Hypertensive extracorporeal limb perfusion (HELP): A new technique for managing critical lower limb ischemia

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Objective: **The concept of repeatedly connecting an extracorporeal blood pump to produce pancycle suprasystolic inflow pressures to ischemic limbs is introduced. Balloon catheters allow for limb isolation from the systemic circulation. In the acute phase, it is assumed that pressure is proportion to flow (Poiseuille's Law) and in the chronic phase that collateral growth is related to endothelial shear stress and wall tension. The primary objective was to establish that increased flow could be achieved through collateral circulation in animals and in man with extracorporeal limb hyperperfusion. The second objective was to develop and test an arterial access system capable of intermittent regional hyperperfusion similar in concept to intermittent hemodialysis. Finally, to demonstrate the translocation of these concepts into humans facing major limb amputation where all standard treatment options had been exhausted.**

Methods: **Twelve sheep (6 hyperperfusion and 6 controls) were attached to a cardiac vortex pump and perfused at 200 mm Hg pancycle with the superficial femoral artery doubly ligated and isolated from the systemic circulation with a balloon catheter. Pressure transducers measured carotid and distal femoral pressures and the carotid-femoral index was calculated. To allow hyperperfusion to be repeated transcutaneously, a peripheral access system (PAS [Allvascular, St Leonards, New South Wales, Australia]) was constructed. This device was implanted in the common carotid artery in 8 sheep and opened approximately 3 days a week for continuous arterial access up to 37 days for 67 openings. To demonstrate these principles in humans, 3 patients with critically ischemic limbs were hyperperfused intermittently. Digital thermography compared the other limb as controls and provided objective evidence of the vascular changes.**

Results: **The mean carotid-femoral index was 0.6 ± 0.01 for controls compared with 1.1 ± 0.28 for the hyperperfusion group ($P < .001$). The collateral flow was superior to normal flow (ie, with the superficial femoral not occluded). Continuous access to the carotid arterial tree via the access device was 25.3 ± 8.8 days with 5 of 8 devices open for the entire observational period (maximum 37 days). The human ischemic limbs were hyperperfused at 2-4 times the mean arterial pressure producing 3-6 times an increase in pump flow measurements intermittently for 53 ± 16 hours. The clinical findings of rest pain, paresthesia, capillary return, and movement showed dramatic improvement as did thermographic emissions. Major amputation was avoided in the cases presented.**

Conclusion: **Blood flow through collaterals can be very significantly augmented by connection to an extracorporeal pump with isolation from the systemic circulation. The pancycle hyperperfusion can be safely repeated by implantation of an arterial access device. In the longer term, there is evidence of collateral development. When amputation is the only alternative, hypertensive extracorporeal limb perfusion should be considered. (J Vasc Surg 2008;48:1156-65.)**

Obstruction to the arterial circulation produces major morbidity and mortality in the community at large. Myocardial, cerebral, and peripheral vascular obstructions have acute and chronic syndromes where outcomes are affected by the "backup circulation" or collaterals. These may also fail as manifested no more vividly than in the lower limb vascular tree. More than 150,000 limb amputations occur annually in the United States (US).[1] Approximately 82% of all amputations are directly related to peripheral vascular disease.[2] The cost to the community is enormous and is estimated to be $120-150,000 US per patient that includes rehabilitation, medication, and loss of working days. In addition to this is the direct cost of the revascularization procedures themselves. Therefore, reducing the number of amputations would greatly benefit not just the potential amputees but also society in terms of reducing the financial burden.

Hypertensive extracorporeal limb perfusion (HELP) involves taking arterial blood and returning it at a pressure higher than the mean cardiac pressure. In doing so, the induced elevated flow results in high fluid shear stresses on the endothelial surface that will theoretically stimulate growth and remodeling of collateral vessels. Importantly, the time course of collateral remodeling needs to be considered. Gene up-

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regulation for remodeling processes occurs optimally at 3 weeks following vessel occlusion in animals.[3]

The aims for the present study were threefold. Firstly, the study sought to demonstrate that by isolating a limb and hyperperfusing the segment proximal to an occlusion, greater flow and pressure could be delivered distal to the occlusion compared to a control. The second aim was to test an implantable arterial access device for intermittent and recurrent connection to a HELP pump. Thirdly, the study tests the efficacy of the HELP technique for 3 patients with gangrenous limbs for whom two independent vascular surgeons could only offer major amputation.

MATERIALS AND METHODS

Animal experiments

In the animal model, 2-3-year-old Merino cross wethers (sheep) weighing between 40 kg to 60 kg were used. This vascular model was chosen due to its similarities with human vasculature and widespread availability. The animals were handled according to the Wellcome Animal Laboratories (Royal North Shore Hospital, Sydney, NSW, Australia) protocols as an accredited animal laboratory with adherence to Good Laboratory Practice principles. Ethics committee permission was obtained prior to the initiation of all experiments.

Inducing high blood flow through collaterals. Twelve sheep were used for this component of the study (6 controls and 6 HELP treatments). Pressure transducers were placed in the distal superficial femoral artery (SFA) and the vessel was occluded. Cannulae were placed in the external iliac artery (Fig 1) and attached to a Jostra Rotaflow Centrifugal Pump (Maquet GMBH & Co. KG, Rastatt, Germany). The pump was then run pancycle at approximately 200 ml/min for 3 hours. The flows and pressures delivered to the occluded SFA and suction pressures at external iliac were recorded via the digital pump readout. The control experiments had the same treatment without pump connection.

