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CHAPTER 6

Gastro-epiploic artery for peripheral revascularization. A study in pigs

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ABSTRACT

Objectives: The purpose of this study was to introduce the autologous gastroepiploic artery (GEA) as arterial bypass graft for peripheral revascularization. We compared the development of intimal hyperplasia and nitric oxide (NO) capacity in GEA and internal jugular vein (IJV) implanted as peripheral grafts.

Materials and methods: In pigs the GEA was implanted into the right peripheral circulation as femoropopliteal bypass graft. In the left peripheral circulation the IJV was implanted as femoropopliteal graft. After 21 days all grafts were harvested. Vascular rings of each graft before and after operation were studied for NO capacity. The distal half of each graft was prepared for histomorphometric studies.

Results: Administration of bradykinin to IJV and GEA induced relaxation. After implantation bradykinin resulted in contraction in IJV grafts whereas in GEA grafts relaxation was reduced. In IJV grafts extensive intimal hyperplasia was formed, whereas in GEA grafts small area's of intimal hyperplasia were formed.

Conclusions: The functional studies showed loss of NO capacity in IJV grafts, whereas NO capacity in GEA grafts remained intact. Intimal hyperplasia in IJV grafts was extensive, whereas GEA grafts demonstrated preservation of pre existent intimal architecture. These results may encourage the application of the human GEA as bypass graft for reconstruction of arteries in lower limb or foot.

INTRODUCTION

The autologous vein is regarded as the bypass graft of choice for peripheral revascularization especially for revascularization in the lower limb or foot. However, vein graft failure due to intimal hyperplasia with ultimately obliteration is a common event.[1]

Functional changes in the vein graft endothelium are also implicated in peripheral vein graft failure. For example it is known that vein graft endothelium is unable to produce nitric oxide. Nitric oxide has an important contribution to the regulation of the vascular tone and helps providing a nonthrombogenic luminal surface. In addition, nitric oxide is able to inhibit vascular smooth muscle cell proliferation.[2] Impairment of nitric oxide release may deprive the vein graft of optimal protection against platelet adhesion and vasospasm and possibly occlusion.

Recently, it has been shown that the short term outcome of the gastroepiploic artery (GEA) utilized for human coronary bypass surgery is comparable with the successful use of the internal mammary artery (IMA) for coronary bypass grafting.[3] Histologic, morphometric and functional similarities allow speculation that their long term patencies may be comparable.[4-6]

We postulate that the gastroepiploic artery is a viable novel bypass graft for peripheral revascularization. Therefore, we compared the intimal morphology and endothelial nitric oxide function in the GEA and internal jugular vein before and after implantation as peripheral bypass grafts in a porcine model.

MATERIALS AND METHODS

Experimental design

Twelve female pigs (42.2 ± 0.9 kg) were used in this study. In the right femoropopliteal circulation the animals received the gastroepiploic artery as autologous arterial bypass graft. In the left femoral circulation the internal jugular vein was implanted as venous bypass graft. After 21 days all grafts were harvested. The proximal half of the grafts before and after grafting were used for determination of endothelial function. The distal half of the grafts was prepared for light microscopic and histomorphometric analysis. The experiments were approved by the committee for judgement of animal experiments of the School of Medicine, University of Groningen.

Animal operations

The animals were anesthetized by an intravenous injection of sodium pentobarbital. The pigs were intubated and inhalation anesthesia was accomplished with 1% halothane.

An incision was made from the last nipple to the knee in both the right and left hind leg, exposuring the popliteal artery. Thereafter the adductor magnus muscle

was partly dissected free from its fascie and mobilized exposuring the femoral artery. A limited laparotomy was made approximately 10 cm distal of the processus xiphoideus. The peritoneal cavity was opened and the GEA was palpated gently to determine its diameter. The GEA was dissected with the use of two surgical clips (Ethicon, Inc., Sommerville, N.Y) on each branch, to the stomach and omentum, respectively. The branches were divided by electrocoagulation. The GEA was dissected to the left, two third of the distance along the great curvature of the stomach. A solution of papaverine (0.1 mg/ ml saline) was gently injected into the the fatty tissue surrounding the GEA preventing spasm of the artery.

