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ORIGINAL RESEARCH

Arterial Blood Flow and Effects on Limb Tissue Perfusion During Endoshunting of the Common Iliac Artery in an Experimental Porcine Model

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Objective: Temporary arterial shunting is an established method to prevent tissue ischaemia. Although less well established, shunting might also be achieved through endovascular and hybrid techniques, known as endoshunting. Endoshunting offers advantages, for example, enabling minimally invasive access and avoiding complete occlusion of the donor artery. In an *ex vivo* bench test, volume flow in various interconnected endoshunt systems has been tested previously. This study aimed to investigate the capacity of the best performing endoshunt system *in vivo*.

Methods: Six anaesthetised pigs had their common iliac arteries (CIAs) explored, with the left CIA serving as the experimental and the right CIA as the control. Mean arterial pressure, regional blood flow, endoshunt flow, and regional oxygen extraction and lactate production were recorded. Distal muscle perfusion was monitored using near infrared spectroscopy (NIRS). Each experiment involved baseline registration, cross clamping of the left CIA, a 120 minute endoshunt session, and restoration of native flow.

Results: During cross clamping, NIRS values on the experimental side reached the lowest measurable value. Following endoshunt activation, there were no NIRS value differences between the experimental and control extremities whereas the average arterial flow decreased in both the experimental (270–140 mL/min, $p = .028$) and control extremities (245–190 mL/min, $p = .25$), with a greater drop on the endoshunted side (48% *vs.* 22%, respectively). Lactate levels temporarily increased by 42% in the endoshunted limb on endoshunt activation but were normalised within an hour. Oxygen extraction remained constant at 55% on the control side but increased to 70% on the endoshunted side ($p = .068$).

Conclusion: In this animal model, a flow optimised endoshunt system appeared to provide sufficient blood flow and restored stable tissue perfusion. Although arterial flow was slightly lower and oxygen extraction slightly higher on the endoshunted side, the endoshunt seemed to deliver adequate perfusion to prevent significant ischaemia.

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INTRODUCTION

Temporary arterial shunting is an established method to prevent tissue ischaemia in vascular surgery.[1,2] This might also be achieved with endovascular and hybrid techniques, so called endoshunting.[3] The benefits of endoshunting include avoidance of complete occlusion of arterial flow in the donor artery, rapid and minimally invasive access to both the donor and in some cases the recipient artery, and easier bridging of longer distances between the donor and recipient arteries. For instance, enabling the use of a donor artery in an unaffected limb becomes a viable option. In cases involving patients with associated injuries or those requiring endovascular reconstruction, where open shunting may not be the most suitable approach, endoshunting may offer a more suitable alternative. In a previous experiment, the volume flow was tested and optimised in various interconnected endoshunt systems within an *ex vivo* experimental heart lung machine circuit.[4]

In this previous study a combination of an 8F Prelude Short Sheath introducer (Merit Medical, South Jordan, UT, USA), a 30 cm long ¼ inch perfusion tubing (Sorin Group, Milan, Italy), and a Distal Limb Perfusion 10F One Piece

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Paediatric Arterial Cannula (Medtronic Inc., Santa Rosa, FL, USA) was found to have the highest flow capacity of all tested endoshunt combinations,[4] explaining why it was concluded that this endoshunt system would be the optimal choice to prevent ischaemic injuries and meet the metabolic demands of most end organs.

The aim with this experimental porcine model study was to investigate the performance of this flow optimised endoshunt *in vivo*, in terms of observed flow rates and effects on tissue perfusion and distal oxygen delivery during endoshunting in the lower extremity, with the ultimate aim of ascertaining safe and effective use in future clinical applications.

