








ORIGINAL RESEARCH

Coronary Circulatory Indexes Before and After Percutaneous Coronary Intervention in a Porcine Tandem Stenoses Model

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BACKGROUND: In tandem stenoses, nonhyperemic pressure ratio pullback is the preferred method to fractional flow reserve (FFR), based on the assumption of stable resting coronary flow. This study aimed to evaluate temporal changes of coronary circulatory indexes in tandem stenoses before and after angioplasty for proximal stenosis.

METHODS AND RESULTS: Coronary tandem stenoses were created by porcine restenosis model with 2 bare metal stents in the left anterior descending artery. Four weeks later, changes in distal coronary pressure (Pd), averaged peak velocity, microvascular resistance, transstenotic pressure gradient across distal stenosis, resting Pd/aortic pressure, and FFR were measured before and 1, 5, 10, 15, and 20 minutes after balloon angioplasty for proximal stenosis. After angioplasty, there were significant changes in both resting and hyperemic Pd, averaged peak velocity, microvascular resistance, and transstenotic pressure gradient across distal stenosis (all P values <0.01). After initial acute changes, hyperemic averaged peak velocity and microvascular resistance did not show significant difference from the baseline values ($P=0.712$ and 0.972 , respectively). Conversely, resting averaged peak velocity remained increased (10.1 ± 0.7 to 17.8 ± 0.7 ; $P<0.001$) and resting microvascular resistance decreased (6.0 ± 0.1 to 2.2 ± 0.7 ; $P<0.001$). Transstenotic pressure gradient across distal stenosis was significantly increased in both resting (13.1 ± 7.6 to 25.3 ± 4.2 ; $P=0.040$) and hyperemic conditions (11.0 ± 3.0 to 27.4 ± 3.3 mm Hg; $P<0.001$). Actual post-percutaneous coronary intervention Pd/aortic pressure and FFR were significantly lower than predicted values (Pd/aortic pressure, 0.68 ± 0.22 versus 0.85 ± 0.14 ; $P<0.001$; FFR, 0.63 ± 0.08 versus 0.81 ± 0.08 ; $P<0.001$).

CONCLUSIONS: After angioplasty for proximal stenosis, transstenotic pressure gradient across distal stenosis showed similar changes between resting and hyperemic conditions. Both actual post-percutaneous coronary intervention resting Pd/aortic pressure and FFR were significantly lower than predicted values.

Key Words: coronary artery disease ■ fractional flow reserve ■ microvascular resistance ■ nonhyperemic pressure ratio ■ tandem stenosis

Coronary physiologic assessments by the pressure-derived fractional flow reserve (FFR) or nonhyperemic pressure ratio (NHPR) such as instantaneous wave-free ratio (iFR) have become standard methods for identifying hemodynamic deprivation

in the interrogated vessel for evidence-based percutaneous coronary intervention (PCI).¹ Although an FFR-guided strategy minimizes unnecessary revascularization and improves patient outcome compared with angiography-guided PCI,²⁻⁴ evaluating functional

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CLINICAL PERSPECTIVE

What Is New?

- The current study evaluated temporal changes of resting and hyperemic coronary circulatory indexes in tandem stenoses before and after angioplasty for proximal stenosis using an experimental animal model.
- After balloon angioplasty for proximal stenosis, there were significant changes in both resting and hyperemic averaged peak velocity, microvascular resistance, and transstenotic pressure gradient across distal stenosis.
- Furthermore, both resting and hyperemic pressure-derived physiologic indexes after proximal stenosis angioplasty were significantly lower than predicted values.

What Are the Clinical Implications?

- These results imply that both resting and hyperemic physiologic indexes could not be accurately predicted in tandem stenosis percutaneous coronary intervention (PCI).
- The significant changes in resting coronary flow after PCI could induce lower-than-expected post-PCI nonhyperemic pressure ratio even after successful PCI.
- Therefore, remeasurement using post-PCI fractional flow reserve would be a practical solution in daily practice.

Nonstandard Abbreviations and Acronyms

APV	averaged peak velocity
CFR	coronary flow reserve
FFR	fractional flow reserve
iFR	instantaneous wave-free ratio
MR	microvascular resistance
NHPR	nonhyperemic pressure ratio
Pa	aortic pressure
Pd	distal coronary pressure
PG	pressure gradient
Pm	coronary pressure between proximal and distal stenosis

significance of individual stenosis in the presence of tandem stenoses or diffuse disease remains problematic.⁵⁻⁷ Under hyperemic condition, treating a stenosis with PCI increases hyperemic flow in the target vessel and transstenotic pressure gradient (PG) across the remaining stenosis. Thus, remeasurement of FFR is required to assess the functional significance of residual stenosis after treating the first stenosis.⁵⁻⁷

Conversely, coronary circulation maintains relatively stable flow in nonhyperemic status according to stenosis severity until critical stenosis develops.^{8,9} Based on this assumption, there have been multiple efforts to evaluate the potential advantage of NHPR to predict post-PCI values by adding a step-up amount across target stenosis to pre-PCI values.^{10,11} Although this potential advantage of NHPR can simplify the procedural planning for tandem stenoses in which individual significance of tandem stenoses can be assessed by a single pre-PCI pullback maneuver, recent studies consistently showed actual post-PCI NHPR value to be lower than predicted value from pre-PCI pullback tracing.¹²⁻¹⁵ Moreover, a recent study showed that the presence of reactive hyperemia after PCI could be related with a suboptimal post-PCI NHPR value, questioning the assumption of stable resting coronary flow after PCI in the cardiac catheterization laboratory.¹⁶

In this context, the current study aimed to evaluate temporal changes of resting and hyperemic coronary circulatory indexes in tandem stenoses before and after angioplasty for proximal stenosis using a porcine tandem stenoses model, seeking to provide practical insights into daily practice.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Protocol

The animal study was approved by the Institutional Animal Care and Use Committee in Korea Research Institute of Bioscience & Biotechnology (AEC-20266) and conformed with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health.¹⁷ In specific pathogen-free swine, the experiments consisted of 2 parts. First, to create tandem stenoses in the left anterior descending artery (LAD), 2 bare metal 3.0×16 mm stents (Coroflex Blue, B. Braun Medical, Inc., Bethlehem, PA) were implanted in proximal and mid-LAD segments 4 weeks before the subsequent experiments. Second, in the subsequent experiment, balloon angioplasty for proximal stenosis with a 3.0×15 mm semicompliant balloon was performed using a standard technique of PCI. During balloon angioplasty, inflation of the balloon was maintained for at least 30 seconds 2 times. Serial changes of resting and hyperemic systemic hemodynamics, distal coronary pressure, Doppler-derived coronary averaged peak velocity (APV), microvascular resistance (MR), transstenotic PG across distal stenosis, and pressure-derived physiologic indexes in LAD were

measured before and 1, 5, 10, 15, and 20 minutes after balloon angioplasty for proximal stenosis (Figure 1).

