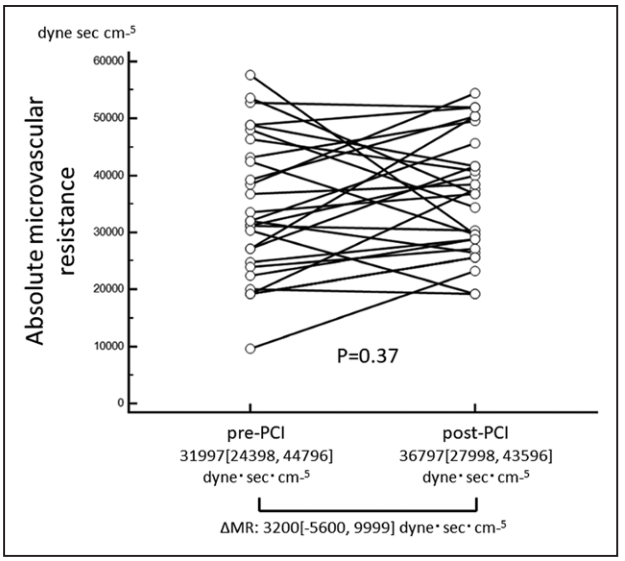

Figure 7. Serial changes in absolute microvascular resistance (MR) after percutaneous coronary intervention (PCI).

effect of coronary perfusion pressure restoration. Therefore, the territories with a high hyperemic MR before PCI could have the capability of vasodilatation, resulting in a coronary flow increase after PCI, as shown in Table 4, in which the increased coronary flow group had significantly higher MR at pre-PCI examinations. However, in the territories showing a lower pre-PCI MR under the presence of epicardial stenosis, the microvasculature might already be fully dilated; thus, coronary flow may not increase after PCI, despite the anatomic reduction of epicardial stenosis. In these territories, pre-PCI hyperemic coronary flow is already high, and a potential coronary flow increase after PCI might be limited by a responsive increase in MR with no capability for further dilation. This may explain lower MR at pre-PCI examination in decreased group in Table 4. These territories may be described as nonflow limiting territories/stenosis despite their pre-PCI FFR values, and PCI might decrease coronary flow because of increased hyperemic MR.[5]

Currently, controversy exists as to whether hyperemic MR in the presence of functionally significant stenosis is equivalent to that after stenosis removal by PCI.[7,8,13] Our results clearly demonstrated that MR was influenced by PCI, and its direction of change had an impact on hyperemic ABF after successful PCI. Multifactorial mechanisms linking MR and coronary hemodynamics may be involved in the determination of the individual functional status of the coronary circulation before and after PCI, and the precise coronary hemodynamic mechanisms remain elusive. Although our previous and present results showed a significant association between the change in MR and the change in ABF after PCI, further study is needed to gain greater mechanistic insights into the relationship between PCI and MR and to clarify its effect on microvascular and coronary hemodynamic status.

It has recently been rigorously debated whether information on coronary physiology and myocardial blood flow in patients with coronary heart disease should inform treatment decisions.[4,6,10,20,21]. However, despite their incorporation into contemporary guidelines, these techniques are still poorly

Table 4. The Baseline Clinical, Angiographic, and Physiological Characteristics According to the Increase or Decrease in Absolute Coronary Flow After PCI