The peripheral access system (PAS). The PAS provides repeatable access to the arterial system. The device, catheters, and connections were supplied by Allvascular (St Leonards, NSW Australia). A schematic of the PAS concept is shown in Fig 2. The essential components comprise a biocompatible tube that can be anastomosed either end-to-end or end-to-side with the inflow donor vessel. The exterior connections allow no flow through the tube when not in use, and an area of tubing that can be clamped to avoid blood loss when the pump is connected.

The principles of operation are:

1. Suction cannula placed through the central lumen.
2. An inflatable balloon is used to isolate the distal limb from the systemic circulation.
3. An extracorporeal (cardiac) pump.
4. A return through the access system into the isolated distal limb with appropriate hemo-reduction valves.

The PAS was tested in eight sheep whose weight varied from 40 to 60 kg. Two operations were required. To allow sufficient flow through the system, a minimal access tube internal diameter (ID) of 21F was required. As the carotid ID in sheep was approximately 4-5 mm, a side-to-side carotid-jugular fistula was created to allow dilatation of the proximal common carotid artery (CCA). The fistula required approximately 4 weeks to mature. Suitability for anastomosis to the access system was determined using duplex ultrasound, ie, when the CCA ID reached 8 mm. The second procedure was the end-to-side anastomosis of the access system with delivery to the exterior.

Fig 3 shows the connections with the suction balloon in situ with hemo-reduction valves. The PAS was opened every few days for 3-4 weeks. On four occasions, the cardiac pump was reconnected to gauge the volume and flow characteristics in the carotid vessel with a low resistance bed (fistula).

The isolation balloon. The isolation balloon was inflated and the blood progressed upward through the center of the balloon catheter and returning via the outside of the same catheter but inside the access system (Fig 2). Suction pressures during flow and inflow were assessed to develop an impression of how much flow could be pumped through the system at different pressures.

Intermittent access. The devices were inspected every 3 days for 39.9 ± 9.0 days. After removal of the plunger and clamping of the silicone tubing, free egress of blood appropriate for possible pump connection was assessed. This procedure continued for approximately 1 month in each sheep, ie, 12 to 15 potential pump connections. Following euthanasia of the sheep, the systems were examined at post-mortem.

Human implantation

The data from 3 patients that received HELP treatment are presented. These patients all had critical ischemia and, in the opinion of two independent vascular surgeons, had no treatment option other than a major amputation. Preoperatively, informed consent was obtained in all patients.

Human procedures

Following design, bench top, and animal testing of the PAS, it was approved for humanitarian use by the Human Research and Ethics Committee of Northern Sydney and Central Coast Area Health Service, Royal North Shore Hospital, Sydney, Australia. The PAS was anastomosed to the common femoral artery (Patients No. 1 and No. 2) or the axillary artery (Patient No. 3). The PAS was tunneled through the subcutaneous tissue and was brought out through the skin. Hemostasis of the anastomosis was achieved and the anastomosis site was flushed with cephalosporin and the wound was closed in layers.

Hyperperfusion. Using the PAS, the patients were connected to the extracorporeal centripetal pump according to the manufacturers operating instructions. Once connected, the patient's limbs were isolated from the systemic flow by the inflation of a catheter in the proximal femoral artery. Before, during, and after the hyperperfusion treatment, blood samples were taken to assess the occurrence of infection (white blood cell count), hemolysis (plasma free hemoglobin), and markers for thrombosis, ie, fibrinogen

