ORIGINAL RESEARCH

Fractional Flow Reserve and Instantaneous Wave-Free Ratio Predict Pathological Wall Shear Stress in Coronary Arteries: Implications for Understanding the Pathophysiological Impact of Functionally Significant Coronary Stenoses

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BACKGROUND: The pathophysiological mechanism behind adverse outcomes associated with ischemia-inducing epicardial coronary stenoses and microcirculatory dysfunction remains unclear. Wall shear stress (WSS) plays an important role in atherosclerotic plaque progression and vulnerability. We aimed to evaluate the relationship between WSS, functionally significant epicardial coronary stenoses, and microcirculatory dysfunction.

METHODS AND RESULTS: Patients undergoing invasive coronary physiology testing were included. Fractional flow reserve, instantaneous wave-free ratio, and the index of microcirculatory resistance were measured. Quantitative coronary angiography was used to obtain the lesion percentage diameter stenosis. Computational fluid dynamics analysis was performed to calculate WSS parameters. Multiple regression analysis was performed to calculate the standardized regression coefficient ($\beta$) for the coronary physiology indices.

A total of 107 vessels from 88 patients were included. Fractional flow reserve independently predicted the total area of low WSS ($\beta$=−0.44; 95% CI, −0.62 to −0.25; $P<0.001$) and maximum lesion WSS ($\beta$=−0.53; 95% CI, −0.70 to −0.36; $P<0.001$) after adjusting for percentage diameter stenosis and index of microcirculatory resistance. Similarly, instantaneous wave-free ratio also independently predicted the total area of low WSS ($\beta$=−0.45; 95% CI, −0.62 to −0.28; $P<0.001$) and maximum lesion WSS ($\beta$=−0.58; 95% CI, −0.73 to −0.43; $P<0.001$). The index of microcirculatory resistance did not predict either low or high WSS.

CONCLUSIONS: Fractional flow reserve and instantaneous wave-free ratio independently predicted the total burden of low WSS and maximum lesion WSS in coronary arteries. No relationship was found between microcirculatory dysfunction and WSS.

Key Words: fractional flow reserve ■ index of microcirculatory resistance ■ instantaneous wave-free ratio ■ wall shear stress

Myocardial ischemia has long been associated with poor outcomes in patients with coronary artery disease. Studies have established fractional flow reserve (FFR) as a more important prognosticator than angiographic severity in patients undergoing revascularization. Coronary microvascular dysfunction, defined by abnormal index of microcirculatory resistance (IMR), is also associated...
with worse outcomes. Yet, the pathophysiological mechanisms underpinning the poor prognosis in patients with functionally significant coronary epicardial and microcirculatory disease are not well understood.

Wall shear stress (WSS), the tangential force exerted on the endothelium by blood flow, has been implicated as a cause of the uneven distribution of atherosclerotic disease throughout the coronary circulation. Low WSS is associated with severe endothelial dysfunction, progression of atherosclerotic plaque, constrictive remodeling, and necrotic core development; whereas high WSS predicts plaque transformation and myocardial infarction.

Currently, it is not known how coronary physiology influences WSS, and determining their relationship may yield insights into the pathophysiological basis for the poor prognosis seen in patients with myocardial ischemia. We therefore performed a study to evaluate whether epicardial and microcirculatory physiology indices can predict abnormal WSS perturbations independent of angiographic severity.

**CLINICAL PERSPECTIVE**

**What Is New?**
- Abnormal fractional flow reserve and instantaneous wave-free ratio were associated with both pathological low and high wall shear stress in coronary arteries, irrespective of the underlying lesion’s angiographic severity.

**What Are the Clinical Implications?**
- Given the known relationship between pathological wall shear stress and atherosclerosis progression, our results provide a potential explanation for the higher incidence of adverse events in patients with ischemia-inducing epicardial coronary stenoses.