	Increase Group (n=22)	Decrease Group (n=6)	*P* Value
Age, y	66±11.6	74±11.2	0.14
Male, n (%)	20 (90.9)	5 (83.3)	0.53
Mean body mass index, kg/m^2	25.0±3.1	22.9±3.7	0.20
Hypertension, n (%)	18 (81.8)	4 (66.7)	0.58
Hyperlipidemia, n (%)	17 (77.3)	3 (50.0)	0.19
Diabetes mellitus, n (%)	4 (18.2)	3 (50)	0.14
History of smoking, n (%)	17 (77.3)	3 (50)	0.31
Lesion location: RCA/LAD/LCx	8/13/1	1/5/0	0.71
Left ventricular ejection fraction (%)	64.5 (58.0–69.0)	58.0 (51.0–63.0)	0.12
Laboratory data			
WBC/μL	6180 (5710–7450)	7210 (5860–10 960)	0.33
LDL-chol, mg/dL	92 (72–152)	106 (96–114)	1.00
HDL-chol, mg/dL	46 (40–49)	38 (34–54)	0.48
TG, mg/dL	157 (88–288)	120 (96–131)	0.14
Creatinine, mg/dL	0.89 (0.72–1.09)	0.82 (0.69–1.10)	0.82
eGFR, mL min^{-1} 1.73 m^{-2}	69.4 (51.7–82.1)	65.8 (51.0–78.5)	0.70
HbA1c, %	5.9 (5.6–6.1)	6.7 (5.6–8.0)	0.42
NT-proBNP, pg/mL	101 (50–207)	142 (68–269)	0.78
peak cTnI, ng/dL	0.325 (0.083–1.048)	1.57 (0.124–2.316)	0.13
QCA analyses			
Pre-PCI MLD, mm	0.81 (0.69–1.17)	1.17 (1.00–1.38)	0.05
Pre-PCI RD, mm	2.88 (2.64–3.33)	2.82 (2.70–3.62)	0.78
Pre-PCI %stenosis, %	71.7 (62.7–78.8)	60.0 (58.3–68.0)	0.08
Lesion length, mm	12.2 (8.0–14.4)	14.8 (11.5–19.1)	0.18
Physiological indices			
Pre-PCI			
Pa, mm Hg	86±14	78±20	0.27
Pd, mm Hg	58±10	55±15	0.63
FFR	0.70 (0.64–0.75)	0.72 (0.66–0.75)	0.82
Absolute hyperemic coronary blood flow (ABF), mL/min	117.3 (84.8–154.9)	208.1 (185.8–307.4)	<0.01
Microvascular resistance (MR), dyne s cm^{-5}	37 597 (31 197–47 996)	19 198 (19 198–27 198)	<0.01
Post-PCI			
Pa, mm Hg	89±13	79±16	0.12
Pd, mm Hg	80±11	68±12	0.02
FFR	0.89 (0.86–0.95)	0.84 (0.81–0.87)	0.09
Absolute hyperemic coronary blood flow (ABF), mL/min	175.9 (141.2–234.1)	158.9 (122.3–258.2)	0.70
Microvascular resistance (MR), dyne s cm^{-5}	36 797 (28 798–45 596)	31 597 (25 598–41 597)	0.43

cTnI indicates cardiac troponin I; eGFR, estimated glomerular filtration rate; FFR, fractional flow reserve; HbA1c, glycohemoglobin; HDL-chol, high density lipoprotein cholesterol; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; LDL-chol, low density lipoprotein cholesterol; MLD, minimal lumen diameter; NT-proBNP, N-terminal pro-B-type natriuretic peptide; Pa, aortic pressure; PCI, percutaneous coronary intervention; Pd, coronary distal pressure; QCA, quantitative coronary angiography; RCA, right coronary artery; RD, reference diameter; TG, triglyceride; and WBC, white blood cells.

understood, and their interpretation for the guidance of revascularization decisions is often ambiguous and difficult to apply at the level of an individual patient or lesion. Deteriorated coronary flow reserve in the reference vessel determined by pressure–velocity wire, which is relevant to impaired microvascular function, has been reported to be associated with an

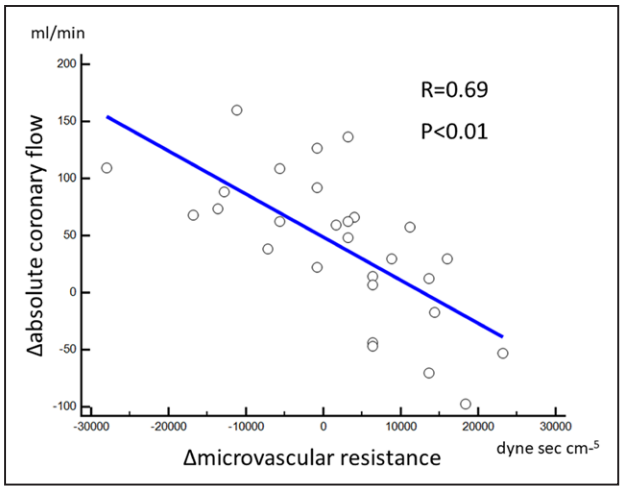

Figure 8. Relationship between the changes in absolute coronary flow and absolute microvascular resistance. △ myocardial resistance=post-PCI MR–pre-PCI MR; △ absolute coronary flow=post-PCI ABF–pre-PCI ABF; The solid line is derived from the linear regression analysis. ABF indicates absolute coronary flow; MR, microvascular resistance; and PCI, percutaneous coronary intervention.

increased all-cause mortality in a long term.[22] In the absence of significant epicardial disease, impairment of coronary flow reserve might be attributable to either an increased basal flow or an impaired flow at hyperemia. It has been speculated that the former is because of a disturbed baseline coronary autoregulation with a relatively preserved hyperemic MR and the latter is because of an impaired vasodilatory function with a high hyperemic MR.[11] Although the reference vessels were not examined in the present study, microvascular parameters might represent the myocardial conditions of whole heart, which may be relevant to the future outcomes of the patients. Further studies were warranted to investigate the impact of these physiological parameters on clinical outcomes.