MATERIALS AND METHODS

Animal model management

This study was an exploratory investigation conducted on six domestic pigs that were approximately three months old and weighed between 62 and 68 kg, approved by the local ethics committee for animal studies at the administrative court of appeals in Gothenburg, Sweden (ref. no. 5.2.18—7209/17); the study was conducted according to the guidelines of the European Parliament directive. The pigs were cared for in accordance with laboratory animal protection regulations and were housed together prior to the experiment. The experiments took place at the University of Gothenburg's Experimental Biomedicine facility, an approved animal research facility. During the experiment, the pigs were premedicated with dexmetomidine/meloxicam in the stables, transported to the operating theatre, and placed under general anaesthesia. Anaesthesia was induced with meloxicam 0.4 mg/kg intravenously and buprenorphine 0.03 mg/kg intramuscularly. Isoflurane (Attane vet, VM Pharma, Guadalajara, Mexico) was administered continuously to maintain anaesthesia. To maintain stable blood pressure, crystalloids and small doses of phenylephrine were infused, with a mean arterial pressure (MAP) goal of 60 mmHg throughout the experiment. A MAP of 60 mmHg was chosen simply because this was the target baseline blood pressure of an anaesthetised pig within the research facility.

Detailed description of the experiment

First, the skin above the musculus tibialis cranialis (equivalent to the tibialis anterior muscle in humans[5]) was shaved, and ultrasound was used to locate the muscle. This allowed for subsequent measurements of tissue perfusion using near infrared spectroscopy (NIRS) and ensured that the muscle was within the NIRS probe registration window. A midline laparotomy was performed where the abdominal aorta, common iliac arteries (CIAs), and iliac veins were dissected free. Each animal received an initial intravenous bolus of heparin (200 IU/kg) and subsequent hourly doses of 100 IU/kg throughout the experiment (i.e., higher than regular human dosing to account for the higher coagulability in the blood of domestic pigs compared with humans[6]). The research was developed in four steps.

Step 1: Baseline measurements

Registration of perfusion in the left and right lower extremities was conducted for 30 minutes.

Step 2: Proximal clamping of the left common iliac artery

After these initial measurements, the left CIA was clamped proximally for 15 minutes, to induce left sided limb ischaemia (whereas the right CIA was left unaffected and thus used as internal control).

Step 3: Endoshunting period

With the proximal clamp of the left CIA in place an 8F Prelude Short Sheath introducer (Merit Medical) was inserted into the infrarenal aorta via retrograde puncture using a standard Seldinger technique (Fig. 1A). This served as the donor introducer for the interconnected shunt system, which was constructed using a 30 cm long ¼ inch perfusion tubing (Sorin Group) and a Distal Limb Perfusion 10F One Piece Paediatric Arterial Cannula (Medtronic Inc.) (Fig. 1B). A transverse arteriotomy was performed in the left CIA distal to the vascular clamp. The distal end of the endoshunt was inserted into the CIA via the arteriotomy and thereby bypassed the CIA following endoshunt activation. Over the subsequent 120 minute period of left CIA endoshunting, continuous measurements of lower limb perfusion were made for both lower extremities. No manipulations were made to the right CIA, which remained unaffected and served as control. The infrarenal aorta and CIA were chosen as experimental vessels in this study, since they best represent the diameters of the human femoral arteries in a 60 kg porcine model.

Step 4: Flow restoration

After 120 minutes of left CIA shunting, the endoshunt was removed, and the left iliac arteriotomy was closed using interrupted vascular sutures. After removing the proximal left CIA clamp, natural blood flow was restored. Subsequently, lower limb perfusion measurements were recorded during the restoration phase lasting 30 minutes. Following completion of the restoration phase, the research animal was euthanised with an injection of 80 mg of pentobarbital sodium (100 mg/mL).

Measurements of iliac artery blood flow and perfusion

To assess iliac artery blood flow and lower limb tissue perfusion, the following parameters were measured:

1. Arterial flow: Real time artery blood flow was measured using ultrasound transit time flow principles. Two MiraQ Vascular (Pacific Medical Systems Ltd., Hong Kong) systems with conventional QuickFit arterial probes were used to determine blood flow in both CIAs, while a HT110 Bypass Flowmeter (Transonic Systems Inc., Ithaca, NY, USA) was used to register blood flow through the endoshunt tubing. Flow rates were recorded every 15 minutes during the experiment, with an additional measurement taken one and five minutes after

