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Research paper

Effect of implantation site on outcome of tissue-engineered vascular grafts

Tornike Sologashvili[a,1], Shahrul A. Saat[b,1], Jean-Christophe Tille[c], Sarra De Valence[d], Damiano Mugnai[a], Jean Pierre Giliberto[a], Jeswant Dillon[b], Azhari Yakub[b], Zamrin Dimon[e], Robert Gurny[d,2], Beat H. Walpoth[a,2,*], Michael Moeller[d,3]

[a] Service of Cardiovascular Surgery, University Hospital of Geneva, Gabrielle-Perret-Gentil 4, 1211 Geneva 14, Switzerland
[b] Department of Cardiothoracic Surgery, National Heart Institute, Jalan Tun Razak, 50400 Kuala Lumpur, Malaysia
[c] Division of Clinical Pathology, University Hospital of Geneva, 1211 Geneva 14, Switzerland
[d] School of Pharmaceutical Sciences, University of Geneva, University of Lausanne, 1211 Geneva, Switzerland
[e] Cardiothoracic Unit, National University of Malaysia, Jalan Yaacob Latiff, 56000 Cheras, Malaysia

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ABSTRACT

Objective: Vascular prostheses for small caliber bypass grafts in cardiac and vascular diseases or for access surgery are still missing. Poly (Ɛ-caprolactone) (PCL) has been previously investigated by our group and showed good biocompatibility and mechanical properties *in vitro* and rapid endothelialisation, cellular infiltration and vascularisation *in vivo* yielding optimal patency in the abdominal aortic position. The aim of the present study is to evaluate our PCL graft in the carotid position and to compare its outcome to the grafts implanted in the abdominal aortic position.

Methods: PCL grafts (1 mm ID/10 mm long) were implanted into the left common carotid artery in 20 Sprague-Dawley rats and compared to our previously published series of abdominal aortic implants. The animals were followed up to 3, 6, 12 and 24 weeks. At each time point, *in vivo* compliance, angiography and histological examination with morphology were performed.

Results: PCL grafts showed good mechanical properties and ease of handling. The average graft compliance was 14.5 ± 1.7%/ mmHg compared to 7.8 ± 0.9% for the abdominal position and 45.1 ± 3.2%/ mmHg for the native carotid artery. The overall patency for the carotid position was 65% as compared to 100% in the abdominal position. Complete endothelialisation was achieved at 3 weeks and cell invasion was more rapid than in the aortic position. In contrast, intimal hyperplasia (IH) and vascular density were less pronounced than in the aortic position.

Conclusion: Our PCL grafts in the carotid position were well endothelialised with early cellular infiltration, higher compliance, lower IH and calcification compared to the similar grafts implanted in the aortic position. However, there was a higher occlusion rate compared to our abdominal aorta series. Anatomical position, compliance mismatch, flow conditions may answer the difference in patency seen.

1. Introduction

Vascular diseases are the leading cause of morbidity and mortality in the Western world. More than 82 million American adults (> 1 in 3) have one or more cardiovascular diseases (CVD) and accounted for one third of all deaths in United States [1]. Cardiovascular and carotid atherosclerotic diseases are particularly prevalent and the stroke rate was 3% within that period (2007). Seven percent of American adults ≥ 20 years of age also had coronary artery disease (CAD) [1]. For both conditions surgery is still the best option and coronary bypass surgery is the state-of-the-art for complex multi-vessel CAD. As no shelf-ready small-calibre vascular prostheses exist to perform such re-vascularisation procedures the patient's own arteries or veins are used. However, they may be diseased or missing due to prior surgeries in up to one third of the patients.

Therefore, the search for better, small-calibre vascular grafts is an

* Corresponding author at: Service of Cardiovascular Surgery, University Hospital of Geneva, 4 rue Gabrielle-Perret-Gentil, 1211 Geneva 4, Switzerland.
E-mail address: Beat.walpoth@unige.ch (B.H. Walpoth).
[1] Both authors have contributed equally.
[2] Emeritus.
[3] Deceased.

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ongoing quest and several approaches have been and are currently investigated.

