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Hypertensive extracorporeal limb perfusion for critical limb ischemia

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Objective: This article reports the early results in humans of hypertensive extracorporeal limb perfusion (HELP) technology in the prevention of major limb amputation due to ischemia. The short-term aim was to dilate pre-existing collateral channels, and the long-term aim was to stimulate remodeling and new collateral development by increasing endothelial shear stress and wall tension.
Methods: This study evaluated 20 patients with critical limb ischemia who were treated with HELP. These patients had no other option but major amputation, as determined by at least two vascular surgeons. The arterial circulation to the ischemic limb was isolated from the systemic circulation by the use of an endoluminal balloon catheter in seven patients and by an implantable, inflatable, occlusive cuff in 13. The limbs were hyperperfused through the peripheral access system with an extracorporeal pump, producing a minimally pulsatile waveform at 200% to 300% of the mean arterial pressure. This was performed repeatedly in sessions of 24 to 36 hours, up to a maximum of 74 hours. The primary end point was avoidance of major amputation. The secondary end points were the clinical improvements in rest pain, ulcer healing, and claudication distance. Patients were analyzed and reviewed using infrared thermography and ultrasound imaging parameters of the limb.
Results: Given adequate arterial access, 39 of 40 connections developed flows four to eight times those supplied to the limb by the normal cardiac output. A progressive decrease was noted in peripheral resistance. All patients developed a pain-free, warm foot or hand while on the pump in the short-term. In the longer term at a mean of 22 months (range, 12-54 months), eight of 20 patients (40%) had avoided major amputation and four more had a delay in amputation of an average of 4 months. The ankle-brachial index changed from 0.04 ± 0.07 (range, 0.00-0.94) to 0.63 ± 0.39 (*t*-test, $P < .05$). Bleeding, infection, premature cessation of the treatment, and poor patient selection resulted in the failures. There were two short-term unrelated deaths that occurred at 1 and 3 months follow-up.
Conclusions: The collateral circulation of ischemic limbs can be augmented and regulated by a connection to an extracorporeal centrifugal pump, with isolation from the systemic circulation provided by balloons and with an access system providing repeatable pump connections. Major amputation may be avoided in selected cases. (J Vasc Surg 2013;58:1244-53.)

Despite advances in endovascular and open surgical techniques for critical limb ischemia (CLI), lower limb amputation, particularly for patients with diabetes, remains a continuing challenge. The escalating costs to the health care system, particularly with repeat vascular procedures, demand a greater scientific effort to achieve a simpler and longer lasting solution.[1] Collateral circulation can be augmented and regulated by connection to an extracorporeal pump at suprasystolic pressures with isolation of the ischemic segment from the systemic circulation by the use of occlusive balloons.[2] This has been achieved by the design of a specific arterial access system to withstand the suprasystolic pressures and high flows similar to those obtained in physiologic peak exercise. In the longer-term, high levels of fluid shear stress (FSS) have been shown to be the moulding force in arteriogenesis.[3] The molecular factors mediating gene upregulation of vascular proliferation have been associated with changes of blood flow at the endothelial interface, particularly via monocyte chemoattractant protein 1.[4-7] Inherent in the concept is that new collaterals may be less susceptible to atheromatous degeneration than the native vessels.

The aims of this article are to:
1. Demonstrate the structure and function of the peripheral access system (PAS) in humans;
2. Report the results in 20 patients for whom major limb amputation was the only option available for their CLI;
3. Report the obstacles encountered in the developmental phase of the technique; and
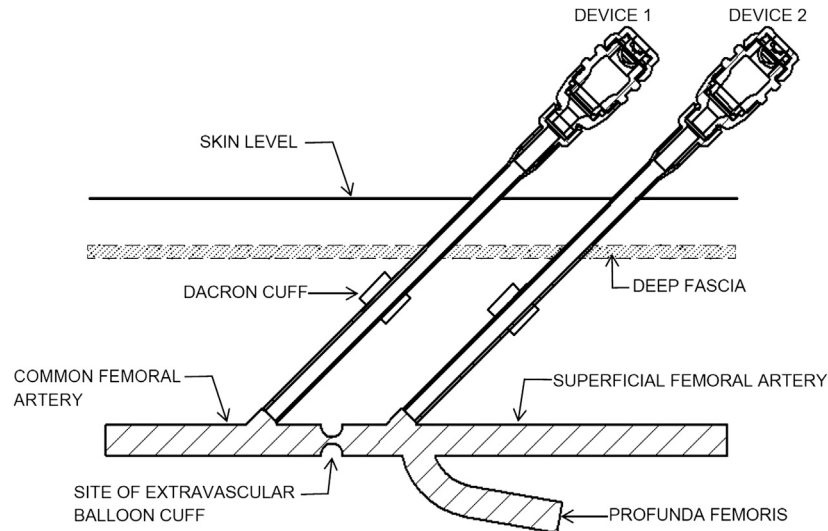
Fig 1. Schematic shows two peripheral access systems (PASs) with isolation from the systemic circulation via an inflatable extravascular balloon. *Device 1* is the inflow from the heart to the pump. *Device 2* takes blood from the pump to the isolated limb at high pressures and flows.