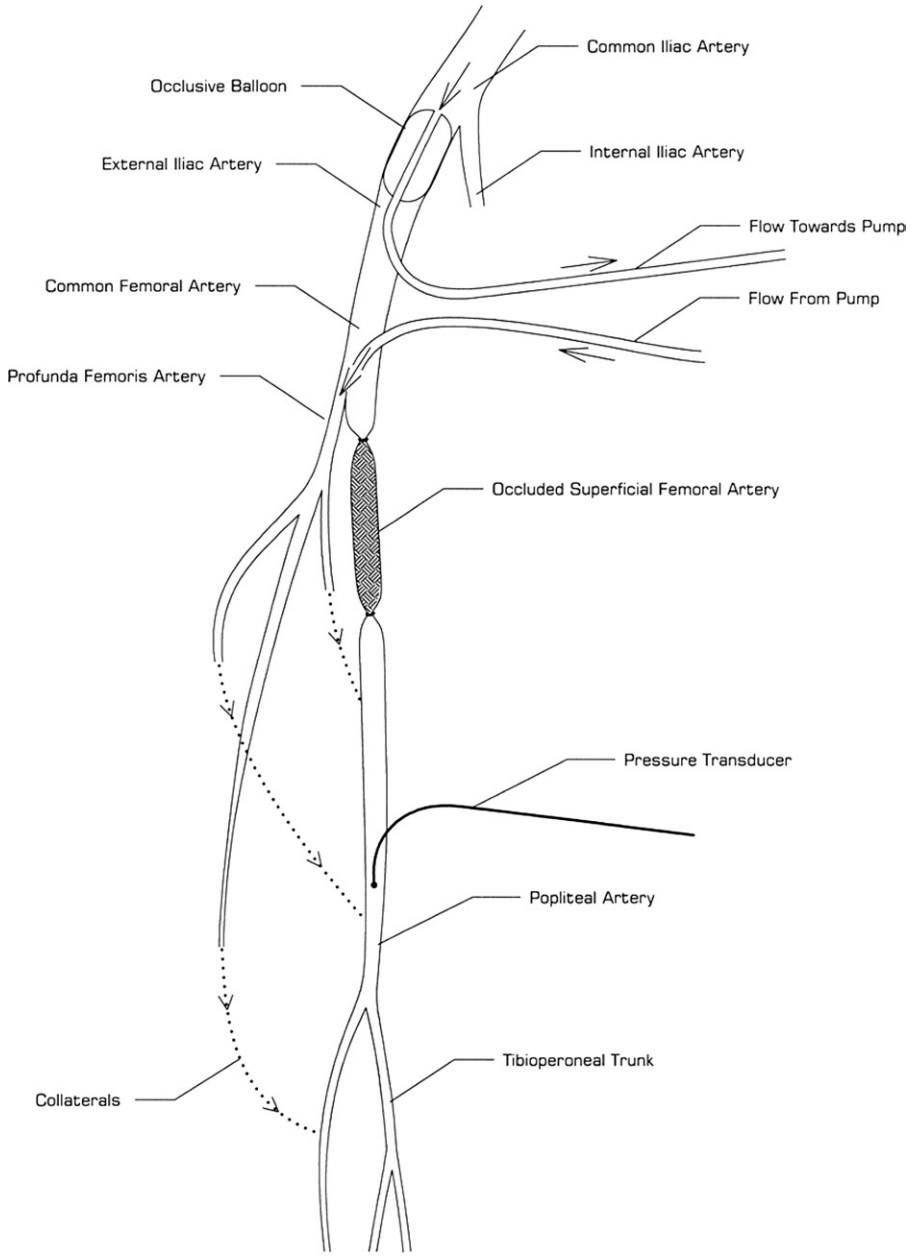

Fig 1. A schematic representation of regional limb hyperperfusion. The superficial femoral artery has been ligated. Pump inflow comes from the external iliac artery under negative pressure. The limb was isolated with an inflated balloon. Pump outflow hyperperfused the collaterals via the profunda femoris artery.

and d-dimer. Additionally activated coagulation time (ACT), normal 150-180 seconds, and activated partial thromboplastin time (APTT) normal 60-80 seconds were regularly measured to ensure that the patient was receiving adequate anticoagulation. All patients were on anti-platelet medication. The other variables "on-pump" were suction pressures, inflow pressures, flows, derived peripheral resistance, and thermographic profiles (Thermo Tracer TH7800N, NEC San-ei Instruments, Tachikawa, Tokyo, Japan). Duplex ultrasound and photoplethysmography were used for anatomical and blood flow assessments including ankle-brachial indices. Pain scores were recorded on the visual analogue scale (VAS). Pump reconnection was on clinical grounds, eg, if pain or discomfort were increasing rather than declining (Fig 4).

Human patients

Patient no. 1 (MB 551). A 52-year-old male with a critical ischemia limb event with a history of chronic occlusion of his distal left popliteal artery. His diagnosis was

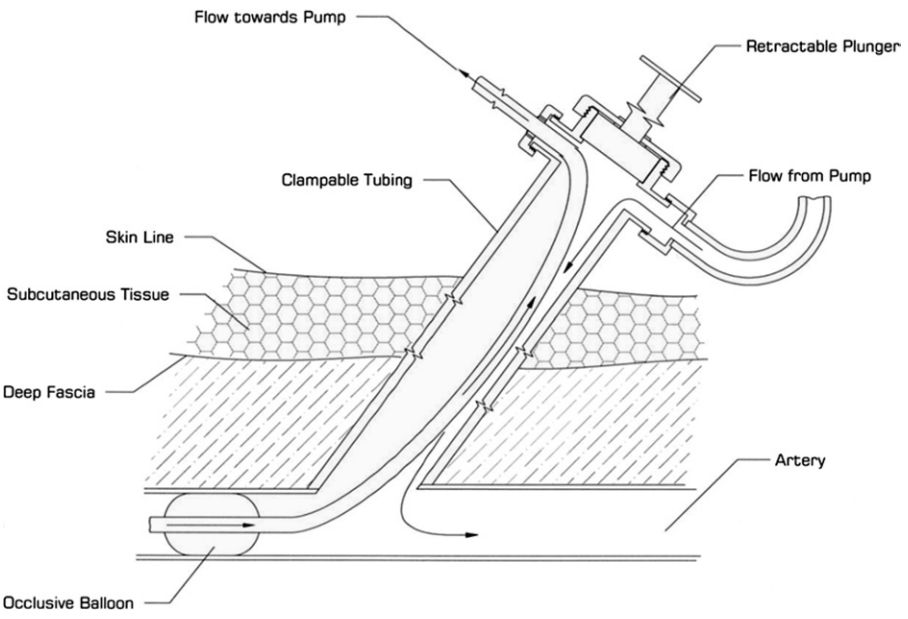

Fig 2. Delivery and access device (PAS. A schematic showing the transcutaneous tube with the blood flow directions indicated by *arrows*. The inflated balloon isolates the systemic circulation from the limb. The plunger is shown in compressed form and the cardiac pump is not shown.

essential thrombocytosis. He previously had angioplasty and stenting of his left common femoral artery and SFA. This patient suffered from gangrene, ischemic ulcers, ischemic neuropathy, and rest pain. In the opinion of two independent vascular surgeons, this patient had no treatment options other than major amputation. The patient's angiogram is shown in Fig 5.

Patient no. 2 (GH 237). A 66-year-old male with critical limb ischemia due to severe atherosclerosis in his left SFA and all major arteries below the level of his knee. He had previously undergone multiple vascular reconstructions including a femoro-distal bypass. This patient suffered from ischemic ulcers, ischemic neuropathy, and rest pain and had a claudication distance of approximately 10 meters. In the opinion of two independent vascular surgeons, this patient had no treatment options other than major amputation.