Synthetic materials such as expanded polytetrafluoroethylene (ePTFE), polyurethane (PU) and polyethylene terephthalate (Dacron) have been widely used as material for the construction of artificial vascular grafts which show acceptable clinical results in the large calibre (> 5mm ID) [2–4]. Such prostheses made of stable polymers, if used for small calibre vascular replacements, will provoke a foreign body reaction during the healing process leading to thrombosis in the early phase and intimal hyperplasia in the late phase, both of which can trigger stenosis and occlusion of the graft. This is particularly true in small-calibre vascular replacements (< 5mm ID) and therefore no commercially available grafts exist for revascularisation procedures such as coronary arteries [2,4,5].

Many approaches have been undertaken to improve the patency of these vascular grafts. These include coatings, inclusion of proteins and drugs as well as cellular seeding and tissue engineering [2,6]. Kannan et al. commented that issues of compliance mismatch, diameter mismatch and the physical properties of vascular grafts may likely affect the formation of intimal hyperplasia (IH) i.e. proliferation of smooth muscle cells in between the endothelial layer and the prosthetic material, mainly in the para-anastomotic areas in the prosthetic wall [3,4,7].

Other materials have been used by several authors to investigate and produce tissue-engineered vascular grafts (TEVG). From our group, Pektok *et al*, Innocente et al. and de Valance et al. utilised Poly (Ɛ-caprolactone) (PCL) to create a TEVG [8–10]. PCL is a synthetic material that has shown good properties as a replacement for native vessel in our previous studies in the rat aortic abdominal model and also compared favourably to ePTFE prostheses [11]. Such grafts had an excellent patency, no aneurysmal dilatation, no stenosis, better endothelialisation, comparable neo-intimal formation, better cellular infiltration and neo-angiogenesis compared to ePTFE [11]. Furthermore, PCL grafts have also been coated with paclitaxel, an anti-proliferative agent, in the rat abdominal aorta model [9]. Results showed a reduced endothelialisation and cell in-growth at 3 weeks and delayed at 12 and 24 weeks. Conversely, the rate of neo-intimal formation (IH) was lower at 12 weeks and delayed at 24 weeks [9]. A long-term study (18 months) also showed good mechanical properties with no stenosis or aneurysmal dilatation [10]. There was good progression of endothelialisation, cell infiltration and neo-vascularisation until 6 months. However, there was cellular regression with chondroid metaplasia within the IH layer at 12 and 18 months [10]. Several authors have implanted small calibre grafts in the carotid arteries, mainly in the rat. Kuwabara et al. added a trimeric peptide sequence of cysteine-alanine-glycine (CAG) to their PCL grafts and showed significantly higher endothelialisation and lower mesenchymal cell adhesion at 6 weeks which has the potential of inhibiting IH [12]. Other novel materials such as polyhedral oligomeric silsesquioxane-poly(carbonate urea) urethane (POSS-PCU), polycarbonate- siloxane polyurethane (PSP) and poly(1,8-octanediol-co-citrate) (POC) have been used as the construct of TEVG and all of them showed good tissue remodeling, mechanical properties and patency [13].

Other approaches to improve TEVGs include seeding polymeric degradable vascular scaffolds with various lineages of cells have been done to improve the tissue remodelling and endothelialisation of the grafts. This can be achieved either by performing a single-stage (direct implantation) or double-stage (seeding followed by culturing of the grafts in static or dynamic condition) seeding method [14–16].

A collaborative group of Deutsch, Meinhart and Zilla et al. produced a clinical series of endothelial cells (ECs) seeded ePTFE grafts in 153 patients over 10 years showing that a double-stage technique for cell seeding of TEVGs is clinically viable and has shown promising result [17,18].

Constructs of pure cellular sheet grafts were also engineered with success [6,19]. Zhao et al. used sheets of mesenchymal stem cells (MSCs) which were rolled into a tubular graft for vascular replacement. This also showed good mechanical properties, endothelialisation, cellular infiltration and ECM formation [20].

The concept of implanting degradable synthetic polymer scaffolds with and without *in vitro* cell seeding, has been pioneered by Shinoka et al. in Japan where they implanted large calibre grafts as right-sided heart conduits (low pressure, high flow) for cardiac malformations in 42 children with excellent mid-term results and 25 with good long-term results [21,22].

More recently, two start-up companies based on university research have initiated clinical implants with decellularized autologous or allogenic scaffolds to be used as AV shunts for dialysis access. The results are promising despite a complex technology [23,24].