4. Demonstrate the device modifications undertaken to maximize the safety and efficacy of the technique.

METHODS

Patients. A cohort of 20 patients were evaluated for this report. Procedures in five patients were approved by the Northern Sydney and Central Coast Human Research Ethics Committee (NSCC HREC) New South Wales, Australia (Protocol 0501-021M). Ten patients were treated under the Special Access Scheme by the Therapeutic Goods Administration Australia, following a similar clinical protocol. Five more patients were part of a registered clinical trial (ACTRN1261000011 8000) approved by the NSCC HREC (Protocol 0911 -306M).

All 20 patients were destined for major amputation. Multiple vascular procedures (mean, 4.5) had failed in 19 of the 20 patients. Six patients had diabetes, and one had essential thrombocytosis.

The inclusion criteria were:
1. All patients had end-stage CLI with any or all of rest pain, tissue loss, or gangrene;
2. All standard operative and endovascular measures had been exhausted;
3. All had been offered amputation by at least one other vascular surgeon;
4. All had high-quality angiography at a small-vessel level with all three calf vessels occluded and no reconstitution distally;
5. There was clinical and angiographic evidence of good inflow.
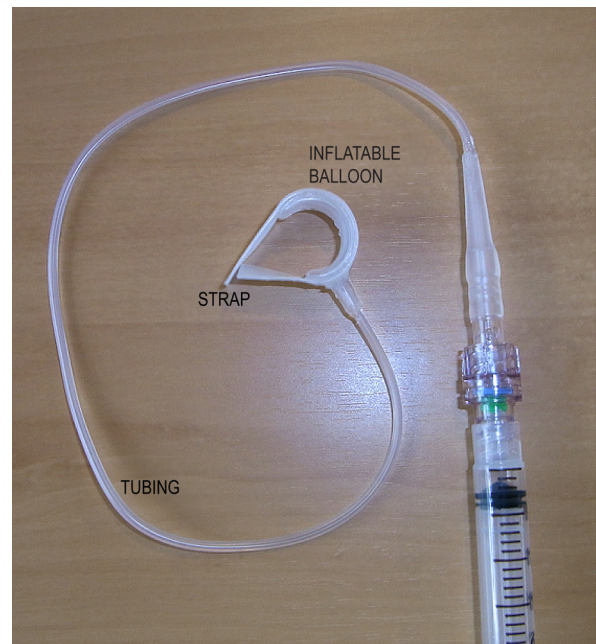

Fig 2. The inflatable balloon is placed circumferentially around the arterial inflow to isolate the ischemic limb. The diameter is fixed via sutures through the strap. The tube is passed externally for manual inflation and deflation as required.

The exclusion criteria were:
1. General cardiac, respiratory, and renal disease of significance;
2. Mental instability;

Fig 3. A polytetrafluoroethylene adventitia "skirt" is placed around the primary anastomosis to minimize bleeding. This is fixed to the adventitia by a continuous PROLENE suture (Ethicon, Somerville, NJ) after appropriate fashioning.

3. Uncontrolled infective/necrotic areas in the affected limb;
4. Vessels not capable of access and anastomosis;
5. Significant myonecrosis.

Materials. All PASs were supplied by AllVascular Pty Ltd (St. Leonards, New South Wales, Australia). The initial approach was to apply a single arterial access system using an endoluminal occlusion and saphenous system.[2] The preferred approach is shown in Fig 1, with inflow and outflow tubes with an extravascular inflatable cuff (Fig 2) between the two access systems. This setup facilitated for high pressure and large volume flows >500 mL/min, particularly where the superficial femoral artery was occluded.

