Validation of pressure gradient and peripheral fractional flow reserve measured by a pressure wire for diagnosis of iliofemoral artery disease with intermediate stenosis

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Objective: To examine the pressure gradient and peripheral fractional flow reserve (pFFR) measured by a pressure wire as indicators of hemodynamic significance in iliofemoral angiographic intermediate stenosis.

Background: The utility of pressure measurements using a pressure wire with vasodilators is unclear in cases with intermediate iliofemoral stenosis.

Methods: The mean pressure gradient (MPG) and mean pressure ratio (MPR) were measured at baseline and after injection of isosorbide dinitrate in 23 lesions with angiographically intermediate iliofemoral stenosis. Patients with complex lesions, infrapopliteal artery lesions, chronic total occlusion, and surgical bypass grafts were excluded. Hyperemic MPR was considered equivalent to pFFR. Changes in parameters in response to vasodilators were assessed and correlations of peak systolic velocity ratio (PSVR) with hyperemic MPG and pFFR were examined using duplex ultrasound.

Results: After injection of isosorbide dinitrate, hyperemic MPG increased significantly (from 9.0±5.7 to 16.3±6.2 mmHg; P<0.05) and hyperemic MPR (pFFR) decreased significantly (from 0.92±0.06 to 0.81±0.07; P<0.05). PSVR was significantly correlated with hyperemic MPG (R=0.52; P<0.05) and pFFR (R=-0.50; P<0.05). The optimal cut-off value of pFFR as an indicator of significant hemodynamic stenosis (PSVR >2.5) was 0.85 (area under the curve 0.72; sensitivity 94%; specificity 50%, P<0.05).

Conclusion: pFFR measured using a pressure wire is reliable for prediction of hemodynamic significance in iliofemoral intermediate stenosis.

Keywords: endovascular therapy, peripheral artery disease, pressure measurements, hyperemia, vasodilators, hemodynamics

Introduction

Endovascular treatment (EVT) for iliofemoral artery lesions has become common in the last decade due to technical developments related to self-expandable nitinol stents, and EVT is now an alternative first-line treatment with long-term outcomes that are not inferior to those after surgery.1,2 The high procedural success rate and reduced invasiveness has encouraged extension of indications for endovascular revascularization, but with little focus on hemodynamic significance. The current guidelines for peripheral artery disease indicate that EVT should be used with optimal drug treatment and supervised exercise therapy when clinical findings suggest a reasonable likelihood of symptomatic improvement. These guidelines also recommend pressure measurements across lesions.
at rest and under induced hyperemia in cases in which the
hemodynamic significance of the target lesion is unclear.\textsuperscript{1,4} Various parameters have been proposed to determine hemody-
namic significance, including mean pressure gradient (MPG), peak-to-peak PG, and ratio of mean pressure (also referred to
as the peripheral fractional flow reserve [pFFR]) with or without
vasodilators.\textsuperscript{5–9} However, the validity of these parameters
for treatment planning is unclear. Therefore, the purpose of
this study was to verify whether trans-stenotic absolute PG
and pFFR measured using a 0.014-inch pressure wire under
hyperemia can be used to establish hemodynamic significance
in iliofemoral angiographically intermediate stenosis.

Methods

Study design and patient population
Pressure measurements were performed for 37 consecu-
tive patients (40 lesions) with claudication and critical limb ischemia who had iliofemoral atherosclerotic artery
disease for which EVT was planned according to com-
prehensive consideration of symptoms, quantitative vessel
angiography results or duplex ultrasound (DUS) study in
advance between April and August 2012 at Kokura Memo-
ral Hospital. Patients who were planning to undergo EVT
for TransAtlantic Inter-Society Consensus (TASC) II class
C or D lesions, infrapopliteal artery lesions, chronic total
occlusion, and surgical bypass grafts were excluded. Based
on these criteria, the subjects were 22 patients (23 lesions)
with intermediate stenosis, defined as $<75\%$ stenosis on
quantitative vessel angiography, identified retrospectively
from our database. We did not defer the EVT from the results
of pressure measurements. Kokura Memorial Hospital review
board/ethics committee approved the study protocol. Written
informed consent was obtained from each patient.

Pressure measurements
Pressure measurements were performed using a 0.014-inch
pressure wire (300 cm PrimeWire Prestage\textsuperscript{®}; Volcano
Corporation, San Diego, CA, USA) following angiography
and just before starting EVT. The pressure wire was calibrated
before the procedure, equalized at the end of the guiding sys-
tem, advanced over the lesion, and positioned in a distal healthy
area. The mean trans-stenotic absolute PG (baseline MPG)
and mean pressure ratio (baseline MPR) were then measured.
Next, 250 $\mu$g of isosorbide dinitrate (ISDN) was injected via
the guiding system to induce a hyperemic state. Hyperemic
MPG and MPR were then measured, usually approximately
1 minute after flushing the guiding system with saline. MPG
was defined as the difference between the mean pressure in
the distal healthy area across the lesion from the pressure
wire (mean distal pressure) and the mean central aorta pres-
sure from the guiding system (mean aorta pressure). MPR
was calculated as mean distal pressure/mean aorta pressure.
Hyperemic MPR was considered equivalent to pFFR.