Supported by our good *in vivo* results of the degradable PCL grafts implanted in the aortic abdominal position, we wanted to evaluate these grafts in the rat carotid position where the diameter is smaller, the flow lower and shear stress different compared to the larger high flow conditions of the abdominal aorta of the rat.

Our aim was to evaluate our PCL graft in the carotid position and to compare the results with our previous series of abdominal aortic implantations for similar implantation duration.

2. Material and methods

2.1. Prostheses preparation

A 1 mm ID PCL prosthesis was prepared by electrospinning with a solution of 15% PCL (Mw 80,000 Da, Sigma, Germany) in $CHCl_3$/ EtOH (70% v:v). The grafts were spun with 20 kV voltage at a rate of 12 ml/hour and 6 min spin time. The detailed description of the fabrication technique has been published previously [25]. All prostheses were sterilised using Gamma irradiation (25 kGy). Average fibre size were measured by scanning electron microscopy (SEM) using standard processing software (ImageJ, National Institute of Health (NIH) USA 2008) [10,25].

2.2. In vivo implantation

After pre-medication the rats were anesthetized with isoflurane (2%) and prepared for surgery. The grafts were implanted in the left common carotid artery (interposition) in 20 Sprague-Dawley rats (400–500 g) with a follow-up period of 3, 6, 12 and 24 weeks (five animals in each group). A 10 mm segment of the native common carotid artery was replaced by the PCL graft using 10–0 polyprolylene (Prolene ®) interrupted sutures. Intra-operative patency was examined visually after the vascular clamps were removed. Animals were kept in separated cages after the surgery with food and water *ad libitum*. No anticoagulation or antiplatelet agent was given.

Animal experimentation followed the guidelines of the Swiss Federal Act on Animal Protection (LPA 2005) [26] and Swiss Animal Protection Ordinance (OPAn 2008) [27] with the experimental protocol number 1081-3232-II2C (Veterinary Office of the State of Geneva, Switzerland).

2.3. Post-operative follow-up studies

At the end of each implantation period, the animals were evaluated under general anaesthesia for the following tests: *in vivo* vascular compliance measurement, angiographic patency assessment and after euthanasia macroscopic evaluation of the peri-graft region with both proximal and distal anastomoses then the graft was opened longitudinally for patency and micro-thrombus assessment. Finally, classical histology and morphometry were performed.

2.4. In-vivo compliance

The pre-explantation compliance was examined under narcosis

utilising high resolution ultrasound (Vevo 770, Visualsonic Canada). The images were processed using the software (ImageJ, NIH USA 2008). One hundred frame video recordings were taken at 71 Hz frame rate at the mid-graft portion. Vessel internal diameter was taken at each frame. The right common carotid artery was used as the control value of the native artery. Blood pressure recording were simultaneously measured by the non-invasive tail cuff system (CODA Monitor, Kent Scientific Corporation, USA). Average internal diameters were noted at systole and diastole for 5 heart cycles. Calculation of the compliance was performed using the formula below.

Compliance of the prostheses was measured as an elastic deformation of the material in response to pressure. It was calculated following the ANSI/ AAMI guideline [28,29].

$$\text{Percentage compliance per 100 mmHg} = \frac{(R_{p2} - R_{p1})/R_{p1}}{P_2 - P_1} \times 10^4$$

R_{p1} – internal diameter at the lower pressure.
R_{p2} – internal diameter at the higher pressure.
P_2-P_1 – pulse pressure/ blood pressure difference (mmHg).

2.5. Digital subtraction angiography (DSA)

Each animal was anaesthetised using an induction with intra-peritoneal Phenobarbitone (1–2 mg/kg) and maintenance with 2% Isoflurane during the procedure. DSA (9800 General Electric Cardiac Series, Salt Lake, USA) was performed *in vivo* with intravenous injection of the contrast agent (Visipaque, Nydomed, Switzerland, 1–2 ml) through the right carotid artery.

