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Hybrid Foot Vein Arterialization in No-Option Patients With Critical Limb Ischemia: A Preliminary Report

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Abstract

Purpose: To describe a preliminary experience in treating no-option critical limb ischemia (CLI) patients with a hybrid foot vein arterialization (HFVA) technique combining open plus endovascular approaches. **Materials and Methods:** Between May 2016 and January 2018, 35 consecutive patients (mean age 68±12 years; 28 men) with 36 no-option CLI limbs underwent HFVA in our center. All limbs had grade 3 WIfI (Wound, Ischemia, and foot Infection) ischemia, and the wound classification was grade 1 in 4 (11%) limbs, grade 2 in 4 (11%), and grade 3 in 28 (78%). Surgical bypass was done on the medial marginal vein or a posterior tibial vein, followed by endovascular removal of foot vein valves and embolization of foot vein collaterals. A "tension-free" surgical approach was used to treat foot lesions. **Results:** At a mean follow-up of 10.8±2 months, limb salvage was achieved in 25 (69%) limbs and wound healing in 16 (44%); 9 patients presented an unhealed wound. Eleven (31%) patients underwent a major amputation (2 below the knee and 9 thigh). One patient with an unhealed wound and open bypass died of myocardial infarction. **Conclusion:** HFVA is a promising technique able to achieve acceptable rates of limb salvage and wound healing in no-option patients generally considered candidates for an impending major amputation. Further studies are needed to standardize the technique and better identify patients who can benefit from this approach.

Keywords

critical limb ischemia, foot vein arterialization, limb salvage, no-option CLI, peripheral artery disease, venous arterialization

Introduction

Lower limb peripheral artery disease (PAD) is the third leading cause of cardiovascular morbidity after coronary artery disease and stroke.[1,2] The clinical manifestations of PAD include claudication and critical limb ischemia (CLI), which includes patients with ischemic rest pain, ulcers, or gangrene. Among patients with PAD of the lower limb, CLI develops in 5% to 10% over 5 years.[3]

Revascularization is the treatment of choice for preventing amputation and resolving rest pain in CLI patients; however, 10% to 50% of CLI patients are considered not suitable for any revascularization treatment due to unreconstructable vascular disease.[3–5] Arterialization of the venous system has been performed in these "no-option" patients as the last attempt to avoid major amputation,[6–9] with an acceptable limb salvage rate at 1 year. Despite these apparently positive results, the procedure has never gained wide acceptance, essentially due to the complexity of the technique, the conflicting results, and the lack of clear technical standardization.[10]

This report describes our preliminary experience in treating no-option CLI patients with a hybrid foot vein

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arterialization (HFVA) technique combining open and endovascular approaches.

Materials and Methods

Study Population

Patients treated between May 2016 and January 2018 who satisfied the following criteria were included: (1) WIfI (Wound, Ischemia, and foot Infection) ischemia classification grade 3, transcutaneous oxygen tension ($TcPo_2$) <30 mm Hg; (2) WIfI wound classification wound grade 1 to 3; (3) severe disease of the foot arteries considered not revascularizable by means of conventional angioplasty or distal bypass after an attempt at endovascular intervention by an experienced operator in contemporary techniques (R.F.); (4) absence of infection or infection completely removed by means of previous surgical and antibiotic treatment; (5) left ventricular ejection fraction >30% at preoperative transthoracic echocardiography; and (6) acceptable life expectancy and walking capacity. Exclusion criteria were (1) extended and irrecoverable foot gangrene, (2) active infection, (3) left ventricular ejection fraction ≤30%, (4) short life expectancy and inability to walk, and (5) patient refusal of the procedure.

Every patient was evaluated by a multidisciplinary team comprising an endovascular operator, 2 vascular surgeons, 2 foot surgeons, and 2 diabetologists. The HFVA procedure was proposed according to the consensus judgment. All patients signed the informed consent prior to the procedure. This study was approved by the Humanitas Hospital ethics committee (approval number 150/17).

In the target period, 951 limbs in 880 patients with CLI were treated in our center. A consecutive series of 35 patients (mean age 68±12 years; 28 men) with 36 no-option CLI limbs underwent HFVA (4% of CLI patients/limbs). Baseline clinical and angiographic characteristics of enrolled patients/limbs are reported in Table 1. The majority of patients had diabetes mellitus and a history of tobacco abuse; a third had chronic kidney disease (2 on hemodialysis). Patients presented with severe ischemic rest pain (average visual analog scale score 8.8±0.3 of 10). All the limbs had grade 3 WIfI ischemia with very low levels of $TcPo_2$ (6.2±5.2 mm Hg). The WIfI wound classification was grade 1 in 4 (11%) limbs, grade 2 in 4 (11%), and grade 3 in 28 (78%) limbs.

Obstructive artery disease was attributed to Buerger disease in 5 (14%) limbs, popliteal aneurysm in 1 (3%), and atherosclerosis in the remaining 30 (83%). Baseline angiographic evaluation showed obstructive disease of the superficial femoral artery in 9 (25%) limbs, popliteal artery in 10 (28%), and tibioperoneal artery in 10 (28%). PAD involved 2 or 3 BTK arteries in the majority of cases. All patients presented with intractable severe obstructive disease of the foot arteries. Diffuse calcification was present in 75%.

