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The effect of percutaneous coronary intervention on endothelial function

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Abstract

Objectives To evaluate the effect of percutaneous coronary intervention (PCI) on endothelial function. **Background** Endothelial injury following PCI remains one of the most common problems. Although previous studies have demonstrated that PCI is usually followed by endothelial damage/dysfunction, the characteristics and influence factors of the changes in endothelial function are not clear except for some biomarkers in blood. **Methods** We performed an observational study on 75 patients including 25 patients undergoing diagnostic coronary angiography and 50 patients undergoing stent-based PCI. In data analysis, we further divided the 50 patients into short-stent group and long-stent group according to the total length of stents. Flow-mediated dilation (FMD) and nitroglycerin-mediated dilation were recorded preoperatively, and at 24 h after procedure, as well as three blood biomarkers high-sensitivity C-reactive protein, von Willebrand Factor (vWF) and Interleukin-6. **Results** After PCI, FMD deteriorated much more significantly in long-stent group than in short-stent group (ΔFMD: 3.2 ± 1.2 *vs.* 1.6 ± 1.0%, $P < 0.01$), whereas FMD did not change significantly in coronary angiography group (9.1 ± 2.0 *vs.* 8.3 ± 2.5%, $P = 0.081$). In addition, an elevation of vWF following PCI was observed both in long-stent group (170 ± 79 *vs.* 207 ± 95 IU/dL, $P < 0.001$) and short-stent group (172 ± 69 *vs.* 194 ± 50 IU/dL, $P = 0.008$). Significant positive correlation existed between the decrease of FMD and increase of vWF ($r = 0.328$, $P = 0.020$). Multiple linear regression analysis showed that FMD deterioration is significantly correlated with total stent length ($P = 0.001$) and total dilation pressure ($P = 0.036$). **Conclusions** A remarkable deterioration of FMD and a proportional increase in vWF level in our study suggests that PCI induced the impairment of endothelial function. The extent of endothelial dysfunction is correlated with stent length and the total dilation pressure.

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Keywords: Coronary stent implantation; Endothelial dysfunction; Flow-mediated dilation; von Willebrand Factor

1 Introduction

Percutaneous coronary intervention (PCI) is one of the most commonly used interventional therapies for the treatment of patients with coronary atherosclerotic heart disease. However, existing researches have shown that cardiovascular interventional procedures do also induce endothelial damage which may be one of the primary causes of adverse events after PCI.[1−4] Some studies have supported the correlation between endothelial injury and PCI. However, most of them have been only focused on the changes in the levels of blood markers.[5−7] With respect to the changes of vascular endothelial function, existing researches are still too sparse to clarify the characteristics and influence factors.

Brachial flow-mediated dilation (FMD) has been one of the most commonly used indicators of nitric oxide-dependent endothelial function.[8, 9] Impaired FMD is associated with coronary disease and its risk factors, as well as in-stent restenosis after PCI.[4,10−13] However, there has been little research regarding the relationship between PCI and the changes of FMD.

In this context, our study is aimed at investigating the endothelium-dependent and -independent vasodilation following PCI and diagnostic coronary angiography, and clarifying the influence factors of FMD deterioration.

2 Methods

2.1 Patients

A total of 75 patients were enrolled, including 25 patients undergoing diagnostic coronary angiography and 50 patients undergoing stent-based PCI at the cardiovascular intervention center affiliated to Chinese PLA General Hospital from November 2012 to March 2013. All patients were

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subjected to coronary angiography for the first time, without a history of myocardial infarction. The patients who had at least one important coronary artery stenosis more than 70% were considered to have the indication for stent implantation. This study was approved by the institutional review boards of the institutions and informed consent was obtained from all participants.

Under local anesthesia with 1% lidocaine hydrochloride, the patients underwent coronary angioplasty using the standard Judkins technique and a movable guide wire system through the right radial artery. All patients received antiplatelet therapy with clopidogrel and aspirin preoperatively and intravenous administration with heparin during the procedure. All patients included into the study had a successful procedure defined as a residual stenosis < 30% in the worse of two orthogonal views, without major cardiac events during peri-procedural phase, such as myocardial infarction, further revascularization and death.