The pumping system used was a Maquet Jostra ROTA-FLOW centrifugal pump system (Hirrlingen, Germany). The thermographic imaging system used was the NECTH7800N Thermotracer (Tokyo, Japan). The thermographic assessment methodology has been described previously.[2]

OPERATIVE METHOD

Implantation. A standard surgical approach to the arteries of the groin or axilla was used. A standard
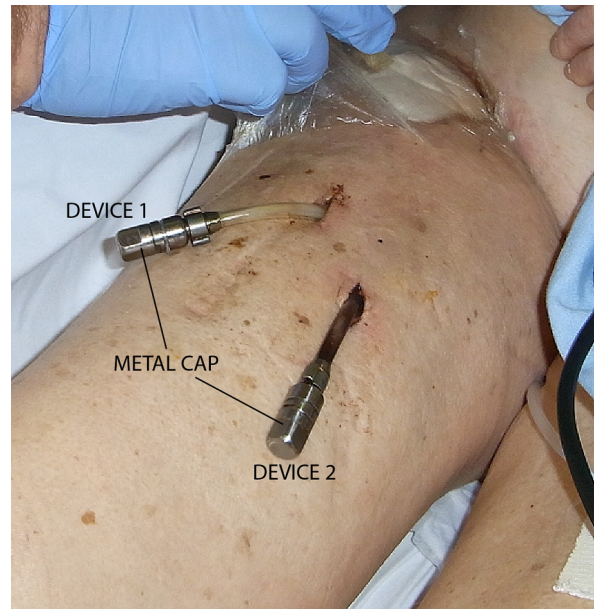

Fig 4. Two flexible access systems in situ in the right common femoral artery with exit cutaneous foramina. The extravascular balloon cuff is not visible. The metal caps lock the internal plunger in position to avoid patient tampering. *Device 1* is the inflow from the heart to the pump. *Device 2* takes blood from the pump to the isolated limb at high pressures and flows.

end-to-side anastomosis was performed, and a further polytetrafluoroethylene "skirt" was sutured around the primary anastomosis to minimize bleeding (Fig 3). These sutures were from the skirt to the adventitia of the host vessels and were circumferential around the primary anastomosis. The input and output PASs have their own individual cutaneous exit (Fig 4) with a hairy Dacron (DuPont, Wilmington, Del) cuff between each PAS and the subcutaneous tissue (Fig 1). The anastomoses were situated at least 1.5 cm apart to allow an inflatable occluder cuff to be implanted in between the two PASs. The inflatable occluder cuff has its own individual subcutaneous exit for its inflation port. The wounds were closed. Extracorporeal pumping was performed in the intensive care unit, and the patients were transferred to the standard ward accommodation after disconnection.

Explantation. Explantation occurred 5 to 18 days after implantation. The access wounds were reopened. After the vessels were controlled, the PASs and occlusive devices were removed, and no foreign bodies were left in situ. The arteriotomies were directly closed or patched with autogenous material. The wounds were irrigated with antibiotic solution and closed with drainage. Intravenous antibiotics were given according to the swab results from the ischemic ulcers during implantation, pump sessions, and explantation. Oral equivalents were given between these times.

Hematologic assessments. Serial full blood counts, biochemistry, and plasma free hemoglobin, D-dimer, and

creatinine phosphokinase were measured daily. During the pumping sessions, careful monitoring of the heparin anticoagulation was afforded by using an hourly measurement of the activated clotting time, which was kept between 160 and 180 seconds. Antiplatelet agents (clopidogrel) were used routinely to inhibit clot formation. Between pumping sessions, the patients had a standard anticoagulation with heparin as a continuous infusion, with a partial thromboplastin time of twice controls, or subcutaneous enoxaparin (1.25 mg/kg) if there was no intravenous access.

Pumping method. Connection can be at the time of the original operation or delayed to allow better hemostasis at the anastomosis. After pump connection, the infusion pressures are established at 300% of the mean arterial pressure (MAP; maximum of 300 mm Hg due to device limits). The MAP was monitored with an arterial catheter in the patient's lower arm. Pump pressure, suction pressure blood flows, and MAP were recorded every 30 minutes.

Baseline and subsequent progress evaluation. When the pump is connected and flow established, the pump revolutions are decreased so that the measured pressure through the system equals the MAP. The measured flow is the baseline. The initial resistance of the system and the limb can be calculated. The inflow pressures were increased to produce a clinically warm, painless limb. As time progresses, the flows increase and the pressures required decrease. When the revolutions are decreased so that the pressures are once again close to the MAP, then the resistance that the heart will face without the pump can be assessed.

When the flows are four to eight times the baseline flow, the pump can be disconnected. The indications for reconnection are recurrence of ischemic symptoms or a decrease in the thermographic and or ultrasound baseline parameters with poor monophasic flow. When the pump is reconnected, a low initial peripheral resistance indicates a good long-term prognosis and early disconnection.

Concerns about infection in recent wounds with transcutaneous foreign material connected to arteries are factors that promote early removal of the devices.