Table 1. Characteristics of the 35 Study Patients.[a]

Demographics and risk factors	
Age, y	68±12
Men	28 (80)
Hypertension	32 (91)
Dyslipidemia	13 (37)
Diabetes mellitus	29 (83)
Smoker	27 (77)
Coronary artery disease	19 (54)
COPD	2 (6)
Chronic kidney disease	12 (34)
ESRD/hemodialysis	2 (6)
Neuropathy	18 (51)
Lesion characteristics (n=36)	
WIfI wound grade	
1	4 (11)
2	4 (11)
3	28 (78)
Buerger disease	5 (14)
Popliteal aneurysm	1 (3)
Atherosclerosis	30 (83)
Location	
Superficial femoral artery	9 (25)
Popliteal artery	10 (28)
Tibioperoneal artery	10 (28)
BTK arteries	
0	1 (3)
1	5 (14)
2	10 (28)
3	20 (56)
Diffuse calcification	27 (75)

Abbreviations: BTK, below the knee; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; WIfI, wound, ischemia, and foot infection.
[a]Continuous data are presented as the mean ± standard deviation; categorical data are given as the number (percentage).

Baseline Angiography

Every patient underwent a baseline digital subtraction angiography study of the target limb using iodixanol (Visipaque 320; GE Healthcare, Waukesha, WI, USA) with multiple oblique views. A below-the-knee (BTK) and foot artery study was performed as previously described.[11,12]

Bypass Surgery Technique

The operations were performed under regional or general anesthesia. Prophylactic antibiotics and perioperative heparin were administered. Inflow was from the most distal patent artery. The medial marginal vein (MMV) (Figures 1–3)

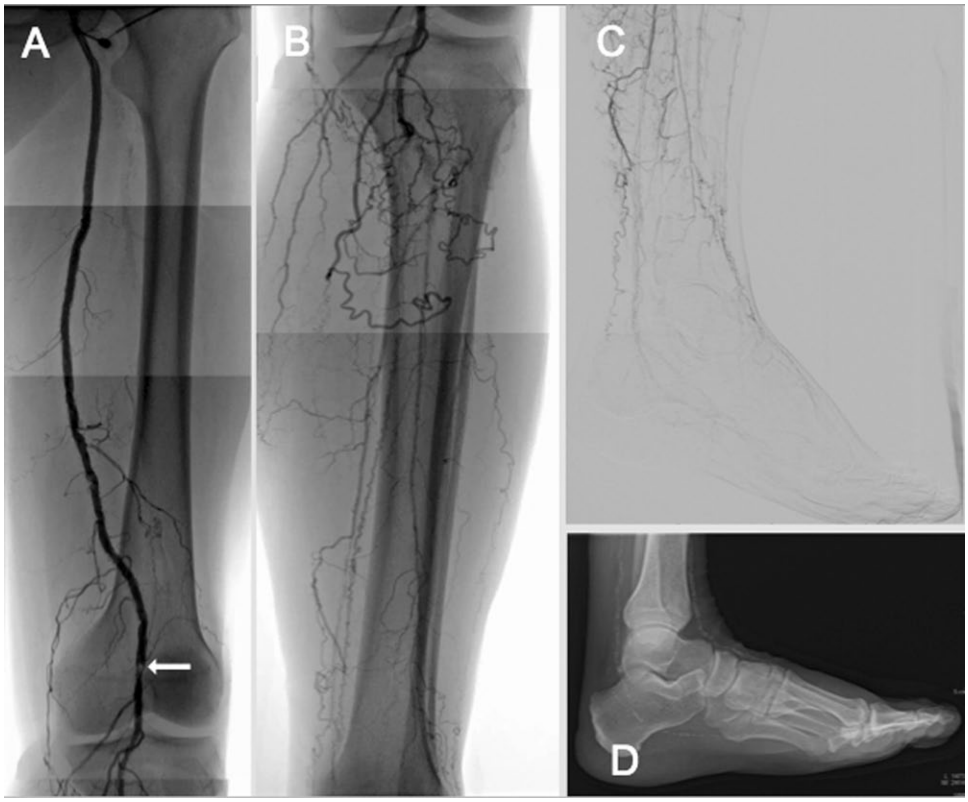


Figure 1. Baseline angiographic study. (A) Femoropopliteal arteries show a focal stenosis of the P2 segment (white arrow), which will be treated by angioplasty before hybrid foot vein arterialization. Severe disease of (B) the below-the-knee and (C) foot arteries. (D) Plain radiography of the foot shows diffuse vascular calcification.

or posterior tibial vein (PTV) was chosen as the distal target vein according to availability (Figure 4). The preferred conduit was the great saphenous vein. When the in situ technique was applied, a LeMaitre valvulotome (Le Maitre Vascular, Burlington, MA, USA) was used to perform retrograde destruction of above-the-ankle valves through phlebotomy at the ankle level. All above-the-ankle collaterals underwent side branch ligation.