Patients were excluded from the study if they met one of the following criteria: (1) severe complications during the procedure; (2) recent surgical history (within six months); (3) decompensated heart failure (ejection fraction < 45%); (4) renal or hepatic failure; (5) recent history of infection; (6) medication with immunosuppressants or hormone replacement therapy; (7) malignant tumors; (8) pregnancy, thyroid disorder or other situations which are known to influence the accuracy of measured values of FMD.

2.2 Blood samples

For each patient, venous blood samples were obtained before and 24 ± 4 h after the procedure from an antecubital vein, using a 21-gauge needle. Plasma samples were immediately analyzed for the levels of von Willebrand Factor (vWF), high-sensitivity C-reactive protein (hs-CRP) and Interleukin-6 (IL-6). Plasma vWF antigen was quantitatively determined by automated latex particle enhanced Immunoturbidimetric assay using commercial reagents (Instrumentation Laboratory Co.; Bedfold; USA). The serum level of hs-CRP was measured by nephelometry immunoassay using commercial reagents (Healthcare Diagnostics Inc.; Newark; USA) and IL-6 was measured by electro-chemiluminescence immunoassay (ECLIA) using commercial reagents (Roche Diagnostics GmbH; Mannheim; Germany). All categorization and management of patients were independent of these results.

2.3 Flow-mediated dilation of brachial artery

Ultrasound assessment of FMD was completed according to the guidelines proposed by the International Brachial Artery Reactivity Task Force.[8]

All vasoactive drugs such as nitrates, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin antagonists, β-blockers and calcium antagonists were withdrawn at least 24 hours prior to the measurement. For all patients, FMD were assessed on the day of the procedure in fasting state. In addition, the patients were prohibited from taking caffeine, high fat food, vitamin C and smoking at least 4-6 h prior to the assessment. For those premenopausal women, menstrual cycle was recorded.

Since coronary angiography was mostly performed via the right radial artery in our hospital, we chose the left brachial artery for the assessment of FMD to prevent hematoma when we rechecked FMD 24 h after the procedure. High-resolution Doppler ultrasound (EF38G; Unex Co. Ltd., Nagoya, Japan) with a 10-MHz linear-array transducer was used to acquire images of the left brachial artery, while the right arm was used to monitor blood pressure. After baseline images were obtained, a forearm blood pressure cuff was inflated to 50 mmHg above the patient's systolic blood pressure for 5 min to occlude the brachial artery. Then the cuff was deflated rapidly. Images were obtained continuously after cuff deflation for 2 min. After the brachial artery diameter returned to the baseline, 10-15 min later, a second scan was recorded. A single dose of nitroglycerin (0.5 mg) was administered sublingually, and the image of brachial artery was serially scanned until the peak vasodilatation occurred. Artery diameter measurements were made at end-diastole in the cardiac cycle (peak of R wave on electrocardiogram) using ECG gating. All assessments and analyses of FMD and nitroglycerin-mediated dilation (NMD) were done by an observer who was blinded to interventional procedures and clinical details. FMD was expressed as the increased percentage in brachial arterial diameter after reactive hyperemia, while NMD as the increased percentage after nitroglycerin administration. FMD was known as the index of endothelium-dependent vasodilation, and NMD was known as the index of endothelium-independent vasodilation. In order to keep the baseline diameter stable over time to reduce the error in rechecking FMD after coronary intervention procedure, we marked the position of the ultrasonic probe and cuff on the left arm.

2.4 Statistical analysis

The normality of all variables was tested using one-sample Kolmogorov-Smirnov test. The measurement data were presented as mean ± SD if they were normally distributed. Otherwise, they were listed as medians (M) with interquartile ranges (IQR). Discrete data was presented as percentages, and compared among groups using chi-square analysis. Comparison for normally distributed data among the

three groups was performed with ANOVA test; otherwise Kruskal–Wallis test was used. Intra-individual comparison between the pre- and post-procedure was performed with a paired *t*-test. A multiple liner regression was performed to determine the correlation between FMD changes and procedure-related factors. All analyses were performed using SPSS 13.0 statistical software. $P \leqslant 0.05$ was considered statistically different.