**METHODS**

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

**Study Population**

We included patients who underwent comprehensive invasive coronary physiological assessment at 2 tertiary referral hospitals for research purposes. This population consisted of patients from 3 separate studies: the first enrolled patients between April 2008 and October 2010 to derive a method of calculating IMR without the coronary wedge pressure; the second evaluated patients between March 2015 and March 2017 to determine the effects of remote ischemic preconditioning on the microcirculation; the third included patients between February 2019 and July 2020 to examine the relationship between the coronary epicardial arteries and the microcirculation (Australian New Zealand Clinical Trials Registry ID: ACTRN12619000450112). Exclusion criteria were culprit vessels in acute coronary syndrome, nonculprit vessels <48 hours after acute ST-segment-elevation myocardial infarction, cardiogenic shock, bypass graft to the target vessel, tortuous vessels precluding safe passage of the pressure guidewire, and any contraindication to adenosine administration. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, and was approved by the human research ethics review boards of both institutions. Written informed consent was obtained from all participants. C.C.Y.W. and A.S.C.Y. had full access to all the data in the study and take responsibility for their integrity and the data analysis.

**Nonstandard Abbreviations and Acronyms**

| Abbreviation | Meaning |
|--------------|---------|
| 3-D          | 3-dimensional |
| CFD          | computational fluid dynamics |
| %DS          | percentage diameter stenosis |
| FFR          | fractional flow reserve |
| iFR          | instantaneous wave-free ratio |
| IMR          | index of microcirculatory resistance |
| WSS          | wall shear stress |

**Coronary Angiography and Physiology Measurements**

Coronary angiography was performed as per standard institutional practice via the radial or femoral route. After diagnostic angiography, a pressure-temperature sensor guidewire (PressureWire X; Abbott Corporation, Chicago, IL) was advanced to the tip of the guiding catheter and equalized to the guide catheter pressure. The guidewire was then advanced to the distal third of the vessel, at least 3 cm downstream from the target lesion. Intracoronary nitroglycerin was administered at a dose of 100 to 200 μg.

The resting mean proximal pressure and distal pressure were recorded. Three boluses of 3 mL room temperature saline were then injected into the coronary artery via the guiding catheter. The transit time of the saline injections was determined using the thermodilution technique, and the average of the 3 resting transit times was recorded as the resting mean transit time.
time. An intravenous infusion of adenosine (140 μg/kg per minute) was then administered via a large-bore peripheral cannula or femoral venous sheath for a minimum duration of 90 seconds to achieve maximal hyperemia. The hyperemic mean proximal pressure and distal pressure were recorded. Thermoclinium curves were then produced in the same manner to determine the hyperemic mean transit time.

All measurements were recorded using the Coroflow system (Coroventis Research AB, Uppsala, Sweden). FFR was calculated as the ratio of hyperemic mean distal pressure/hyperemic mean proximal pressure. The corrected IMR was calculated in all patients using the following formula: IMR=hyperemic mean proximal pressure×hyperemic mean distal pressure/hyperemic mean proximal pressure–0.32. In vessels with significant epicardial stenoses, the commonly used simplified formula (IMR=hyperemic mean distal pressure×hyperemic mean transit time) can overestimate IMR by neglecting the significant contribution of collateral flow. The corrected IMR formula accounts for the contribution of collateral flow toward IMR calculation without requiring the additional invasive step of obtaining coronary wedge pressure, and has been shown to have excellent correlation and agreement with true IMR.4,11,13

The corrected IMR formula (IMR=hyperemic mean distal pressure×hyperemic mean proximal pressure×hyperemic mean transit time×1.35×[hyperemic mean distal pressure/hyperemic mean proximal pressure×hyperemic mean transit time]) can overestimate IMR by neglecting the significant contribution of collateral flow. The corrected IMR formula accounts for the contribution of collateral flow toward IMR calculation without requiring the additional invasive step of obtaining coronary wedge pressure, and has been shown to have excellent correlation and agreement with true IMR.4,11,13

WSS Calculation

The WSS calculation was performed by an independent analyst blinded to the coronary physiology indices. Three-dimensional (3-D) reconstructions of the target vessels were performed using a Leonardo workstation (IC3D; Siemens, Forchheim, Germany). End-diastolic images from 2 orthogonal angiographic views at least 30° apart were selected for reconstruction. Of the 137 available vessels, 30 were excluded because of inadequate image quality for accurate 3-D reconstruction.

