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Fractional flow reserve in below the knee arteries with critical limb ischemia and validation against gold-standard morphologic, functional measures and long term clinical outcomes

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ABSTRACT

Introduction: The aim of this study was to assess the applicability of fractional flow reserve measurement (FFR) in below-the-knee (BTK) arteries and to evaluate its correlation with non-invasive functional parameters before and after angioplasty.
Methods: We enrolled 39 patients with severe BTK arterial lesions. Inclusion criteria were critical limb ischemia (Rutherford 4–6) and angiographically proven arterial stenosis of the distal lower limb (percent diameter stenosis ≥70%). Exclusion criteria were chronic total occlusion, diabetic foot syndrome and non-viable distal lower limb. The transstenotic distal/proximal pressure ratio was measured under resting (Pd/Pa) and hyperemic (FFR) conditions induced by 40 mg intra-arterial Papaverin and was compared with quantitative angiography-, laser Doppler- and duplex ultrasound-derived measurements before and after percutaneous angioplasty (PTA).
Results: Comparing measurements before and after PTA, we found significant improvements in the resting Pd/Pa values (0.79 [0.67–0.90] vs 0.90 [0.85–0.97]; $p < 0.001$) and FFR values (0.60 ± 0.19 vs 0.76 ± 0.15; $p < 0.001$), respectively. At baseline, Pd/Pa ratio and FFR were significantly albeit weakly correlated with % area stenosis (r:−0.31, p = 0.05 and r:−0.31, p = 0.05, respectively). After PTA, neither Pd/Pa nor FFR remained correlated with % area stenosis. Similarly, prior PTA, Pd/Pa ratio and FFR were significantly correlated with TcO2% and perfusion unit change (r:0.48, $p < 0.01$ and r:0.34, $p < 0.05$, respectively), but after intervention, these significant correlations vanished. Pd/Pa and FFR values did not show correlation with duplex ultrasound-derived measurements. At 1 year, major adverse events (MAEs) and major adverse cardiovascular and cerebrovascular (MACCEs) were observed in 7 (17.9%) and in 9 (23.1%) patients, respectively.
Conclusion: CLI due to severe BTK arterial disease was associated with several impediments of baseline pressure measurements which were significantly improved after successful PTA and stenting. Significant relationships between pressure data and functional and imaging parameters existed prior intervention but vanished after. Further studies are required to determine the clinical value of pre- and post-PTA pressure measurements in BTK arterial disease.

1. Introduction

Translesional pressure measurement with pressure sensor wires was first validated in peripheral arteries [1], followed by intracoronary [2] and renal arteries [3]. Translesional pressure measurement was primarily focused on systolic gradient and remained the gold standard in peripheral arteries for years. In coronary and renal arteries, a novel pressure-derived metric, the fractional flow reserve (FFR), was introduced and was found to be more closely correlated with coronary physiology [2–4]. However, the application of FFR measurement in the peripheral circulation has not been thoroughly investigated [5–10].

Abbreviations: AS, area stenosis; BTK, below-the-knee; CLI, critical limb ischemia; DPU, Doppler perfusion units; FFR, fractional flow reserve; stress FFRperiph, Peripheral fractional flow reserve; LL, lesion length; MLD, minimum lumen diameter; PTA, percutaneous transluminal angioplasty; PW, Pressure wire; %DU, Percentage change in DPU; %TcO2, Percentage change in TcO2; PTA, Percutaneous transluminal angioplasty; DS, percent diameter stenosis; RVD, reference vessel diameter; SPP, segmental skin perfusion pressure; tcO2, transcutaneous O2 pressure.

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Despite these early attempts to determine an invasive metric, the traditional functional diagnostic approach to peripheral vascular disease is still non-invasive. As described previously, critical limb ischemia (CLI) is associated with an ankle systolic pressure ≤ 50 mmHg or a toe systolic pressure of 30 mmHg or less [11]. Generally, a toe-brachial pressure index (TBPI) of <0.75 is predictive of the presence of hemodynamically significant peripheral artery disease [12]. Numerous studies have shown that a transcutaneous O2 (TcO2) pressure < to 30 mm Hg is consistent with poor wound healing [13].