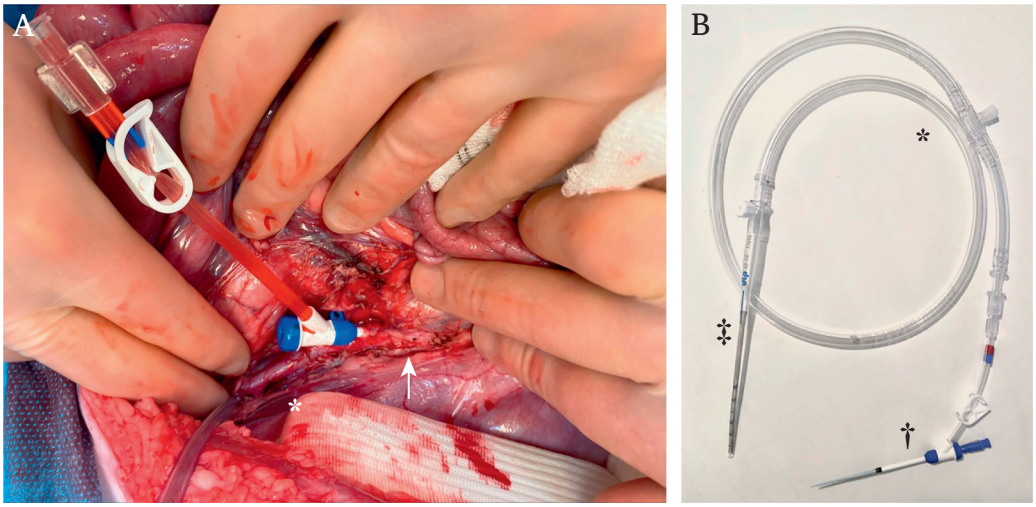

Figure 1. (A) 8 F Prelude Short Sheath introducer (Merit Medical) inserted into the porcine infrarenal aorta (arrow) via a retrograde puncture. *Left Common iliac artery (CIA). (B) The endoshunt system used in the experiment consisting of *30 cm long ¼" perfusion tubing (Sorin Group). †8 F Prelude Short Sheath introducer (Merit Medical, South Jordan, UT, USA). ‡Distal Limb Perfusion 10 F One Piece Paediatric Arterial Cannula (Medtronic Inc., Santa Rosa, FL, USA).

endoshunt activation, and after restoration of native blood flow. These additional measurements aimed to capture the rapid effects of reperfusion.

2. Tissue perfusion: NIRS was used to continuously record tissue perfusion in the striated musculature of the lower extremities. The INVOS 5100C Regional Oximeter (Somanetics, Medtronic Inc.) with cerebral/somatic oximetry adult sensors was used.
3. Lower extremity oxygen extraction: Arterial and venous blood gas sampling were performed every 30 minutes to measure lower extremity oxygen extraction. An extra blood gas sample was collected after seven minutes of arterial clamping. Arterial blood gas was obtained from the carotid artery, while selective catheters inserted directly into the common iliac veins allowed for the calculation of oxygen extraction rates in the lower extremities. The RAPIDPoint 500 (Siemens Healthcare, Erlangen, Germany) was used for sample analysis.
4. Lactate levels: The same arterial and venous blood gas samples as described above were used to analyse the arterial and venous lactate of the left and the right lower extremities selectively. The RAPIDPoint 500 (Siemens) was used for sample analysis.
5. MAP: MAP was measured continuously using an arterial line placed in the carotid artery.

Experimental protocol deviations

The blood gas analyser failed to measure haemoglobin and oxygen saturation on one experimental day, resulting in the calculation of oxygen extraction being based on four research animals. During the latter part of step 3, one research animal experienced an unprovoked cardiac arrest. Although successful resuscitation was achieved, the arterial and venous blood gas sample at the 165 minute measurement point could not be recorded because of this event. In another research animal, an arterial dissection occurred distal to the arteriotomy, prolonging the shunt removal phase before distal perfusion could be restored.

Statistics

Descriptive summary statistics of categorical variables are presented as absolute or relative frequencies whereas continuous data are presented as median (range). The Mann—Whitney U test was used to compare independent variables of interest and the Wilcoxon signed rank test was used for pairwise comparisons. A p value $<.050$ was considered to be statistically significant. Calculations were performed in SPSS Statistics 29 (IBM Corp., Armonk, NY, USA).