Patient no. 3 (EC 968). An 85-year-old male with critical ischemia of his left hand following embolization to the distal brachial artery 5 months previously. This patient suffered from gangrene, ischemic ulcers, and rest pain. In the opinion of two independent vascular surgeons, this patient had no treatment options other than major amputation.

Statistical analysis. Statistical analysis using ANOVA with Turkey's post-hoc test was performed. This compared values between the controls and the hyperperfusion group, as well as the values between the different time points within each group in the animals. A *t* test compared general flow rates and a Mann Whitney test was employed to assess thermographic parameters.

Fig 3. The PAS with pump connections.

RESULTS

Animals

Inducing high blood flow through collaterals. The femoral-carotid index (FCI) is the ratio between the femoral arterial and carotid arterial pressures. This was plotted against time and is shown in Fig 6. The mean and standard deviations of the hyperperfusion system were compared with controls. In the first 30 minutes after establishment of baseline values, the mean FCI in the control group was 0.64 ± 0.048. The mean FCI during the first 30 minutes of hyperperfusion (after baseline values were achieved) was 0.79 ± 0.065. The mean FCI for the last 30 minutes of the 3-hour observation period were 0.68 ± 0.010 and 1.1 ± 0.028 for the control and hyperperfusion groups respectively. There was no significant difference in control group between the first and last 30 minutes ($P > .05$). There were

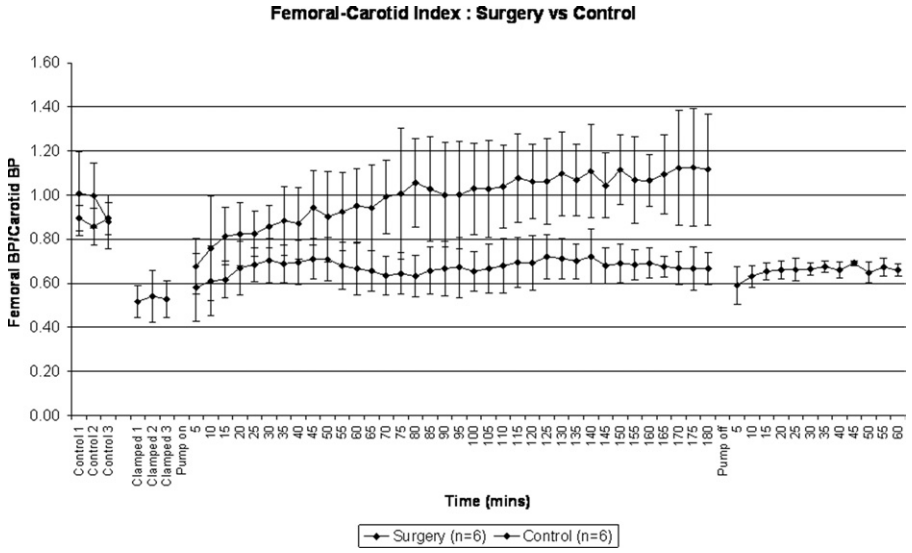

Fig 4. Hyperperfusion treatment compared with controls. This graph shows the change in relative femoral blood pressure over the experimental time (240 minutes). The ratio of femoral pressure to carotid pressure was used as the measure because it controls for normal variations in the sheep systemic blood pressure during the experiment.

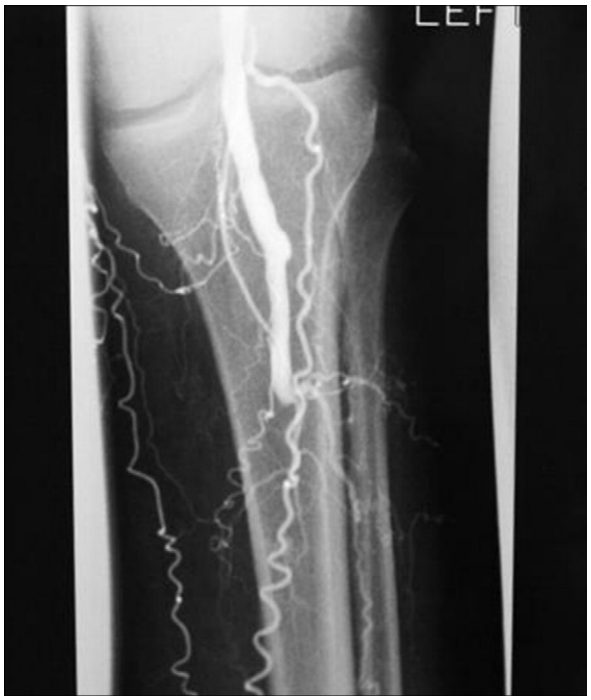

Fig 5. Angiogram of the leg revealing interrupted flow in the popliteal artery.

significant differences between the first and last 30 minutes in the hyperperfusion group ($P < .001$); between the control and hyperperfusion groups in the first 30 minutes ($P < .001$); and between the control and hyperperfusion groups in the last 30 minutes ($P < .001$).

Assessment of the PAS for biocompatibility and repeated access. In subsequent experiments investigating the suitability of a prototype to provide vascular access, eight devices were assessed in vivo using an ovine model. The devices were observed over a period of 4 weeks. Although the primary device patency was lost at a median of 20.5 days (average 25.3 ± 8.8), arterial access was available for the entire 4-week period for five out of eight devices implanted. These five devices remained functional up to the day they were explanted. Two devices were not regularly inspected for arterial access due to problems with the devices' components. This did not affect flow through the host artery and upon explantation of these two devices, an intimal layer was found to have developed across the anastomoses of both devices. There were no infective or hemorrhagic complications associated with any of the eight devices. The mean time that the device remained implanted was 39.88 ± 9.0 days (range, 28 to 58).

