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Preferential Use of Infrapopliteal Angioplasty for Critical Limb Ischemia: Vascular Surgeons' Perspective

Toshiya Nishibe[1,2], Kiyohito Yamamoto[1], Kayo Toguchi[1], Yoshimasa Seike[1], Naoki Ito[2], Masayasu Nishibe[2], Jun Koizumi[3], Alan Dardik[4], Hitoshi Ogino[1]

[1]*Department of Cardiovascular Surgery, Tokyo Medical University, Tokyo, Japan*

[2]*Department of Surgery, Eniwa Midorino Clinic, Eniwa, Japan*

[3]*Department of Diagnostic Radiology, Tokai University School of Medicine, Isehara, Japan*

[4]*Department of Vascular Surgery, Yale University School of Medicine, New Haven, Connecticut, USA*

The purpose of this study was to describe the vascular surgeons' experience with an endovascular-first approach for critical limb ischemia (CLI) due to arteriosclerotic disease involving infrapopliteal vessels. From April 2006 to September 2013, 55 limbs with CLI in 45 consecutive patients who had undergone infrapopliteal percutaneous transluminal angioplasty (PTA) were evaluated. All limbs presented with ulcers or gangrenes (Rutherford 5 or 6), and were treated with infrapopliteal PTA as the initial treatment. Clinical outcomes of major adverse limb event (MALE) + perioperative death (POD), amputation-free survival (AFS), limb salvage, and survival were analyzed with the Kaplan–Meier method. Multivariable perioperative predictors of MALE + POD and AFS were identified using the stepwise Cox proportional hazards regression model. The technical success rate was 95% (52/55). Clinical success was attained in 37 of 55 limbs (67%). Freedom from MALE + POD, AFS, limb salvage, and survival were 89%, 84%, 92%, and 92% at 6 months, respectively, and 82%, 68%, 89%, and 78% at 12 months, respectively. Clinical success (HR, 0.06; 0.01–0.50; $P = 0.009$) was associated with freedom from MALE + POD. Rutherford 6 (HR, 3.0; 95% CI, 1.1–8.3; $P < 0.004$) and clinical success (HR, 0.19; 95% CI, 0.07–0.49; $P < 0.0007$) were associated with AFS. These results suggest that infrapopliteal PTA can be offered as a first therapeutic option for a significant proportion of patients with CLI. Vascular surgeons must embrace and validate

Corresponding author: Toshiya Nishibe, MD, PhD, 6-7-1 Nishi-shinjuku, Shinjuku-ku, Tokyo 160-0023, Japan.
Tel.: +81 3 3342 6111; Fax: +81 3 3345 1437; E-mail: toshiyanishibe@yahoo.co.jp

endovascular technology if they are to remain competitive in treatment of peripheral artery disease.

Key words: Peripheral artery disease – Critical limb ischemia – Endovascular therapy

Critical limb ischemia (CLI) is associated with a high risk of limb loss in the absence of revascularization.[1] Although bypass surgery has been currently considered the most durable and effective therapy for limb salvage in patients with CLI, percutaneous transluminal angioplasty (PTA) is becoming as a first-line therapy for CLI with rapid advances of endovascular technology.[2,3] There are a number of theoretical advantages to PTA; it may be safer, is quicker, can be repeated, is possibly less expensive, and may not preclude surgical bypass if it is unsuccessful.

Infrapopliteal and tibial artery occlusions are more commonly associated with CLI due to owing to the paucity of collateral vascular pathways beyond these lesions. Recently, an increasing number of series of PTA reported by cardiologists and interventional radiologists have shown acceptable limb salvage rates even in the most challenging target area such as these infrapopliteal segments.[4,5] Stimulated by these favorable results, we have grown to favor infrapopliteal PTA for patients with CLI since 2006, while reserving distal bypass surgery only when infrapopliteal PTA is not possible or failed. The purpose of this study was to describe our experience of an endovascular-first approach for CLI due to arteriosclerotic disease involving infrapopliteal vessels, and to give perspective for this entity from a vascular surgeons' point of view.