3 Results

3.1 Patient demographics

A total of 75 patients were included into the study group (52 males, 23 females) with an average of 59 ± 8 (39 to 77) years. In our study, all females were postmenopausal, and none of them were receiving estrogen replacement therapy. Ten patients presented with unstable angina pectoris while the others with stable one. No statistical differences were found in basic clinical characteristics among all three groups. However, there was a high prevalence of risk factors including cigarette-smoking ($P = 0.032$), hypertension ($P = 0.002$) and hypercholesterolemia ($P = 0.028$) in the patients of long-stent group compared with the other two groups. In the long-stent group, application of beta-blockers ($P = 0.039$) and statins ($P = 0.030$) were much higher than that in the short-stent group and angiography group. That may partially explain why there was no significant difference in the baseline of blood lipid and blood pressure level between the long-stent group, which include more hypertensive and hyperlipidemic patients, and the other groups. Clinical characteristics and cardiovascular risk factors of the 75 patients are presented in Table 1.

Table 1. Baseline characteristics of different groups.

	Angiography group (n = 25)	Short-stent group (n = 25)	Long-stent group (n = 25)	P value
Age, yrs	58 ± 11	57 ± 8	60 ± 8	0.412
Female	10(40)	8(32)	5(20)	0.304
Body mess index, kg/m^2	26.94 ± 3.38	25.98 ± 3.74	25.88 ± 2.90	0.471
Systolic pressure, mmHg	130 ± 12	127 ± 13	129 ± 17	0.792
Diastolic pressure, mmHg	81 ± 10	76 ± 10	79 ± 9	0.195
Heart rate, beats/min	71 ± 7	69 ± 7	72 ± 6	0.377
Ejection fraction, %	58 ± 8	59 ± 6	59 ± 6	0.710
Stable angina	22(88)	22(88)	21(84)	0.891
Risk factors				
Hypertension	13(52)	9(36)	21(84)	0.002
Hyperlipidemia	5(20)	11(44)	14(56)	0.028
Diabetes mellitus	8(32)	6(24)	12(48)	0.192
Current smoker	5(20)	10(40)	14(56)	0.032
Familial history of coronary artery disease	0(0)	2(8)	4(16)	0.114
Medication on admission				
Nitroglycerine or nitrates	3(12)	6(24)	6(24)	0.472
Beta-blockers	1(4)	5(20)	8(32)	0.039
ACEIs	0(0)	3(12)	4(16)	0.129
ARBs	2(8)	6(24)	6(24)	0.245
CCBs	4(16)	5(20)	9(36)	0.215
Aspirin	6(24)	11(44)	11(44)	0.175
Clopidogrel	2(8)	3(12)	5(20)	0.446
Statins	5(20)	11(44)	14(56)	0.030
Total cholesterol, mg/dL	168.8 ± 33.2	157.8 ± 43.4	166.6 ± 44.1	0.617
Triglyceride, mg/dL	109.0 ± 53.0	132.6 ± 74.3	185.4 ± 143.0	0.080
HDL cholesterol, mg/dL	48.3 ± 9.6	42.0 ± 9.9	44.9 ± 19.1	0.761
LDL cholesterol, mg/dL	102.3 ± 26.1	93.9 ± 35.1	93.8 ± 33.8	0.542
Apolipoprotein A1, g/L	1.19 ± 0.29	1.19 ± 0.21	1.19 ± 0.24	0.999
Apolipoprotein B, g/L	0.79 ± 0.22	0.76 ± 0.26	0.89 ± 0.19	0.297

Data are expressed as mean ± SD or n(%). ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; CCB: calcium channel blocker; HDL: high-density lipoprotein; LDL: low-density lipoprotein.

3.2 Coronary angiography results

A total of 75 patients underwent diagnostic coronary angiography and 50 of them had indications for stent implantation. All procedures were successfully completed without complications. For the 50 patients who had stent implantation, the maximum total length of stent was 135 mm and the minimum was 14 mm, with a median length of 41 mm. Thus the patients receiving stent implantation of total length $\leqslant$ 41 mm were defined as short-stent group, the others were defined as long-stent group. The average length of the stents was 67.1 ± 24.7 mm in long-stent group and 24.9 ± 7.9 mm in short-stent group ($P < 0.001$).