Endovascular Technique

After bypass surgery, patients underwent one or more staged endovascular procedures, with different hemodynamic targets. In the primary post-bypass procedure, distal vein devalvulation was performed immediately after bypass surgery, with the aim to destroy the venous valves downstream of the distal bypass anastomosis/phlebotomy. Foot vein collaterals stealing blood were not touched because high blood flow through the bypass at this stage was considered a good sign of early patency.

In a secondary procedure, focalization of blood flow to the wound was performed 14 to 28 days later, with the aim of creating forward pressure of the blood flow by embolizing the proximal foot vein collaterals. If necessary, the operator refined distal valve destruction. Maintenance procedures were performed during follow-up to reestablish patency if hemodynamic impairment (stenosis, occlusion) of the arterialized circuit was detected by duplex scan.

The procedures were performed under local anesthesia using an antegrade femoral approach[12] and a 4-F to 5-F introducer sheath. The bypass was crossed using a 0.014- or 0.018-inch wire (Command; Abbott Vascular, Redwood City, CA, USA) and a diagnostic 4-F Berenstein catheter (Tempo Aqua; Cordis Corporation, a Cardinal Health company, Milpitas, CA, USA). Caution was taken in crossing the fresh anastomoses. Closure was obtained by manual compression.

For valve crossing, the Berenstein catheter was advanced 1 to 2 cm in front of the valve and then gently pushed a nitinol-tipped wire toward the valve flaps. This maneuver was constantly repeated, changing the wire direction by rotating the catheter tip ("dancing wire technique") until the tip of the wire occasionally crossed the valve flaps (Figure 2C-H); afterward, advancing the

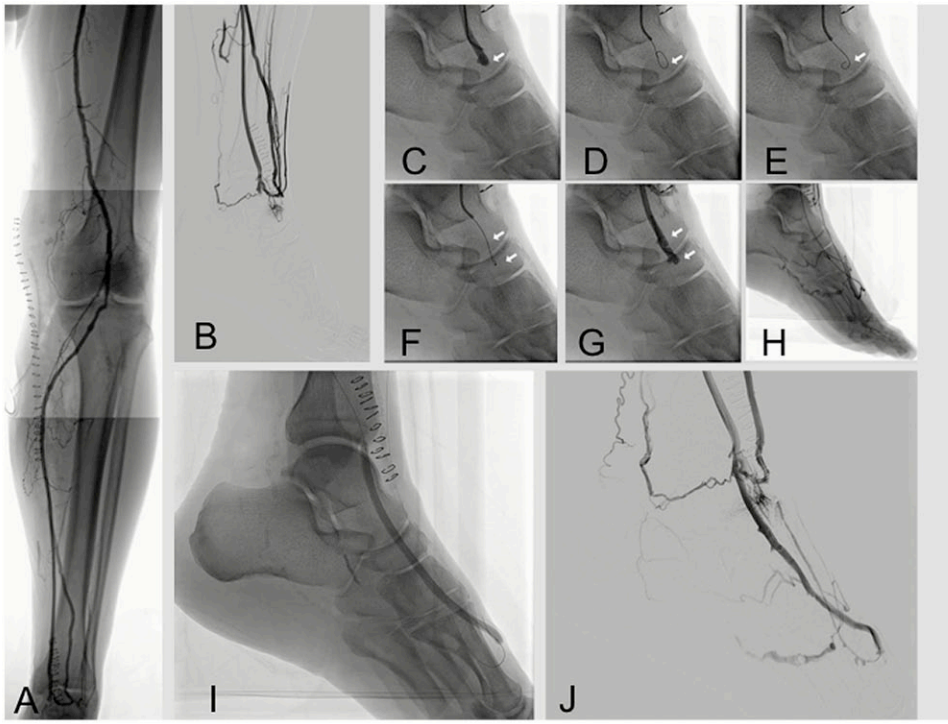


Figure 2. Same patient as Figure 1. Hybrid foot vein arterialization on the medial marginal vein (MMV), postsurgery procedure. (A) In situ saphenous bypass with proximal anastomosis on the P3 segment. (B) Blood flow at the ankle level goes into proximal collaterals, not into foot veins. (C-H) "Dancing wire" technique: the first 2 valves of the MMV are crossed (white arrows), and the wire reaches the dorsal venous arch. (I) A 4-×120-mm-long balloon is inflated in the MMV at 14 atm for 2 minutes. (J) Final result with slow flow due to diffuse spasm of the distal veins.

catheter tip through the valve was generally easy by gently rotating and pushing it. Crossing the vein valves with extreme delicacy is essential because vein perforation is frequent, and aggressive maneuvers can precipitate diffuse vein spasm (Figure 2J).

Local injection of a contrast agent allowed the identification of valves and ostia of collateral vessels. The distal target was chosen according to the type of bypass. If a bypass was on the MMV, the valves of this vein (3–5 valves) were crossed to arrive at the dorsal arch, which is generally avalvulated. Crossing collateral vessels connecting the MMV with the dorsalis pedis vein or with some deep or superficial plantar veins to expand the arterialization network was sometimes possible.