Patients and Methods

From April 2006 to September 2013, 55 limbs in 45 consecutive patients with CLI due to arteriosclerotic disease involving infrapopliteal vessels were treated with infrapopliteal PTA as the initial treatment at Fujita Health University, Eniwa Midorino Clinic, and Tokyo Medical University. The limbs were stratified by clinical symptoms according to Rutherford's classification: all limbs presenting with life-threatening nonhealing ulceration or gangrene (Rutherford 5 or 6). All the procedures were performed by or under the supervision of 1 board-certified vascular surgeon (T.N.) in an angiographic suite or an operating room with a portable imaging system. The aim of the procedures was to achieve a direct-line flow from the common iliac artery to the foot ulcer either based on the angiosome concept,[6,7] or, if not possible, to feed the ulcerated angiosome with collaterals from other angiosomes. Iliac artery lesions were first treated if necessary, and then infrainguinal artery lesions were treated in a separate session.

Infrapopliteal artery lesions were treated with plain old balloon angioplasty. Access was obtained through an ipsilateral femoral approach by using a 6 to 7 Fr sheath. The lesions were first crossed by using a 0.035-inch angled or straight guidewire supported by a 4 Fr straight catheter, or, if not possible, a 0.014 straight guidewire supported by a 2.5 Fr straight catheter. Small-diameter and extra-long balloons such as Savvy (Cordis Endovascular, Warren, New Jersey), Genity (Kaneka Medics, Osaka, Japan) and Sterling or Coyote (Boston Scientific, Natick, Massachusetts) were used for infrapopliteal artery lesions. Balloon inflation pressures ranged from 3 to 4 atmospheres and were held for at least 180 seconds to prevent arterial injury or dissection. An example of revascularization of infrapopliteal PTA is shown in Figs. 1 and 2.

Iliac artery lesions were treated with primary stenting, while superficial femoral artery lesions were preferentially treated with balloon angioplasty and selective stenting.[8–10] Stents were placed in superficial femoral artery lesions only when residual stenosis and flow-limiting dissections were noticed after balloon angioplasty. Rigid balloon expandable stents such as Palmaz (Cordis Endovascular) and Express LD (Boston Scientific) were used for most common iliac artery lesions, and flexible self-expanding stents such as SMART (Cordis Endovascular) and Luminexx (BARD, Murray Hill, New Jersey) for most external iliac or superficial femoral artery lesions. Multiple stents were placed if necessary.

Typically, 70 units/kg of heparin sodium was administered intravenously during PTA, and 200 units/h of heparin sodium were continued for 48 hours after PTA. Alprostadil (10 μg/d), which had proven to improve healing of ischemic ulcers and reduction in amputation,[1,11] was administered intravenously for up to 28 days after PTA. Aspirin

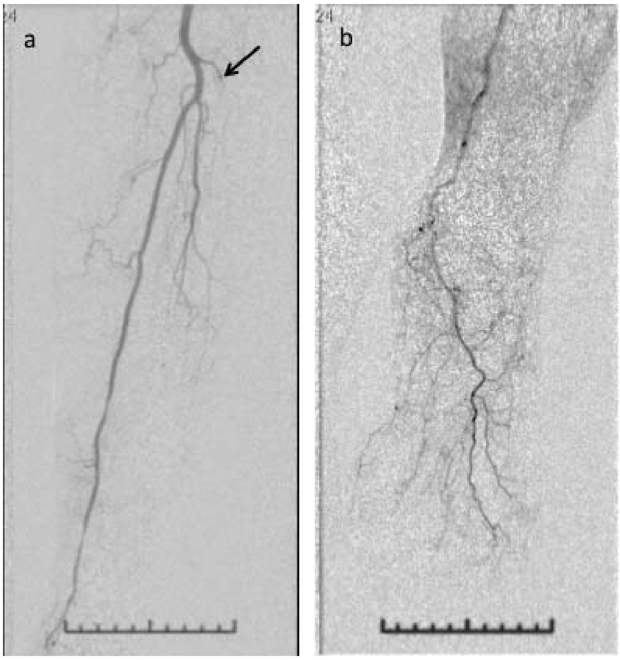

Fig. 1 (a) Preoperative arteriograms performed in a 62-year-old woman with a nonhealing ulcer of the right first digit and rest pain. The anterior tibial artery was occluded from just below origin to level of the ankle (arrow). (b) The dorsalis pedis artery was not visualized.