De Bruyne et al[23] recently reported that intracoronary saline infusion through a dedicated catheter with 4 lateral small side holes induces steady-state maximal hyperemia at a saline flow ≥15 mL/min. Their study raised an important and critical issue on new possibilities of measuring maximal hyperemic ABF and minimal MR without vasodilator drugs. In our study, saline infusion at the speed of 20 mL/min through a catheter with a distal end-hole did not induce maximal hyperemia, and we measured ABF at maximal hyperemia under saline infusion on top of adenosine administration. The difference in the mode of saline infusion because of the difference in the infusion catheter might be a dominant cause of this phenomenon although other factors, such as the difference in the atherosclerotic burden and the presence or absence of significant stenosis, should be considered. Further investigation is warranted to study the effect of the mode of saline infusion and its hyperemic effect in the different population both at pre- and post-PCI.

The results of the present study may help to suggest a potential strategy for classifying patients with epicardial coronary artery disease, with or without a concomitant abnormal microcirculatory status. Our results from using an approach to measure ABF and MR provide a novel insight into the serial dynamic behavior of the coronary microcirculation at an individual lesion level in the presence of epicardial stenosis and after stenosis removal by successful PCI. Furthermore, MR interrogation on the basis of FFR assessment may clarify the existence of differentiated pattern of ischemic heart disease that harbor epicardial and microvascular dysfunction, which potentially benefit revascularization decision making for individual lesion levels.

Study Limitation

The results of the present study should be interpreted with consideration of some limitations. First, this study prospectively but not consecutively included subjects from a single center, making selection bias unavoidable. Second, this study comprised a small sample size that may not be enough for the assessment of safety concerns. Further studies might be needed to prove the safety of this method. Third, ABF may have no meaning without knowledge of the extent of the perfusion area or determination of a normal value, and there are no available data using this method to provide a reference value. Further study combining this method for ABF with positron emission tomography scanning or MRI of the perfusion territory could provide valuable information on ABF per unit myocardium although there are no definitive data available to suggest clinically significant absolute hyperemic blood flow level to relieve myocardial ischemia. Fourth, the present study used an end-hole catheter instead of the dedicated catheter with side holes. Although an acceptable mixture of circulating fluid and infused fluid from the end-hole catheter in our experimental study (Movies in the Data Supplement), incomplete mixture of fluids cannot be completely ruled out in a living body. Fifth, for routine practice and decision making in the catheterization laboratory, this method of measuring ABF and MR might not add any clinical value because FFR elegantly describes the influence of the epicardial stenosis on myocardial perfusion. Furthermore, suboptimal hyperemia is induced by saline infusion even in the baseline in the present study (Table 2). Therefore, it is difficult to determine coronary flow reserve using thermodilution method by saline infusion. Furthermore, the direct saline infusion into coronary artery on top of intravenous adenosine infusion increases the circulatory volume, which may influence coronary flow velocity over significant stenosis and might worsen the functional outcome. However, given our finding that the hyperemic MR clearly changed after PCI and influenced ABF, further investigation of coronary hemodynamics should be explored at individual patient level.

Conclusions

The technique of a thermodilution method using a continuous intracoronary infusion of saline allows feasible measurement of ABF and MR. It allowed us to elucidate the changes in ABF and MR after PCI. Serial changes in MR significantly influenced the increase or decrease in ABF after elective PCI. Further studies using this method may shed new light on coronary hemodynamics.

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Disclosures

None.

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Effect of Elective Percutaneous Coronary Intervention on Hyperemic Absolute Coronary Blood Flow Volume and Microvascular Resistance

Yoshihisa Kanaji, Tadashi Murai, Taishi Yonetsu, Eisuke Usui, Makoto Araki, Junji Matsuda, Masahiro Hoshino, Masao Yamaguchi, Takayuki Niida, Masahiro Hada, Sadamitsu Ichijyo, Rikuta Hamaya, Yoshinori Kanno, Mitsuaki Isobe and Tsunekazu Kakuta

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SUPPLEMENTAL MATERIAL.

Supplemental video files

Video files show a pressure-temperature sensor-tipped wire placed in the experiment model composed of silicon tubes, an infusion pump, and a dialysis machine, which simulated the mixture of the room temperature saline (red colored, 20ml/min, 25°C) and pulsatile flow saline of body temperature (pulsation flow auxiliary circulation system, 150ml/min, 37°C).

Supplemental video file 1: After a steady temperature was recorded by the sensor-tipped wire, the wire was moved upward and downward in the silicon tube to determine homogeneity of fluid temperature within the tube. Temperature fluctuation was limited within 0.08°C, which was less than 5% of temperature deviation.

Supplemental video file 2: the pressure-temperature sensor-tipped wire was moved proximally and distally in the silicon tube to ensure the longitudinal homogeneity of fluid temperature. Temperature fluctuation range was below 0.08 °C.