Of the 25 patients in the coronary angiography group, 10 had no prominent stenosis, one was diagnosed as coronary atherosclerosis (stenosis < 50%) and 14 were diagnosed as coronary atherosclerotic heart disease. Three of the 14 patients had multi-vessel disease and the stenosis was so severe that we advised them to receive coronary artery bypass grafting surgery. The remaining 11 patients did not have the indications for stent implantation with either stenosis less than 70% or reserved coronary artery flow. There were much more cases of multi-vessel diseases in the long-stent implantation group than in the angiography group (68% *vs.* 12%, $P < 0.001$) and short-stent implantation group (68% *vs.* 24%, $P = 0.002$). The total coronary atheroma burden of coronary artery disease assessed by Gensini score was much higher in the long-stent implantation group in comparison with the other two groups ($P < 0.001$). The coronary angiography results were shown in Table 2.

Table 2. Results of coronary angiography.

	Angiography group *n* = 25	Short-stent group *n* = 25	Long-stent group *n* = 25	*P* value
No. Coronary diseased vessels				< 0.001
0	11(44)	0(0)	0(0)	
1	11(44)	11(44)	2(8)	
2	0(0)	8(32)	6(24)	
3	3(12)	6(24)	17(68)	
Target vessel				0.701
LAD	-	18(66.7)	48(75.0)	
LCX	-	6(22.2)	10(15.6)	
RCA	-	3(11.1)	6(9.4)	
Types of stents				0.719
Rapamycin-eluting stent	-	22(81.5)	50(78.1)	
Paclitaxel-eluting stent	-	5(18.5)	14(21.9)	
Gensini Score	5(0–8)	24(12–51)	46(27–70)	< 0.001
No. stents	-	1.1 ± 0.3	2.6 ± 0.9	< 0.001
Total length of stents	-	24.9 ± 7.9	67.1 ± 24.7	< 0.001

Data are expressed as mean ± SD or *n*(%). LAD: left anterior descending coronary artery; LCX: left circumflex coronary artery; RCA: right coronary artery.

3.3 Brachial-artery ultrasound results

For all groups of patients, average FMD was 8.0 ± 2.3% ($n = 75$), and average NMD was 13.4 ± 5.1% ($n = 75$). The FMD before the procedure were significantly lower in long-stent group than the other two groups ($P < 0.01$), while there were no obvious differences in the responses to nitroglycerin among all three groups ($P = 0.682$). In addition, we found that basic brachial FMD was closely correlated with the total coronary atheroma burden assessed by Gensini score ($r = –0.735$, $P < 0.01$) (Figure 1).

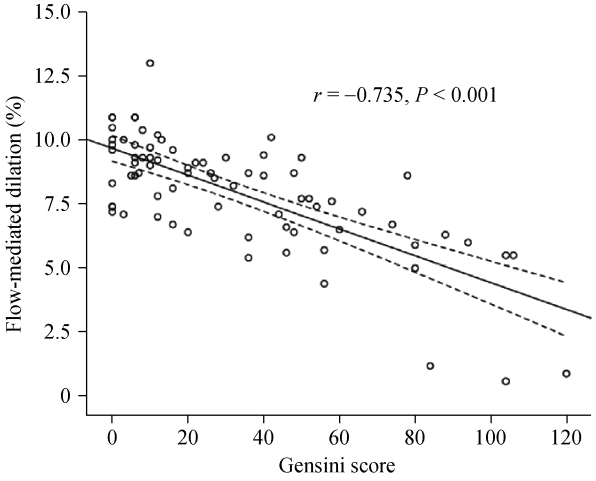

Figure 1. Correlation (Pearson *r*, 95% CI) between FMD and Gensini score. There was a negative correlation between FMD and Gensini score ($r = –0.735$, $P < 0.01$). FMD: flow-mediated dilation.