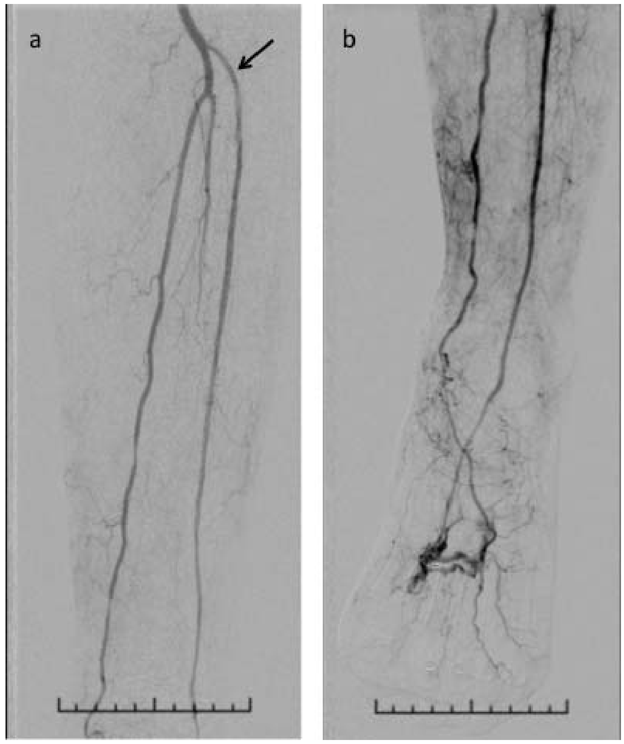

Fig. 2 (a) Postoperative arteriograms. Successful infrapopliteal percutaneous transluminal angioplasty (PTA) of the anterior tibial artery occlusion was performed (arrow). (b) The dorsalis pedis artery was well visualized.

(100 mg/d) and cilostazol (100 to 200 mg/d) and or beraprost sodium (60 to 120 μg/d) were orally administered after PTA, and were continued as long as side effects did not occur. Hemodynamic change before and after the procedure was assessed with ankle brachial pressure index (ABI) when possible.

All limbs were followed every 1 or 2 weeks for clinical assessment. Clinical success was defined as when an expected toe or transmetatarsal amputation was performed and healed well or ischemic ulcers were healed or remarkably reduced. When clinical success was not achieved within a few months, bypass surgery or major amputation was considered. Freedom from major limb adverse event (MALE) plus perioperative (30 days) death (POD), amputation-free survival (AFS), limb salvage, and survival rates were determined. Major adverse limb event was a composite of either major amputation or major reintervention. Major reintervention included the creation of a new surgical bypass graft, the use of thrombectomy or thrombolysis, or a major surgical graft revision such as a jump graft or an interposition graft, while minor reintervention included endovascular procedures (PTA, atherectomy, stenting) without thrombectomy/thrombolysis, and minor surgical revisions (patch angioplasty). Limb salvage was defined as when no ipsilateral major amputation proximal to the ankle was performed. AFS was a composite endpoint defined as freedom from ipsilateral major amputation proximal to the ankle and freedom from all-cause mortality.

Statistical Review

Data are shown as means ± standard deviation for continuous variables. Statistical software package Mac Multivariate Analysis (Esumi, Tokyo, Japan) and GraphPad Prism version 5.0d (GraphPad Software, Inc, San Diego, California) were used for statistical analysis. For continuous data, the normality of the distribution was examined by the Kolmogorov–Smirnov test. Intergroup comparison was made by Student's t test for normally distributed data, and by Mann-Whitney U test for other data. Clinical outcomes of limb-based MALE + POD, AFS, limb salvage, and survival were analyzed with the Kaplan–Meier method. Multivariable perioperative predictors of limb-based MALE +

Table 1 Baseline characteristics of study population

Variables	Limb, % (N)
Age >75 yrs	18 (33)
Male	42 (76)
Current smoking	13 (23)
Hypertension	32 (58)
Dyslipidemia	12 (22)
Diabetes mellitus	35 (64)
Cerebral infarction	27 (49)
Ischemic heart disease	42 (76)
Hemodialysis	37 (66)
Rutherford	
5	45 (82)
6	10 (18)
Iliac artery lesion	5 (9)
TASC II A/B	4/1
Superficial femoral artery lesion	18 (33)
TASC II A/B/C	8/5/5

POD and AFS were identified using the stepwise Cox proportional hazards regression model. Clinically prescribed predictors (age >75 years, female, Rutherford 6, hypertension, dyslipidemia, diabetes mellitus, cerebrovascular disease, ischemic heart disease, end-stage renal failure on hemodialysis, active smoking, iliac artery lesions, superficial femoral artery lesions, and clinical success) were entered into the multivariate model.