DUS study
The peak systolic velocity ratio (PSVR) on duplex (DUS)
was used to define the hemodynamic severity of lesions. Tests
were performed by certified sonographers within 30 days
before pressure measurements. PSVR was calculated by divid-
ing the velocity measured at the point of maximum stenosis by
the velocity in the closest adjacent healthy vessel segment.

Outcomes
Comparisons of baseline MPG to hyperemic MPG, and
baseline MPR to hyperemic MPR (pFFR) were performed
to assess responses of these parameters to vasodilators.
Correlations of PSVR on DUS with hyperemic MPG and
pFFR were examined. Optimal cut-off values were deter-
mained for hyperemic MPG and pFFR as indicators of hemo-
dynamically significant stenosis (PSVR $>2.5$ on DUS).

Statistical analysis
Continuous variables are presented as means with stan-
dard deviation and categorical variables as numbers with
percentages. Continuous variables were compared by
Student’s $t$-test and correlations between continuous variables
were examined using simple linear regression. A receiver
operating characteristic analysis was used to determine the
optimal cut-off values for hyperemic MPG and pFFR. $P<0.05$
was regarded as significant. All analyses were performed using
JMP® version 10.0 (SAS Institute Inc., Cary, NC, USA).

Results
The characteristics of the patients are shown in Table 1 and
the characteristics of lesions are shown in Table 2. The patients
had a mean age of 72.2±6.8 years (range: 61–86 years) and 19 were
male. Almost half of the patients had coronary artery disease
(CAD) and three were receiving hemodialysis. All patients
had intermittent claudication, except for four with critical limb
ischemia. The mean % stenosis diameter was 57.3±13.2\%,
and 91\% of the lesions were classified as TASC II A.

MPG increased significantly after injection of ISDN
(from 9.0±5.7 to 16.3±6.2 mmHg; $P<0.05$, Figure 1).
Baseline MPG was not significantly correlated with PSVR
($R=0.33; P=0.12$); however, hyperemic MPG was signifi-
cantly correlated with PSVR ($R=0.52; P<0.05$, Figure 2).
MPR decreased significantly after injection of ISDN (from 0.92±0.06 to 0.81±0.07; P<0.05, Figure 3). Baseline MPR was not significantly correlated with PSVR (R=-0.32; P=0.16); however, hyperemic MPR (pFFR) was significantly correlated with PSVR (R=-0.50; P<0.05, Figure 4).

The optimal cut-off value for pFFR for hemodynamically significant stenosis (defined as PSVR >2.5) was 0.85 (area under the curve [AUC] 0.72; sensitivity 94%; specificity 50%, P<0.05, Figure 5). Hyperemic MPG was not a significant predictor of hemodynamically significant stenosis (AUC 0.48; sensitivity 71%; specificity: 87%, P=0.95).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient characteristics for pressure measurements (N=22)</th>
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<tbody>
<tr>
<td>Age, years</td>
<td>72.2±6.8</td>
</tr>
<tr>
<td>Sex, male</td>
<td>19 (86)</td>
</tr>
<tr>
<td>Left lower extremity</td>
<td>14 (64)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>19 (86)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>13 (59)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>14 (64)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>6 (27)</td>
</tr>
<tr>
<td>Previously smoked</td>
<td>12 (55)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>13 (59)</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>59±13</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>6 (27)</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>3 (14)</td>
</tr>
<tr>
<td>Rutherford classification</td>
<td>0 1 (5) 1 1 (5) 2 6 (27) 3 11 (50) 4 3 (14) 5 1 (5) 6 0</td>
</tr>
<tr>
<td>Abbreviation: SD, standard deviation.</td>
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<tr>
<th>Table 2</th>
<th>Lesion characteristics (N=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum lesion length (mm)</td>
<td>2.1±1.3</td>
</tr>
<tr>
<td>Reference vessel diameter (mm)</td>
<td>5.2±2.9</td>
</tr>
<tr>
<td>Diameter stenosis (%)</td>
<td>57.3±13.2</td>
</tr>
<tr>
<td>Lesion length (mm)</td>
<td>32.0±19.0</td>
</tr>
<tr>
<td>Lesion location</td>
<td>Iliac 8 (35) Femoropopliteal 15 (65)</td>
</tr>
<tr>
<td>Restenosis</td>
<td>8 (35)</td>
</tr>
<tr>
<td>Below the knee runoff</td>
<td>0/3 0 1/3 6 (26) 2/3 7 (10) 3/3 10 (43)</td>
</tr>
<tr>
<td>TASC II classification</td>
<td>A 21 (91) B 2 (9)</td>
</tr>
<tr>
<td>Abbreviations: SD, standard deviation; TASC, TransAtlantic Inter-Society Consensus.</td>
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</table>
Discussion

The major findings in this study of iliofemoral angiographically intermediate stenosis were that hemodynamic significance can be established more accurately under hyperemia induced by ISDN, compared to a resting state; that hyperemic MPG and hyperemic MPR (pFFR) are both significantly correlated with PSVR on DUS; and that the optimal cut-off value for pFFR as an indicator of hemodynamic significance (PSVR > 2.5) was 0.85.