The aim of this study was to evaluate the usefulness of resting Pd/Pa ratio and FFR measurements in the evaluation of peripheral artery disease and to evaluate its correlation with non-invasive functional metrics and with invasive morphological parameters before and after percutaneous transluminal angioplasty (PTA).

2. Methods

2.1. Study population

We prospectively enrolled 39 consecutive patients with CLI and angiographically proven below-the-knee (BTK) stenosis. Inclusion criteria were chronic critical limb ischemia (Rutherford 4–6) and angiographically proven significant lesion of the distal lower limb (Diameter stenosis ≥70%) [12]. Exclusion criteria included chronic total occlusion or other morphologic appearance of the wound that makes FFR periph measurement impossible or unacceptably risky, diabetic foot syndrome and non-viable distal lower limb. Our Institutional Review Committee approved the study, and all patients provided written informed consent prior to study inclusion.

2.2. Angiographic findings

Peripheral angiography was performed following routine techniques. Vessels and lesions were analyzed using a quantitative computerized analysis (QCA) system (Innova 3100, General Electric Healthcare, US) with contrast filled guiding catheter used for calibration. Minimum lumen diameter (MLD), reference vessel diameter (RVD), percent area stenosis (AS), percent diameter stenosis (DS) and lesion length (LL) were measured before and after angioplasty.

2.3. Pressure measurements, calculation of fractional flow reserve and angioplasty

Pressure measurements were performed as follows: Following peripheral angiography, a 55 cm long 5F hydrophilic sheath was advanced into the popliteal artery through an anterograde common femoral artery access. All patients received a bolus of intravenous unfractionated heparin at doses determined according to body weight. After calibration and equalization, the 0.014″ PressureWire™ Certus (St. Jude Medical, St. Paul, MN, USA) was advanced as indicated through the sheath, distal to the stenosis, in the most distal segment as possible. The following measurements were taken at baseline and during maximal hyperemia, which was induced by administration of 40 mg intraarterial papaverin bolus: systolic pressure gradient (Dp), resting Pd/Pa ratio and peripheral FFR (FFR periph). Systolic peripheral wedge pressure (Pwedge) was also measured during balloon dilatation.

After calibration, equalization and FFR measurement we have done a balloon angioplasty with a dedicated below-the-knee balloon and in cases when the angiographic result showed significant recoil, or dissection or the flow was slow, balloon expandable drug eluting stent implantation was done. The revascularization strategy was direct revascularization of the wound related artery, but in complex CTO cases we have done an indirect revascularization with improving the collateral flow from the major feeding artery.

2.4. Laser Doppler examination

Laser Doppler examination was performed with a commercially available laser Doppler system (PeriFlux system 500, Järfälla, Sweden). Pre- and post-interventional segmental skin perfusion pressures in Doppler perfusion units (DPU) and transcutaneous O2 pressure (tcO2) were measured. DPU was measured at rest and after local heating (Stress DPU), while TcO2 was measured at rest and after O2 inhalation. The percent changes in DPU (%DPU change) and TcO2 (%TcO2 change) were calculated before and 3 days after intervention.

2.5. Doppler ultrasound measurements

Peak systolic velocity (PSV) was measured in the distal portions of the anterior and posterior tibial arteries, as appropriate.

2.6. Follow-up

The follow-up included a clinical examination, laser Doppler measurements, and Doppler ultrasound prior to intervention, after intervention, at 2 and 12 months after intervention. Follow-up included control angiography at 12 months.

2.7. Endpoints and definitions

2.7.1. Clinical success

Primary clinical success was defined as an improvement in at least one clinical category in the Rutherford-Becker classification at the 12-months follow-up [14]. Primary patency was defined as persistent patency without clinical indication for re-intervention at the 12-month follow-up, including angioplasty, surgical procedures performed on or at the margins of the treated lesion, and amputation. Limb salvage was defined as prevention of any amputation. Major amputation was defined as limb loss below or above the knee level, while minor amputation was defined as an amputation at or distal from the trans metatarsal level.

2.7.2. Technical success

Technical success was defined as PTA resulting in <30% residual stenosis with normal anterograde flow. Accordingly, a suboptimal result was defined as sluggish flow and/or residual stenosis of 30% to 50% after repeated dilatation.

2.7.3. Major adverse events (MAE)

MAEs were a composite of death, repeat revascularization of the target vessel by PTA or artery bypass graft operation or major amputation during the hospital stay and up to 12 months of follow-up.