RESULTS

Distal tissue perfusion

All six research animals had a consistent measured distance of 0.4 cm from the skin to the muscle fascia and 3 cm from the skin to the underlying bone, indicating that all muscles were comfortably within the NIRS probe measurement window. At baseline, the median NIRS values on both the experimental (left) and control (right) sides were comparable at 50% (range 44—54%, right side, and 39—53%, left side). During the period of left CIA clamping, the NIRS values on the experimental side dropped significantly to the lowest detectable value of system (15%; range 15—20%) for all but one research animal, confirming the acute tissue ischaemia caused by cross clamping. In one animal, the NIRS value dropped to 20%; this, however, still represents a clear indication of severe ischaemia. This particular observation was interpreted as being the result of favourable collateral circulation in the pelvic region in this research animal.

After insertion and activation of the endoshunt on the experimental left side, the median NIRS value recovered to 42% (36—53%). There was a relative NIRS value decrease of

16% during the endoshunting period compared with the baseline registration, but the observed NIRS values on the experimental side did not differ significantly from those of the control extremity (see Fig. 2).

Arterial blood flow rates

On endoshunt activation, the median arterial volume flow decreased in both the experimental left CIA (from 270, range 138—409, to 140, range 103—335 mL/min, $p = .028$) and in the control right iliac artery (from 245, range 159—278, to 190, range 83—235, mL/min, $p = .25$). The observed median volume flow drop was more pronounced on the experimental left side (48%) than on the right control side (22%) (Fig. 3 and Table 1).

Regional lactate production and oxygen extraction

On endoshunt activation, the median venous lactate levels in the endoshunted left limb temporarily increased by 0.5 (0.09—0.9) mmol/L (42%), but within one hour after shunt activation the lactate level venous returns had again normalised to baseline levels. The venous lactate level on the control side remained largely unaffected during the entire experiment (Fig. 4A).

The median per cent oxygen extraction rates during the experiments remained relatively constant on the control side 55% (range 41—75) but increased on the experimental side on clamping to 70% (range 63—81 %, $p = .068$) and then remained consistently higher throughout the endoshunting period (Fig. 4B).

Arterial pressure drop over the endoshunt system (ΔP)

During one of the experimental sessions, measurements of arterial pressure were conducted both proximal to the endoshunt and simultaneously in the side port of the ¼ inch perfusion tube. At a MAP of 60 mmHg, the pressure drop across this section of the endoshunt system was 3 mmHg. Taking into account that the measuring point was positioned midway between the two inflow and outflow components with similar flow resistance, the following calculations were performed to estimate $\Delta P = (3 \pm 1) \times 2$ mmHg $< 4 \times 2$ mmHg $= 8$ mmHg. This calculation provided an approximation of the pressure difference (ΔP) and indicated that it was less than 8 mmHg at a MAP of 60 mmHg.

DISCUSSION

In this *in vivo* experimental study, it has been demonstrated that shunting with an optimised endoshunt system appeared to deliver adequate arterial flow volumes, restored stable muscle tissue perfusion, and caused only a temporary increase in lactic acid production in the shunted limb that was mainly attributable to the 15 minutes of cross clamping before the endoshunt was activated.