Computational fluid dynamics (CFD) analysis was subsequently performed using methods described in our previous studies.18,19 In brief, the reconstructed 3-D models were imported into mesh generation software (ANSYS CFX 12.1, PA). The surfaces of the vessels were triangulated with a node distance between 0.01 and 0.02 mm, and a boundary layer mesh with 4 rows and a growth factor of 1.2 was generated.

For the CFD simulation, flow was considered to be 3-D, steady, and turbulent. Blood was modeled as a noncompressible Newtonian fluid with a dynamic viscosity of 0.0035 Pa·s and a density of 1050 kg/m³. Walls were considered rigid, and a no-slip boundary condition was applied. The inlet and outlet boundary conditions were individualized and set to the patients’ invasively measured aortic and distal coronary pressure, respectively. The fluid motion equations were solved using the finite volume-based software ANSYS CFX 12.1.

The maximum WSS at the lesion site along with the total area of low WSS in each vessel were measured. On the basis of previous studies, a threshold of <1 Pa was chosen to define low WSS: Samady et al demonstrated greater progression of plaque area, necrotic core, and constrictive remodeling in coronary segments with WSS <1 Pa in a longitudinal intravascular ultrasound study; similarly, Stone et al found coronary segments with WSS <1.2 Pa exhibited plaque progression and constrictive remodeling on serial intravascular ultrasound examinations; lastly, Kumar et al showed a higher prevalence of endothelial dysfunction in coronary segments with WSS <1 Pa. An example of a coronary artery with CFD-derived WSS color mapping is provided in Figure 1.

Statistical Analysis

Continuous variables were expressed as mean±SD for normally distributed data, and median (interquartile range) for nonnormally distributed data. Categorical variables were expressed as frequencies (percentages). The study cohort was divided into nonobstructive (%DS <50) and obstructive (%DS ≥50) lesions, and the Mann-Whitney U test was used to compare differences in the total area of low WSS and maximum lesion WSS between ischemic and nonischemic vessels. Spearman rank correlation was used to assess the relationship between different WSS parameters and coronary physiology indices. Multiple regression analysis was performed with 2 separate models to determine whether the coronary physiology indices independently predicted WSS. Model 1 adjusted for FFR, %DS, and IMR, whereas model 2 adjusted for iFR, %DS, and IMR. Results were expressed as standardized coefficients (β) with 95% CIs. All analyses were performed using SPSS version 23 and Graphpad Prism version 8.4.0. A 2-tailed probability value <0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

A total of 107 vessels from 88 patients were included in this study. The mean age was 63±11 years, and
28% were women. Most patients had stable coronary artery disease (72%), and the left anterior descending artery was the most commonly studied vessel (70%). The median lesion %DS was 47% (interquartile range, 37%–57%), and median FFR and iFR were 0.85 (interquartile range, 0.73–0.90) and 0.89 (interquartile range, 0.83–0.95), respectively. There were 40 (37%) lesions with FFR ≤0.80, and 54 (51%) with iFR ≤0.89. FFR correlated significantly with iFR ($r_s=0.91; P<0.001$), whereas IMR did not correlate with FFR ($r_s=0.02; P=0.87$) or iFR ($r_s=-0.02; P=0.82$). Details of patient comorbidities and lesion characteristics are summarized in Table 1.

**Coronary Physiology Indices and Low WSS**

Vessels with ischemic FFR and iFR values had larger total area of low WSS compared with nonischemic vessels (FFR: 73 versus 28 mm²; $P<0.001$; iFR: 68 versus 26 mm²; $P<0.001$) (Figure 2A). There was no significant difference in the total area of low WSS between vessels with abnormal or normal IMR (63 versus 38 mm²; $P=0.16$).