2.7.4. Major adverse cardiac and cerebral events (MACCE)

MACCE were a composite of death, myocardial infarction, stroke, coronary intervention or bypass operation.

2.7.5. Vascular complications

Major vascular complication was defined as diminished or lost arterial pulse or the presence of any pseudoaneurysm or arteriovenous fistula following the procedure or during clinical follow-up. Minor vascular complication was defined as a hematoma of <5 cm in diameter over the femoral puncture area that did not require further treatment. Bleeding complication was defined as any bleeding with a fall in hemoglobin level of >3 g/dl requiring a blood transfusion.

2.8. Statistical analysis

All statistical analyses were performed with Graph Pad Prism 6. Continuous variables are presented as the mean ± standard deviation (SD) or mean and interquartile ratio, as appropriate. Differences between continuous variables were analyzed using Student's *t*-test or Mann-Whitney test, as appropriate. Correlations between variables were analyzed using the Pearson or Spearman rank test, as appropriate. Probability values lower than 0.05 were considered to be significant.

3. Results

3.1. Demographic and clinical data

The baseline demographic and clinical characteristics of the study population are shown in Table 1. The clinical indications for the procedures were rest pain in 12 patients (30.7%), arterial ulcer in 10 cases (25.6%) and gangrene in 17 patients (43.6%).

3.2. Angiographic and procedural data (see Table 2)

The interventions were completed with technical success in all patients. Balloon angioplasty was performed in all cases, and additional drug-eluting stent implantation was indicated in 20 cases (51.3%). After the procedure, % area stenosis improved from 82.35 [76.2–88.5] % to 42.9 ± 18.5% ($p < 0.001$), and the toe-to-brachial index increased from 0.45 ± 0.21 to 0.54 ± 0.20 ($p < 0.05$) compared to prior PTA. The clinical success rate at one year was 61.5%. Control angiography was performed in 32/39 (82%) patients. Angiographic restenosis (>50% diameter stenosis) was found in 13 patients (41%) at one year angiographic follow up (4 in-stent restenosis and 9 restenosis after balloon angioplasty.

3.3. Pressure wire measurements (see Table 3)

The mean systolic pressure gradient decreased from 45 [35.7–54.4] mmHg before PTA to 20 [14.3–25.4] mmHg after intervention ($p < 0.001$). Resting Pd/Pa improved significantly from 0.79 [0.67–0.9] to 0.90 [0.85–0.97] ($p < 0.001$), and FFR periph significantly improved from 0.60 ± 0.19 to 0.88 ± 0.12 ($p < 0.01$) (see Fig. 1). An 0.52 FFR value (AUC: 0.724, sensitivity 88.9%, specificity 60%) had the best cut-off value to predict area stenosis >70%. One year MAEs and MACCEs were observed in 7 (17.9%) and in 9 (23.1%) patients. Neither the laser, nor the pressure wire measurements were found significantly different when direct or indirect revascularisation was done. The average systolic wedge pressure (Wp) during balloon inflation was 37.4 [28.6–46.2] mmHg, but in patients with at least one parallel chronic total occlusion the systolic wedge pressure was significantly lower (parallel CTO Wp: 32.47 ± 19.5 mmHg vs nonparallel CTO: 70.80 ± 41.2 mm Hg, $p = 0.002$). Significant difference was found between FFR derived wedge pressures in patients with rest pain, crural ulcer and pedal gangrene (46.3 ± 34.4 vs. 40.1 ± 26.6 vs. 28.5 ± 26.6 Hgmm, $p < 0.05$). FFR values pre 0.64 [0.31–0.98] vs 0.59 [0.53–0.66] and post interventions 0.80 [0.6–1.0] vs 0.75 [0.69–0.81] were not significantly different between the patients with parallel and non-parallel CTO, respectively (Table 5).

Table 1
Demographic and clinical data.

Demographic and clinical data n (%)		
Demographic data	Age (years)	68 [65–71]
	Male	30 (77)
	BMI	29 ± 5
	Hypertension	37 (95)
	Smokers	29 (74)
	Diabetes mellitus	26 (67)
	Dyslipidaemia	35 (90)
	Renal failure	12 (31)
	Coronary artery disease	13 (33)
	Atrial fibrillation	7 (18)
Indication	Ischemic rest pain	12 (31)
	Ulcer	10 (26)
	Gangrena	17 (44)
Rutherford classification	II4	14 (36)
	III5	19 (49)
	III6	6 (15)

Table 2
Angiographic and procedural data.