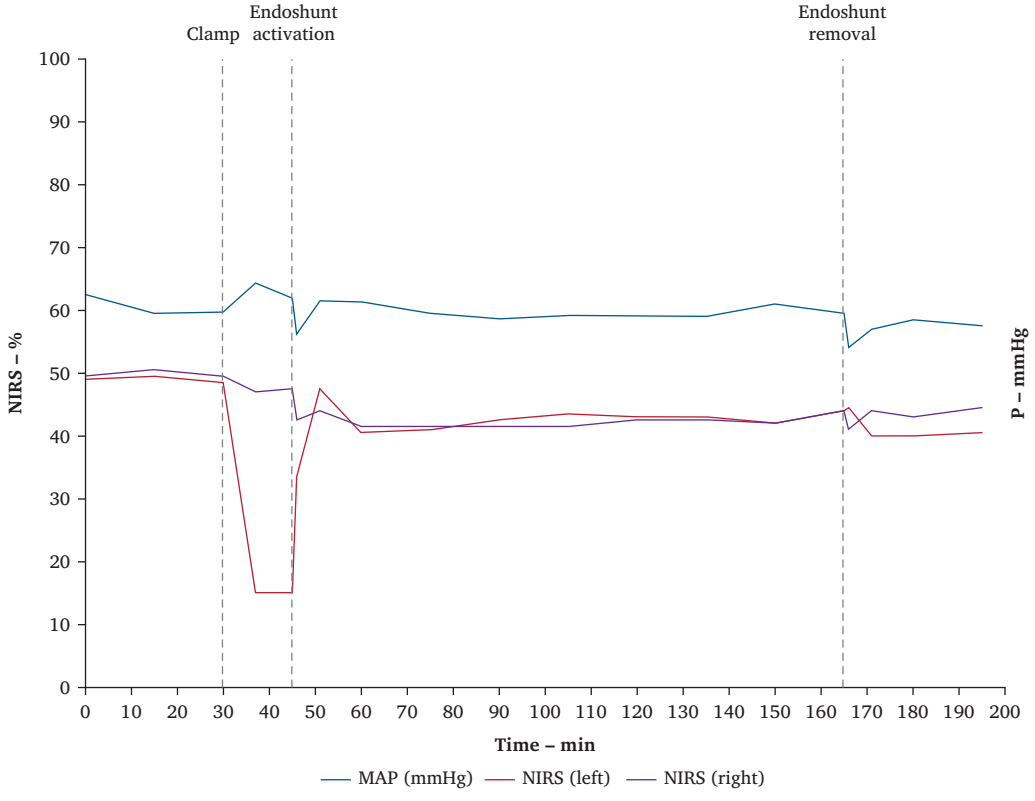

Figure 2. Observed median near infrared spectroscopy (NIRS) values for experimental left leg (red) and control right leg (purple). P = pressure; MAP = mean arterial pressure (blue).