Results

All infrapopliteal artery lesions were treated with PTA as the initial treatment, while no bypass surgery was performed as the initial treatment. The median duration of follow-up was 222 days (range, 7–903 days). The baseline clinical characteristics were listed in Table 1. The limb-based population consisted of 42 men and 13 women with a mean age of 70.5 years (range, 45 to 87 years). Forty-five limbs (82%) were complicated with ischemic ulceration not exceeding ulcer of the digits of the foot defined as Rutherford 5 while 10 (18%) limbs with severe ischemic ulcers or frank gangrene defined as Rutherford 6. All limbs had multiple concomitant risk factors, including older age >75 years (33%), male (76%), current smoking (64%), hypertension (58%), dyslipidemia (22%), diabetes mellitus (64%), cerebrovascular disease (49%), ischemic heart disease (76%), and end-stage renal failure on hemodialysis (67%). All patients were categorized as American Society of Anesthesiologists (ASA) physical status more than III. Eighteen limbs had superficial femoral artery lesions (33%), of which 8 were classified as TASC II A, 5 as TASC II B, and 5 as TASC II C. Five limbs had iliac artery lesions (9%), of which 4 were classified as TASC II A and 1 as TASC II B.

The technical success rate was 95% (52/55). The affected arteries treated by infrapopliteal PTA were the below-knee popliteal artery in 12 limbs (22%), the anterior tibial artery in 41 limbs (75%), the peroneal artery in 10 limbs (18%), and the posterior tibial artery in 6 limbs (11%), respectively. Concomitant procedures including plain old balloon angioplasty or stent placement of the superficial femoral artery were performed in 18 limbs; plain old balloon angioplasty was performed in 7 limbs, while stent placement was performed in the other 11 limbs. Separate sessions of stent placement of the iliac artery were performed in all 5 limbs. The ABI increased from 0.55 $\pm$ 0.37 pre-intervention to 0.82 ± 0.24 postintervention (n = 46, $P < 0.001$).

Clinical success was attained in 37 of 55 limbs (67%). The 30-day survival rate was 98% (54/55), with no severe complications. There were no complications due to local access, including no hematomas, pseudoaneurysms, dissections, or emboli. Freedom from MALE + POD, AFS, limb salvage, and survival were 89%, 84%, 92%, and 92% at 6 months, respectively, and 82%, 68%, 89%, and 78% at 12 months, respectively (Fig. 3a–d). Major or minor re-intervention was performed in 7 limbs, including below-knee femoropopliteal bypass (n = 1), distal bypass surgery (n = 1), and re-infrapopliteal PTA (n = 5). Major amputation above the knee was carried out in 8 limbs. Twelve patients with 15 treated limbs died: 6 patients due to myocardial ischemia, 4 due to sepsis, 1 due to pancreatic cancer, and 1 due to gastric ulcer bleeding.

Results of the multivariate stepwise Cox proportional hazard regression analysis for freedom from MALE + POD and AFS are shown in Tables 2 and 3. Clinical success (HR, 0.06; 0.01–0.50; $p = 0.009$) was associated with freedom from MALE + POD, while Rutherford 6 (HR, 3.0; 95% CI, 1.1–8.3; $P < 0.004$) and clinical success (HR, 0.19; 95% CI, 0.07–0.49; $P < 0.0007$) were associated with AFS.