Animal Preparation

The study animals were specific pathogen-free minipigs weighing 25–35 kg. For the in vivo experiments, the swine were anesthetized with zolazepam and tiletamine (2.5 mg/kg; Zoletil50, Virbac, Caros, France) and azaperone (6 mg/kg; Stresnil, Janssen-Cilag, Neuss, Germany). The animals received supplemental oxygen via endotracheal intubation throughout the procedure by isoflurane inhalation (2%). The anesthetic depth was monitored clinically as previously described.^{18,19} Hemodynamic and surface electrocardiographic monitoring was performed continuously throughout the procedure.

In the first part of the experiment, the left carotid artery was accessed via cutdown procedure, and a 6-Fr sheath was inserted after subcutaneous

injection of 2% lidocaine. After engagement of the left coronary artery using a 6-Fr Judkins left guide catheter, baseline coronary angiography was performed after intracoronary administration of 100 µg of nitroglycerin. To exclude animals with severe endothelial dysfunction, an acetylcholine challenge test was performed. When coronary vasoconstriction was absent under the administration of acetylcholine, the wiring was continued, and 2 bare metal stents were implanted in the proximal and mid-LAD segments. Intraprocedural anticoagulation was maintained with intravenous injection of heparin (100 U/kg). Before the stents were implanted, overstretch injury was induced using a slightly larger 1.3–1.5:1 predilatation balloon compared with the reference vessel size. To prevent stent thrombosis, 100 mg of aspirin and 75 mg of clopidogrel once daily were given for 5 days before the procedure and maintained until the second experiments.

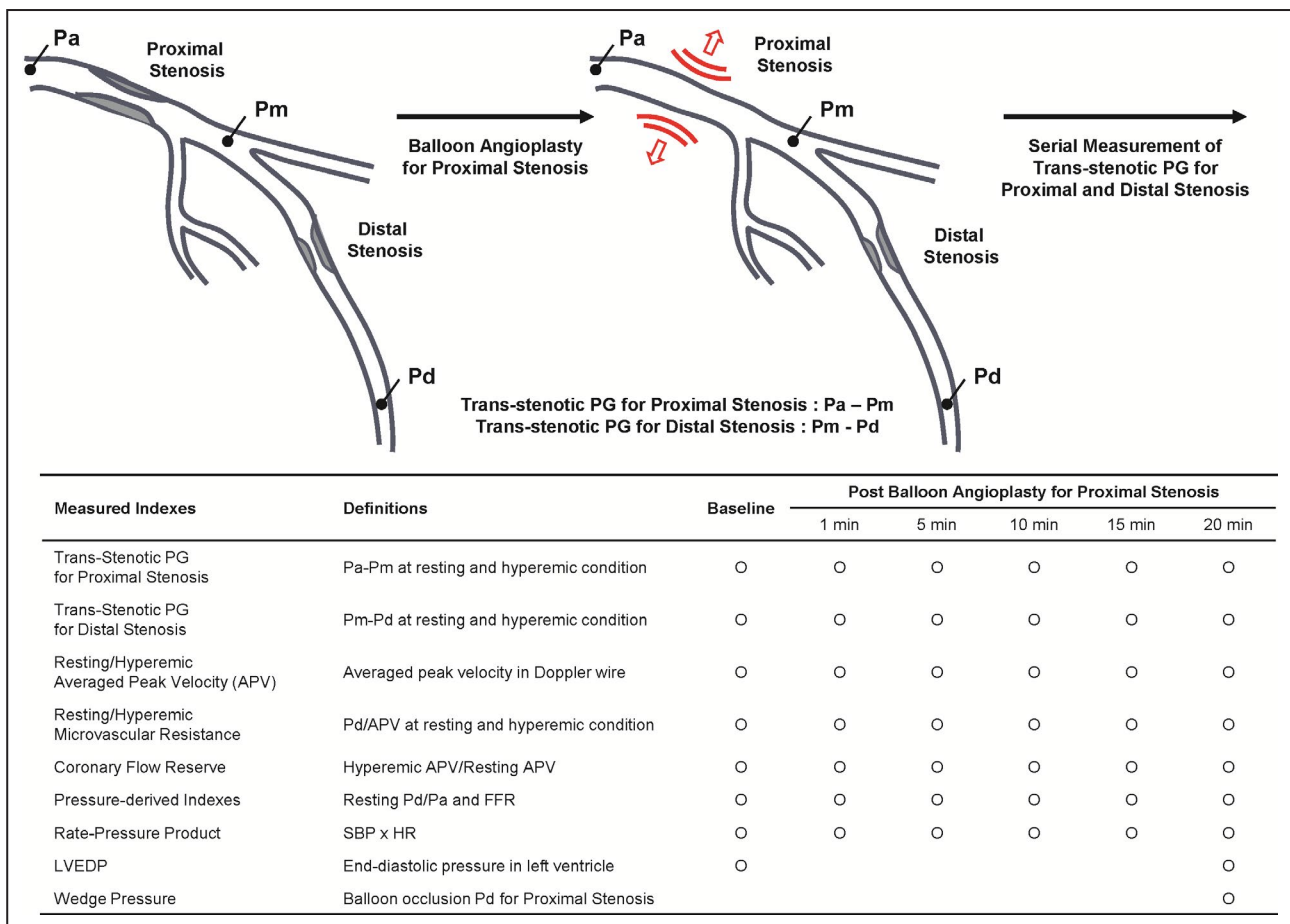


Figure 1. Schematic illustration of experiment protocol.

In a porcine tandem stenoses model, temporal changes in resting and hyperemic coronary circulatory indexes before and after angioplasty for proximal stenosis were evaluated. After balloon angioplasty of proximal stenosis, measurements were repeated at 1, 5, 10, 15, and 20 min. LVEDP was measured at baseline and at 20 min, and wedge pressure with balloon occlusion was measured at 20 min after balloon angioplasty. APV indicates averaged peak velocity; CFR, coronary flow reserve; FFR, fractional flow reserve; HR, heart rate; MR, microvascular resistance; LVEDP, left ventricular end-diastolic pressure; Pa, aortic pressure; Pd, distal coronary pressure; PG, pressure gradient; Pm, coronary pressure between proximal and distal stenosis; and SBP, systolic blood pressure.

The main experiments were performed 4 weeks after the bare metal stent implantation. After subcutaneous injection of 2% lidocaine, the contralateral carotid artery was exposed via cutdown procedure, and a 6-Fr sheath was inserted. After intracoronary administration of 100 µg of nitroglycerin and systemic anticoagulation with intravenous injection of heparin, the aortic pressure (Pa), distal coronary pressure (Pd), coronary pressure between proximal and distal stenosis (Pm), and Doppler-derived coronary APV were recorded continuously using ComboMap (Philips Volcano, San Diego, CA) and RADI analyzer (Abbott Vascular, Temecula, CA). The left ventricular end-diastolic pressure was measured using a standard 5-Fr pigtail catheter (Cordis Corporation, Miami Lakes, FL) before and 20 minutes after balloon angioplasty for proximal stenosis.

The initial experiment was performed in 6 subjects; however, 2 subjects suffered sudden cardiac death before the second experiment. There was no intraprocedural event during the first and second experiments among the remaining 4 subjects.