Quantitative measurements – Diameter stenosis (%)	
Popliteal artery (P3 segment)	27 [13–30]
Anterior tibial artery	86 [78–94]
Peroneal artery	64 [54–75]
Tibiofibular artery	34 ± 32
Posterior tibial artery	87 [78–95]
Quantitative measurements and angiography at lesion site	
Diameter stenosis (%)	65 ± 23
Area stenosis (%)	82 [76–89]
Reference vessel diameter (mm)	2.93 [2.6–3.25]
Minimum lumen diameter (mm)	1.0 ± 0.7
Lesion length (mm)	31 [23.4–37.8]
Severe calcification n (%)	9 (23.1)

3.4. Doppler ultrasound measurements (see Table 3)

3.4.1. Laser Doppler measurements (see Table 3)

Before and 3 days after the intervention, the rest DPU were 26 [20–31] and 27 [22–33] (p = ns), and the stress DPU were 141 [115–168] and 165 ± 86 (p = ns), respectively. Before and after the intervention, the rest TcO_2 values were 31 ± 18 and 30 ± 16 (p = ns) and the TcO_2 values after O_2 inhalation were 116 [83–149] and 124 [90–159], respectively (Fig. 2). Significant improvement in toe pressure (mmHg) was observed from before to after the intervention (67 [57–77] vs. 79 [70–88] ($p < 0.01$)).

3.4.2. Correlations (Fig. 3, Table 4)

Distal pressure, Pd/Pa and FFR periph were significantly but weakly correlated with %TcO_2 change (r: −0.33, −0.36 and 0.34, respectively ($p < 0.05$)). Furthermore, Distal pressure, Pd/Pa and FFR periph were also significantly correlated with stress DPU (r:-0.44, 0.44, and 0.34, respectively ($p < 0.05$)). Pd/Pa and FFRperiph were significantly correlated with % area stenosis and % diameter stenosis ($p < 0.05$ for all). Pressure wire measurement was not significantly correlated with lesion length. Toe pressure was significantly correlated with distal pressure, Pd/Pa and FFRperiph (r: −0.30, r:0.37 and 0.33 ($p < 0.05$), respectively).

Table 3
Procedural and Laser Doppler results.

	Before intervention	After intervention
Angiographic result		
Diameter stenosis (%)	65 ± 23	26 ± 13 ***
Area stenosis (%)	82 ± [76–89]	43 ± 19 ***
Pressure wire measurements		
Systolic pressure gradient (mm Hg)	45 [36–54]	20 [14–25] **
Pd/Pa	0.74 [0.67–0.81]	0.88 [0.84–0.92] **
FFRperiph	0.60 ± 0.19	0.77 ± 0.12 **
Wedge pressure (Hgmm)	37 [29–46]	–
Laser Doppler measurements		
rest DPU	26 [20–31]	67 [57–77]
stress DPU	141 [115–168]	165 ± 86
% DPU change	625 [435–816]	693 [515–872]
rest TcO2	31 ± 18	30 ± 16
TcO2 after O2 inhalation	116 [83–149]	124 [90–159]
%TcO2 change	243 ± 219	318 [154–482]
Toe pressure	27 [21–33]	79 [70–88]
Doppler US (dilated artery)		
Distal anterior tibial artery (PSV- mm/s)	21 [21–33]	44 [34–54] **
Distal posterior tibial artery (PSV- mm/s)	26 [19–32]	29 [22–36]