There was good tissue ingrowth into the Dacron felt cuff, providing desired anchorage for the device. In four different animal preparations where the carotid vessels were hyperperfused, the flow rates were 463 ± 149 mL/minute using a 12 French (Fr) perfusion catheter. Suction pressures exceeding 120 mm Hg (negative) were avoided, as it was known that platelet activation could occur at negative pressure levels when the pumps are used for normal pediatric cardiac applications. The PAS withstood pressures of up to 200 mm Hg without any adverse affects.

Human hyperperfusion

Perfusion pressures and flows or the various vessels are summarized in Table I. In total, these patients received 53.3 ± 4.6 hours of hyperperfusion treatment each, over two sessions (treatment 1 of 26.0 ± 6.6 hours; treatment 2

Table I. Various flow and pressure relationships in different anatomical sites

Vessel	*Base flow (ml/min)*	*Pump flow*	*Change*	*Map*	*Pump pressure (mm Hg)*	*Change*
SFA	86	309 ± 41	×3.6	94 ± 6	286 ± 27	×3.0
Profunda	122	780 ± 110	×6.4	82 ± 6	180 ± 20	×2.2
Axillary	206	494 ± 98	×2.4	87 ± 8.7	153 ± 7.6	×1.8

SFA, Superficial femoral artery.

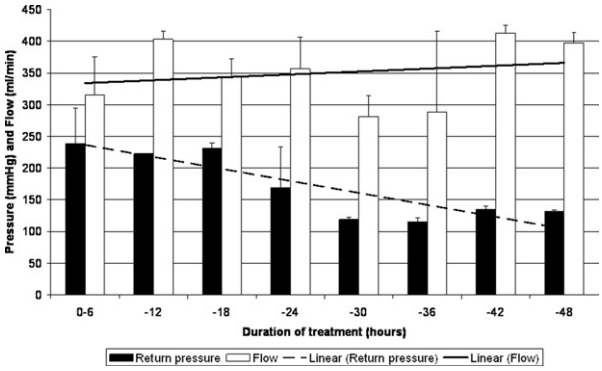

Fig 6. Pressure and flow measurements of both hyperperfusion treatments showing a continuously decreasing trend in pressure with a slight increase in overall blood flow.

of 27.3 ± 2.9 hours). The two HELP treatment sessions were separated by approximately 7 days 'non-treatment'. Fig 6 is an example of the pressure and flow relationships over time. The short-term thermographic results are demonstrated in Fig 7. Initial pre-pump emissions on the left are less than the asymptomatic right limb (Fig 7, *a*). On pump, the situation reverses (Fig 7, *b* and *c*). In Fig 7, *d*, the surface temperature is greater than the patent contralateral anterior tibial bypass graft. Fig 8 demonstrates the long-term outcomes at 10 months following hyperperfusion. The salvaged limb is warmer than the contralateral normal limb (ABI >1.0). Fig 8, *b* demonstrated the superior temperature gradients in the hyperperfused limb. The thermographic emissions in the upper limb patient were compared with a reference point, these results are summarized in Table II. The ischemic finger without gangrene was the fifth finger, left hand. The control was the corresponding finger on the right hand. The finger had tenderness and rest pain. There was a significant reduction in thermal emissions of the left fifth finger compared to the right fifth finger ($P <$ .01). On-pump, the affected finger became warmer ($P <$ .01). Initially off-pump, temperatures resumed to the pre-pump levels. Gradually the temperatures became the same as the control after 4 weeks ($P = .4$). The clinical findings only vaguely followed this improvement cycle, which tended to be continuous.

Clinical findings. The pain scores (1-10) are shown at Fig 9. At 2 months, pain scores were (0, 0, and 1). Improvement continued post-pump with demarcation of gangrene, improvement of claudication, and improvement of ischemic neuropathy. The gangrenous toes were removed in 1 patient.

Complications. Excessive suture-hole bleeding was a common problem when connected to the pump and perfused at pancycle suprasystolic pressures – especially with systemic anticoagulation. There were no clinical infections. When the access system was removed from the axillary artery in the hand hyperperfusion patient, the vessel was very friable and replaced with a polytetrafluoroethylene (PTFE) interposition graft.

DISCUSSION

The acute sheep flow model demonstrates that high inflow pressures can be propagated to the distal arterial tree. The strengths of the system relate to its simplicity, reproducibility, cost effectiveness, and easy pump attachments. The main weakness is the difficulty in creating a chronic model because of arterial size discrepancy. This is shown no more dramatically than the need to create a carotid arteriovenous fistula initially, to test biocompatibility with the access system.

The human examples demonstrate some translation of concept from the animal experiments. The main feature is the ease of creating increased distal flow by increasing proximal flow (Table I). The 3 patients suggest long-term effectiveness (longest follow-up 20 months). There is only minor improvement in distal pressures long term, although symptoms, thermographic findings, and ultrasonic velocities (particularly diastolic) are encouraging (Table III).

Material requirements

The pump. The selection of HELP pump was central to intermittent use of regional hyperperfusion. A portable cardiac pump with heparin-bonded connections to the delivery and access device, causing minimal red cell damage with digitized flow and pressure measurements selected. The flow dependency of the pump was an added safety feature. In cases of high resistance, the pressure would remain constant with a consequent reduction of flow. A vortex pump was optimal for regional hyperperfusion. During all of the hyperperfusion episodes, the plasma-free hemoglobin was normal.