The parameters of brachial-artery of the patients pre- and post-procedure are displayed in Table 3. As shown, in patients with stent implantation, FMD decreased significantly while there were no obvious changes of the basic brachial artery diameter, reactive hyperemia and the time to peak. In the long-stent group, the impairment of FMD was much worse than that in the short-stent group (ΔFMD: 3.2 ± 1.2 *vs.* 1.6 ± 1.0, $P < 0.01$) (Figure 2). In contrast to PCI group, FMD was not influenced by diagnostic coronary angiography (9.1 ± 2.0 *vs.* 8.3 ± 2.5, $P = 0.081$). There were no obvious changes in the level of NMD before and after procedure in all three groups (Figure 3). Impaired FMD had been shown to be associated with longer stent length, longer balloon length and higher total dilation pressure by univariate linear regression analysis. For multiple linear regression analysis, the covariates were selected on the basis of prior evidence of an association with decreased FMD in the present study (inclusion a priori $P < 0.20$). The covariates included total stent length, total balloon length, total dilation pressure, history of diabetes mellitus and family history of coronary artery disease. The results of multiple linear regression analysis showed that only total stent length ($P =$

Table 3. Results of brachial-artery ultrasound.

	Pre-procedure	Post-procedure	*P* value
Angiography group			
Baseline brachial artery diameter, mm	3.96 ± 0.61	3.86 ± 0.54	0.163
Reactive hyperemia, % increase	383 ± 123	367 ± 96	0.492
Time at max diameter, s	57.5 ± 13.6	60.1 ± 18.7	0.293
Flow-mediated dilation, %	9.1 ± 2.0	8.3 ± 2.5	0.081
NTG-mediated dilation , %	14.0 ± 4.9	13.8 ± 3.9	0.850
Short-stent group			
Baseline brachial artery diameter, mm	3.72 ± 0.62	3.79 ± 0.65	0.571
Reactive hyperemia, % increase	385 ± 98	368 ± 117	0.269
Time at max diameter, s	62.2 ± 19.0	65.6 ± 23.6	0.358
Flow-mediated dilation, %	8.1 ± 2.5	6.5 ± 2.2	< 0.01
NTG-mediated dilation, %	12.7 ± 5.3	12.5 ± 4.8	0.703
Long-stent group			
Baseline brachial artery diameter, mm	3.92 ± 0.54	3.86 ± 0.62	0.291
Reactive hyperemia, % increase	386 ± 82	374 ± 80	0.216
Time at max diameter, s	61.6 ± 15.7	59.0 ± 17.2	0.338
Flow-mediated dilation, %	6.8 ± 2.1*,**	3.6 ± 1.8	< 0.01
NTG-mediated dilation, %	13.6 ± 5.3	12.7 ± 4.5	0.102

Data are expressed as mean ± SD. $^{*}P < 0.01$ compared with short-stent group; $^{**}P < 0.01$ compared with angiography group. NTG: nitroglycerin.

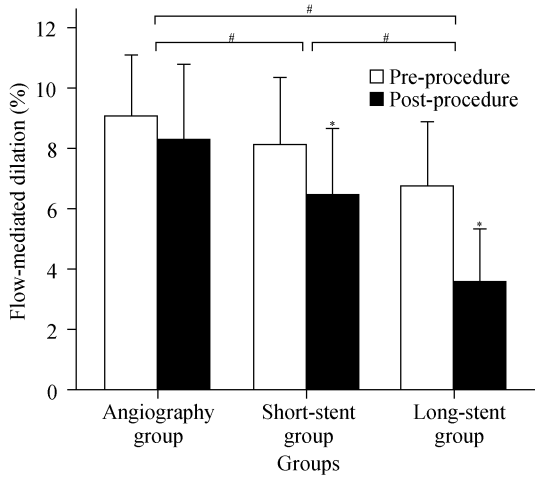

Figure 2. Changes in FMD levels after procedure. Data are present as mean ± SD. $^{*}P < 0.01$ *vs*. before PCI; $^{\#}P < 0.01$ compared between two groups by the changes of FMD. FMD: flow-mediated dilation.