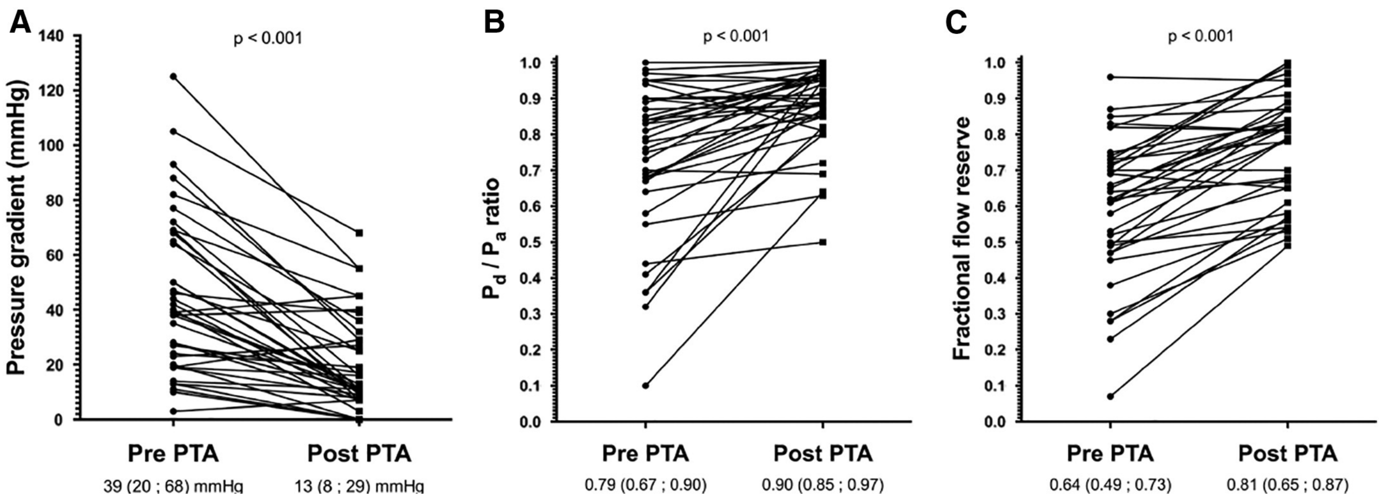

Fig. 1. Pre- and post-interventional measurements. A: Pressure gradient. B: Pd/Pa ratio. C: FFRperiph.

3.4.3. Procedural complications

The rate of MAE during 12 months of follow-up was 23.7% (4 deaths, 2 major amputations, 4 re-interventions). The rate of MACCE up to 12 months after intervention was 17.9% (4 deaths, 2 strokes, 3 coronary interventions). FFR periph final value >0.66 (AUC: 0.624, sensitivity 77.8%, specificity 70%) had the best cut-off value to predict freedom from 12 month MAEs. FFR derived wedge pressure was significantly lower (7.5 ± 10.6 vs. 39 [30.5–47.9] Hgmm, $p < 0.05$) in patients underwent major amputation at one year ($n = 2$), while other pressure wire measurements were not statistically different.

4. Discussion

Severe peripheral artery disease is often the result of multisegment occlusive disease in the arteries supplying the involved lower extremity. While the aorta, iliac, femoral, and popliteal arteries can be involved, there is a particularly high prevalence of tibioperoneal and pedal disease in patients with CLI. The diagnosis of CLI is straightforward and is based on vascular examination, including measurement of the ankle brachial index (ABI) and TBPI and a number of imaging modalities, but all of these examinations have limitations; thus, the gold standard for CLI diagnosis is still digital subtraction angiography (DSA). DSA clearly depicts the anatomy of the BTK segment, but does not provide information about the severity of the functional impairment caused by the lesion or about leg perfusion or viability. Foot perfusion can be analyzed with TBPI, TcPO2, transcutaneous carbon dioxide and DPU. TcPO2 and TcPCO2 are established indicators of local cutaneous perfusion, but measurements of tcPO2 are often unreliable because they are influenced by many physiological, methodological, and technical factors [15]. Of note, measurements of DPU have no such limitations, and DPU is useful for predicting wound healing in limbs in which neither ABP nor TBPI can be measured. Despite the reliability of laser Doppler measurements, there is no functional test available in the catheterization laboratory to obtain immediate information about the functional significance of a singular BTK lesion or to assess the results of angioplasty. Despite pressure improvements, we observed non-significant improvements in the laser Doppler parameters at 3 days after intervention because the microcirculation was still damaged at that time and more time was necessary for the microcirculation abnormality to resolve.