Discussion

Options for revascularization for limb salvage in patients with CLI include bypass surgery, PTA, or both. Less-invasive PTA, including balloon angioplasty and stent placement, has been established as a valid alternative to bypass surgery in high-risk patients. Several authors, including ours, advocated

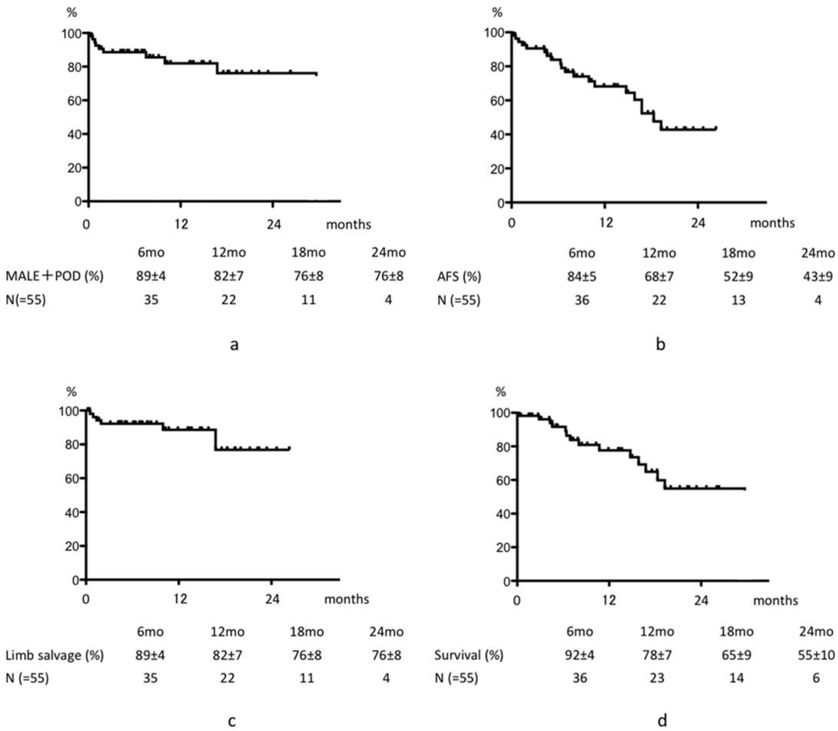

Fig. 3 (a) Freedom from major adverse limb events plus perioperative death (MALE + POD). (b) Amputation-free survival (AFS). (c) Limb salvage. (d) Survival.

that PTA can be a feasible, safe, and effective procedure even in patients who are elderly or frail or whom bypass surgery poses high risks because of multiple medical problems such as cerebrovascular, cardiac, pulmonary, renal, and other diseases; there is no need for general or spinal anesthesia, there are no or fewer surgical wounds, and procedural morbidity and mortality rates are quite low.[8,12,13]

PTA has been considered as a first-line therapy even for CLI attributable to the infrapopliteal lesions with the continued evolution of catheter-based technologies. In 2001, Dorros *et al* first reported that tibioperoneal angioplasty could be used as primary treatment in 235 patients with CLI.[4] In 2008, Romiti *et al* performed a recent meta-analysis of infrapopliteal angioplasty for CLI and demonstrated the 3-year limb salvage and survival rates of 86% and 98%, respectively, which were comparable to those of bypass surgery.[5] Recently, Söderström *et al* used a propensity matching analysis to decrease confounder bias and showed similar 5-year limb salvage and AFS rates between endovascular and surgical procedures for CLI attributable to infrapopliteal lesions.[14]

Conte *et al* developed a set of suggested objective performance goals (OPG) for evaluating new catheter-based treatments in CLI, based on evidence from historical controls.[15] Bypass with autogenous vein was considered the established standard, and data compiled from 3 individual randomized, controlled trials, including PREVENT III,[16] CIRACUSE,[17] and BASIL,[18] was analyzed. Perioperative death or any MALE was considered to be primary and AFS as the key secondary endpoint, which together best captured the clinical efficacy of the initial procedure for treatment of CLI. The suggest-

Table 2 Association of clinical characteristics with MALE + POD

	Univariate analysis HR, 95% CI	Multivariate analysis HR, 95% CI
Age >75 yrs	0.55 [0.11–2.66]	
Male	0.42 [0.05–3.35]	
Current smoking	2.18 [0.45–10.69]	
Hypertension	1.52 [0.38–6.14]	
Dyslipidemia	2.93 [0.17–4.93]	
Diabetes mellitus	0.41 [0.11–1.56]	
Cerebral infarction	0.27 [0.06–1.31]	
Ischemic heart disease	1.34 [0.27–6.55]	
Hemodialysis	4.55 [0.57–36.47]	
Rutherford 6	4.68 [1.23–17.75]*	
Iliac artery lesion	1.74 [0.22–14.04]	
Superficial femoral artery lesion	0.71 [0.14–3.41]	
Clinical success	0.05 [0.01–0.40]*	0.06 [0.07–0.50]*

CI, confidence interval; HR, hazard ratio; MALE, major adverse limb event; POD, perioperative death.