Hemodynamic and Coronary Physiological Measurements

During the experimental procedure, systemic hemodynamics were monitored continuously by systemic pressure and rate-pressure product (systolic blood pressure, mm Hg×heart rate, beats/min) and recorded at each stage. Coronary physiologic evaluation was performed using an 0.014-inch guidewire equipped with a Doppler flow velocity sensor (FlowWire, Philips Volcano) for APV measurements and a pressure-sensored wire (PressureWire X, Abbott Vascular) for Pa, Pm, and Pd signals. The Doppler-sensored wire was positioned at the distal segment of the interrogated vessel beyond the distal stenosis and carefully manipulated circumferentially to acquire optimal Doppler flow signal; however, the axial position of the sensor was not changed. The pressure-sensored wire was positioned at the distal segment for Pd and between proximal and distal stenoses for Pm signal. The APV, Pa, Pm, and Pd were simultaneously recorded in both resting and hyperemic conditions at each stage of the experiment. Intracoronary nitrate (100 µg) was administered before each physiologic measurement. Hyperemia was induced with intracoronary bolus administration of nicorandil (2 mg) to avoid hypotension and heart rhythm disturbance.^{20–23} Previous clinical and preclinical studies demonstrated a hyperemic plateau time after intracoronary nicorandil of 32.3±15.2 seconds in humans²³ and 30.3 (quartile 1–3, 27.0–33.0) seconds in pigs.²¹

Mean Doppler flow velocity was averaged over a minimum of 3 consecutive heartbeats (APV).

Coronary flow reserve (CFR) was calculated as hyperemic APV/resting APV. Resting and hyperemic MR were calculated as Pd/APV at resting and hyperemic conditions, respectively. Transstenotic PG across proximal and distal stenoses were calculated as Pa-Pm and Pm-Pd, respectively, in both resting and hyperemic conditions. Pressure-derived physiologic indexes in the vessel were measured in both resting and hyperemic conditions as resting Pd/Pa (the ratio of the mean Pd to mean Pa in resting condition) and FFR (the lowest average of hyperemic Pd/Pa during 3 consecutive beats during maximal hyperemia). At each stage of the experiment, 5 repeated measurements were acquired. After each measurement, the pressure-sensored wire was pulled back to the guide catheter, and the presence of drift was checked. With a drift >0.03 unit of FFR, reequalizations and repeated measurements were performed. After measurement of coronary circulatory indexes at 20 minutes after proximal stenosis angioplasty, balloon occlusion pressure (wedge pressure) was measured while occluding proximal stenosis with an angioplasty balloon, and collateral flow index was calculated as balloon occlusion pressure divided by Pa.²⁴ Predicted value of FFR after proximal stenosis angioplasty was calculated as previously reported using the alleged equation of predicted $FFR = 1 - \frac{(Pm - Pd) \times (Pa - \text{wedge pressure})}{Pa \times (Pm - \text{wedge pressure})}$.⁵ Predicted value of resting Pd/Pa after proximal stenosis angioplasty was calculated by adding Δ resting Pd/Pa across proximal stenosis into pre-PCI resting Pd/Pa value.^{8,9}

Statistical Analysis

Continuous values were expressed as median with first and third quartiles depending on distribution. For comparing coronary circulatory indexes, a generalized estimating equation was used to adjust for intrasubject variability of repeatedly measured and clustered data from the same subject. This correlation structure assumes that animals are independent, and that all measurements within animals are correlated equally. Estimated means and 95% standard errors were presented as summary statistics (estimated mean±standard error). The overall temporal changes of resting and hyperemic indexes were illustrated as a line graph. In head-to-head comparison of coronary circulatory indexes before and after balloon angioplasty for proximal stenosis, values from immediately after balloon angioplasty (1, 5, and 10 minutes after balloon angioplasty) were excluded. Mean difference of coronary circulatory indexes between baseline phase versus values from 15 to 20 minutes after balloon angioplasty was tested by paired T-test and illustrated as box and whisker plots. All analyses were 2-tailed, and

statistical significance was defined as a $P < 0.05$. All statistical analyses were performed using R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS 25.0 for Windows (SPSS-PC, Chicago, IL).

RESULTS

Characteristics of Experimental Animals and Coronary Tandem Stenoses

Table 1 summarizes the baseline characteristics of experimental animals and coronary arteries with tandem stenoses. The median body weight of animals was 29.0 kg (quartile 1–3, 25.8–31.5 kg). The median systolic and diastolic blood pressure was 106.0 mm Hg (quartile 1–3, 82.5–137.8 mm Hg) and 58.5 mm Hg (quartile 1–3, 48.0–78.4 mm Hg), respectively. Both proximal and distal stenoses were intermediate in stenosis severity (proximal stenosis, 55.5%; quartile 1–3, 34.3%–64.8%; distal stenosis, 65.5%; quartile 1–3, 57.5%–71.3%). At baseline, resting and hyperemic pressure-derived physiologic indexes in LAD were resting Pd/Pa of 0.78 (quartile 1–3, 0.62–0.86) and FFR of 0.75 (quartile 1–3, 0.63–0.77), respectively. Baseline CFR was 2.6 (quartile 1–3 2.2–2.9) (Table 1). After balloon angioplasty for proximal stenosis, diameter stenosis was significantly decreased in proximal stenosis ($51.5 \pm 7.2\%$ to $17.8 \pm 2.4\%$; $P < 0.001$), but there was no significant change in distal stenosis ($64.8 \pm 3.2\%$ to $66.4 \pm 2.5\%$; $P = 0.210$). The interrogated vessel showed balloon occlusion pressure of 6.0 mm Hg (quartile 1–3, 5.0–7.0 mm Hg) and collateral flow index of 0.10 (quartile 1–3, 0.09–0.13).

Serial Changes in Coronary Circulatory Indexes After Angioplasty for Proximal Stenosis

Table 2 summarizes temporal changes of systemic hemodynamics and coronary circulatory indexes at baseline and 1, 5, 10, 15, and 20 minutes after balloon angioplasty for proximal stenosis. Hyperemic APV decreased and hyperemic MR increased initially after angioplasty. However, hyperemic APV and MR did not show significant difference from the baseline values at 15 minutes after balloon angioplasty. Conversely, changes in resting APV and MR were more persistent than those of hyperemic indexes. Resting APV increased immediately after balloon angioplasty and remained increased throughout 20 minutes ($P = 0.006$). Also, immediate decrease in resting MR lasted until 20 minutes after proximal stenosis balloon angioplasty ($P = 0.001$). Accordingly, CFR decreased at 1 minute after the balloon angioplasty and remained depressed until 20 minutes ($P < 0.001$). The

Table 1. Baseline Characteristics of Experiment Animals and Coronary Arteries With Tandem Stenoses