RESULTS

The pumping hours, mean flow rates, peak flows (mL/min), mean perfusion pressures, and peak pressures (mm Hg) are summarized in Table I. Peak pressures of up to 366 mm Hg (mean ± standard deviation: 240.6 ± 53.77 mm Hg) creating flows up to 1400 mL/min (694 ± 265.6 mL/min) were delivered safely to 19 of 20 ischemic limbs. One of the 20 limbs could not be perfused due to an unrecognized iliac dissection that prohibited adequate inflow. The overall mean perfusion pressure was 191 ± 39.54 mm Hg delivering 523 ± 195.4 mL/min through collaterals. These values were four to eight times the flow provided to the limb by the normal cardiac output. Patient outcomes at a mean of 12 months (range, 1-29 months) are summarized in Table II. While

being treated with the pump, 18 of 19 patients (94.74%) were noted to have an essentially pain-free, well-perfused, warm extremity. The single exception was the patient with underestimated myonecrosis at the onset.

Limbs were intact in eight of the 19 who had adequate pump connection. Four patients had a mean delay of 4 months in the below-knee amputation, despite significant improvement in their initial post-treatment clinical picture (Table II). Seven of the eight patients had healed ulcers at the latest follow-up, with improvement in the single residual, who had a neurogenic component. Creatinine phosphokinase was elevated in two patients, one with pre-existing myonecrosis and the other with inadvertent balloon deflation due to a transient increase in distal ischemia. There was no evidence of hemolysis, with normal plasma free hemoglobin, or platelet activation due to pump-induced negative pressures. There were two long-term deaths >30 days. Complications are summarized in Table III.

Pain assessment documented in the visual analog score changed from 9.0 ± 0.1 to 1.1 ± 0.3 (*t*-test, $P < .05$) at the latest follow-up. The ankle-brachial index (ABI) measurements changed from 0.04 ± 0.07 (range, 0.0-0.94) to 0.63 ± 0.39 (*t*-test, $P < .05$) at the latest follow-up visit. Claudication was improved, but this variable was confounded by other factors such as coexisting osteoarthritis in the knee or contralateral peripheral vascular disease (Table II). The thermographic imaging system showed noticeable differences between the treated limb and the untreated limbs in 19 of the 20 patients while connected to the pump and in 11 patients at the last follow-up visit.

A typical pumping sequence for 24 hours is shown in Fig 5. There is progressive improvement in flow, with a decreasing pressure required to produce that flow. Fig 6 shows the relationship between pressure and flow at different times and at various pump speeds. The gradient is the peripheral resistance. When the limbs are initially hyperperfused, the resistance is high. If the pump speed is varied so that the inflow pressure equates to the MAP, the flow through the limb is almost undetectable. Because the pressure-flow relationship is a straight line, retrograde projection of the resistance gives an estimate of the resistance of the pump itself and its associated tubing at the MAP. In this example, the initial flow rates are <200 mL/min, but the flow rate at the MAP is ~450 mL/min after 24 hours of pumping. This has been designated as short-term pressure-induced collateral dilatation (PICD). The temporary PICD, along with the pressure gradient, results in an increased flow rated during the pumping session and thus greater FSS at the arterial walls to stimulate arteriogenesis and collateral growth. When the pump is initially reconnected after 3 or 4 rest days off the pump, the resistance resumes a similar, but improved, value from the base value. Thereafter, there is a gradual and long-term affect of the temporary PICD with each individual connection.

Table I. Pump flows and pressures

	Patient	Age/sex	Pumping sessions	Pumping hours			
				S1[a]	S2	S3	Total
Protocol 0501-021M	MB551[b]	52/M	2	19	28	…	47.0
	RB567	57/M	1	59.5	…	…	59.5
	FW853	85/M	2	6.5	18	…	24.5
	GH237[b]	61/M	2	33.5	24	…	57.5
	MM565	86/F	2	24	11.5	…	35.5
Special Access Scheme,	EC968[c]	86/M	2	27	29	…	56.0
Therapeutic Goods Administration	MB840	86/F	2	28.5	24.25	…	52.8
	IM879	79/M	1	17.5	…	…	17.5
	JV313[b]	65/M	2	26	36	…	62.0
	MI731	76/M	2	26.5	30	…	56.5
	GC319	72/M	2	19.75	22.75	…	42.5
	KH592[b]	73/M	2	24	24.75	…	48.8
	ED238[b]	62/M	2	26	25.42	…	51.4
	BB002	67/M	2	25	32.5	…	57.5
	SL314	67/F	3	23	23.5	24.33	70.8
	LP301	68/M	3	18.5	18.5	24	61.0
Protocol 0911-306M	GB304	79/M	1	20	…	…	20.0
	KW307	76/M	1	23.5	…	…	23.5
	CM305	70/F	3	25	24	27.5	76.5
	MP306	82/F	3	24	26	21	71.0

F, Female; *M,* male.
[a]Sn, nth pumping session.
[b]Superficial femoral artery open.
[c]Upper limb patient.