0.001) and total dilation pressure ($P = 0.036$) were independent determinants of FMD deterioration. The determination coefficient R^2 was 0.556. The statistics were shown in Table 4 and Table 5.

3.4 hs-CRP and IL-6 levels pre- and post-PCI

To investigate the association between systemic inflammation and PCI, the quantifications of hs-CRP and IL-6 were performed in all three groups (Table 6). Baseline IL-6 level was too low to detect in 11 of 75 patients. Baseline hs-CRP and IL-6 levels were comparable. Following PCI, there were no prominent changes of these two inflammation

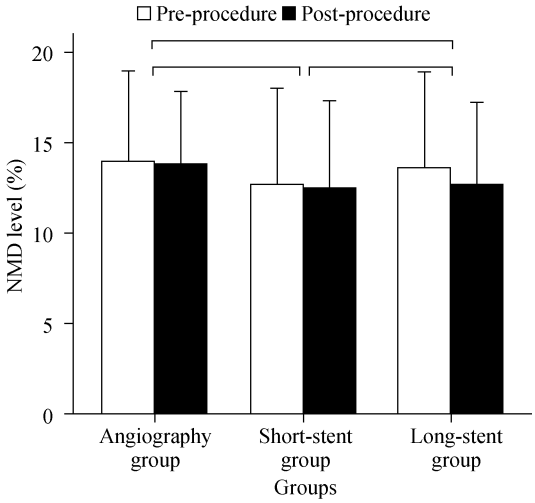

Figure 3. Changes in NMD levels after procedure. No difference was found in NMD levels among the three groups by coronarography after PCI. NMD: nitroglycerin-mediated dilation.

Table 4. Univariate linear regression analysis for predictors of FMD deterioration.

	Univariate linear regression analysis	
	Correlation coefficient	*P* value
Average stent diameter, mm	$r = 0.245$	0.087
Total stent length, mm	$r = 0.706$	< 0.001
Average balloon diameter, mm	$r = 0.130$	0.369
Total balloon length, mm	$r = 0.438$	0.001
Total dilation pressure, atm	$r = 0.615$	< 0.001
Types of stents (Paclitaxel-eluting stent)	$r = -0.010$	0.944
Current smoker	$r = 0.170$	0.237
Hypertension	$r = 0.086$	0.552
Hyperlipidemia	$r = 0.134$	0.355
Diabetes mellitus	$r = 0.268$	0.060
Familial history of coronary artery disease	$r = 0.215$	0.134
Aspirin	$r = –0.072$	0.620
Clopidogrel	$r = 0.034$	0.813
Nitroglycerine or nitrates	$r = 0.085$	0.557
Statins	$r = -0.024$	0.867
Beta-blockers	$r = 0.073$	0.615
ACEI	$r = -0.061$	0.675
ARB	$r = 0.057$	0.696
CCB	$r = 0.072$	0.620
Diuretic	$r = 0.100$	0.489

ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; CCB: calcium channel blocker; FMD: flow-mediated dilation.

Table 5. Multiple linear regression analysis for predictors of FMD deterioration.

	Univariate linear regression analysis	
	Correlation coefficient	***P* value**
Total stent length, mm	β = 0.539	0.001
Total balloon length, mm	β = 0.105	0.469
Total dilation pressure, atm	β = 0.329	0.036
Diabetes mellitus	β = 0.028	0.807
Familial history of coronary artery disease	β = 0.124	0.262

Determination coefficient $R^2 = 0.556$. FMD: flow-mediated dilation.

Table 6. Results of the biomarkers in blood.