4.1. Direct pressure measurement in the peripheral circulation

The use of DSA in the BTK segment also has limitations because lesions in that location are very complex, a true reference segment has

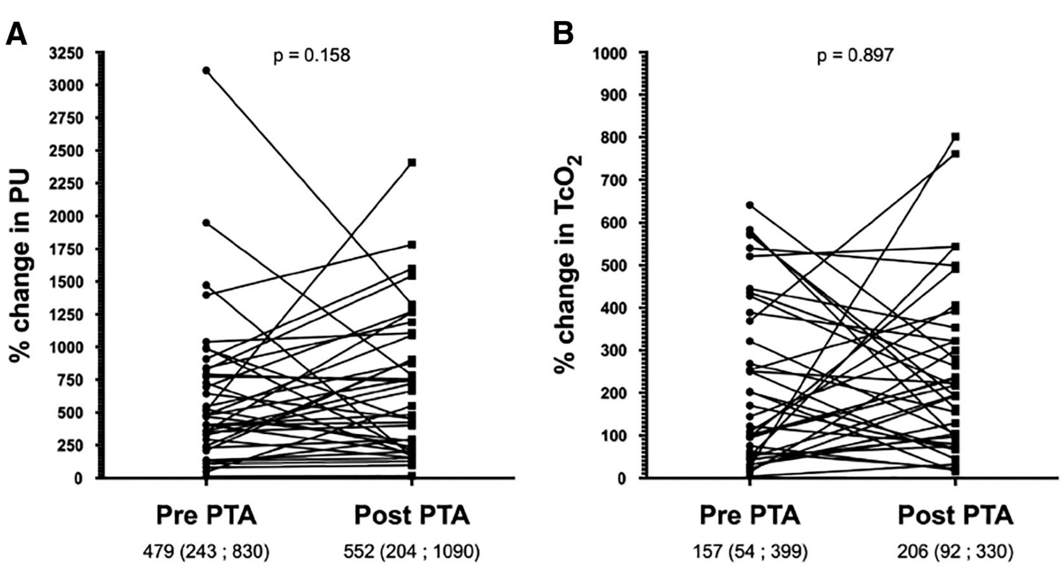

Fig. 2. Pre- and post-interventional laser Doppler measurements. A: Percentage change in DPU. B. Percentage change in TcO2.

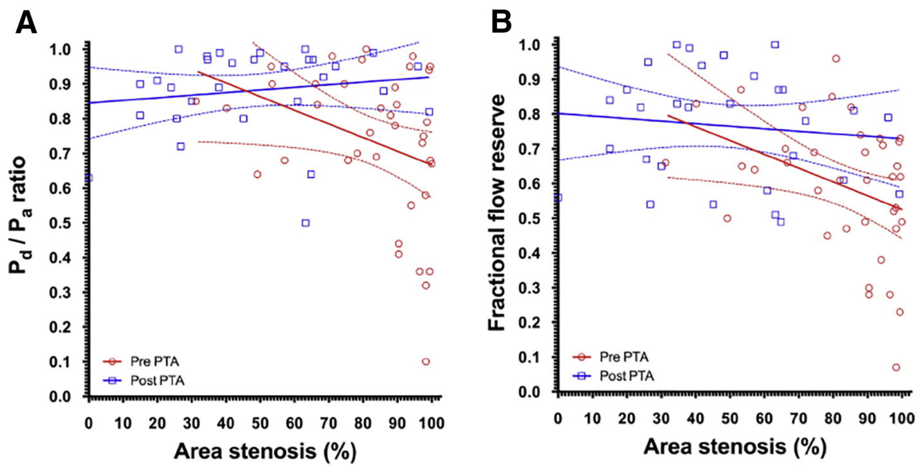

Fig. 3. Correlation analysis curves of the correlations of resting Pd/Pa ratio (A) and FFRperiph (B) with area stenosis.

Table 4
Correlational data – baseline measurements.

	DPU	DPU at stress	% Change in DPU	TcO2	TcO2 at stress	% Change in TcO2	Toe pressure
QCA (AS)	0.09	−0.19	−0.19	0.03	−0.14	−0.12	−0.12
QCA (DS)	0.16	−0.19	−0.28	−0.01	−0.20	−0.09	−0.20
QCA (LL)	−0.03	−0.10	−0.03	0.17	0.16	0.17	0.08
DP	0.18	−0.33*	−0.44**	−0.14	−0.29	−0.44**	−0.45**
Pd/Pa	−0.14	0.36*	0.44**	0.09	0.35*	0.56***	0.53***
FFRperiph	−0.01	0.38*	0.34*	0.05	0.29	0.48**	0.49**