Table II. Clinical outcome of 20 patients

Patient	1 week	Latest follow-up	Outcome at latest follow-up
MB551[a]	Immediate pain relief	29 months	Forefoot amputation; leg viable, healed ulcer
RB567	Leg amputated	1week	AKA
FW853	No pain	3 days	BKA 3 months after treatment
GH237[a]	Pain negligible	15 months	Leg viable; ulcers healed
EC968 [b]	Pain-free fingers	13 months	Hand saved
MB840	Pain "low to medium;" gangrenous 1st toe amputated	4 months	Post-treatment infection; AKA
MM565	Minimized pain	1 month	Died of exacerbation of pre-treatment respiratory failure
IM879	No access, pumping abandoned	12 months	BKA
JV313[a]	Pain-free leg	18 months	Leg viable
MI731	Pain 4/10; leg appears warmer	3 months	Ulcer healed; forefoot amputated Amputation site viable, leg viable
GC319	Ulcer still sore; foot feels warmer than before	5 months	BKA at 5 months
KH592[a]	No pain when lying down; pain 3/10 in toe upon contact, 0/10 in leg	5 months	Delayed BKA
ED238[a]	Pain in ulcer negligible	3 months	Ulcer improved; some pain
BB002	Leg pain 2/10	6 weeks	BKA 6 weeks post-treatment
SL314	Pain absent	5 weeks	Infection, AKA at 5 weeks
LP301	Leg amputated; BKA	3 months	BKA
GB304	Leg viable; pain 1/10	6 months	Limb viable
KW307	Leg viable; pain 1/10	6 months	Limb viable
CM305	Leg viable; pain 8/10	3 months	BKA
MP306	Leg viable; pain 4/10	3 months	Died of cardiac and renal failure

ABI, Ankle-brachial index; *AKA,* above-knee amputation; *BKA,* below-knee amputation; *NA,* not applicable; *PPG,* photoplethysmograph; *VAS,* visual analog scale.
[a]Superficial artery open.
[b]Upper limb patient.

Table I. Continued.

Mean flow per treatment, mL/min			Mean pressure, mm Hg			Peak flows, mL/min			Peak pressure, mm Hg		
S1	*S2*	*S3*	*S1*	*S2*	*S3*	*S1*	*S2*	*S3*	*S1*	*S2*	*S3*
349	355	...	234	121	...	430	450	...	366	150	...
294	...	...	196	...	...	520	...	...	279	...	...
276	193	...	179	303	...	294	300	...	220	350	...
308	788	...	285	184	...	400	1006	...	330	233	...
894	474	...	181	200	...	1100	700	...	228	245	...
498	372	...	154	169	...	650	410	...	167	190	...
437	444	...	211	217	...	670	560	...	263	296	...
112	...	...	130	...	...	240	...	...	145	...	...
567	686	...	175	171	...	670	860	...	267	212	...
615	601	...	187	206	...	760	880	...	306	243	...
385	393	...	244	290	...	490	470	...	302	313	...
468	448	...	187	175	...	740	670	...	262	196	...
558	518	...	166	147	...	730	770	...	290	222	...
711	756	...	148	152	...	870	1000	...	179	190	...
486	656	634	205	204	188	690	770	770	221	230	207
808	744	858	204	198	206	1110	1020	1060	237	276	247
695	...	...	169	...	...	920	...	...	196	...	...
366	...	...	140	...	...	470	...	...	170	...	...
724	663	773	207	196	194	900	760	1400	248	257	299
326	433	258	149	187	181	450	510	290	180	204	209

Table II. Continued.

Post-op walking distance, mm	ABI (PPG)		Ulceration	VAS pain score
	Before	*After*		
≥500	(0.2)	(0.36)	Healed	0/10
NA	NA	NA	NA	NA
≥100	0.1	0.3	NA	NA
≥100	0	(0.21)	Healed	1/10
Unrestricted	0	1	Healed	0/10
≥100	0	NA	NA	NA
NA	0.1	0.35	NA	NA
≥100	0	NA	NA	NA
≥500	0.2	1	Healed	0/10
500	0	0.74	Healed	0/10
≥100	0	0.27	Ulcer neurogenic	NA
Contralateral BKA	0	0.3	Healed	1/10
≥100	0	1 (0.43)	Yes	3/10
50	0	0.47	Toe	2/10
50	0	0.4	NA	3/10
NA	0	NA	NA	NA
≥500	0	0.62	Healed	0/10
50	0	1.47	2 healing	0/10
NA	NA	NA	NA	NA
NA	0.94 (calcification)	NA	NA	NA