If the bypass was on the PTV, the valves of the lateral plantar vein (3–6 valves) were crossed or, if impossible, the medial plantar vein to the plantar arch. At the level of the dorsal or plantar arches, attempts were made to cross the ostial valves of the metatarsal veins, especially the first one, to arrive at the distal digital level.

For valve destruction, balloon inflation at 14 to 16 atm was used, starting with a 3- to 4-mm-diameter balloon, checking the result with contrast injection after inflation, and, in case of persistent valve competence, repeating the inflation with a bigger balloon (5–6 mm). Sometimes leakage of blood outside the vessel was observed without hemodynamic consequences.

Foot Lesion Treatment

After HFVA, the foot was elevated to reduce the edema, and a waiting strategy was chosen to give the venous arterialization time to develop and to let the wound demarcate. According to our previous experience with CLI patients, a "tension-free" surgical approach was applied when debridement or minor amputation was needed, avoiding any primary intention wound closure and pursuing a secondary intention closure. Dermal substitute (collagen) was used for covering exposed bone in transverse amputations, or the edges were closed with

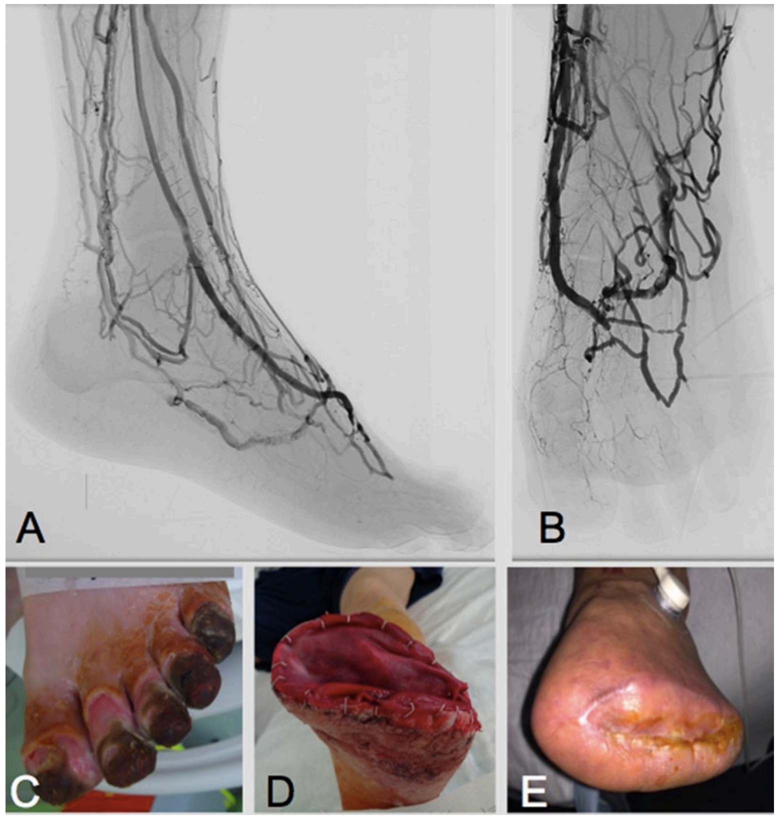


Figure 3. Same patient as Figures 1 and 2. (A, B) Lateral and anteroposterior views of the final result after embolization of proximal collateral vessels at day 18. Blood flow goes to the dorsal venous arch and reaches the deep plantar and dorsal systems through collaterals. Wound status (C) preoperatively, (D) after transmetatarsal amputation and dermal substitute at day 27, and (E) day 196 (fully healed).

just a subcutaneous suture in transverse or longitudinal amputations (Figures 3D and 4F).

Follow-up

Patients were assessed postoperatively by clinical examination, $TcPo_2$ measurements, and duplex scan. Wounds were evaluated in the diabetic foot outpatient clinic every 1 to 3 weeks according to clinical status. Duplex scan evaluation was done before discharge and every month thereafter for at least 6 months.

Statistical Analysis

Quantitative data are presented as mean ± standard deviation, and categorical data are given as counts and percentage. The chi-square test or Fisher exact test was used to analyze categorical variables. Continuous variables were analyzed with the *t* test or Mann-Whitney *U* test as appropriate. Primary patency, secondary patency, and limb salvage were estimated using Kaplan-Meier analysis. The log-rank test was employed to compare Kaplan-Meier curves. The threshold for statistical significance was $p<0.05$. All statistical analyses were performed using SPSS software (version 20.0; IBM Corporation, Armonk, NY, USA).

Results

Arterialization Procedure and Foot Surgery

The donor artery was the common femoral artery in 6 (17%) limbs and the BTK popliteal artery in 30 (83%). An angioplasty of the superficial femoral or popliteal artery above the anastomosis site preceded the bypass procedure in 3 cases. The great saphenous vein was used in 26 (72%), and polytetrafluoroethylene or a combined bypass was used in 10 (28%). The distal anastomosis was made on the PTV in 18 (50%) limbs and on the MMV in 18 (50%). All patients underwent endovascular venous valve destruction. Once adequate foot perfusion was achieved, patients underwent foot surgery.