(r values, $p < 0.05$ *, $p < 0.01$ **)

not been identified and conventional quantitative measurements cannot properly predict the severity of the stenosis before and after angioplasty. Direct pressure measurement may help resolve this problem, but performance of this measurement is limited in the catheterization laboratory. There is no consensus on the diagnostic translesional pressure gradient criteria, but the most widely accepted criteria utilize a mean gradient of 15 mm Hg before or after vasodilators and a peak systolic gradient of 10–20 mm Hg [9]. Garcia et al. reported their experience with comparing catheter-derived pressure gradients to pressure wire gradients in 20 lesions in 16 patients [5]. The catheter-derived pressure gradients overestimated the pressure gradients compared to the pressure wire derived gradients. Lotfi et al. demonstrated that the peripheral vascular bed responds to vasodilation and found that a post-intervention pFFR of <0.95 predicted a more rapid PSV over time, which is a reasonable surrogate for restenosis [6]. Recently, Hioki conducted a study on iliac stenosis and found a significant linear correlation between post-exercise ABI and p-FFR at hyperemia, which was stronger than the correlation between post-exercise ABI and peak-to-peak pressure gradient at hyperemia [8]. Banerjee S et al. found that translesional gradient measured using a pressure wire after administration of 100 μg of adenosine was strongly correlated with rest ABI ($r = -0.748$); exercise ABI ($r = -0.888$), exercise duration ($r = -0.711$), and percent angiographic stenosis ($r = -0.818$) ($p < 0.01$ for all) [10].

4.2. Drug used for hyperemia

Functional lesion severity can be assessed with the use of vasodilators to simulate exercise and induce a more accurate physiologic gradient. Administration of nitroglycerin, adenosine or papaverin may be given in an attempt to simulate stress-induced vasodilatation in the peripheral circulation. In peripheral studies with pFFR measurement, 200 μg of adenosine was used to induce hyperemia and resulted in a good hemodynamic response [6–10]. Papaverin is a strong vasodilatator in the peripheral arteries [16] that causes long-term vasodilation, and it is used for FFR measurement in the coronary and renal vessels [3,17]. In our study, 40 mg papaverin was used to initiate vasodilation in the BTK segment, and we achieved a good hemodynamic response.

Potential clinical applications of pressure wire measurement in the peripheral circulation include: first to assess stenosis severity of

Table 5
Pre and post-procedural pressure wire measurements in patients with and without the presence of parallel artery CTO.

	No CTO (n = 5)	One vessel CTO (n = 18)	Two vessel CTO (n = 16)
Pre-procedural measurements			
- Dp	41 ± 42.9	42.2 [30.1–54.3]	49.4 [24.2–43.2]
- Pd/Pa	0.73 ± 0.32	0.77 [0.66–0.88]	0.71 [0.61–0.80]
- FFR Periph	0.64 ± 0.31	0.63 [0.52–0.73]	0.54 [0.46–0.62]
- PWedge	70.8 ± 41.16**	33.7 [24.24–43.2]**	31.01 [20.1–42.05]**
Post-procedural measurements			
- Dp	21.6 ± 26.18	16.11 [10.3–21.9]	23.63 [13.36–33.89]
- Pd/Pa	0.86 ± 0.20	0.90 [0.85–0.94]	0.87 [0.80–0.93]
- FFR Periph	0.80 ± 0.17	0.81 [0.74–0.88]	0.70 [0.62–0.78]