The right internal jugular vein was harvested via a longitudinal incision medial of the right sternocleidomastoid muscle. During the preparation of the IJV, the vein did not spasm. Therefore we did not use papavarine in the preparation of the IJV.

After systemic heparinization with 5000 units heparin (LEO Pharmaceuticals Weesp, the Netherlands) the GEA was implanted as peripheral arterial bypass graft with the help of optical magnification (x2). There was an evident mismatch between the internal diameters of the GEA and the femoral artery. The GEA with a length of approximately 5 cm was implanted as bypass graft with end to side anastomosis in the femoral artery and end-to- side in the popliteal artery above the knee using running 7-0 polypropylene sutures (Ethicon, Inc.) (Figure 1). The femoral artery between the bypass graft was clipped (Ethicon, Inc.), allowing blood flow only through the bypass. Approximately 5 cm of the

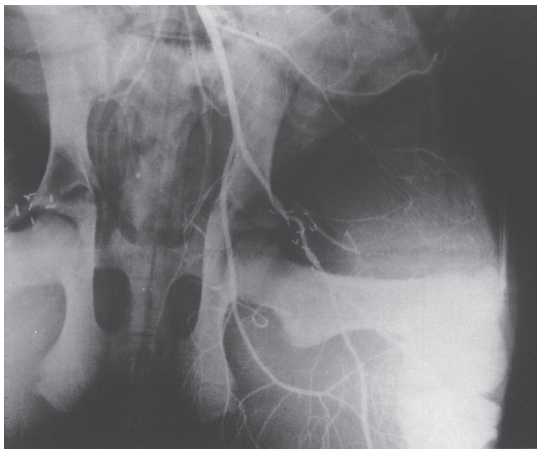

Figure 1. Angiography demonstrating the gastroepiploic artery (arrow) as arterial bypass graft in the femoral artery

internal jugular vein was implanted as venous bypass graft into the left femoropopliteal arterial circulation using the same implantation technique as described above. The internal diameter of the venous graft matched closely with the recipient femoral artery.

The patency of all bypass grafts immediately after implantation was confirmed by Doppler. The wounds were closed in layers using 2-0 polyglactin suture (Ethicon, Inc.). Postoperative anticoagulation treatment consisted of acetyl salicylic acid 200 mg daily starting the day after operation. Twenty-one days after the operation all the animals were re-anesthetized. The grafts were dissected and gently rinsed with normal saline. Subsequently the graft was divided in a proximal half for in vitro endothelial studies and a distal half for histologic examination.

Histology

The part for histologic examination was fixed by immersion in 4% formalin for 48 hours. The grafts were paraffin embedded and orientated for transversal sectioning. Sections were cut at 4 μm and stained for light microscopic examination with hematoxylin and eosin, and with modified Verhoeff's elastic tissue stains. The thickness and the area of the intima and the media of each graft were quantified by videomorphometry. The inner intimal boundary was the luminal surface, and the intima-media boundary was identified by the internal elastic lamina demarcated by the Verhoeff elastin staining. The outer border of the IJV graft was defined by the perivascular capillaries, whereas the outer border of the GEA graft was the outer elastic lamina.

Endothelial function

Both during the initial operation for peripheral revascularization and at the time of sacrifice, segments of the internal jugular vein and gastroepiploic artery were harvested for determination of pre-operative (i.e. control) versus post-operative (i.e. graft) vessel function. The collected blood vessels were placed in a buffer solution of the following composition (mM): NaCl, 120.4; KCl, 5.9; $CaCl_2$, 2.5; $MgCl_2$, 1.2; glucose 11.5; $NaHCO_3$, 25.0; continuously aerated with 95% O_2 - 5% CO_2. Indomethacin (10 μm) was added to the buffer solution to block the cyclooxygenase pathway. Vessels were dissected free from surrounding tissue and cut into rings (2 mm) with a sharp razor blade. Rings were mounted in 15 ml organ baths containing the above mentioned buffer at 37º C and connected to a transducer for measurement of isotonic displacements. They were given a preload of 14 mN and allowed to equilibrate for 45 minutes, during which regular washings were preformed. All rings were primed and checked for viability by evoking an initial contraction with 10 μM phenylephrine followed by

repeated washing and renewed stabilization for 45 minutes. Subsequent relaxatory studies (below) were all preformed in 10 μM phenylephrine-precontracted rings, with different series of measurements being separated by repeated washing and stabilization.