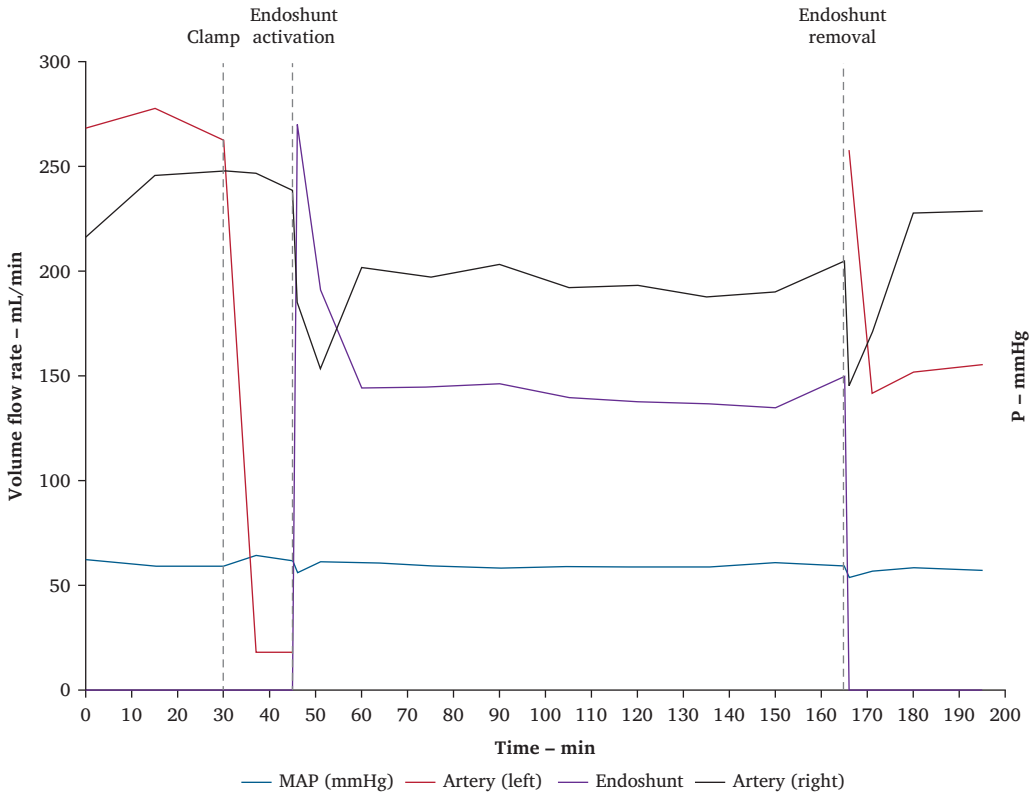

Figure 3. Median volume flow rates for experimental left common iliac artery (red), control right common iliac artery (black) and endoshunt from aorta to left iliac artery (purple). P = pressure; MAP = mean arterial pressure (blue).

Table 1. Left and right common iliac artery volume flow for the six research animals during the main phases of the experiment.

	Baseline (0—30 min)	Endoshunting phase (45—165 min)	Restoration of native vessel flow (165—195 min)
Left (experimental side) arterial flow — mL/min	270 (138—409)	140 (103—335)	150 (81—330)
Right (control side) arterial flow — mL/min	245 (159—278)	190 (83—235)	225 (97—360)

Data are presented as median (range).

In a previous study, the flow capacity of different endoshunt systems was tested,[4] and it was observed that the most important factors for efficient volume flow are the radius of the inner lumen of the shunt, followed by the overall length of the endoshunt, i.e., in accordance with the predictions in the Haugen—Poiseuille equation ($Q = dV/dt = \pi r^4 \Delta p/(8\mu L)$), where Q is the volumetric flow rate. The factors of the equation determine the pressure drop over the endoshunt, ΔP. Another important factor that determines the volume flow rate is the driving pressure, in this case defined by the MAP. The relationship between MAP, the drop in pressure over the endoshunt system and the peripheral resistance can be written as: MAP = ΔP + peripheral resistance.[7] In conclusion a high driving pressure (MAP) and a low pressure gradient (ΔP) over the endoshunt system are the major determinants of volume flow rates,[4] assuming a constant peripheral resistance. In this animal study the aim was to keep the MAP at 60 mmHg. During the experiment the ΔP was measured to $\leq$8 mmHg at a MAP of 60 mmHg. Under the experimental conditions, the median flow rate during the shunt period was 140 mL/min but ranged from 103 to 335 mL/min. The highest volume flows were observed immediately after shunt activation, due to the low peripheral resistance induced by the preceding ischaemia in the lower extremity. This type of immediate short lived high volume flow rate after restoration of blood flow after shorter ischaemic periods has been described in previous studies.[8,9] Haemodynamically, there was quite an evident impact of this short lived reperfusion with both a drop in the MAP and in the volume flow of the contralateral leg at the time of shunt activation. This leads to the conclusion that the endoshunt system can deliver at least 335 mL/min under *in vivo* conditions, i.e., substantially higher than the median flow rate that was observed during the experiment (140 mL/min). One explanation for this volume blood flow decrease compared with both baseline and the right control extremity may be the observed phenomena of raised peripheral resistance and subsequent