Table III. Complications: Device and procedural modifications

Complication	Incidence	Etiology	Effect	Device/procedure change
Hemorrhage	3	High infusion pressure Anticoagulation Repeat operation site Multiple exit cannulas	Blood transfusion required	Double "skirt" anastomosis Delay in pumping Suction drainage External compression
Infection	4	Gangrenous ulcers in feet	Amputation at a higher level (n = 1)	Dacron isolation rings on PAS
		Infected lymphatic Repeat groin procedures	Transient (n = 2) bacteremia	Early removal of device No residual foreign material Longer subcutaneous tunnel
Fistula	1	Inadvertent balloon deflation	Transient superficial skin ulceration (groin)	Routine balloon checks especially high flow with low resistance on monitors
Embolization	1	Long flow times Long pump lines Poor anticoagulation control	Transient muscle pain Transient CPK elevation Delay in ulcer healing	Use high-flow double PAS systems Limit pump time to 24 hours

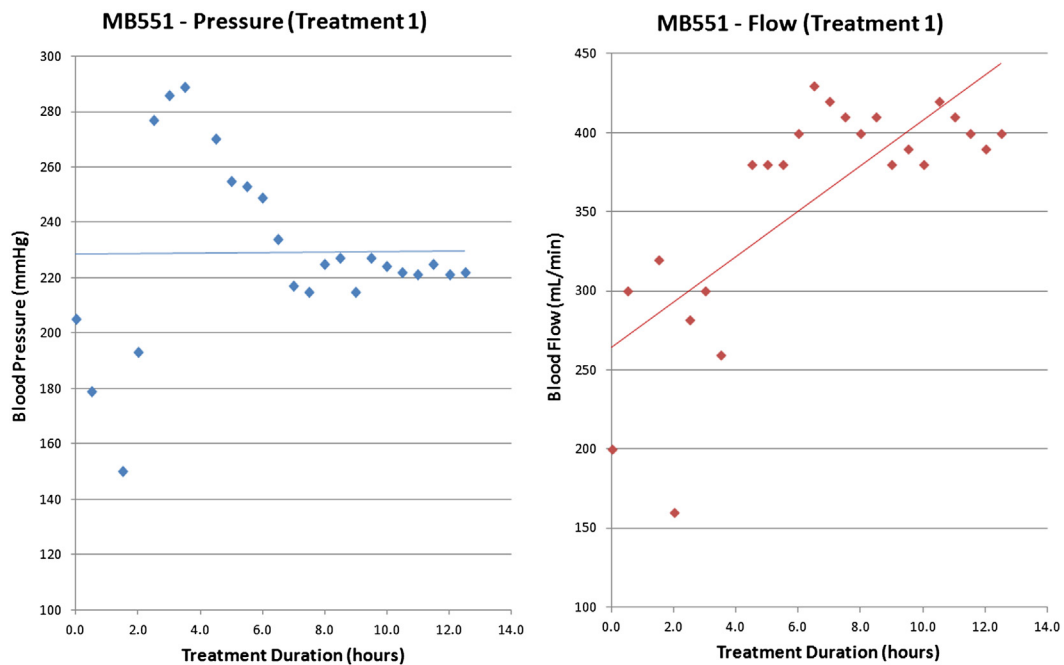*CPK,* Creatine phosphokinase; *PAS,* peripheral access system.

Fig 5. A 24-hour sequence with pressure and flow variation plotted against time. As time progresses, there is a gradual increase in flow with an associated decrease in the required pump pressure. This relationship reflects a decrease in peripheral resistance.

DISCUSSION

Given adequate inflow, the 40 connections to the pump allowed regulation, augmentation, and variation of the collateral circulation as required clinically in the short-term. The gradual reduction in peripheral resistance during a 24-hour period is shown in Fig 5. The changes are reflected in the clinical picture, with resolution of rest pain and the rapid development of a warm, pink limb. Thermography (Fig 7) is a simple noninvasive way to compare the preoperative superficial flow using the other limb as a control. Similarly, this imaging mode can be used to monitor postperfusion progress. The thermography was found to be helpful in deciding whether to reconnect the pump. The groin areas were scanned but uniformly showed increased temperature that did not correlate with the clinical situation.