	Before procedure	**After procedure**	***P* value**
vWF (IU/dL)			
Angiography group	142 ± 70	150 ± 77	0.330
Short-stent group	172 ± 69	194 ± 50	0.008
Long-stent group	170 ± 79	207 ± 95	< 0.001
hs-CRP (mg/L)			
Angiography group	1.83 ± 1.18	1.80 ± 1.32	0.837
Short-stent group	2.03 ± 1.47	2.15 ± 1.49	0.649
Long-stent group	2.69 ± 2.64	3.00 ± 2.94	0.093
IL-6 (pg/mL)			
Angiography group	2.91 ± 1.88	2.65 ± 1.60	0.082
Short-stent group	3.03 ± 1.59	3.27 ± 1.75	0.156
Long-stent group	3.50 ± 1.66	3.73 ± 2.09	0.173

Data are expressed as mean ± SD. hs-CRP: high-sensitivity C-reactive protein; IL-6: Interleukin-6; vWF: von Willebrand Factor.

markers in all three groups. However, there was a trend that hs-CRP and IL-6 levels increased in the stent-implantation group after procedure, although the differences were not significant.

3.5 vWF levels pre- and post-PCI

The levels of vWF in three groups pre- and post-procedure were listed in Table 6. The average level of vWF increased from 172 ± 69 pre-PCI to 194 ± 50 post-PCI in the short-stent group ($P = 0.008$), and 170 ± 79 pre-PCI to 207 ± 95 post-PCI in the long-stent group ($P < 0.001$). But we found that there was no significant difference in ΔvWF level between the long-stent group and the short-stent group (ΔvWF: 23.0 ± 39.5 vs 36.4 ± 40.0, $P = 0.226$). In coronary angiography group, there were no significant changes (142 ± 70 *vs.* 150 ± 77, $P = 0.330$) in vWF level after procedure. Notably, there was a correlation between FMD deterioration and vWF elevation although correlation coefficient was a little bit weak ($r = 0.328$, $P = 0.020$) (Figure 4).

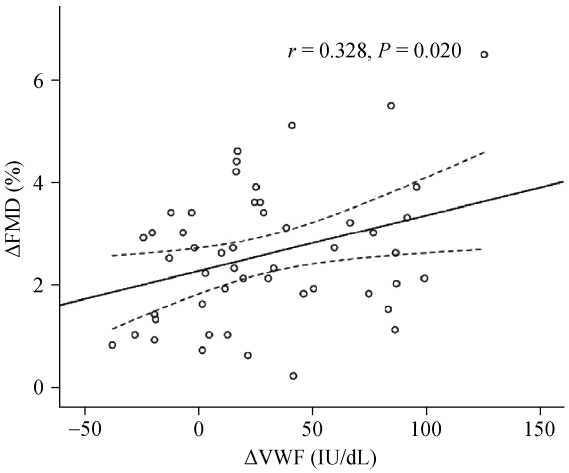

Figure 4. Correlation (Pearson *r*, 95% CI) between change in FMD and change in vWF after stent implantation. There was a weak but significant positive correlation between ΔFMD and ΔvWF ($r = 0.328$, $P = 0.020$). FMD: flow-mediated dilation.

4 Discussion

Although PCI has become one of the most commonly used treatments for atherosclerotic heart diseases, endothelial injury after the stent implantation remains to be a prominent problems. Evidence suggests that endothelial dysfunction play an important role in the development and progression of atherosclerotic diseases, acute coronary syndrome and restenosis after PCI.[12–15] Theoretically, PCI itself was considered to lead to substantial endothelial cell injury with complex mechanisms including systemic inflammatory, activation of the platelets, ischemia and reperfusion injury, plaque rupture, arterial wall damage and the like.[16–18] Although previous researches have demonstrated that PCI is followed by endothelial damage/dysfunction, most of them have been focused on the biomarkers in blood, such as Endothelin-1, vWF, circulating endothelial cells (CECs) and endothelial microparticles (EMPs). Some previous studies have shed some light on the effects of PCI on FMD levels, but none of them have investigated the factors associated with the decrease of FMD, let alone the interrelationships between the impaired FMD and other circulating endothelial markers. So we pay attention to define the correlation between impaired FMD, related factors and circulating endothelial injury markers.

Spiro *et al.*[19] has found that there was an significant decrease of FMD immediately after PCI, even when there were no obvious changes in blood inflammatory markers. But it must be pointed out that only 10 patients were enrolled in that study. In our research, we found a significant decrease in FMD level and an increase in vWF level in the patients who received stent implantation. No significant changes were observed in the patients who only had an angiography. We also found that in the long-stent group, the impairment of FMD was much worse than that in the short-stent group. Univariate linear regression analysis show-

ed that impaired FMD induced by PCI was positively correlated with procedure-related factors including the total length of stents and balloons, and the total dilation pressure. The results of multiple linear regression also showed that the total length of stents and total dilation pressure acted as significant influence factors.