Access system design. The requirement for safety and efficacy of the access system related to the minimization of thromboembolic phenomena, infection, and ease of recurrent use, ie, connection and disconnection to the arterial system.

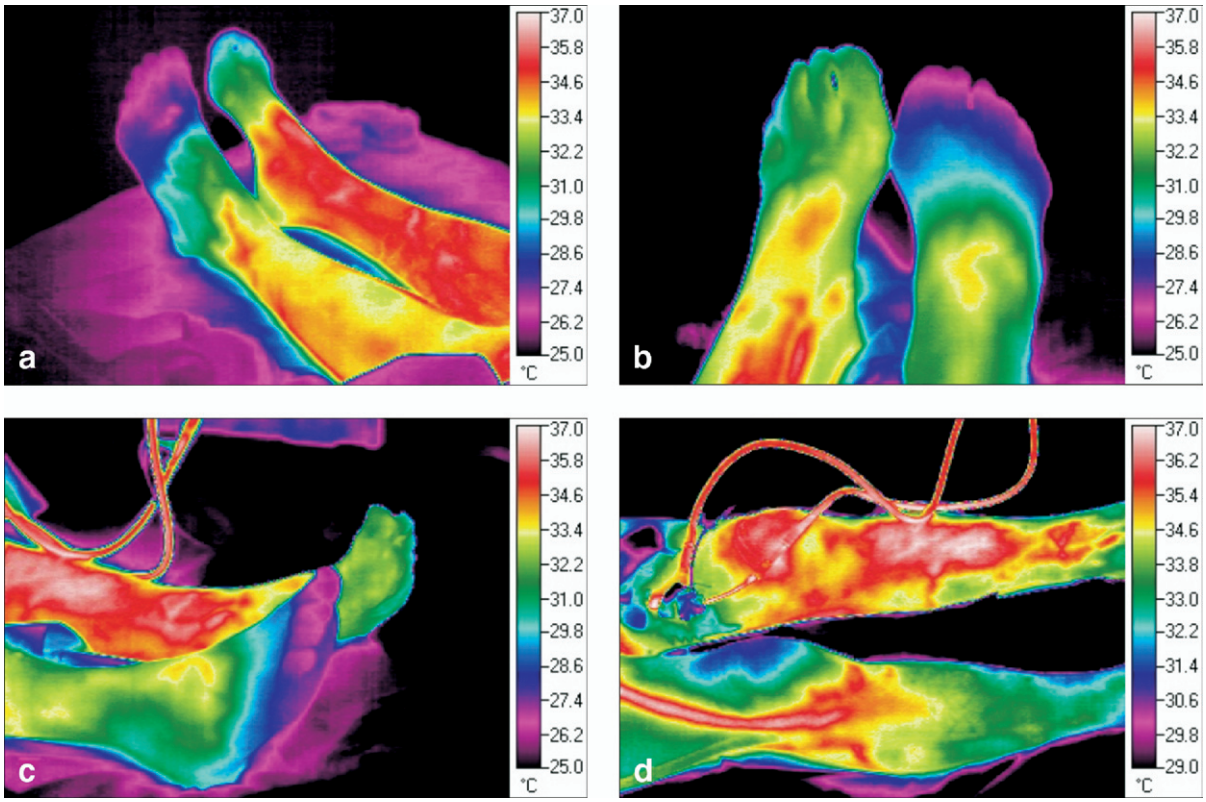

Fig 7. Thermographic study of patient FW with an ischemic left lower limb. In (**a**), the patient is resting, off-pump while (**b**), (**c**), (**d**) demonstrate skin perfusion during the hyperperfusion phase.

Physiological justification of concept. During peak exercise, systolic pressures in normal people may reach 250 mm Hg with very low diastolic pressures reflecting maximal peripheral vasodilatation. At foot level, the hydrostatic column may add up to 100 mm Hg, ie, a total at the foot level of 350 mm Hg. Regional hyperperfusion imitates peak exercise pancycle with the patient lying supine. The normal flow in the lower limb is 350 ml/min and may reach 6 L/m during exercise. The calf flow is approximately 125 ml/min.[4] At calf level through a 7 mm ID with a 12Fr central catheter, it is possible to achieve flow through collaterals, which were in excess of non-diseased vessels at rest.

Thermography. The monitoring of the regional hyperperfusion effects on ischemic limbs assumes considerable importance. To initiate collateral development, the PAS was designed to provide intermittent multiple treatments for 10-12 hours three times a week. The concept is similar to that of hemodialysis in chronic renal failure. The role of thermography was to determine how often regional hyperperfusion had to be initiated by assessing the rate of decline of flow through collaterals after removal of the pumps. The relationship between temperature isotherms and skin blood flow has been well established. Compared to Zenon 133 which is regarded as the "Gold Standard",[5] computerized thermography is a rapid, non-invasive technique where associated software enables the statistical analysis of the recorded image. The optimal use of this device is selection of amputation level[6] that is of great relevance in monitoring the effects of regional hyperperfusion.

Pressure and flow findings

The animal HELP experiments indicated an increase of pressure can be propagated through collateral pathways. The 3 patients also confirm that HELP can result in clinical improvement. Development of an implantable access device for recurrent intermittent access also appears to be feasible up to 28 days. The marriage of these two separate concepts is underpinned by many animal experiments and human observations related to collateral development. Elevated endothelial shear stress has been implicated as the crucial factor in collateral development.[7-10] Shear is directly related to the pressure gradient across a collateral bed. The need for intermittent access relates to the time course requirements for "up regulation" of the genetic control of collateral development. This appears to be approximately three weeks.[11] The modulating effect of wall tension also needs to be considered as collateral development dilates collateral vessels due to increased perfusion pressure. Shear stress decreases as vessels dilate, thereby reducing the stimulus for collateral development.