Animals (n=4)	
Body weight, kg	29.0 (25.8–31.5)
Systolic blood pressure, mm Hg	106.0 (82.5–137.8)
Diastolic blood pressure, mm Hg	58.5 (48.0–78.4)
Baseline heart rates, beats/min	90.5 (90.0–112.8)
Coronary artery with tandem stenoses (n=4)	
Proximal stenosis	
Reference vessel diameter, mm	3.0 (2.7–3.2)
Diameter stenosis, %	55.5 (34.3–64.8)
Lesion length, mm	8.5 (7.3–8.9)
Distal stenosis	
Reference vessel diameter, mm	2.5 (2.4–2.7)
Diameter stenosis, %	65.5 (57.5–71.3)
Lesion length, mm	10.7 (8.1–13.4)
Pressure-derived indices	
Resting Pd/Pa	0.78 (0.62–0.86)
Fractional flow reserve	0.75 (0.63–0.77)
Flow velocity, cm/s	
Resting averaged peak velocity	10.0 (9.8–11.0)
Hyperemic averaged peak velocity	25.0 (22.8–29.0)
Transstenotic pressure gradient for proximal stenosis, mm Hg	
Resting transstenotic pressure gradient	7.0 (6.0–8.8)
Hyperemic transstenotic pressure gradient	8.5 (6.5–11.0)
Transstenotic pressure gradient for distal stenosis, mm Hg	
Resting transstenotic pressure gradient	6.0 (2.0–30.0)
Hyperemic transstenotic pressure gradient	8.0 (7.0–15.8)
Microvascular resistance, mm Hg/cm/s	
Resting microvascular resistance	6.0 (5.6–6.3)
Hyperemic microvascular resistance	1.7 (0.6–1.9)
Coronary flow reserve	2.6 (2.2–2.9)
Rate-pressure product, mm Hg × beats/min	10211.0 (7559.8–14188.8)

Values are median (interquartile ranges, 25th–75th). Pa indicates aortic pressure; and Pd, distal coronary pressure.

depression of CFR was mainly driven by increased resting APV (Table 2 and Figure 2).

Serial Changes in Systemic Hemodynamics, Intracoronary Pressures, and Transstenotic Pressure Gradients After Angioplasty for Proximal Stenosis

After balloon angioplasty for proximal stenosis, resting Pa showed no significant change ($P = 0.191$); conversely, hyperemic Pa decreased significantly from baseline until 15 minutes and partially recovered at 20 minutes ($P = 0.002$). Both resting and hyperemic Pd decreased

Table 2. Changes in Systemic Hemodynamics and Coronary Circulatory Indexes Before and After Angioplasty for Proximal Stenosis

Circulatory Indices	Baseline	Measurements After Angioplasty of Proximal Stenosis					P Value*
		1 min	5 min	10 min	15 min	20 min	
Resting mean pressure, mm Hg							
Pa	73.7±2.1	69.4±1.9	67.5±1.6	67.9±2.2	67.2±4.2	65.5±2.8	0.191
Pm	66.4±2.3	65.2±3.3	65.4±2.4	64.9±2.7	64.1±3.3	62.1±3.6	0.674
Pd	53.4±2.9	52.0±6.4	46.3±6.9	45.2±7.0	39.1±4.2	36.6±4.2	0.003
Hyperemic mean pressure, mm Hg							
Pa	66.3±4.2	64.0±3.8	60.9±1.2	60.6±1.5	59.5±1.7	64.1±1.6	0.002
Pm	57.3±3.1	58.6±3.4	57.9±2.2	57.7±1.7	55.9±1.1	61.1±2.6	0.302
Pd	46.3±1.5	43.5±6.4	38.4±7.4	38.0±6.0	30.2±4.1	32.0±4.0	0.005
Averaged peak velocity, cm/s							
Resting	10.1±0.7	16.7±0.7	14.3±0.7	21.7±2.8	17.3±0.6	18.2±0.8	0.006
Hyperemic	25.6±1.8	18.7±1.5	19.9±0.2	26.6±0.4	24.9±2.5	25.4±2.1	<0.001
Microvascular resistance, mm Hg/cm/s							
Resting	6.0±0.1	2.7±0.2	2.7±0.8	1.9±0.7	2.3±0.7	2.1±0.7	<0.001
Hyperemic	1.3±0.4	2.4±0.1	1.8±0.5	1.2±0.5	1.4±0.6	1.3±0.6	<0.001
Transstenotic PG for proximal stenosis, mm Hg							
Resting	7.3±0.7	4.2±1.5	2.1±1.1	3.0±1.1	3.1±1.1	3.4±0.8	<0.001
Hyperemic	9.0±1.2	5.4±1.7	3.0±1.9	3.0±1.3	3.6±1.0	3.0±1.0	<0.001
Transstenotic PG for distal stenosis, mm Hg							
Resting	13.1±7.6	13.2±6.8	19.1±8.4	19.8±8.8	25.0±5.5	25.5±5.4	0.001
Hyperemic	11.0±3.0	15.1±5.2	19.5±6.9	19.7±7.7	25.7±4.3	29.1±4.4	0.008
Pressure-derived indices in vessel							
Resting Pd/Pa	0.75±0.06	0.75±0.09	0.69±0.11	0.67±0.11	0.61±0.19	0.57±0.20	<0.001
FFR	0.71±0.04	0.67±0.08	0.63±0.12	0.64±0.11	0.51±0.19	0.51±0.21	0.013
Coronary flow reserve	2.55±0.20	1.14±0.07	1.39±0.08	1.27±0.15	1.44±0.09	1.39±0.05	<0.001
Rate-pressure product, mm Hg × beats/min	10721.3±1555.3	9890.2±801.1	8964.1±481.2	9373.2±475.7	9327.8±547.6	9064.4±577.4	0.103
Left ventricular end diastolic pressure, mm Hg	3.8±0.4	NA	NA	NA	NA	3.5±0.4	0.424

Data are presented as estimated mean and 95% standard error (estimated mean±standard error), calculated using the generalized estimating equation. FFR indicates fractional flow reserve; NA, not applicable; Pa, aortic pressure; Pd, distal coronary pressure; Pm, coronary pressure at midpoint between proximal and distal stenosis; and PG, pressure gradient.

*P value was derived from the generalized estimating equation for overall comparison of repeated measures.

significantly without recovery until 20 minutes ($P=0.003$ and 0.005 , respectively). Transstenotic PG of proximal stenosis decreased significantly in both resting and hyperemic conditions (both P values <0.001), demonstrating successful relief of proximal stenosis after balloon angioplasty without subsequent recoil. Conversely, transstenotic PG of distal stenosis significantly increased in both resting ($P=0.001$) and hyperemic conditions ($P=0.008$). This increase in transstenotic PG across distal stenosis led to significant decrease in resting Pd/Pa ($P<0.001$) and FFR ($P=0.013$) after proximal stenosis balloon angioplasty despite unchanged stenosis severity of distal stenosis (Table 2 and Figure 3). Actual post-PCI Pd/Pa and FFR after proximal stenosis angioplasty were significantly lower than predicted values on the basis of predicted values (Pd/Pa, 0.68 ± 0.22 versus 0.85 ± 0.14 ; $P<0.001$; FFR,

0.63 ± 0.08 versus 0.81 ± 0.08 ; $P<0.001$). Throughout the entire experiment, there were no significant changes in rate-pressure product ($P=0.103$).