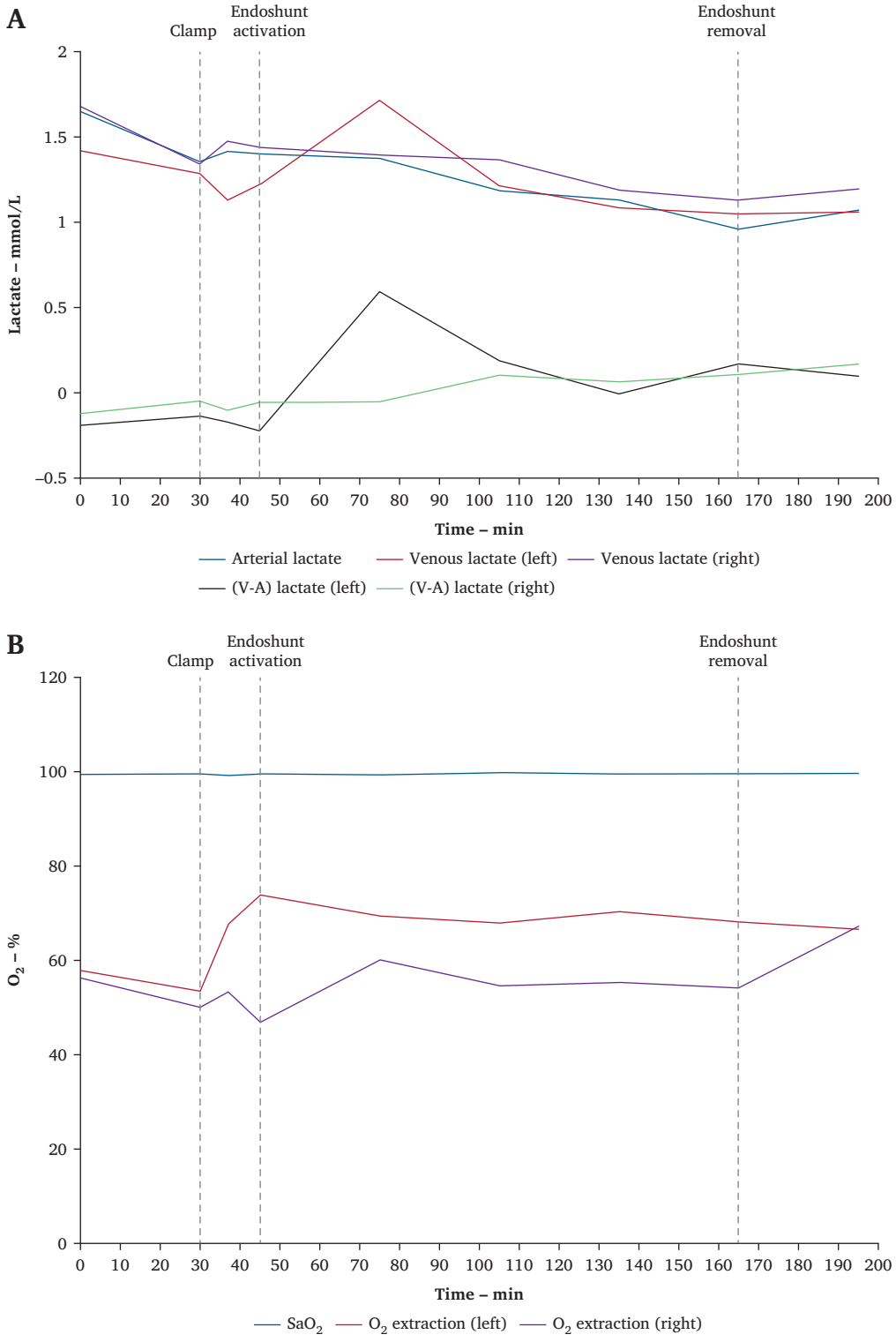

Figure 4. (A) Arterial lactate levels measured in the carotid artery (blue), in the (experimental) left iliac vein (red), and in the (control) right iliac vein (purple). The arterial lactate level subtracted from the venous lactate level on the (experimental) left side is displayed in black. The arterial lactate level subtracted from the venous lactate level on the (control) right side is displayed in green. (B) Observed regional oxygen extraction levels in the left (experimental) and right (control) limbs during the experiment. Oxygen (O_2) extraction on experimental left side (red). O_2 extraction on control right side (purple). SaO_2 = oxygen saturation (blue).

lower volume blood flow in the post-ischaemic tissue bed.[10–12] This phenomenon of higher peripheral resistance has been reported to stay in effect for up to 30—240 minutes, depending on duration and severity of ischaemia.[10,12] Further evidence for this assumption is that the volume flow did not fully return to baseline levels in the experimental left leg after removal of the endoshunt and restoration of native vessel flow.