The variation of pump speed allows control of the inflow pressure. Higher flow rates indicate a good PICD,
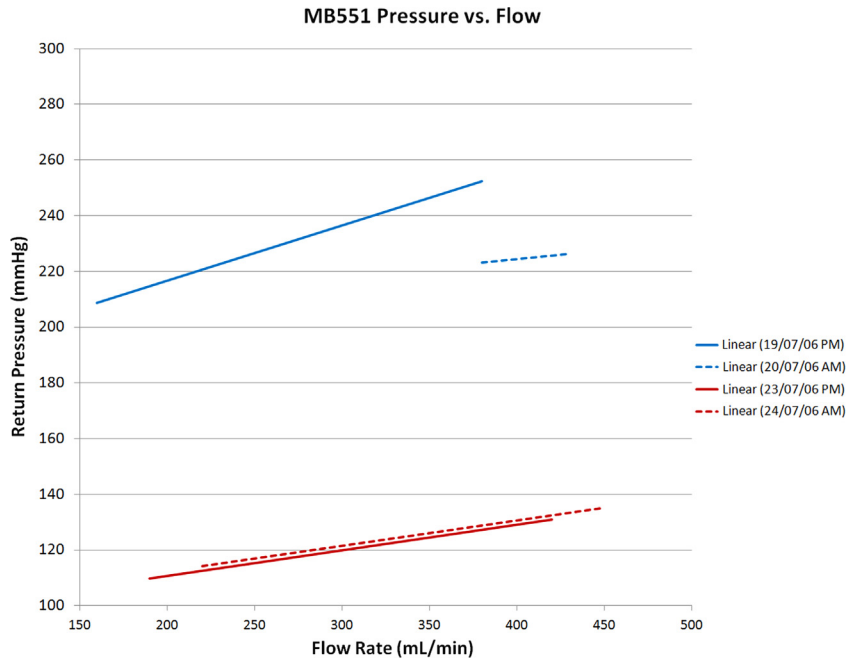
Fig 6. Graph shows pressure vs flow at different times. Initial flow rates are compared with those 12 hours later, after a rest period and after pump reconnection, and then again after 24 hours. Peripheral resistance improved after different pumping sessions.
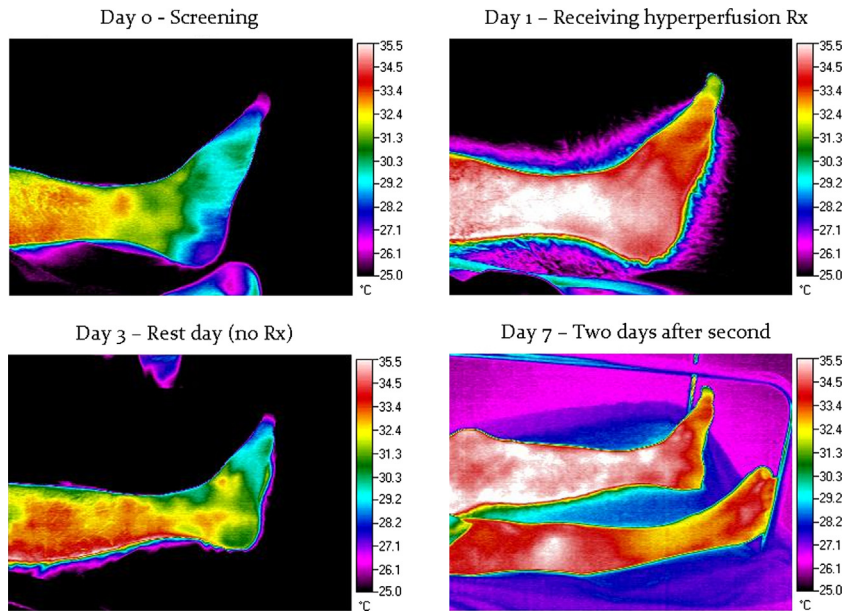

Fig 7. Monitoring thermogram is used to indicate the need for pump reconnection. This system is helpful for long-term follow-up. These images correspond to the clinical presentation. After receiving hyperperfusion, thermographic improvement is maintained.

and pump disconnection is appropriate. Similarly, when the pump is reconnected, the degree of return of collateral smooth muscle tone is reflected in the initial peripheral resistance. It is interesting that the pressure-flow rate gradient reduces slightly at different pump speeds (Fig 6). These changes suggest that the increased pressure induces dilatation of the vascular smooth muscle, which leads to a drop in the peripheral resistance, similar to that

induced by exercise.[2] After pump disconnection, there is recovery of smooth muscle tone. At the vascular endothelial level while on the pump, there is an enormous increase in blood flow velocity. Because velocity and FSS are intimately related and linked to the gradual upregulation of genes, there is an expectation of an increase in the formation of collaterals.[4-7]

The pump. The centrifugal pump was the pump of choice primarily due to its added safety measures. In an event of a blockage or obstruction in the circuit, a centrifugal pump would not continuously increase the pressure, which could lead to rupture of the PAS or the vessel(s), or both. In addition, it allowed for a heparinized circuit, was portable, and was easily connected to standard tubing. It also has automated alarm systems and a digitized reading of suction pressures, flows, and inflow pressures. Finally, it has been safely used for extended periods (days) for extracorporeal membrane oxygenation (ECMO) for cardiac patients, with minimal hemolysis. There was no significant cooling of the patient, as measured by standard temperature readings.