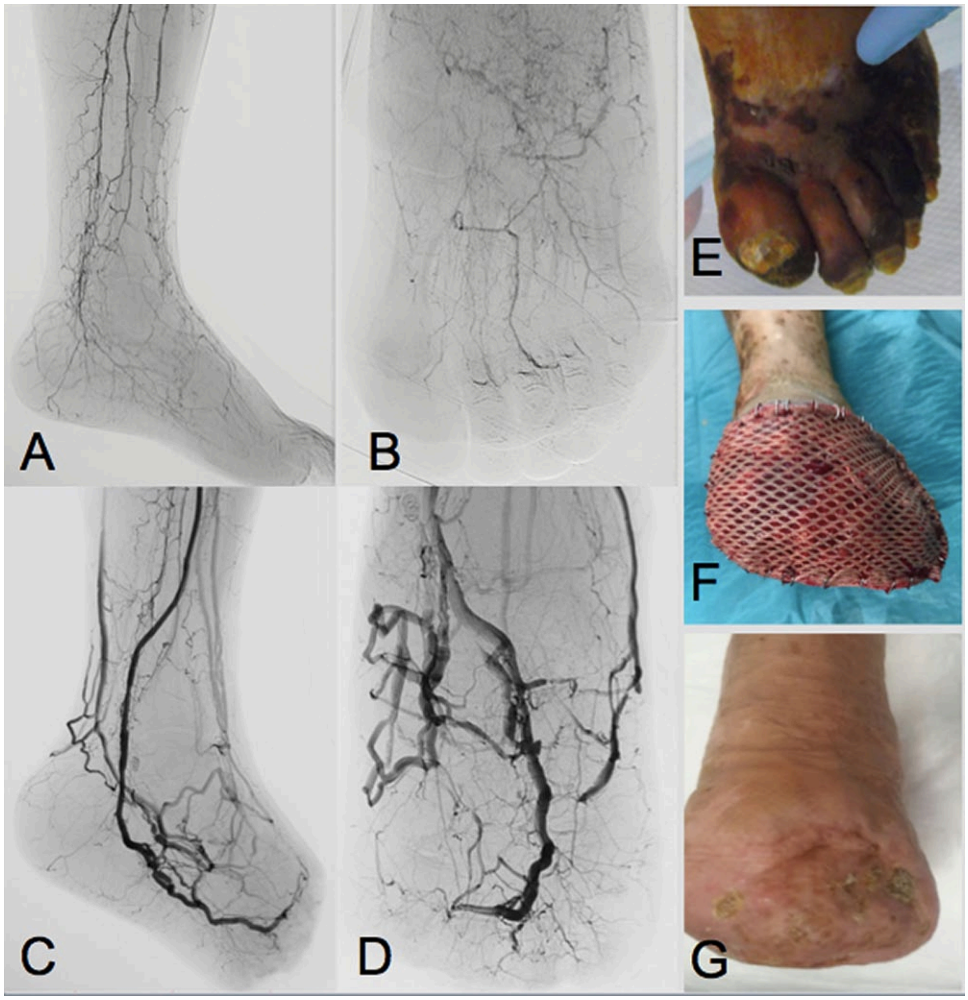


Figure 4. Hybrid foot vein arterialization on the posterior tibial vein. (A, B) Baseline angiographic study shows diffuse disease affecting below-the-knee and foot arteries. (C, D) Final result after a maintenance procedure at day 128 aimed at treatment of a distal anastomosis restenosis. Wound status (E) preoperatively, (F) after transmetatarsal amputation and skin graft at day 34, and (G) fully healed at day 197.

Clinical Outcomes

The clinical outcomes are reported in Table 2. Nine (25%) patients presented an early occlusion of the bypass in the first 3 weeks, generally associated with increasing pain and pedal cyanosis. After a failed attempt to reestablish durable and reliable patency, all of these patients underwent major amputation. The remaining 27 patients had a focalization procedure after 16±12 days in which 36 collateral veins were embolized (1.3 per procedure). Two patients had infectious complications affecting the foot stump and underwent major amputation with a pulsatile bypass. Overall, 11 (31%) patients had a major amputation (2 BTK and 9 thigh) after HFVA. In the 5 patients with Buerger disease, 4 presented healing and limb salvage (1 still smoking), and 1 still smoking patient underwent a major amputation.

At a mean follow-up of 10.8±2 months, limb salvage was achieved in 25 (69%) limbs, wound healing in 16 (44%), and 9 (25%) patients presented a wound that was still open. One patient, with a healing wound and an open bypass, died of myocardial infarction. The post-HFVA peak of $TcPo_2$ was 46±4.2 mm Hg in the nonamputated limbs. During follow-up, 14 maintenance procedures were done in not-healed patients presenting at duplex scan with stenosis (7 limbs) or occlusion (7 limbs) of the arterialized circuit.