In vessels with angiographically nonobstructive stenoses (%DS ≤50%, $n=62$), the total area of low WSS was significantly larger in those with ischemic FFR (63 versus 26 mm²; $P=0.002$) and iFR (53 versus 24 mm²; $P=0.01$) values compared with nonischemic vessels (Figure 2B). Similarly, in vessels with obstructive lesions (%DS ≥50%, $n=45$), the total area of low WSS was larger in those with ischemic FFR (90 versus 40 mm²; $P=0.01$) and iFR (90 versus 30 mm²; $P<0.001$) values (Figure 2C).

The total area of low WSS correlated significantly with FFR ($r_s=-0.58; P<0.001$), iFR ($r_s=-0.64; P<0.001$), and %DS ($r_s=0.65; P<0.001$), but not with IMR ($r_s=0.09; P=0.34$) (Figure 3). In a multiple regression model incorporating FFR, %DS, and IMR, both FFR and %DS were independent predictors of the total area of low WSS (FFR: $\beta=-0.44$; 95% CI, −0.62 to −0.25; $P<0.001$; %DS: $\beta=0.34$; 95% CI, 0.16–0.53; IMR did not correlate).
P<0.001) (Table 2). Similarly, after incorporating iFR, %DS, and IMR in a separate model, iFR and %DS were also independent predictors of the total area of low WSS (iFR: $\beta$=-0.45; 95% CI, −0.62 to −0.28; P<0.001; %DS: $\beta$=0.37; 95% CI, 0.20–0.54; P<0.001) (Table 3). IMR did not predict the total area of low WSS in either model.

**Coronary Physiology Indices and High WSS**

Vessels with ischemic FFR and iFR values had significantly greater maximum lesion WSS compared with nonischemic vessels (FFR: 95 versus 39 Pa [P<0.001]; iFR: 89 versus 37 Pa [P<0.001]) (Figure 4A). There was no significant difference in maximum lesion WSS between vessels with abnormal or normal IMR. In vessels with angiographically nonobstructive stenoses, maximum lesion WSS was significantly greater in those with ischemic FFR (90 versus 37 Pa; P<0.001) and iFR (76 versus 28 Pa; P=0.002) values compared with nonischemic vessels (Figure 4B). Similarly, in vessels with obstructive stenoses, maximum lesion WSS was significantly greater in those with ischemic FFR (104 versus 49 Pa; P=0.001) and iFR (103 versus 43 Pa; P<0.001) values (Figure 4C).

Maximum lesion WSS correlated significantly with FFR ($r_s$=−0.64; P<0.001), iFR ($r_s$=−0.70; P<0.001), and %DS ($r_s$=0.66; P<0.001), but not with IMR ($r_s$=0.07; P=0.49) (Figure 5). In a multiple regression model incorporating FFR, %DS, and IMR, both FFR and %DS were independent predictors of maximum lesion WSS (FFR: $\beta$=−0.53; 95% CI, −0.70 to −0.36; P<0.001; %DS: $\beta$=0.30; 95% CI, 0.12–0.47; P<0.001) (Table 2). Similarly, after incorporating iFR, %DS, and IMR in a separate model, iFR and %DS were also independent predictors of maximum lesion WSS (iFR: $\beta$=−0.58; 95% CI, −0.73 to −0.43; P<0.001; %DS: $\beta$=0.31; 95% CI, 0.16–0.45; P<0.001) (Table 3). IMR did not predict maximum lesion WSS in either model.

**DISCUSSION**

To the best of our knowledge, this is the first study to demonstrate a significant independent relationship between ischemia-inducing epicardial coronary stenoses and pathological WSS. On the other hand, we did not find any relationship between microcirculatory dysfunction and pathological WSS. Given the established evidence for low WSS in plaque progression\(^5,7,8\) and high WSS in vulnerable plaque transformation\(^9,10\) our results provide a potential explanation for the higher incidence of adverse events in vessels with functionally significant epicardial coronary stenoses.