Endothelium dependent and independent relaxations

In the first series of measurements, all rings were stimulated with 1 μM bradykinin, followed by subsequent addition of 10 mM sodium nitrite. In the second series of measurements, individual rings were stimulated in a parallel fashion with one of the following different agonists: ATP (10 nM - 100 μM), ADP (10 nM - 100 μM), calcium ionitric oxide phore A23187 (30 nM - 1 μM), and sodium nitrite (1 μM - 10 mM). Following the response to the final concentration of the aforementioned agonists, 10 mM sodium nitrite was added (except in case sodium nitrite was the first agonist). Endothelial-dependency and -independency for agonist-induced relaxations in IJV and GEA had been determined in previous pilot-experiments. It was demonstrated by the loss of relaxation to bradykinin , ATP, ADP and A23187 in endothelium-denuded rings (data not shown).
The involvement of nitric oxide was similar demonstrated by the loss of relaxation to bradykinin, ATP, ADP, A23187 and in endothelium-intact rings in the presence of the nitric oxide -synthetase inhibitor NG-mono-methyl-L-arginine (100 μM). Interference by agonist-induced release of vasoactive prostaglandines was prevented by the continuous presence of indomethacin (10 μM) to block formation of cyclooxygenase products. Following the final concentration of aforementioned agonists, 10 mM sodium nitrite was added to demonstrate the relaxatory capacity of the ring preparations in the above experimental condition, and to exclude possible defects at the level of smooth muscle cells to respond to nitric oxide .

Statistics

Relaxation-related displacements were calculated as percentage of the previously established phenylephrine induced contraction. All data are expressed as mean ± standard error of the mean. Differences in means were tested for significance using a two tailed Student's t-test or F-ANOVA, and p values < 0.05 were regarded as significant.

RESULTS

General

Concerning the surgical procedure; the GEA is accompanied by gastroepiploic veins (Figure 3A). During the implantation these veins make it difficult to get the GEA à vue for the implantation procedure. The surgical manipulation of

the GEA make the GEA spastic reducing the diameter to less than 1 mm which is presenting a difficulty for the anastomosing procedure. We first explored the possibility to use the saphous vein as venous bypass graft. In this porcine model the saphous vein is limited in length and has multiple side branches. On the contrary the internal jugular vein has adequate length with almost no side branches.

All animals survived the experimental period, and had an increase in body weight (42.2 ± 0.9 versus 46.2 ± 1.0 kg body weight before and after operation; $p< 0.001$). Six internal jugular vein grafts and 6 GEA grafts were occluded at harvest 3 weeks after the operation. In the first 4 operated pigs both the GEA and IJV were occluded. In pigs 5-7 the GEA graft or IJV graft was occluded. The graft failures may in part be attributed to a learning curve. The remaining 6 patent IJV grafts and the 6 patent GEA grafts were used for histologic and functional studies.

Histology

Internal jugular vein

Light microscopic examination of the internal jugular vein demonstrated a single layer of endothelial cells and a media consisting of approximately four layers of smooth muscle cells surrounded by collagen and elastin. Three weeks after the implantation all vein grafts showed an extensive concentric intimal thickening. Endothelial cells could be identified on the luminal surface of the vein grafts.

The (myo)fibroblasts or smooth muscle cells in the intima were arranged in a random pattern within expanded extracellular matrix. The media of the vein grafts underwent concentric thickening. Medial area was 0.35 ± 0.04 vs. 3.83±0.31 mm^2 ($n=6$, $p<0.0001$) before and after implantation, respectively. Representative cross-sections of the internal jugular vein before and after bypass grafting are shown (Figure 2).