For vWF, our findings were consistent with several previous studies that have shown an increase in the level of vWF in the patients who had received PCI.[20, 21] Boos, *et al.*[20] has found that 24 h after coronary stent implantation there was an elevation on the level of vWF and CECs, in addition, there was a significant correlation between the changes in vWF and CECs. Vargová, *et al.*[21] observed that the plasma vWF level was still elevated even 96 h after the procedure, and argued that the change in vWF was also attributed to the general vascular system rather than only the coronary endothelial cells in response to the procedure. In our study, there were no significant differences in baseline vWF level among the three groups, but an elevation of vWF level was found in the patients undergoing stent implantation. We also found that after PCI, there was a positive correlation between the increase of vWF and the decrease of FMD. So our study showed agreement with Vargová's theory that the increase vWF level was much more likely to be a systemic reaction after PCI rather than a local damage of coronary endothelial cells, since the function of peripheral endothelial cells was also impaired.

Interestingly, although some previous studies have suggested that there would be a systemic inflammatory reaction after PCI procedure, in our study, we did not find an elevation of hs-CRP and IL-6 level. We summarize the possible reasons as follows. First, patient demographics were different. Previous researches enrolled more patients with unstable angina pectoris, non-ST segment elevation myocardial infarction and high risk status. Liuzzo, *et al.*[22] has suggested that for individuals who had severe unstable angina, there would be a marked increase in IL-6, CRP and SAA level after coronary intervention. However, for patients with stable angina, there were no obvious changes. In our study, there were only about 13.3% of our patients were unstable angina, and no acute myocardial infarction patient was enrolled, as may partly explain the absence of significant increase in hs-CRP and IL-6 after PCI. Second, the baseline level of the inflammatory factors in our study was relatively low. There was only 12% of the individuals presenting with a hs-CRP level above 3 mg/L. Previous studies have shown that patients with an elevated CRP were particularly "sensitive" to coronary intervention. Even coronary angiography is sufficient enough to cause an CRP elevation in the patients with an elevated baseline CRP level[22]. Versaci, *et al.*[23] and Sciahbasi, *et al.*[24] has reported that in the patients with a high pre-procedural serum level of CRP were much more likely to present with a robust elevation of CRP after the procedure than patients who had normal pre-procedural serum levels of CRP. Last, but not the least, all the biomarkers in the blood were only measured at two time points (pre-PCI and 24 h after PCI). Since the trend of hs-CRP after the procedure was not fully understood, we cannot rule out the possibility that we may have missed an abrupt rise in release of hs-CRP, which might otherwise have been observed by more frequent and protracted sampling after PCI. Since we measured two inflammatory markers only, which may be affected by PCI at two time points, we could not rule out the possibility that there was actually a systemic inflammatory response after PCI.

4.1 Study limitations

Our study has some limitations. First, we measured FMD and the blood biomarkers at two time points only, so the trends of changes in these indexes after PCI were not fully investigated, especially FMD. As far as we know, there is only one research showing the time course of the endothelial function in response to coronary stents which is performed on pigs by Plass, *et al.*[25] Second, in this study, we only use vWF as the indicator for endothelial cell damage. Although vWF is one of the most common markers used for endothelial injury, the result would be much more convincing if we had included some other markers such as EMPs. Finally, there was only a small part of the patients presenting with unstable angina, so the representativeness of the sample may not be good enough.

4.2 Conclusions

We found that a significant deteriorated FMD was observed in the patients who had stent implantation, and that the changes of FMD were correlated with total stent length and total dilatation pressure. That is to say, PCI induced the impairment of endothelial function, the extent of which is correlated with stent length and total dilation pressure. In addition, FMD impairment was accompanied with an elevated level of vWF which suggests that PCI induces both endothelial cells damage and endothelial dysfunction.

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