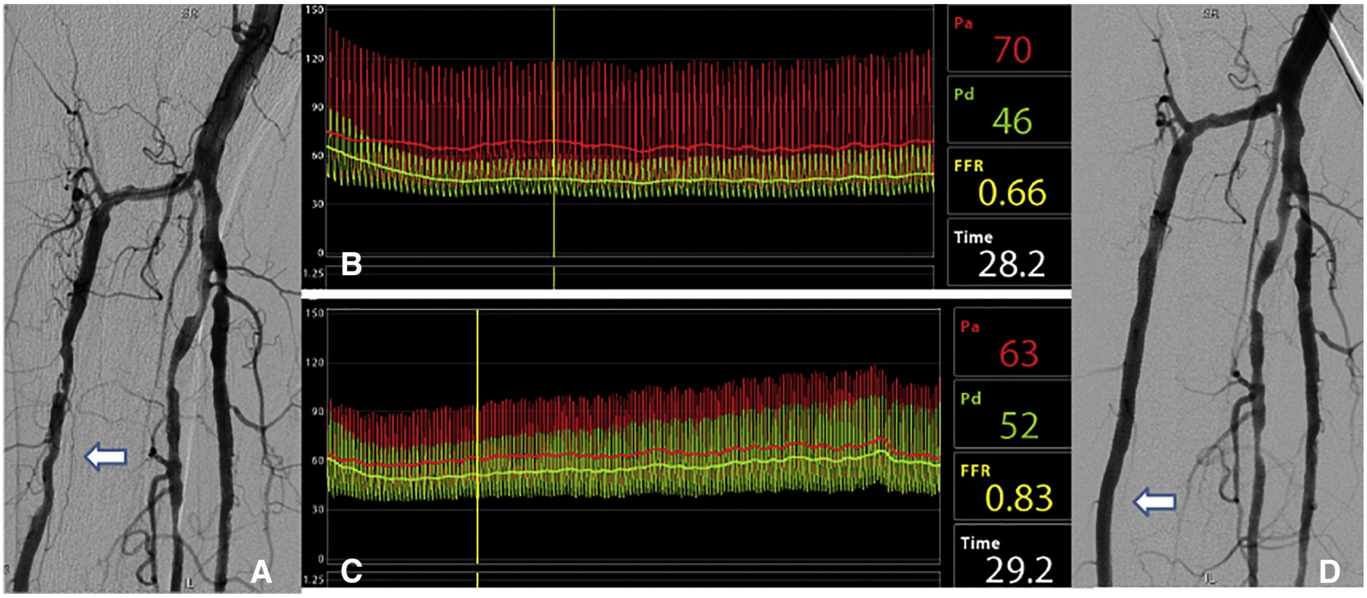

Fig. 4. A 62-year-old male patient with rest pain. DSA shows critical tibioperoneal trunk stenosis (A). FFRperiph measurement before (B) and after stent implantation (C). Final angiography shows no residual stenosis after stent implantation (D).

indeterminate lesions and therefore help guide revascularization procedures, second to assess the immediate efficacy of the revascularization procedure, which in turn can help predict long-term outcomes after revascularization and assessment of individual contribution of each stenosis in segments that contain long, diffuse disease. Fig. 4 presents the findings of a representative case in which we used the pressure wire in a significant BTK lesion before and after angioplasty.

4.3. Further investigations

A dose response analysis comparing the abilities of different agents and doses to induce maximal hyperemia is necessary. It is also necessary to clarify the true cut-off value of FFRperiph that indicates a significant lesion in the BTK segment. In the coronary arteries, a FFR value of <0.80 has been accepted to indicate a significant lesion in recent trials [18]; however, in patients with CLI, many other factors can influence FFRperiph, such as developed collaterals, microvascular disease (infection, inflammation, and diabetic microangiopathy), and rheological state. The systolic wedge pressure in the current study population was 37.4 [28.6–46.2] mmHg, indicating that highly developed collaterals are present in CLI patients. Pwedge was negatively correlated with Dp ($r = 0.42$, $p = 0.007$) and significantly positively correlated with Pd/Pa and FFRperiph ($r = 0.47$, $p = 0.002$ and $r = 0.43$, $p = 0.005$, respectively). Highly developed collaterals can cause false high FFRperiph values; therefore, Pwedge must be taken into consideration during FFR measurement. Pwedge was significantly lower in patients underwent major amputation (7.5 ± 10.6 vs. 39 [30.5–47.9] Hgmm, $p < 0.05$), which means that the low wedge pressure increase the risk of major amputation due to incomplete collateral system of the lower limb.

4.4. Study limitations

This was a proof of concept study investigating the feasibility of FFR measurement in peripheral arteries; however, a small number of cases were included in this study. Another limitation of this study is the lack of a dose response analysis and the lack of a comparison of adenosine to papaverin for the induction of hyperemia.

5. Conclusion

Peripheral fractional flow reserve measurement is feasible and correlates well with standard morphologic and indirect functional parameters. Additional studies with larger patient series are necessary to clarify the true value of fractional flow reserve for the guidance of below-the-knee interventions.

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