Table 2. Clinical Outcomes of the 36 No-Option Limbs in 35 Patients.[a]

Major amputations	11/36 (31)
Above the knee	9/36 (25)
Below the knee	2/36 (6)
Infection related	2/36 (6)
Time to amputation, mo	1.8±1.2
Limb salvage	25/36 (69)
No minor amputation	1/36 (3)
Rays	5/36 (14)
Transmetatarsal	14/36 (39)
Lisfranc	1/36 (3)
Chopart	4/36 (11)
Healed	16/36 (44)
Not healed	9/36 (25)
Death	1/35 (3)
Time to healing, mo	7.6±1.5

[a]Continuous data are presented as the mean ± standard deviation; categorical data are given as the number (percentage).

The procedure was successful in reestablishing patency in 12 cases.

Estimated primary patency at 1, 6, and 12 months was, respectively, 86.1% (95% CI 54% to 84%), 20.7% (95% CI 2% to 26%), and 6.9% (95% CI 0% to 18%); secondary patency was 91.7% (95% CI 83% to 100%), 30.3% (95% CI 15% to 46%), and 8.1% (95% CI 0% to 22%). The limb salvage estimates were 91.7% (95% CI 77% to 100%), 68.1% (95% CI 39% to 77%), and 68.1% (95% CI 39% to 77%; Figure 5).

The patients were divided into a limb salvage group and a major amputation group (Table 3). Log-rank analysis showed statistical differences in primary ($p<0.001$) and secondary ($p<0.001$) patency at 6 months in the 2 groups.

Discussion

The HFVA described in this report differs from the other published techniques of vein arterialization, although it incorporates parts of them. The surgical bypass on the dorsal or plantar foot veins was proposed by Lengua[13] in 1975 and by Taylor et al[14] in 1999. Both techniques were applied in other studies with promising although sometimes discordant results.[15–26] In all these studies, valvulectomy of the distal foot veins during the surgical procedure was by phlebotomy under direct visual control and/or retrograde passage of arterial dilators, irrigating cannulas, valvulotomes, cutting balloons, Fogarty catheters, or Parsonnet probes.

Recently, totally percutaneous approaches were described by other authors. Kum et al[27] reported the initial clinical experience with percutaneous deep vein arterialization using a dedicated, ultrasound-guided crossing method to create the arteriovenous fistula and long covered nitinol stents (LimFlow, Paris, France). Gandini et al[28] described an endovascular distal plantar vein arterialization: from a subintimal channel in the occluded plantar artery they intentionally pursued an entry in the distal plantar vein, pointing the tip of the guidewire opposite to the arterial wall calcifications. Once the guidewire was advanced in the satellite vein, a plantar arteriovenous fistula was created by angioplasty of the arteriovenous anastomosis and the occluded arterial segment. The technique was attempted in 9 consecutive diabetic dialysis patients and was successful in 7; however, an average of 15 minutes of fluoroscopy was necessary to access a vein lumen, and there are no data on the reproducibility of the procedure.

Our study combined 3 complementary techniques: a surgical bypass on the dorsal or plantar foot veins, a percutaneous technique for valvulectomy of the foot veins with balloon angioplasty, and the embolization of collaterals to focalize blood distally. The embolization resembles the technique of Alexandrescu et al,[29] who focalized blood flow to the wound according to an "angiosome-oriented" approach. Because of the distal landing position of our bypass, only ankle and foot veins were embolized, trying to push blood flow as distal as possible. Eventually, the key point of our approach was the replacement of a single-step vascular procedure with multiple staged endovascular steps aimed at different pathophysiological targets and the combination of HFVA with a dedicated foot surgical treatment.

The definition of a no-option CLI patient changes according to the available techniques in a certain era and place. In the Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial in 2005,[5] for example, 34% of the patients were still considered not revascularizable by surgery or angioplasty. Very strict vascular criteria were applied in our study, selecting patients with severe disease of the foot outflow arteries and at high risk for major amputation according to the WIfI classification. Moreover, our center is a national referral center for CLI, has a high case load of CLI patients, and had an extensive experience in their treatment.[30,31]

The selection of no-option patients was made by a multidisciplinary team based on a consensus judgment. Given these selection criteria, our results should be considered encouraging. No-option CLI patients treated conservatively on a wait-and-see basis present a 10% to 20% spontaneous wound healing at 1 year[32,33] vs 44% wound healing observed in our patients at 10 months.

The early patency of the arterialized circuit was a key factor for limb salvage in our series. A 25% rate of early unrepairable bypass failure was encountered, leading in all cases to major amputation. These data are similar to the experience with MMV arterialization by Lengua et al,[34] who described a 20% rate of early thrombosis leading to

Table 3. Comparison Between Limb Salvage Group and Major Amputation Group.[a]

Variables	Limb Salvage (n=25)	Major Amputation (n=11)	p
Age, y	67.5±11.1	70.7±14.1	0.51
Men	18 (72)	10 (91)	0.15
Smoking	18 (72)	5 (55)	0.09
Hypertension	22 (88)	10 (91)	>0.99
Diabetes mellitus	21 (84)	8 (73)	0.65
Duration, y	14.4±9.6	16.4±9.6	0.76
Chronic kidney disease	8 (32)	4 (36)	0.38
Coronary artery disease	13 (52)	6 (55)	>0.99
COPD	2 (8)	0	>0.99
Neuropathy	14 (56)	5 (45)	0.72
Retinopathy	5 (20)	2 (18)	>0.99
Bypass on			>0.99
Medial marginal vein	13 (52)	5 (45)	>0.99
Posterior tibial vein	12 (48)	6 (55)	>0.99
Bypass patency at 6 months			
Primary, %	25.7	9.1	0.001
Secondary, %	38.4	18.2	0.001