Manipulation of collateral pathways. The pressure and flow data suggests direct relationship between pressure

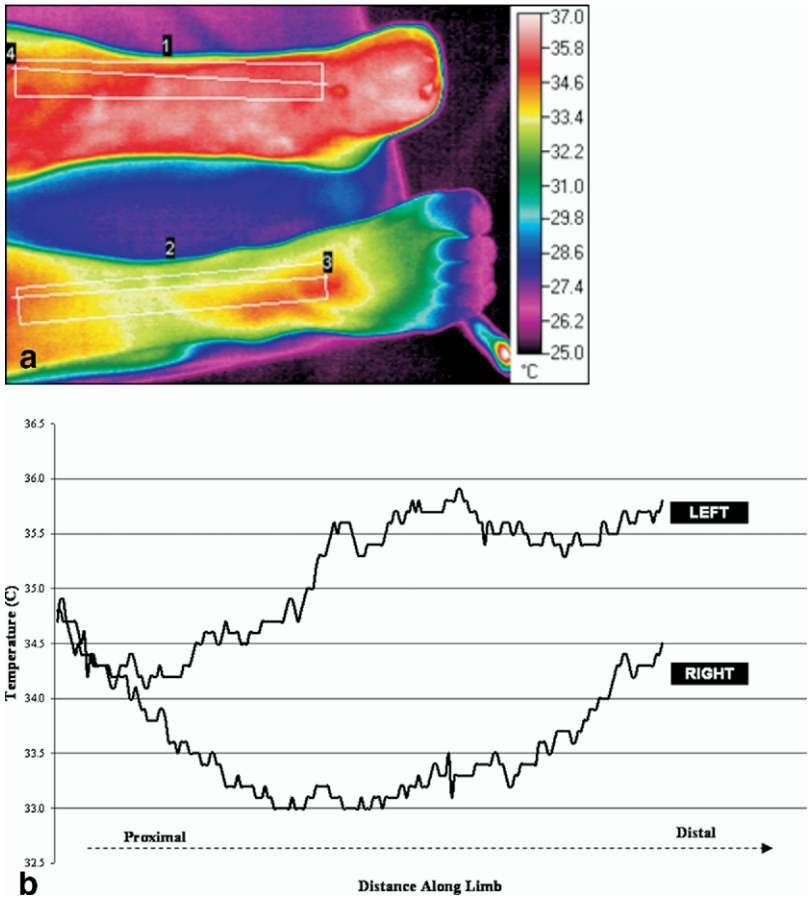

Fig 8. Thermographic study of (**a**) of left lower limb tibial line of Patient MB eight months post-hyperperfusion compared to the normal contralateral limb (ankle brachial index >1.0). Skin blood flow on the treated leg was superior as demonstrated in (**b**) when compared to the "normal" limb.

Table II. Area analysis-comparison of the left and right hands in patient 3. Thermographic readings of a left upper limb hyperperfusion for ischemic gangrene. The right fifth finger was used as a control. The analysis illustrated the time period to regain normal perfusion

Date	*Pump status*	*Right*	*Left*	*Difference*	P *value*
Aug 28, 2007	Pre	30.1	27.8	−2.3	>.01
Sep 10, 2007	Pre	30.5	32.9	+2.4	>.01
Sep 11, 2007	Post	34.8	32.2	−2.6	>.01
Oct 11, 2007	Post	26.9	26.8	−0.1	=.4

and flow (Poiseuille's Law and Ohm's Law) in collateral pathways (Table I). What is not clear is the optimal approach to maximize long-term collateral stimulation. Flow can be defined and the pressure varied (Fig 6) or the pressure made constant and the flow varied. Another imponderable is the role of simultaneous pharmacological infusions. Vasodilators have been used occasionally, usually in between infusions. Do they have a negative impact on collateral growth as they reduce the shear stress? Further data is required to determine the optimum parameters such as maximum pressures and flows for stimulating collateral growth. The replacement of the normal pulsatile flow for continuous flow also may have a beneficial impact. The capillary fragility is related to the pulse pressure. As the flow is continuous, this may mitigate against high inflow pressures. Especially important is improvement in diastolic flow which may have applications in cerebrovascular disease where hemorrhagic infarct conversion is an important consideration-flow can be increased without increasing peak pressures.

The importance of increasing the pressure gradients across a collateral bed has many clinical analogies. Patients routinely hang their ischemic limbs over the end of the bed to improve rest pain using the hydrostatic effect to increase the pressure gradient across the collateral bed. This is also evident in the common symptom of nocturnal rest pain. The pain does not occur during the day because of the gravitational effects across an occluded major vessel. Pa-