Comparison of Resting and Hyperemic Coronary Circulatory Indexes Before and After Angioplasty for Proximal Stenosis

To exclude influence from acute changes before stabilization of coronary circulation, values obtained 1, 5, and 10 minutes after balloon angioplasty were excluded for these comparisons. Although hyperemic APV and MR did not show significant difference from the baseline values ($P=0.712$ and 0.972 respectively), changes in resting APV and MR persisted (both P values <0.001). Depressed CFR also lasted longer than 15 minutes after

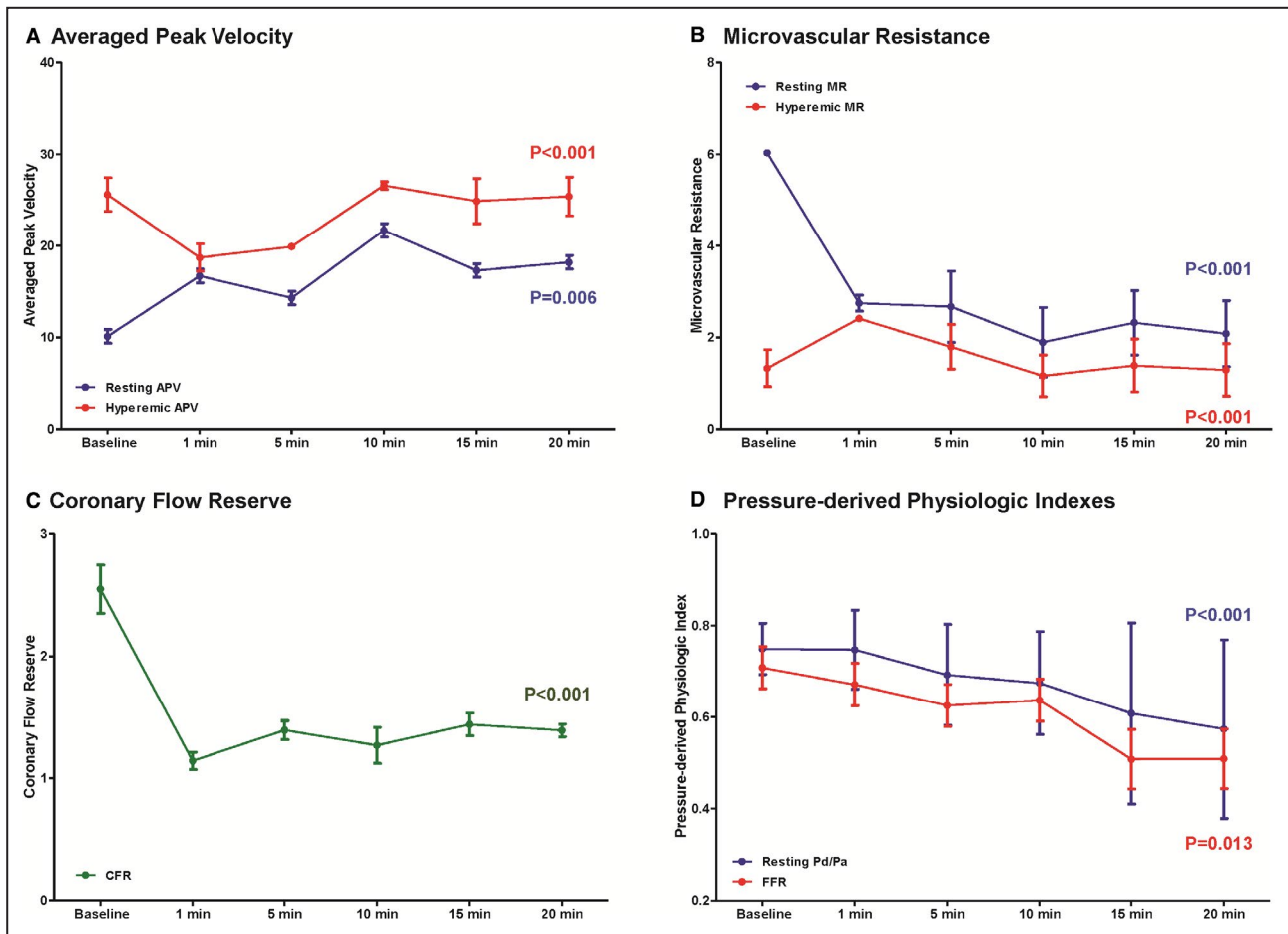


Figure 2. Changes in coronary circulatory indexes after angioplasty of proximal stenosis.

Changes in (A) APV, (B) MR, (C) CFR, and (D) pressure-derived physiologic indexes during resting and hyperemic conditions are demonstrated at baseline and 1, 5, 10, 15, and 20 min after angioplasty for proximal stenosis. Red, green, and blue circles represent means of coronary circulatory indexes, and error bars represent 95% standard errors. *P* values were derived from the generalized estimating equation for overall comparison of repeated measures. APV indicates averaged peak velocity; CFR, coronary flow reserve; FFR, fractional flow reserve; MR, microvascular resistance; and Pd/Pa, resting distal coronary pressure/aortic pressure.

balloon angioplasty ($P < 0.001$) because of persistently elevated resting APV. In a comparison of transstenotic PG across distal stenosis, both resting and hyperemic transstenotic PG showed significant increase from baseline values (resting transstenotic PG, 13.1 ± 7.6 – 25.3 ± 4.2 mm Hg; $P = 0.040$; hyperemic transstenotic PG, 11.0 ± 3.0 – 27.4 ± 3.3 mm Hg, $P < 0.001$). Pressure-derived physiologic indexes also showed significant decrease after balloon angioplasty for proximal stenosis (resting Pd/Pa, 0.75 ± 0.06 – 0.59 ± 0.19 ; $P = 0.018$; FFR, 0.71 ± 0.04 – 0.51 ± 0.20 ; $P = 0.002$) (Figure 4). There was no significant change in left ventricular end-diastolic pressure ($P = 0.424$) (Table 2).

DISCUSSION

The current animal experiment evaluated the serial changes in resting and hyperemic coronary circulatory indexes in tandem stenoses before and after balloon

angioplasty for proximal stenosis. The major findings were as follows (Figure 5): First, following balloon angioplasty for proximal stenosis, there were significant changes in both resting and hyperemic APV, MR, and distal coronary pressures. Second, unlike the hyperemic coronary circulatory indexes, which recovered to baseline values after the initial phase, changes in resting coronary circulatory indexes lasted until 20 minutes after balloon angioplasty for proximal stenosis. Third, transstenotic PG across distal stenosis significantly increased and showed similar changes between resting and hyperemic conditions after balloon angioplasty for proximal stenosis. Fourth, both resting Pd/Pa and FFR after proximal stenosis angioplasty were significantly lower than predicted values before proximal stenosis angioplasty.