2.6. Histology and morphometry

Explanted prostheses were opened longitudinally including proximal and distal anastomoses and fixed in 4% formaldehyde, then embedded in paraffin. Longitudinal sections of 4 μm were stained with Hematoxylin-Eosin (H&E), Miller-Masson (collagen and elastin) and von Kossa (calcium) stains. Immuno-histochemical staining with anti-CD34 (Santa Cruz Biotechnology Inc., sc-7045, dilution 1:2000) and anti-alpha smooth muscle actin (αSMA) (DAKO, N1584, dilution 1:800) was performed. Slides were scanned in high resolution (Mirax scanner, Carl Zeiss MicroImaging GmbH, Göttingen, Germany) and quantified with software (ImageJ, NIH USA 2008). The following measurements were performed (percent of the whole length of the graft): percentage of endothelial coverage, percentage of intimal hyperplasia (IH) coverage, average IH thickness, percentage of cell invasion, average graft thickness and percentage of calcification length. Results are expressed as the average for all the animal ± standard error of the mean. Quantification of the number of capillaries was performed after the CD34 staining. Capillaries number was quantified using 10 randomly positioned field of view (magnification x400), for each graft. The average was then calculated for each time end points.

2.7. Statistics

Results were expressed as average ± standard error of the mean. Comparison was made with the data from the intra-abdominal PCL implantation study [10]. The non-parametric Mann-Witney *U* test was used to measure the differences between the time points and the groups. A p value < 0.05 was taken as significant.

3. Results

3.1. Implantation and in vivo characterisation

The grafts were all implanted by the same surgeon with a mean cross-clamp time of 28.9 ± 1.3 min. These grafts had good mechanical handling during implantation and had an average thickness of 424 ± 20 μm. The mechanical properties of these grafts were the same as in our previous studies [8,10,25].

3.2. In vivo compliance

Compliance was measured in all patent prostheses. Fig. 2 shows the compliance of the PCL grafts implanted in the left carotid and compared to the native right carotid artery. The average value of the carotid graft was 14.5 ± 1.7%/mmHg, which was significantly less than the value for the native right carotid artery of 45.1 ± 3.2%/ mmHg ($p < 0.05$).

3.3. Angiography & patency

Seven grafts were occluded at the time of ex-plantation yielding an overall patency of 65%. One at 3 weeks, 2 at 6 weeks, 3 at 12 weeks and 1 at 24 weeks. Fig. 3 (left panel) shows an angiogram of the rat with a patent PCL graft on the left side and the native carotid artery on the right side. The middle panelshows an occluded graft (arrow), with some back filling of the distal carotid artery. On the right panel a patent carotid PCL graft showing some narrowing of the prosthesis is represented.

3.4. Histology

Fig. 1 shows a representative macroscopic and histologic section of grafts at various time points.

3.5. Thrombosis, endothelialisation and intimal hyperplasia

The patent grafts did not show any macroscopic thrombus formation

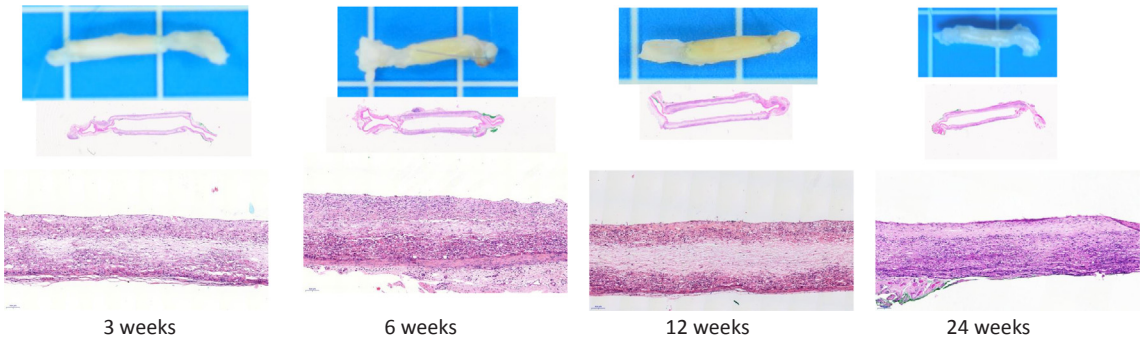

Fig. 1. Macroscopic and histologic pictures of a PCL graft after various durations of implantation (3, 6, 12 and 24 weeks). Upper part: macroscopy of the grafts. Middle part: histologic longitudinal section of the graft with the proximal (right side) and distal anastomosis. Lower part: histology (H & E) of the graft wall (magnification 100 ×). Upper part is the luminal side with endothelial coverage. The middle portion shows the cellular infiltration in the PCL graft and the lower part represents the adventitia.