The evolution of the PAS. Repeated surgical groin dissections and anastomoses with expanded polytetrafluoroethylene grafts immediately subjected to high pressures, high flows, and aggressive anticoagulation create a strong predisposition for bleeding. The double skirt anastomosis was thus designed to address this issue. Since this concept has been instituted, bleeding at this site has been minimal. The development of separate input and output access systems allows for greater inlet and outlet diameters, thus eliminating the risk of hemolysis and platelet activation when using small catheters with a high negative pressure. This type of configuration also allows for more than one vascular bed to be isolated and hyperperfused, for example, a superficial femoral and profunda artery together, or by using another occlusive balloon, the profunda alone.

The use of an external inflatable occluder cuff also decreases the chance of thrombus compared with an endovascular occlusive balloon because no foreign body is in direct contact with the blood flow. No thromboembolic complications have been associated with external balloon occlusion. The disadvantage of having an external inflatable occluder cuff is the need for an additional small exit foramen, which, although only 2 mm, is nevertheless predisposed to skin bleeding at very high infusion pressures.

Because 19 of the 20 limbs had tissue loss or gangrene, the patients had a high infection potential due to colonization of their ulceration and potentially infected lymphatics. These patients often had multiple groin procedures, which also predisposes to an infective risk. In addition to appropriate antibiotics, technical changes have been instituted to minimize the infective complications. The length of the PAS and the length of the subcutaneous tunnel were increased with the addition of multiple circumferential Dacron infection shields. Other measures include a separate exit wound for the access system and the use of autogenous materials for arterial patches to close arteriotomies when

the devices are removed. Often, the endarterectomized superficial femoral artery or residual autogenous grafts were used.

Repeatability. The long-term development of collateral circulation depends on the FSS. The optimal time for development of gene upregulation is ostensibly 3 weeks.[4-6] In 10 patients, despite very successful pumping procedures, the result was limb loss with the gradual redevelopment of rest pain, and the ulcer failed to heal completely in one patient.

External arteriovenous shunts have been used for long-term hemodialysis for periods of many months and years without insurmountable adverse events.[8-10] The HELP technology is an advancement of this but still requires a better understanding of collateral development to tailor flow requirements in the short-term and long-term. Further investigations could include analysis of the overall duration of the treatment, individual treatment durations, frequency of cycles, pressure profiles, and optimal adjuvant therapy (ie, physiotherapy or drug therapy, or both). There is an urgent need for measurable biochemical markers to reliably predict the development of adequate collateralization, thereby defining treatment repeatability. The ABI increase in these patients reflects this inadequacy. However, because many of these vessels were heavily calcified, no flow could be detected on presentation, then after hyperperfusion, the increased flow might be artificially elevated in the ABI.

Future developments. Optimization of the access system is ongoing. Pump specialization and size minimization may allow greater portability. The concept of regional hyperperfusion can be used for other ischemic organs and has already been shown in the carotid circulation.[2] Furthermore, the continuous perfusion dramatically increases the total flow through a vessel without the peak perfusion pressure having to be increased, largely due to increased diastolic flow. Theoretically, this may minimize the risk of intracerebral hemorrhage while increasing collateral flow for occlusive cerebral disease. Further basic research is required to demonstrate applicability in stroke patients and other ischemic vascular beds. In retrospect, shorter multiple hyperperfusion episodes (perhaps 8 hours, similar to hemodialysis) and accessing the blood flow from a remote source (axilla or either leg) might improve collateral distribution and growth.

CONCLUSIONS

The collateral circulation can be augmented and regulated by connection to an extracorporeal cardiac pump. Isolation from the systemic circulation provided by balloons and the PAS allows intermittent pump connection. Major amputation may be avoided in selected patients when all other measures have failed. Further research and definition of confounding variables are being defined in a prospective controlled clinical trial.

AUTHOR CONTRIBUTIONS

Conception and design: RL, NK, MP
Analysis and interpretation: RL, NK, MP, DM, MD

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