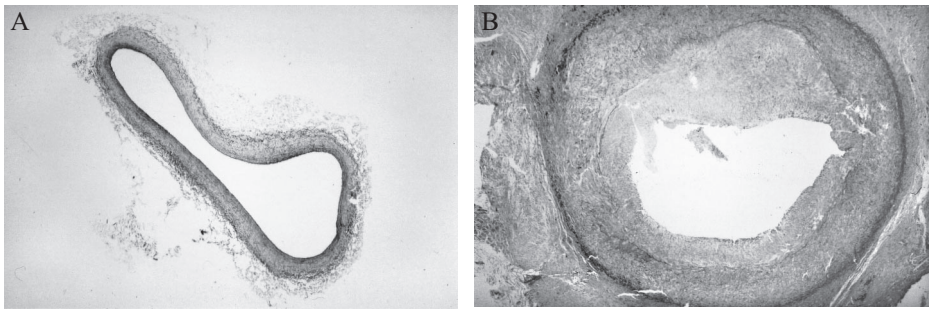

Figure 2
Light microscopy of internal jugular vein before (A) and after (B) implantation as bypass graft. Note the extensive intimal hyperplasia in the vein graft. Verhoeff's elastin staining. Original magnification x20.

Gastroepiploic artery

The intima of the gastroepiploic artery consisted of a single layer of endothelium with the internal elastic lamina. The media consisted of 20 to 25 concentric layers of smooth muscle cells separated by concentric orientated elastic fibers. Three weeks after implantation 2 GEA grafts had developed no intimal hyperplasia whereas four GEA grafts had developed only few small area's of intima hyperplasia (Figure 3B). Both the endothelial layer and the internal elastic lamina were intact. The media increased in thickness and cellularity and the concentric elastic fibers appeared unchanged suggesting that the integrity of the artery was preserved. Medial area was 0.59±0.06 vs. 3.14±0.21 mm^2 (n=6, $p<0.0001$) before and after implantation, respectively.

Gastroepiploic artery graft versus internal jugular vein graft

The internal jugular vein implanted into the peripheral circulation caused extensive intimal thickening, whereas the GEA reacted mainly with medial thickening and minimal or absent intimal hyperplasia. The thickness of the intima was 644±46 versus 33±11 μm ($p<0.0001$) for IJV grafts and GEA grafts, respectively. Thickness of the media was 435±98 versus 448±56 μm ($p=0.80$) for IJV grafts and GEA grafts, respectively. The results of dimensional morphometric analysis are shown in figure 4.

Endothelial function

In a number of experiments preceeding the present study, we established that relaxations induced by ATP, ADP, bradykinin (all receptor-dependent) and

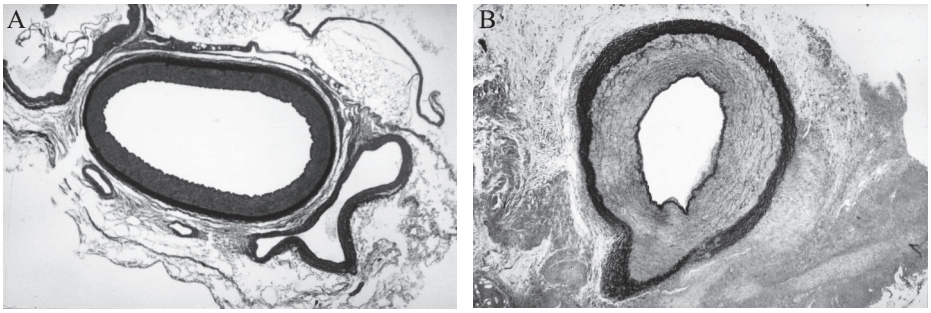

Figure 3
Light microscopy of the gastroepiploic artery (arrow) with accompanying veins (A).
The right gastroepiploic artery 3 weeks after implantation into the peripheral circulation showed minor intimal hyperplasia (B). Tissue sections stained with Verhoeff's elastin staining. Original magnification x20.

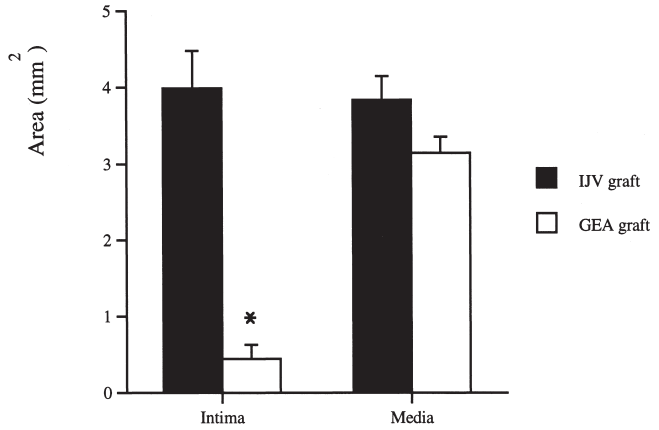

Figure 4
Bar graph indicating cross-sectional area of intima and media of pig jugular vein bypass grafts (dark bars) and gastroepiploic artery bypass (GEA) grafts (white bars), harvested at 21 days after peripheral implantation. Development of intimal hyperplasia was significantly less in GEA grafts. Values represent mean ± SEM. Asterisk indicates $p<0.0001$.