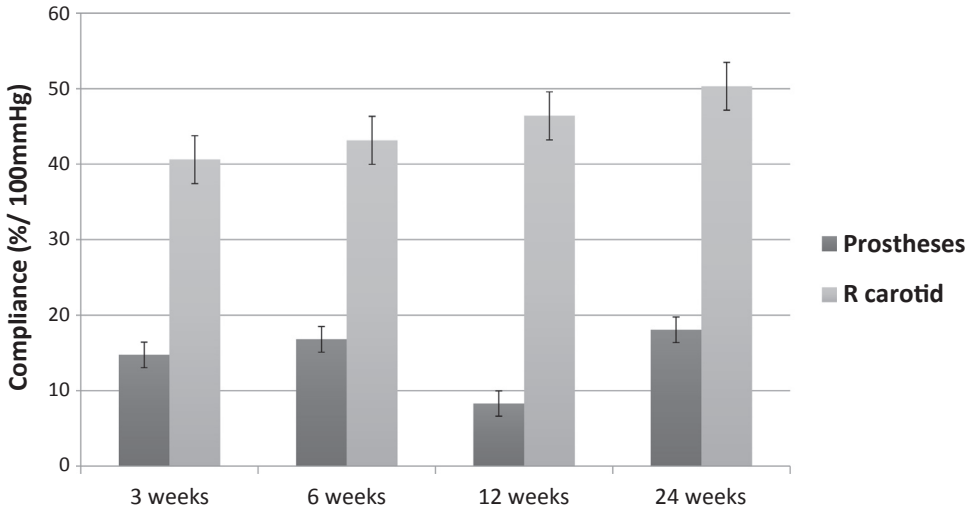

Fig. 2. *In vivo* compliance of PCL grafts implanted in the left carotid artery (prosthesis) compared to native right carotid artery (r carotid). There is a significant difference between the compliance of the grafts and the native artery in the same location.

and histological examination did not reveal micro-thrombi. The occluded grafts showed partial re-canalised thrombus with sub-acute micro-thrombi. All the patent grafts showed complete and confluent endothelialisation as early as 3 weeks and for all longer implantation periods (Fig. 4).

Intimal hyperplasia was seen at the sub-endothelial level. After 3 weeks, it was 7 ± 3.6% of the graft. This increased to 8 ± 3.9% at 6 weeks, then decreased to 5.9 ± 4.2% at 12 weeks and yielded 6.5 ± 4.7% at 24 weeks (ns). The average IH thickness was initially 39 μm but then stabilised to 4.6–17.8 μm throughout the study period.

3.6. Cellular infiltration and tissue regeneration

The nano and micro-fibre structure of the graft has been shown to allow rapid cellular infiltration [8,10,25]. After 3 weeks of implantation the wall of the graft showed a dense cell infiltration (95 ± 3.2%) by macrophages and myofibroblasts. These values varied slightly (ns) over time (90 ± 2.3% at 6 weeks, 95 ± 3.3% at 12 weeks, and 85 ± 4.6% at 24 weeks).

In the peri-graft tissue there were signs of mild chronic inflammation with foreign body reaction (giant cells (GCs) and macrophages present surrounding the grafts).

3.7. Vessel density in the PCL graft

Fig. 5 shows the vessel numbers per high power field with constant vascular density until 12 weeks and a regression at 24 weeks ($p < 0.05$). Fig. 6 shows the regression of the vascularisation (CD34 stained endothelial cells in brown) and cellularity at 24 weeks compared to 3 weeks.

3.8. Calcification

Our group has previously described PCL grafts to develop scarce chondroid metaplasia (CM) (process of differentiation of smooth muscle cells into chondrocyte) [8,10]. Calcification in this material may develop from sites of chondroid metaplasia. In the carotid position, one sample had a small area of CM and calcification at 3 weeks (3.4 ± 3.4%). This was not seen in the 6 weeks group but was clearly present in the 12 weeks group (12.2 ± 5.9%). CM is more frequently found in areas of IH and near anastomoses [8,10].

4. Discussion

In the present study the results of the small calibre, degradable, PCL grafts in the carotid position were assessed and compared to those obtained previously from implantation of the same graft in the aortic abdominal position.