Although FFR or NHPR-guided strategy to determine the necessity of revascularization has been supported by the current guidelines,^{1,25} it should be noted that FFR or NHPR reflects cumulative hemodynamic

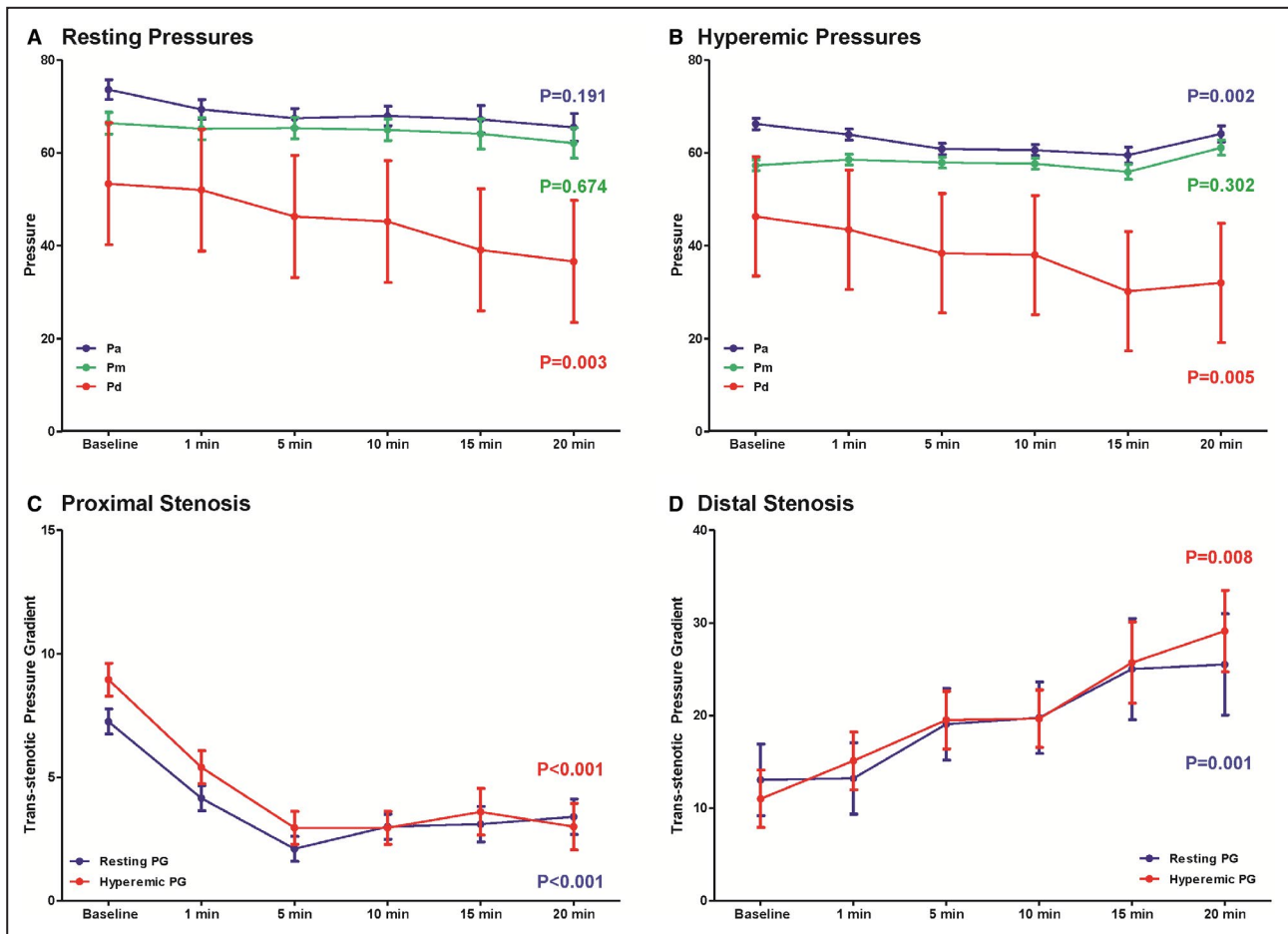


Figure 3. Changes in systemic hemodynamics, intracoronary pressures and transstenotic pressure gradients after angioplasty for proximal stenosis.

Changes in (A) resting coronary pressures, (B) hyperemic coronary pressures, (C) transstenotic PG across proximal stenosis, and (D) transstenotic PG across distal stenosis during resting and hyperemic conditions are demonstrated at baseline and 1, 5, 10, 15, and 20 min after angioplasty for proximal stenosis. Red, green, and blue circles represent means of coronary pressures and pressure gradients, and error bars represent 95% standard errors. *P* values were derived from the generalized estimating equation for overall comparison of repeated measures. Pa indicates aortic pressure; Pd, distal coronary pressure; PG, pressure gradient; and Pm, coronary pressure between proximal and distal stenosis.

impact of coronary atherosclerosis in the target vessel.^{26,27} Therefore, true functional significance of individual stenosis or underlying diffuse atherosclerotic disease can be underestimated in the presence of tandem stenoses. During maximal hyperemia, coronary flow is affected by changes in stenosis severity, and treating a stenosis with PCI will increase hyperemic flow and transstenotic PG across the remaining stenosis.^{5,6,28} This effect was demonstrated by an initial report by Pijls et al⁵ in which the transstenotic PG across the secondary stenosis was significantly increased after relieving primary stenosis (from 10 ± 7 to 19 ± 11 mm Hg). A later report by Kim et al⁶ showed similar results of increased transstenotic PG across the secondary stenosis after stenting for primary stenosis (from 7.7 ± 5.9 to 10.9 ± 7.8 mm Hg). In this regard, repeated measurements of FFR after stenting the primary stenosis have been a standard recommendation

to accurately assess the functional significance of residual disease.^{6,7}

Conversely, coronary flow remains relatively stable in nonhyperemic status according to stenosis severity until critical stenosis develops.^{8,9} Based on this, it has been suggested that a relatively small change in coronary flow under nonhyperemic conditions induces a more predictable change in transstenotic PG and NHPR after PCI.⁹ This means that post-PCI NHPR value after treatment of first stenosis can be approximated by adding a step-up amount across the stenosis to the pre-PCI NHPR value without the need for measuring balloon occlusion pressure or a complex equation.⁹ Indeed, an initial pilot study by Nijjer et al¹⁰ showed close correlation ($r=0.97$; $P<0.01$) between predicted and observed post-PCI iFR step-up amount, and the difference between predicted and observed post-PCI iFR was 0.016 ± 0.004 in 32 vessels. However,