A23187 (receptor-independent) in porcine GEA and IJV were suppressible by inhibition of nitric oxide -synthetase and depend on the presence of the endothelium (data not shown).

The above endothelium-dependent relaxations therefore reflect the biological activity of nitric oxide released from the stimulated endothelium, and the subsequent responsiveness of vascular smooth muscle cells to nitric oxide. The latter is reflected by relaxatory response to the endothelium-independent vasodilator sodium nitrite. In the present study, the receptor-dependent relaxations induced by ATP (Figure 5) and ADP (not presented) were significantly decreased in GEA and IJV grafts. Similarly, bradykinin -induced relaxation (in % precontraction) in GEA was significantly decreased ($p<0.001$) from 70±5% (n=12) to 27 ±3% (n=6) after grafting, whereas in IJV it decreased from 58±7% (n=10) to -48±11% (n=6); i.e. relaxation in IJV turned into contractions after grafting. Receptor-independent stimulation with calcium ionophore A23187 resulted in comparable relaxatory responses in GEA before and after grafting. In contrast, A23187 induced relaxations were virtually abolished in IJV grafts (Figure 6). The above changes in endothelium-dependent relaxatory responses after grafting seemed not to be due to experimental conditions or decreased vascular responsiveness to nitric oxide since sodium nitrite -induced relaxation directly following ATP/ADP/bradykinin /A23187 was not decreased, neither in GEA grafts nor in IJV grafts (data not presented). This was confirmed by the relaxatory responses of the rings stimulated with increasing concentrations of sodium nitrite, displaying an increased

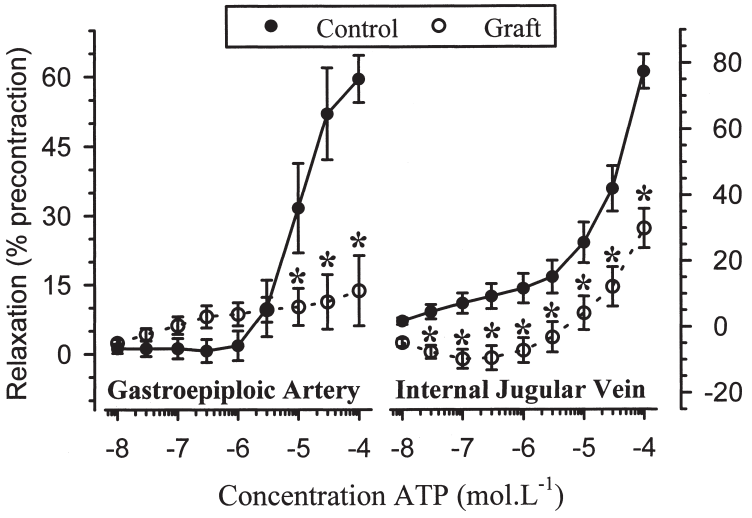

Figure 5
Endothelium-dependent relaxation to ATP in the gastroepiploic artery (left y axis) and internal jugular vein (right y axis) before (control=closed circles; n=9 and n=9 for GEA and IJV respectively) and 21 days after (graft= open circles; n=6 and n=5 for GEA and IJV respectively), grafting. Relaxations are expressed as a percentage of phenylefrine-induced precontraction, and data represent the mean ± SEM. Asterisk indicates $p<0.05$.