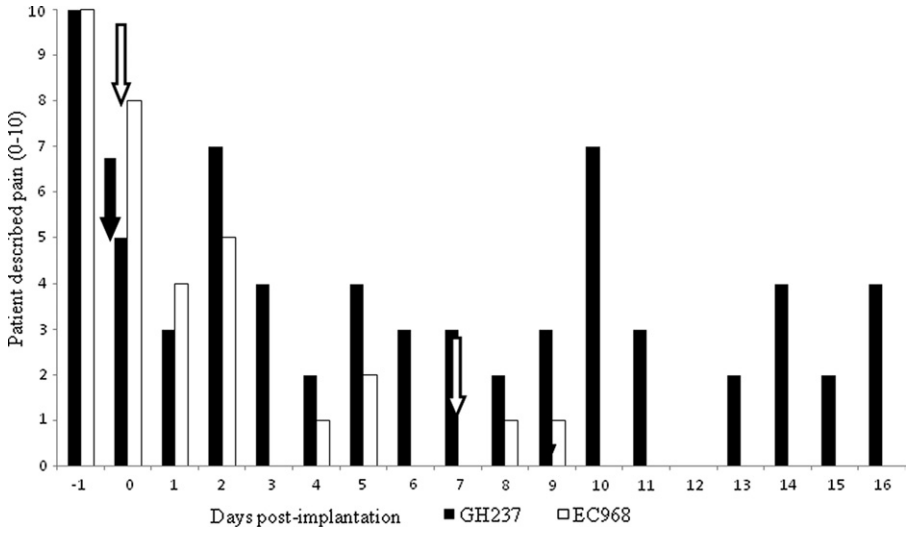

Fig 9. Patient pain level (1-10) and timeline. The *arrows* indicate "on pump" periods.

Table III. I. Patient clinical outcomes pre and post hyperperfusion

	Patient 1		*Patient 2*		*Patient 3*	
Pump status	*Pre*	*Post*	*Pre*	*Post*	*Pre*	*Post*
Rest pain	Yes	No	Yes	No	Yes	No
Gangrene	Yes	No	Yes	No	Yes	No
Ulceration	Yes	Healed (Toes lost)	Yes	Healed	Yes	Healed
Claudication (m)	15	>500	10	200	Nil	Nil
ABI/PPG	0.20	0.36	0	0.3	0	160 (mm Hg)
Peak/end diastolic velocity (cm/sec)	60/21 (popliteal)	123/60	121/19 (profunda) 43/25 (popliteal)	295/35 (profunda) 153/100 (popliteal)	N/A	N/A
Follow-up (months)		20		10		8

ABI, Ankle-brachial index; *PPG,* photoplethysmography; *N/A,* not applicable.

tients on beta-blockers or patients with low cardiac output have worsening of their ischemic presentation, either ulceration or claudication, which usually reverses with the reversal of the pump failure. In patients with aorto-bifemoral disease and SFA occlusion, bypassing of the aorto-femoral segment provides an increased pressure head at the femoral level, which may avoid distal bypass.

Most patients who present with a SFA occlusion do not lose their limb due to the development of collaterals. However, time is required for these collaterals to develop. In fact many patients are not aware that occlusion of a major vessel has occurred as they remain asymptomatic due to collateral development. Where critical limb ischemia is treated with a bypass procedure that is initially successful but then occludes at 3 to 4 weeks, the limb will usually be saved.

CONCLUSIONS

Collateral blood flow in a limb can be augmented by connection to an extracorporeal blood pump. The PAS allows safe and repeated access to the arterial tree. Hyperperfusion can be suspended when the peripheral resistance declines so that the pressure required to create a specific flow is similar to the normal mean cardiac pressure. Reinstitution of hyperperfusion is based upon clinical grounds. Isolated regional hyperperfusion is suggested when amputation is the only treatment alternative.

AUTHOR CONTRIBUTIONS

Conception and design: RL, MP, SL, MH, MC
Analysis and interpretation: RL, MP
Data collection: SL, DM, MC
Writing the article: RL, MP, SL, MC
Critical revision of the article: RL, MP, DM, MC
Final approval of the article: RL, MP
Statistical analysis: RL, MP, SL
Graphics: MC, SL, MH
Obtained funding: RL, MP
Overall responsibility: RL

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INVITED COMMENTARY

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Critical limb ischemia (CLI) remains a major unmet public health concern in the United States. Despite therapies that include bypass surgery and a vast array of endovascular options, there remain a substantial number of patients that because of distal extent of disease, absent autogenous conduit, or associated co morbidities do not have revascularization options. These patients are left with poor quality of life and the frequent need for major amputation. To date, several pharmacologic and biologic therapies have demonstrated the ability to improve limb perfusion but have not as yet demonstrated a beneficial effect on the clinically meaningful endpoint of amputation-free survival. As such there remains a dire need for an effective minimally invasive therapy for the no-option or poor-option patient with CLI.

The authors have described a highly innovative procedure that could potentially meet this need. They have developed a minimally invasive technique to temporarily perfuse the ischemic extremity at supra-physiologic blood pressures that are isolated to the affected extremity. This technique, described as Hypertensive Extracorporeal Limb Hyperperfusion (HELP), can be developed for chronic use. The appeal of HELP is that it may have an acute beneficial effect on perfusion as well as a delayed effect through increased formation of collateral blood vessels due to the temporary elevation in shear stress that occurs with therapy. They have reported convincing preclinical data that perfusion improves with HELP in a large animal hind limb ischemia model and have provided evidence of feasibility in a small safety study in no-option patients.

The next step in the development of this technique would be to perform a clinical trial. Unfortunately this is a significant hurdle in the "no-option" CLI patient population. It is difficult to conduct trials in patients with CLI because of patient heterogeneity and frequent associated co-morbidities. This group of patients that may present with rest pain through extensive tissue loss and adverse events are common in such trials. Currently available surrogate endpoints to measure limb perfusion are not accurate. Though the natural history of untreated CLI is poor, adjudicated outcomes data in this patient population are lacking. The need for a control group to truly assess the efficacy of this therapy further complicates study design and patient recruitment. In the current study, the few patients treated by the authors had very different vascular pathologies and proof of efficacy is lacking.

The authors are to be congratulated for bringing forward an exciting concept for the treatment of a cohort of patients with few options and a poor quality of life. The next step, to conduct a well-designed clinical trial to demonstrate proof of efficacy will be equally challenging.