**Clinical Relevance of Pathological WSS in Coronary Arteries**

Despite being a systemic process, atherosclerosis preferentially affects specific regions of the coronary arterial circulation. For example, the culprit lesion in acute myocardial infarction is often located near bifurcations and major curvatures, where increased
blood flow disturbances occur. Studies using CFD analysis have implicated WSS as a potential explanation for this phenomenon. In addition, the presence of a coronary stenosis further modulates local WSS perturbations; high WSS generally occurs at the throat of the lesion, whereas low and oscillatory WSS occurs proximal and distal to the site of maximal stenosis. Natural history studies of WSS in human coronary arteries demonstrated that coronary segments with low WSS, variably defined as <1 to 1.2 Pa, were associated with plaque progression, constrictive remodeling, and necrotic core development. This phenomenon was postulated to be secondary to endothelial activation of the protein kinase and nuclear factor-κB signaling pathways in response to low WSS, with subsequent expression of proinflammatory and apoptotic genes. Furthermore, coronary segments with low WSS have been shown to be

| Table 2. Multiple Regression Model Adjusted for %DS, FFR, and IMR |
|------------------|------|------|------|------|------|------|------|------|
| WSS parameters  | %DS β | 95% CI | P value | FFR β | 95% CI | P value | IMR β | 95% CI | P value |
| ALWSS, mm²       | 0.34  | 0.16 to 0.53 | <0.001 | −0.44 | −0.62 to −0.25 | <0.001 | 0.02  | −0.12 to 0.16 | 0.79  |
| Maximum WSS, Pa  | 0.30  | 0.12 to 0.47 | 0.001  | −0.53 | −0.70 to −0.36 | <0.001 | 0.06  | −0.08 to 0.17 | 0.47  |

ALWSS indicates area of low WSS; %DS, percentage diameter stenosis; FFR, fractional flow reserve; IMR, index of microcirculatory resistance; and WSS, wall shear stress.
associated with endothelial dysfunction, a precursor to the development of atherosclerosis.\textsuperscript{7,24} Therefore, it is evident that low WSS leads to atherosclerosis progression and endothelial dysfunction in the coronary arteries.

Apart from low WSS, abnormally high WSS within coronary lesions also carries deleterious effects. A serial virtual histological intravascular ultrasound study has shown that high WSS induced excessive expansive remodeling with greater necrotic core and calcium progression, leading to the development of vulnerable plaques.\textsuperscript{5} More importantly, high WSS has been found to be associated with adverse clinical outcomes. In a subgroup analysis of the Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) II study, Kumar et al identified high WSS in the proximal lesion segment to be an independent predictor of future myocardial infarction in unrevascularized patients.\textsuperscript{9} In a separate study utilizing computed tomography coronary angiography, Lee et al identified coronary lesions with high WSS to be a significant predictor of future acute coronary syndrome (Please insert reference 10 here: Lee et al. JACC Cardiovasc Imaging. 2019 Jun;12(6):1032-1043)

### FFR and iFR Independently Predicted Burden of Low WSS and Maximum Lesion WSS

Our finding of a significant relationship between abnormal FFR/iFR and pathological WSS provide a potential explanation for the could be explained as follows: by virtue of Ohm’s law, the pressure gradient (voltage) between the guide catheter and distal pressure sensor is influenced by the amount of flow (current) and stenosis severity (resistance). In the setting of lesions with identical stenosis severity, a vessel supplying a larger amount of myocardium has proportionally larger flow and higher pressure gradient (ie, lower FFR/iFR). This leads to increased flow velocity, Reynolds number ($[\text{velocity} \times \text{lumen diameter}] / \text{viscosity}$), and flow reattachment length,\textsuperscript{21} resulting in both higher maximum lesion WSS and a larger area of flow recirculation zone with low and oscillating WSS (Figure 6). Furthermore, FFR