*$P < 0.05$.

Table 3 *Association of clinical characteristics with AFS*

	Univariate analysis HR [95% CI]	Multivariate analysis HR [95% CI]
Age >75 yrs	1.51 [0.61–3.74]	
Male	0.66 [0.19–2.28]	
Current smoking	4.29 [1.24–14.83]*	
Hypertension	1.19 [0.48–2.93]	
Dyslipidemia	0.61 [0.18–2.12]	
Diabetes mellitus	0.81 [0.33–2.00]	
Cerebral infarction	0.91 [0.37–2.24]	
Ischemic heart disease	1.71 [0.57–5.14]	
Hemodialysis	4.74 [1.10–20.49]*	
Rutherford 6	5.91 [2.41–14.48]*	2.97 [1.06–8.29]*
Iliac artery lesion	1.71 [0.70–4.23]	
Superficial femoral artery lesion	1.45 [0.55–3.82]	
Clinical success	0.16 [0.07–0.43]*	0.19 [0.07–0.49]*

AFS, amputation free survival; CI, confidence interval; HR, hazard ratio.

*$P < 0.05$.

ed OPG of MALE + POD, AFS, limb salvage, and survival at 1 year were 71%, 71%, 84%, and 80%, respectively, while those were 67%, 68%, 81%, and 80%, respectively, for high-risk anatomy (infrapopliteal lesions).

Recently, Iida *et al* reported a retrospective series of 884 patients (1057 limbs) who underwent infrapopliteal angioplasty for CLI.[19] At 1 year, AFS was 71%, which was equivalent to the suggested OPG of 68%, while freedom from MALE + POD was 81%, which surpasses the suggested OPG of 67%. Our study also revealed that freedom from MALE + POD and AFS at 1 year were 82% and 68%, respectively, which were comparable to the previously-mentioned results.

Our study identified that clinical success was independently associated with freedom from MALE + POD. There is beyond doubt reasonable relationship between freedom from MALE and clinical success; if clinical success should not be achieved, amputation or bypass surgery or both must be done. Also, our study found that two clinical factors, namely clinical success and Rutherford 6, were independently associated with AFS. This finding may be explained by that acute infections are associated with a transient increase in the risk of vascular events including myocardial infarction and stroke.[20] Clinical unsuccessfulness and Rutherford 6, which reflect sustained and profound infections, possibly cause myocardial infarction and stroke, thereby leading to death. Several studies also identified presence of tissue loss or Rutherford 6 as an independent risk factor for AFS.[14,15,19]

Vascular surgeons have played a primary role in decision-making and overall management in patients with PAD. However, cardiologists and interventional radiologists are competing among themselves and sometimes viewing vascular surgeons as irrelevant in the light of endovascular therapy (EVT). Thus, vascular surgeons must embrace and validate EVT technology if they are to remain competitive in treatment of PAD.[21]

This study has several limitations that may have influenced the results. First, this was a retrospective study, which can create the potential for selection and information bias. Second, the wound care was not standardized, which might have influenced ulcer healing time. Third, we did not perform follow-up angiography for patency in asymptomatic patients. This may have overestimated the efficacy of infrapopliteal PTA.

In conclusion, infrapopliteal PTA showed favorable clinical outcomes in terms of freedom from MALE + POD, AFS, limb salvage, and survival. Together with other previous reports, this result suggests that infrapopliteal PTA may be offered as a first therapeutic option for a significant proportion of patients with CLI. We stress that vascular surgeons must adopt EVT technology as one of therapeutic modalities if they are to remain competitive in treatment of CLI.

Acknowledgments

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