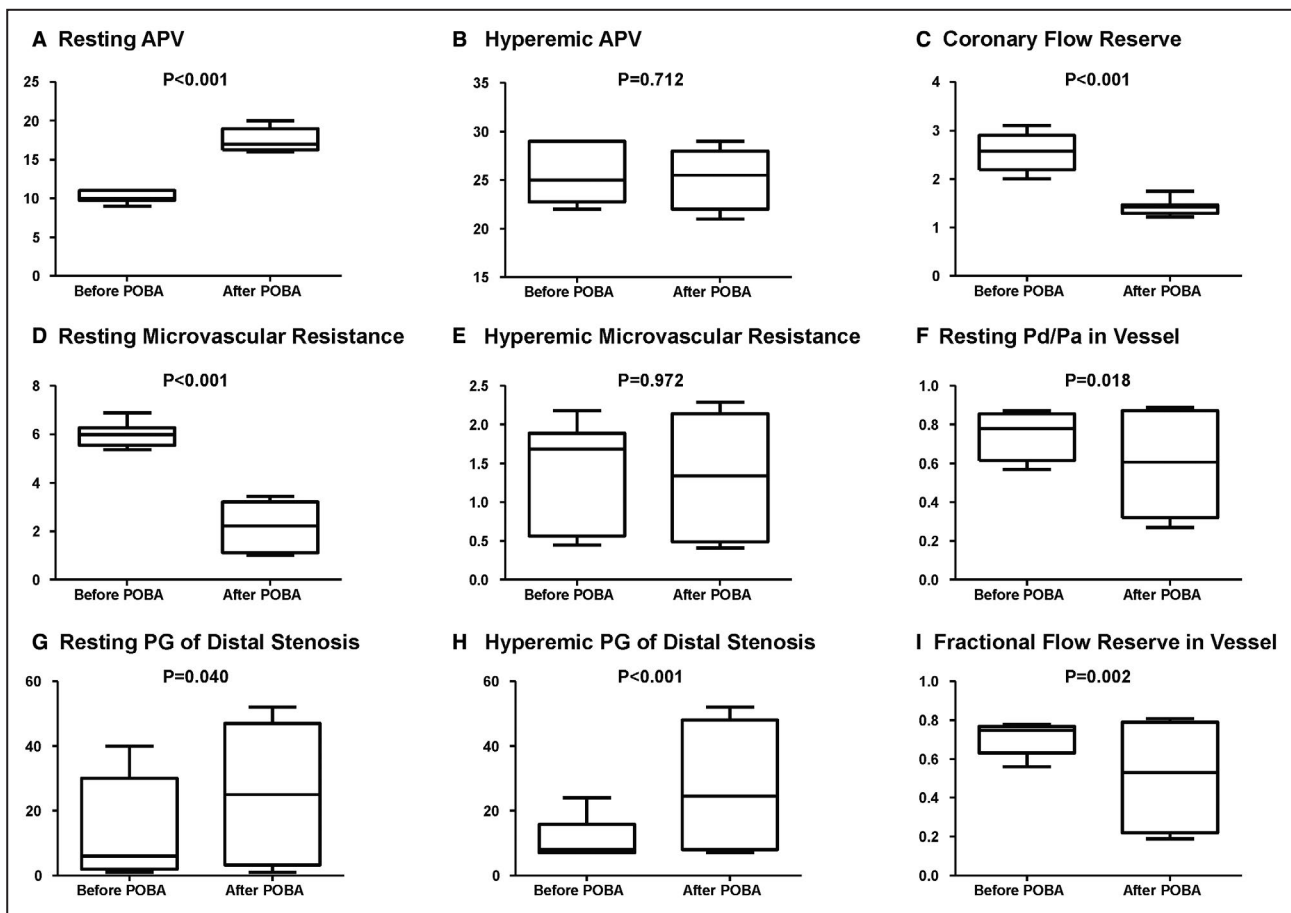


Figure 4. Comparison of resting and hyperemic coronary circulatory indexes before and after angioplasty for proximal stenosis.

Comparisons of coronary circulatory indexes including (A and B) resting and hyperemic averaged peak velocity (APV), (C) coronary flow reserve (CFR), (D and E) resting and hyperemic microvascular resistance (MR), (F) resting Pd/Pa, (G and H) resting and hyperemic PG of distal stenosis, and (I) fractional flow reserve (FFR) are presented as box and whisker plots before and after balloon angioplasty for proximal stenosis. Baseline and mean values from 15 and 20 min after balloon angioplasty for proximal stenosis are compared. In box and whisker plots, the horizontal line indicates median value, box indicates the interquartile range, and whiskers indicate the 2.5 and 97.5 percentiles. APV indicates averaged peak velocity; CFR, coronary flow reserve; FFR, fractional flow reserve; MR, microvascular resistance; Pd/Pa, resting distal coronary pressure / aortic pressure; PG, pressure gradient; and POBA, plain old balloon angioplasty.

the difference between predicted and observed post-PCI iFR values in later studies was reported up to 0.036, and the observed post-PCI values were consistently lower than predicted values.^{12–15}

Although suboptimal stent expansion might be one of the possible causes for difference between predicted and observed post-PCI NHPR values,¹² Matsuo et al¹⁴ presented that 57% of post-PCI iFR gradients occurred in the nonstented segments among patients with ≥ 0.03 difference between predicted and observed post-PCI iFR values. This result implies that discordance between predicted and observed post-PCI NHPR values is not entirely attributable to suboptimal stent implantation, but increased pressure gradients across residual stenosis also contributed to the significant difference between predicted and observed values. Indeed, PGs across residual stenosis increased

at rest as well as a hyperemic state after PCI in this experiment. Part of the increased PG at rest can be explained by increased resting flow represented by increased resting APV. Furthermore, actual resting Pd/Pa values after proximal stenosis angioplasty were significantly lower than predicted values.

Earlier preclinical and clinical studies demonstrated the phenomenon of increased resting coronary flow even after brief occlusion of the coronary artery during PCI.^{29,30} Schwartz et al performed a preclinical study using 11 conscious dogs in which brief coronary occlusion of 0.2 seconds induced significant reactive hyperemic response. Similarly, Marcus et al³⁰ showed that brief coronary occlusion for < 2 seconds consistently produced hyperemic response, and duration of the reactive hyperemia progressively increased with increasing duration of occlusion, which was