#### Table 3. Multiple Regression Model Adjusted for %DS, iFR, and IMR

| WSS parameters | %DS | iFR | IMR |
|----------------|-----|-----|-----|
| ALWSS, mm$^2$ | β   | 95% CI | P value | β   | 95% CI | P value | β   | 95% CI | P value |
|                | 0.37 | 0.20 to 0.54 | <0.001 | −0.45 | −0.82 to −0.28 | <0.001 | −0.06 | −0.16 to 0.12 | 0.77 |
| Maximum WSS, Pa | 0.31 | 0.16 to 0.45 | <0.001 | −0.58 | −0.73 to −0.43 | <0.001 | −0.00 | −0.12 to 0.11 | 0.95 |

ALWSS indicates area of low WSS; %DS, percentage diameter stenosis; iFR, instantaneous wave-free ratio; IMR, index of microcirculatory resistance; and WSS, wall shear stress.

![Figure 4. Difference in maximum lesion wall shear stress (WSS) between ischemic and nonischemic vessels.](image)

**A**. The difference in maximum lesion WSS between ischemic and nonischemic vessels in the entire cohort (n=107). **B**. The difference in maximum lesion WSS between ischemic and nonischemic vessels with angiographically nonobstructive stenoses (n=62). **C**. The difference in maximum lesion WSS between ischemic and nonischemic vessels with angiographically obstructive stenoses (n=45). The Mann-Whitney U test was used to compare differences between groups. %DS indicates percentage diameter stenosis; FFR, fractional flow reserve; and iFR, instantaneous wave-free ratio.
and iFR are summation indexes that assess the cumulative effect of atherosclerotic disease in the epicardial compartment of the coronary circulation by measuring the total pressure loss along the interrogated length of vessel. This allows integrated assessment of the effects of diffuse disease beyond the main lesion, a common and important contributor to myocardial ischemia. The presence of diffuse disease upstream or downstream to the main lesion has the potential to further modulate the local WSS milieu, and may explain the additive value of FFR and iFR over an idealized model of isolated focal stenosis in predicting WSS changes.

Although FFR and iFR both evaluate the epicardial component of the coronary circulation, there are distinct differences between the two tests that account for the 10% to 30% discordance rates observed in previous studies. FFR measures the distal/proximal pressure ratio during pharmacologically induced hyperemia, a state in which the microcirculatory resistance is minimized; whereas iFR measures the distal/proximal pressure ratio during the diastolic wave-free period at rest, a state that is significantly influenced by the additional effects of coronary autoregulation. Therefore, there may be differences between FFR and iFR in their ability to predict WSS. In our study, both ischemic FFR and iFR values were significantly associated with pathological WSS; further studies comparing resting and hyperemic shear stress may be helpful to evaluate the differences between the two tests.

Clinical Implications: A Potential Explanation for the Prognostic Impact of Myocardial Ischemia

Observational studies involving treadmill and myocardial perfusion stress have demonstrated an association
between ischemia severity and clinical outcomes in patients with stable coronary artery disease. The advent of FFR has further enabled localization of ischemia-inducing coronary lesions, thus influencing treatment decisions in multivessel disease. The FAME study demonstrated superiority of FFR-guided percutaneous coronary intervention over angiography-guided percutaneous coronary intervention, while the FAME II study showed increased clinical events in patients with FFR ≤0.80 randomized to medical therapy. Collectively, studies to date have established myocardial ischemia to be an important prognostic factor. Yet, the pathophysiological mechanism underpinning this phenomenon has not been clearly elucidated. Our results provide a potential explanation for the additive prognostic impact of ischemia over angiographic severity alone, by demonstrating a significant relationship between ischemic FFR/iFR and pathological WSS that persisted after adjusting for lesion stenosis severity. Future studies to investigate whether percutaneous coronary intervention or novel drug therapies, such as those that specifically target shear-dependent von Willebrand factor–glycoprotein Ib receptor ligand interaction, could improve clinical outcomes in lesion subsets exhibiting pathological WSS would help further our fundamental understanding of WSS and its impact in coronary artery disease.

CONCLUSIONS

FFR and iFR predicted pathological low and high WSS within coronary arteries, irrespective of the angiographic severity of the underlying lesion. No relationship was found between microcirculatory dysfunction and pathological WSS.

ARTICLE INFORMATION

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