Abbreviations: COPD, chronic obstructive pulmonary disease; FU, follow-up.
[a]Continuous data are presented as the mean ± standard deviation; categorical data are given as the number (percentage).

precocious major amputation. The complexity of the procedure on the foot vein system and the learning curve could explain the reason for these early failures, along with the crude method used to break distal valves, inducing heavy barotrauma into the vein wall that led to spasm, early thrombosis, and restenosis.

Once the acute phase is over, bypass patency remains poor despite a consistent number of successful maintenance procedures. Lengua et al[34] observed a mean patency of 8 months in patients who passed the acute phase. Surgical bypass on the PTV in the Mutirangura et al[24] series had a mean patency of 49% at 24 months. Kum et al[27] described a median time to loss of primary patency of 3.3 months in their preliminary experience with percutaneous deep vein arterialization, with most patients requiring reinterventions to maintain patency. Despite this short patency period, our experience confirms an acceptable limb salvage rate, supporting the hypothesis of a persistent positive effect on tissue nutrition after bypass occlusion.

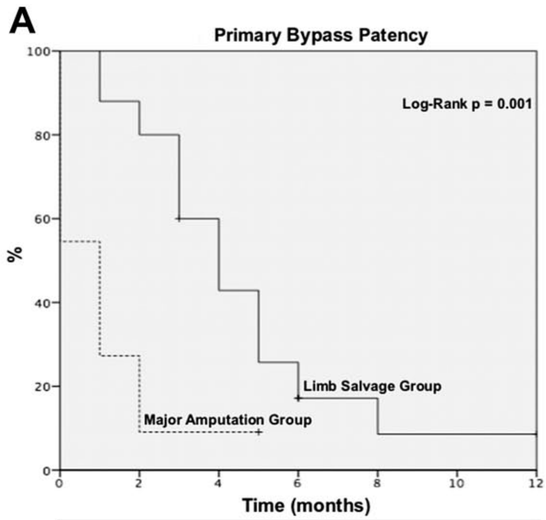
The exact mechanism of action of vein arterialization is still unclear. One theoretical explanation includes direct tissue nutrition supplied by reverse perfusion through capillaries, collaterals, and arteriovenous shunts[35,36] or the stimulation of angiogenesis.[37] The first post-HFVA angiography in our series did not show any tissue blush or significant blood flow into small veins, making it difficult to hypothesize any acute positive tissue nutrition. Later, focalization and maintenance procedures demonstrated a remodeling of the distal vascular network (Figure 4C and D), suggesting plausible direct tissue feeding. These images, alongside the persistent healing and high $TcPo_2$ values of patients with an occluded bypass, support the hypothesis of a neoangiogenetic process triggered by the arterialized circuit.[34] As observed by other authors,[24,27,34] temporary vein arterialization in no-option CLI patients with a "desert" foot could promote the growth of a new vascular foot distribution system and protect them from recurrent ischemia after graft occlusion (Figure 6).

Limitations

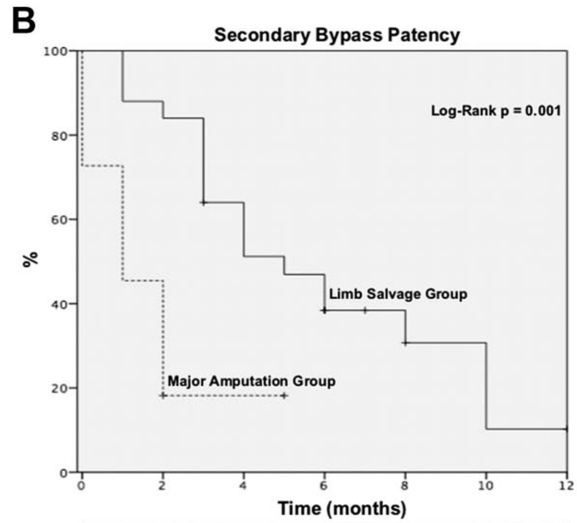
This cohort study is limited in its potential to standardize the procedure. The lack of a hybrid surgical room explains why the primary endovascular procedure occurred after the surgical bypass and not concomitantly, which would have been more proper. Finally, only a better standardization of the technique and a randomized multicenter trial could determine whether our results are reproducible and improvable.