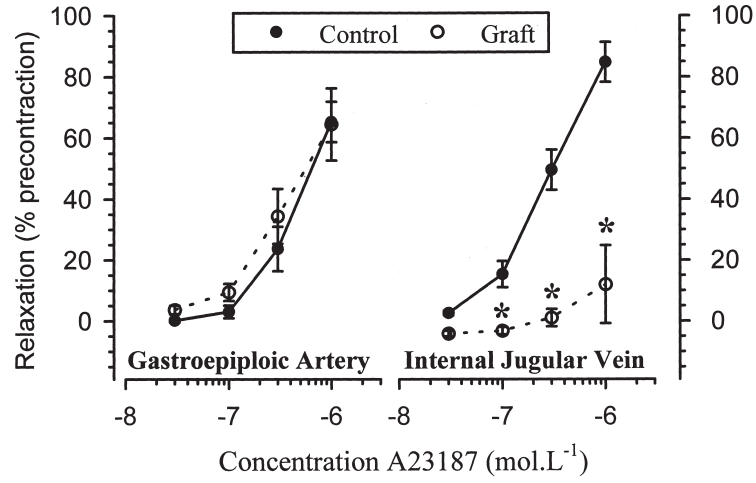

Figure 6
Endothelium-dependent relaxation to calcium ionophore A23187 in the gastroepiploic artery (left y axis) and internal jugular vein (right y axis) before (control=closed circles; n=8 and n=8 for GEA and IJV respectively) and 21 days after (graft=open circles; n=6 and n=4 for GEA and IJV respectively) grafting. Relaxations are expressed as a percentage of phenylephrine-induced precontraction, and data represent the mean ± SEM. Asterisk indicates $p<0.05$.

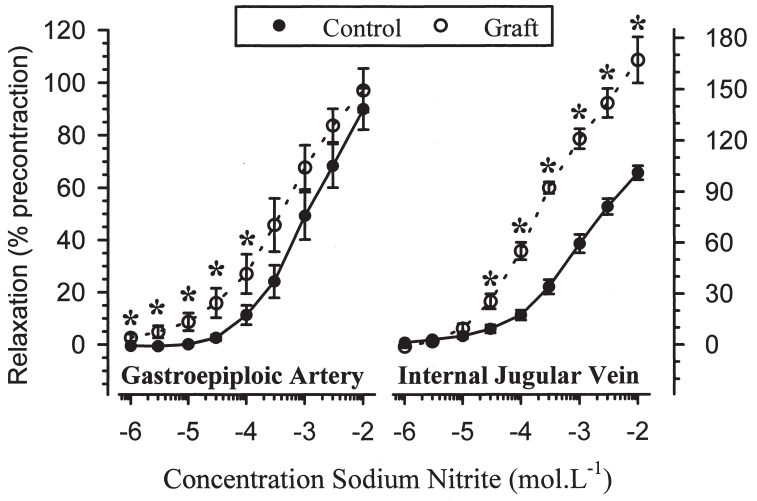

Figure 7
Endothelium-dependent relaxation to sodium nitrite in the gastroepiploic artery (left y axis) and internal jugular vein (right y axis) before (control=closed circles; n=10 and n=10 for GEA and IJV respectively) and 21 days after (graft=open circles; n=5 and n=6 for GEA and IJV respectively) grafting. Relaxations are expressed as a percentage of phenylephrine-induced precontraction, and data represent the mean ± SEM. Asterisk indicates $p<0.05$.

rather than decreased sensitivity to nitric oxide after grafting, especially in IJV (Figure 7).

DISCUSSION

In this experimental model the gastroepiploic artery was successfully introduced as peripheral bypass graft. The development of intimal hyperplasia in the internal jugular vein grafts was extensive, whereas intimal hyperplasia in the gastroepiploic artery grafts was minimal or absent. The results of functional vascular studies demonstrate loss of endothelial nitric oxide function in the IJV grafts, while endothelial capacity to generate biologically active nitric oxide in GEA grafts remained intact.

Intimal hyperplasia, the universal response after vein graft implantation in the arterial circulation, is held responsible for vein graft stenosis and occlusion in the initial years after implantation.[6] Intimal hyperplasia starts with myofibroblast proliferation two days after graft implantation or arterial wall injury, this is followed by extracellular matrix secretion in the second week leading to intimal thickening.[7] The minimal or absent intimal hyperplasia in GEA grafts after three weeks suggests that the intimal hyperplasia will remain at this low level. This hypothesis is supported by the clinical observation that the development of intimal hyperplasia in internal mammary arterial bypass grafts and gastroepiploic arterial bypass grafts is not significant 2 years after implantation and beyond.[8,16] It is hypothezised that the