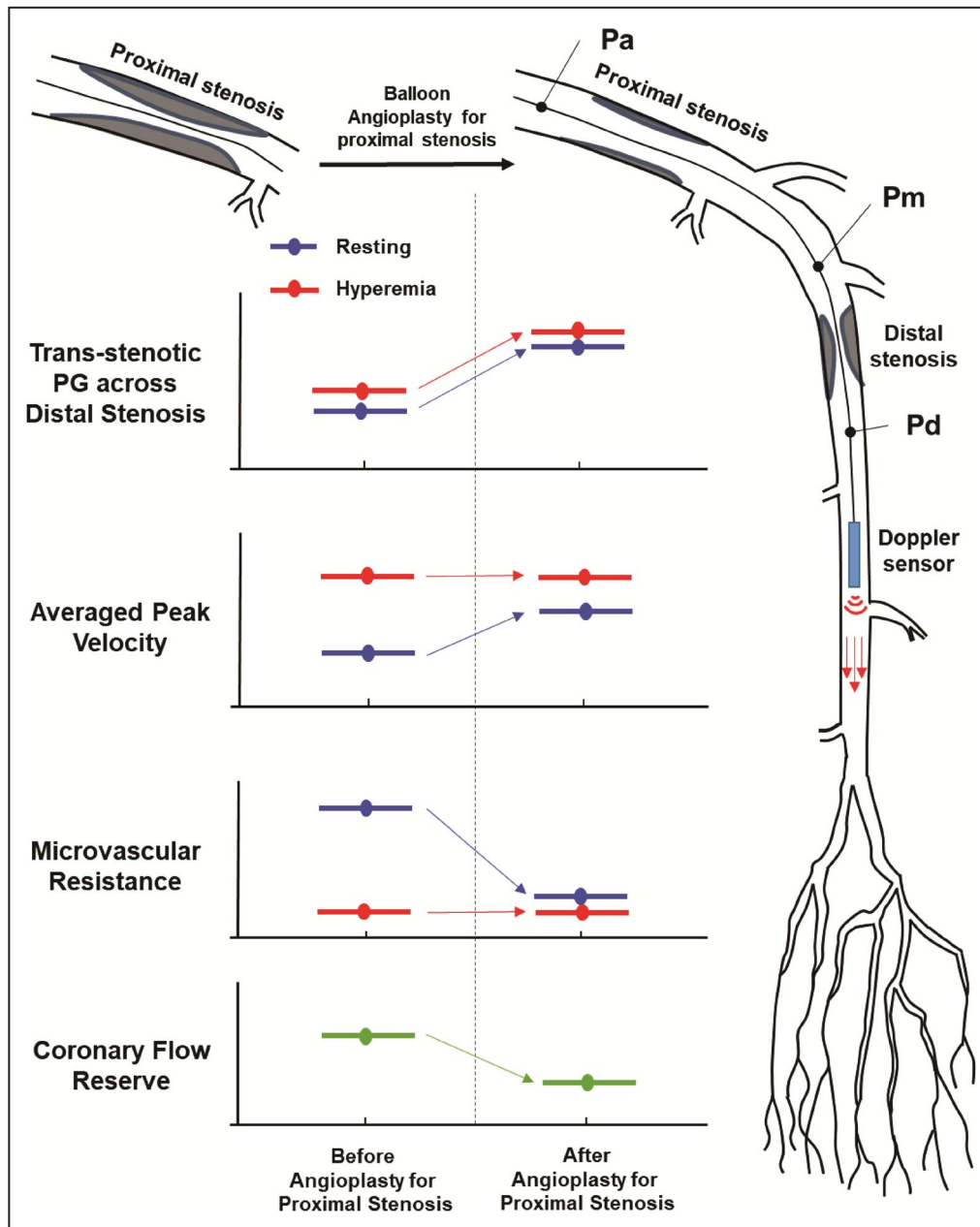


Figure 5. Changes in coronary circulatory indexes before and after angioplasty for proximal stenosis in tandem stenoses.

Current study evaluated temporal changes of resting and hyperemic coronary circulatory indexes in tandem stenoses before and after angioplasty for proximal stenosis using an experimental animal model. After balloon angioplasty for proximal stenosis, there were significant changes in both resting and hyperemic distal coronary pressure, averaged peak velocity, microvascular resistance, and transstenotic PG across distal stenosis. Unlike hyperemic coronary circulatory indexes, changes in resting coronary circulatory indexes did not recover to baseline values after proximal stenosis angioplasty. Transstenotic PG across distal stenosis showed similar changes between resting and hyperemic conditions after proximal stenosis angioplasty. PG indicates pressure gradient. Pa indicates aortic pressure; Pd, distal coronary pressure; and Pm, coronary pressure between proximal and distal stenosis.

corroborated by a later study.³¹ Recent studies also reported that 15 to 20 seconds of coronary occlusion can produce maximal hyperemic response, which could be significantly longer than that induced by intracoronary administration of adenosine.^{32,33}

The influence of post-occlusion reactive hyperemia to post-PCI NHPR and its clinical implications were recently demonstrated using the PERSPECTIVE-PCI (Prognostic Perspective of Invasive Hyperemic and Nonhyperemic Physiologic Indices Measured After Percutaneous

Coronary Intervention) registry.¹⁶ Among 588 patients who underwent both resting and hyperemic post-PCI physiologic index measurements, >60% of patients with an ischemic range of post-PCI Pd/Pa (≤ 0.92) showed non-ischemic FFR (> 0.80). At 2 years, patients with post-PCI Pd/Pa ≤ 0.92 but FFR > 0.80 had low event rates, and TVF risk in this group was not significantly different from that of the post-PCI Pd/Pa > 0.92 group. In a comparison of thermodilution-based coronary flow–derived indexes, patients with post-PCI Pd/Pa ≤ 0.92 but FFR > 0.80 showed significantly shorter resting mean transit time but similar hyperemic mean transit time than those with post-PCI resting Pd/Pa > 0.92 . These results imply that abnormal post-PCI resting Pd/Pa values might not be caused entirely by residual ischemia, and increased resting coronary flow in the post-PCI phase might be a suitable explanation.¹⁶ Although the duration of postocclusion reactive hyperemia varies among studies, the present experiment showed that measurement of NHPR during this period would overestimate the functional significance of residual stenosis.

Clinical Implications

The current results do not contradict the relatively stable resting coronary flow than hyperemic flow according to stenosis severity. A previous Iberian-Dutch-English study demonstrated that resting APV remained stable until the anatomic stenosis reached 90% diameter stenosis with compensatory reduction of resting MR.⁸ Therefore, it might be reasonable to predict post-PCI NHPR from pre-PCI NHPR pullback maneuver. However, the predicted value should be regarded as the maximally achievable value under 2 assumptions. First, PCI should be optimized with no or minimal pressure gradient across an implanted stent. Second, the post-PCI coronary flow should return to its baseline resting value before measuring post-PCI NHPR. However, the current and previous results suggest that there is variable duration of increased resting flow in the post-PCI phase. In addition, the significant changes in resting coronary flow after PCI could induce lower-than-expected post-PCI NHPR even after successful PCI. Therefore, when the post-PCI NHPR is lower than expected, even after successful PCI without stent underexpansion, measuring FFR under maximal hyperemia would reduce the possibility of overestimating lesion severity of residual stenosis.

LIMITATIONS

Some limitations of the current study should be acknowledged. First, the current study was an animal experiment model and not a human study. Second, although the current study excluded animal subjects with significant

epicardial coronary vasospasm or endothelial dysfunction by acetylcholine challenge test, and intracoronary nitroglycerin was administered before measurements of coronary circulatory indexes, microvascular spasm after balloon angioplasty could influence the study results. Third, the current experiment measured coronary circulatory indexes until 20 minutes after angioplasty for proximal stenosis. It is unclear whether extended measurement time beyond 20 minutes would provide different results. Fourth, the current experiment used coronary circulatory indexes acquired from 4 experimental subjects. Although it is a relatively limited sample size, it is unethical to expand the sample size of experimental subjects after acquiring statistically significant results for the study hypothesis based on the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health.¹⁷

CONCLUSION

In a porcine tandem stenoses model, angioplasty for proximal stenosis induced significant changes in both resting and hyperemic APV, MR, and transstenotic PG across distal stenosis. Transstenotic PG across distal stenosis showed a similar increase in resting and hyperemic conditions after angioplasty for proximal stenosis. Both resting and hyperemic pressure-derived physiologic indexes after proximal stenosis angioplasty were significantly lower than predicted values.

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