Conclusion

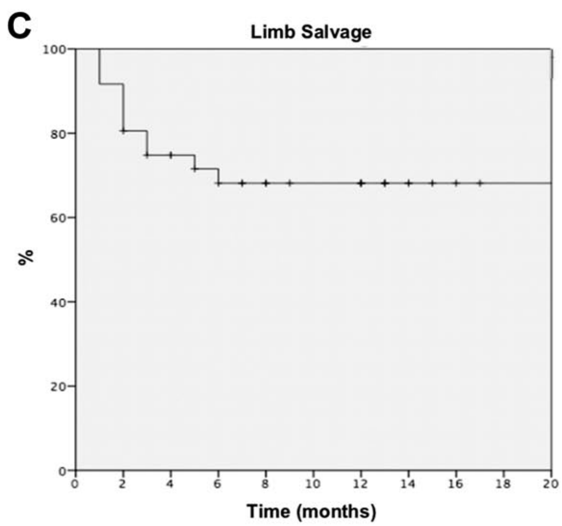
HFVA is a promising technique able to achieve acceptable limb salvage and wound healing in no-option CLI patients generally considered candidates for an impending major amputation. Further studies are needed to better identify patients who can benefit from this approach and standardize the technique.



	1 month	6 months	12 months
MA Group: PP %	54.5	9.1	-
MA Group: n. at risk	6	1	-
MA Group: SE (%)	8.7	8.7	-
LS Group : PP %	88	17.1	8.6
LS Group : n. at risk	22	4	1
LS Group : SE (%)	6.5	7.2	7.8



	1 month	6 months	12 months
MA Group: SP %	72.7	18.2	-
MA Group: n. at risk	8	2	-
MA Group: SE (%)	7.6	11.6	-
LS Group : SP %	88	46.9	10.2
LS Group : n. at risk	22	11	1
LS Group : SE (%)	6.5	9.1	10.2



	1 month	6 months	12 months	18 months
Limb Salvage: PP %	91.7	68.1	68.1	68.1
Limb Salvage: n. at risk	33	20	11	1
Limb Salvage: SE (%)	4.6	8	8	8

Figure 5. Kaplan-Meier curves for (A) primary bypass patency, (B) secondary bypass patency, and (C) limb salvage.

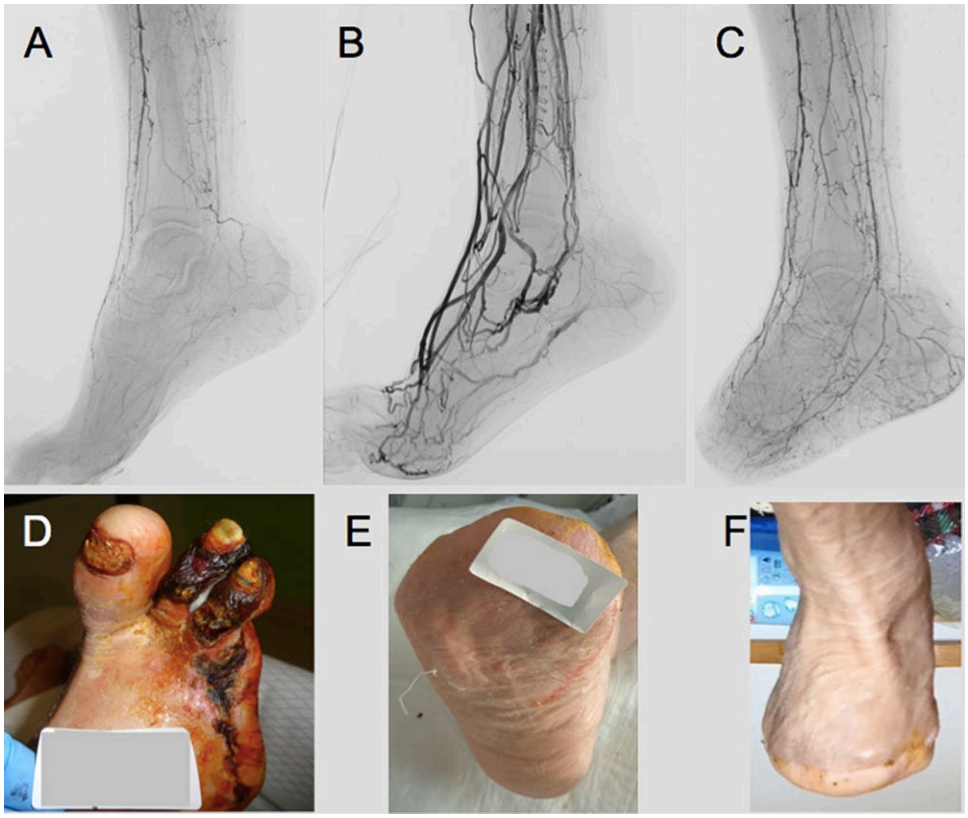


Figure 6. Hybrid foot vein arterialization on the medial marginal vein. (A) Baseline angiographic study shows diffuse disease affecting the below-the-knee and foot arteries. (B) Final result after focalization procedure at day 22. (C) Angiographic study at day 96 showing occlusion of the bypass and development of a new vascular distribution system. (D) Wound status preoperatively; transcutaneous partial pressure of oxygen ($TcPO_2$) was 6 mm Hg. (E, F) After transmetatarsal amputation and skin graft, the foot is fully healed at day 135. The $TcPO_2$ was 56 mm Hg.

Declaration of Conflicting Interests

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