intimal proliferative response forms the basis for vein graft accelerated atherosclerosis, an important cause of late vein graft failure.[7,9,10] The extensive intimal hyperplasia in the peripheral IJV grafts in this study is likely to predispose to graft stenosis and accelerated vein graft atherosclerosis. Improvement of peripheral revascularization especially below the knee can be realized by either measures to control vein graft intimal hyperplasia or by the introduction of alternative bypass conduits. Experimental studies reported successful inhibition of vein graft intimal hyperplasia with the use of systemic or local pharmacologic compounds.[6] So far no clinical study reported inhibition of intimal hyperplasia. The clinical application of small diameter synthetic vascular grafts with or without endothelial seeding is still disappointing.[11]

The endothelium is an important modulator of the vessel tone, prevents blood vessel thrombosis, and controls vascular smooth muscle cell proliferation.[2] Endothelium exercises these functions through the production of endothelium derived products like prostacyclin and nitric oxide.

For instance, nitric oxide reduces platelet adhesion and is by itself a potent antiaggregatory mediator. Both experimental and clinical studies revealed that vein grafts in the arterial circulation undergo functional changes leading to incapacity of production of prostacyclin and nitric oxide.[2] Oral suppletion with L-arginine, precursor of nitric oxide, inhibited vein graft intimal hyperplasia in an experimental study. [12] This observation further stresses the importance of nitric oxide in vein remodelling after bypass grafting. Long term follow-up studies in cardiac surgery have shown that the patency rate of pedicled and free internal mammary artery grafts was better than that of saphenous vein grafts.[8] It is suggested that differences in endothelial function may contribute to this higher patency rate among arterial grafts than among venous grafts.[13] Recently, we reported the ability of the human GEA to produce nitric oxide and the resemblance of the activation and behaviour of the L-arginine pathways in the human GEA and the IMA.[4]

In the present study, both receptor-dependent and -independent induction of endothelium dependent (nitric oxide-mediated) relaxation was markedly impaired in IJV after grafting. This impairment seemed not to be due to a defect at the level of vascular smooth muscle cells since vascular sensitivity of IJV grafts to exogenous nitric oxide was increased rather than decreased. Such increased sensitivity to exogenous nitric oxide may also be observed in endothelium-denuded vascular preparations, and is believed to reflect a diminished inhibitory effect of endogenous nitric oxide on exogenous nitric oxide. Sodium nitrite induced relaxations were also intact in GEA grafts, thus indicating that decreased

responsivity to exogenous nitric oxide can neither account for the decrease in endothelial receptor relaxation in GEA after grafting.

In contrast to IJV grafts, receptor independent induction of endothelium dependent relaxation was intact in GEA graft, suggesting a normal formation of biologically active nitric oxide. These data are indicative for selective alterations at endothelial receptor level in arterial grafts, and a general loss in endothelial capacity to generate biologically active nitric oxide in venous grafts. This endothelial dysfunction may in part explain the extensive intimal hyperplasia in the IJV grafts, and the low intimal hyperplasia in GEA grafts presumably associated with the capacity to produce nitric oxide.

Besides the minimal intimal hyperplasia formation and the capacity to produce nitric oxide, is the low susceptibility of the GEA to atherosclerosis[5] another characteristic making the GEA an attractive alternative for peripheral reconstruction. In the human situation approximately 16 to 26 cm of the GEA can be used for revascularization.[14] In the clinically setting the flow rates of GEA grafts for coronary bypass grafting ranged from 141-210 ml/ min depending on the size of the distal anastomosis. [14] Another human study demonstrated that the average intraoperative flow rates in femorotibial and femoropopliteal venous bypass grafts were 150-180 ml/ min, respectively. [15] These data indicate that despite the small diameter of the GEA graft this arterial graft is capable to transport equivalent blood volumes as venous grafts. The problem of spasm of the GEA graft during implantation can clinically be prevented by the intraluminal use of papavarine and verapamil.[14] Laparoscopic preparation of the GEA may further facilitate its use for human peripheral reconstruction.

In summary, in this study the gastroepiploic artery was introduced as peripheral bypass graft. The investigated parameters, thought to be crucial for long-term graft patency, were significantly better in the GEA grafts than in the IJV grafts in this animal model. These results may encourage the application of the human GEA for reconstruction of arteries in the lower limb or foot

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