The next crucial question to address is whether the volume flow in the endoshunt circuit is sufficient to avert permanent lower extremity ischaemic damage. To ascertain this, regional lactate production, oxygen extraction, and limb muscle oximetry were assessed. NIRS is a commonly used method to evaluate both cerebral and peripheral muscle perfusion[13] and with the probe used, with two receiving detectors, foremost oxygenation of muscle tissue is measured.[14] During cross clamping of the left CIA, the NIRS value drop indicated acute striated muscle tissue ischaemia. After endoshunt activation there was a short period were the NIRS value exceeded that of the control side suggestive of reperfusion, and thereafter the observed NIRS values of the experimental and control sides were comparable throughout the experiment. The interpretation of these measurements is that the arterial circulation is sufficient during endoshunting. This conclusion was also further supported by the observed regional patterns of lactate production, where a transient lactate increase was observed in the left limb after endoshunt activation that rose slightly during the first 30 minutes of endoshunting (median increase at 0.7 mmol/L, Fig. 4A) but thereafter returned to baseline levels. This pattern is interpreted as washout of the lactate that was produced during the 15 minutes of cross clamping (and subsequent ischaemia) but that additional lactate did not accumulate during the endoshunt period. The fact that the regional oxygen extraction increased (from 55 to 70%) in the experimental left limb following cross clamping of the CIA but did not fully return to baseline during the two hours of endoshunting still suggests a need for some metabolic adaptation to meet the oxygen demand in the peripheral muscle. This slightly higher oxygen extraction level could still be interpreted as adequate against the background of the observed lowered lactate production. It has been reported previously that skin and subcutaneous tissue might alter their oxygen consumption in the event of lower blood flow whereas the oxygen consumption in striated muscle does not have this ability.[15] The higher peripheral resistance in the post-ischaemic tissue, the oxygen debt collected during the ischaemic period, and the constant demand for oxygen in the striated muscle might explain why the oxygen extraction rate decreased slowly in the experimental leg. In the future, given that it was not done in this study, it would be interesting to also measure myoglobin, creatinine kinase, and to collect muscle biopsies to further evaluate the level of muscle ischaemia.

One potential limitation regarding the endoshunt system that was used in this experiment is that the distal component (Distal Limb Perfusion 10F One-Piece Paediatric Arterial Cannula, Medtronic Inc.) is a bit sharp at its distal end. Even if the included dilatator like introducer system had been used, one of the research animals suffered an arterial dissection distal to the arteriotomy. The assessment is that the dissection occurred when re-suturing the arteriotomy, but it cannot be fully excluded that the dissection was caused by this distal endoshunt component. Another limitation with the distal component used in this experiment is that it needs to be inserted via an arteriotomy. In some cases, for example when an embolectomy is required prior to shunt insertion, this is appropriate. In other cases, an endovascularly inserted distal component might be more suitable. Other obvious limitations are that the sample size in this study with only six research animals hampers the possibility for statistical inference of the observed changes.

The clinical implication of the study is that the endoshunting method is an attractive and versatile alternative to the more established method of conventional arterial shunting that has mainly been used in acute extremity ischaemia, trauma, and during carotid artery surgery. Besides the already mentioned benefits, endoshunting allows very rapid donor (and sometimes recipient) artery access and shunt system activation, as well as making it possible to keep both ends of the shunt system out of the surgical field and the site for the ongoing vascular reconstruction. Depending on the diameters of the donor and recipient arteries, different inflow and outflow components can be easily adapted to the surgical situation, keeping in mind that smaller components inevitably lead to lower volume flow rates. Moreover, it is possible to keep the shunt activated throughout the entire arterial reconstruction, whereas a conventional shunt commonly needs removal prior to completion of, for example, a bypass reconstruction. In future studies the aim is to test the hypothesis that endoshunting might also be an alternative technique when a shunt is needed for visceral arteries during, for example, complex open aortic surgical procedures. In conclusion, endovascular shunting using an optimised endoshunt system appeared to deliver adequate flow volumes in an experimental pig model and restored stable muscle tissue perfusion. Although the arterial blood flow on the endoshunted side was slightly lower than on the control side during the endoshunting period, the endoshunt seemed to deliver sufficient arterial flow that avoided significant ischaemia.

CONFLICT OF INTEREST

None.

FUNDING

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