In CAD, common physiological findings are included in planning a revascularization strategy for non-severe stenosis. We routinely employ stress tests for coronary blood flow through exercise or pharmacologic stimulation, and coronary pressure measurements are commonly used for assessment of the ischemic potential of a stenosis in our daily practice. Recent large clinical trials have established fractional flow reserve (FFR) measured using a pressure wire as a standard diagnostic tool in patients with non-severe stenosis.10,11 In peripheral artery disease, hyperemic translesional MPG and renal FFR are important as physiological parameters in endovascular revascularization for renal artery stenosis (RAS). Current American College of Cardiology/American Heart Association guidelines recommend pressure measurements for understanding the functional significance in RAS.12,13

Unlike in CAD or RAS, pressure measurements are not commonly used for iliofemoral disease with intermediate stenosis although there might be high frequencies of visual-functional mismatch between moderate morphologic stenosis (>50% in angiography) and pressure ratio.14 A residual MPG < 10 mmHg after intervention has been suggested as an indicator of hemodynamic significance in iliac arteries.4 However, this criterion is based on findings obtained using MPG and hyperemic MPR (pFFR) are both significantly correlated with PSVR on DUS; and that the optimal cut-off value for pFFR as an indicator of hemodynamic significance (PSVR > 2.5) was 0.85.

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5 Fr catheters, and large diameter catheters always overestimate the PG compared with a pressure wire. In addition, there are no data on the clinical value of using vasodilators and pFFR measurements for iliofemoral disease with intermediate stenosis. In contrast, DUS is frequently used for planning of iliofemoral artery revascularization (both endovascular and surgical) in daily practice. The quality of this examination depends on the experience of sonographers and data interpretation can be time-consuming; but the method is noninvasive, and provides information on lesion locations and stenosis in two dimensions, and on hemodynamic severity based on PSVR. The results of the current study revealed the importance of inducing a hyperemic state in evaluation of iliofemoral artery circulation. The findings support our hypothesis that pressure measurements for iliofemoral angiographic mild to moderate stenosis can be used in place of DUS to evaluate hemodynamic significance. Thus, measurement of hyperemic MPG and pFFR using a pressure wire can be used to assess the hemodynamic severity of a lesion (which was not evaluated in DUS before EVT) in a catheter laboratory and to perform intervention with the pressure wire across the lesion based on pFFR reaching the threshold described above. We note that modern pressure wires have improved durability and torque, and thus EVT using a pressure wire is not stressful for operators, except for treating complex lesions such as those in the TASC II C/D class. Hyperemic MPG also had a significant correlation with PSVR on DUS, but we were unable to establish a threshold MPG as an indicator of hemodynamic significance in the current study. This parameter is an absolute value that depends strongly on blood pressure. Therefore, there is likely to be a wide range of hyperemic MPG values in iliofemoral arteries that may or may not reflect hemodynamic significance (Figure 2). Thus, we conclude that hyperemic MPR (pFFR) is a better measure of hemodynamic significance.

Limitations
There were several limitations in the study. First, the study population was identified retrospectively and the sample size was small. Second, correlations between hyperemic pressure measurements and PSVR on DUS were significant, but only moderate. Third, some cases had diffuse long lesions (especially for superficial femoral lesions); thus, some of the lesions on which pressure measurements were performed in our catheter laboratory did not strictly correspond to the positions of lesions evaluated on DUS by sonography in the vascular laboratory. This inadequate correspondence might be one of the reasons behind the poor specificity in pFFR measurement (only 50%) in the present study. Finally, a dose of 250 µg of ISDN was used to induce hyperemia, but a different dose of ISDN or another vasodilator (nitroglycerine, papaverine, adenosine) may alter the results. In the future, a validation study examining the type and dose of vasodilator would be needed.

Conclusion
Induction of a hyperemic state is required for pressure measurements in iliofemoral artery circulation. Hyperemic MPR (pFFR) measured using a 0.014-inch pressure wire is reliable for prediction of hemodynamic significance in iliofemoral angiographically mild to moderate stenosis. The optimal cutoff value of pFFR for hemodynamic significance was 0.85.

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Disclosure
The authors have no conflicts of interest to disclose.

References


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