4.1. Implantation and angiography result

After respective duration of implantation, the angiographic patency rate revealed 7 occluded grafts yielding a patency rate of 65%. Our previous series of PCL grafts implanted in the intra-abdominal aorta showed 100% patency [8,10]. There were no major complications during the implantation and the cross-clamp time did not show any significant difference between the two sites of implantation. The handling of the smaller diameter (1 mm ID) for carotid compared to 2 mm ID for abdominal aortic location may influence the outcome but more likely the difference in flow and shear rate may explain the higher occlusion rate in the carotid position.

Other studies have reported patency rates of 75% at 6 weeks for TEVG placement in rat carotid model [12].

4.2. In vivo compliance

Native carotid arteries showed a trend of gradual increase of compliance over the 24 weeks. The average compliance of the carotid PCL grafts was about one third of the native right common carotid artery (Fig. 2). However, the average compliance of 14.7 ± 1.7% in the carotid grafts was twice as high as the compliance of the same grafts implanted in the abdominal aorta (7.8 ± 0.9%; $p < 0.05$) [10]. The radial compliance mismatch at the anastomotic site is one of the causes of intimal hyperplasia and luminal narrowing hence reduced longevity of the grafts [3,4]. Other authors have reported compliance measurements in TEVG revealing values between 5 and 11% [13]. Prosthetic compliance will be affected by the degradation of the synthetic material. Fibre fragmentation and molecular weight reduction was previously seen in our prosthesis at 18 months [10]. However, the fibres never completely disappeared at 18 months. Elastin was only seen in the IH layer and collagen was mainly seen in the medial layer of the prosthetic wall [10]. Production of collagen and elastin fibres will greatly affect the compliance.

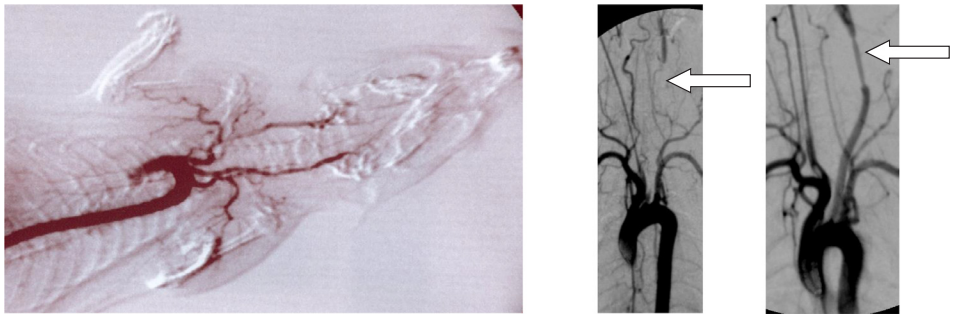

Fig. 3. Angiographic images showing an aortic arch with a patent PCL graft in the left carotid artery and a right carotid artery filled with contrast (left panel). The middle panel shows an occluded carotid artery graft (arrow) and the right panel shows a stenosed carotid artery graft (arrow).

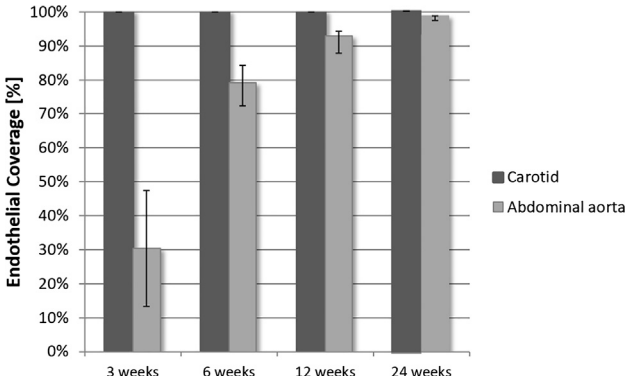

Fig. 4. Shows the percent of endothelialisation of PCL grafts implanted in the carotid artery as compared to the ones implanted in the abdominal aorta. Of interest is that the endothelialisation in the carotid artery is confluent (100%) and occurs as early as 3 weeks compared to a much slower process in the abdominal aorta.

4.3. Endothelialisation

The carotid grafts showed complete endothelialisation at 3 weeks and continued until 24 weeks (Fig. 4). In contrast, the abdominal aortic grafts only reached full endothelialisation after 24 weeks [10].

Zilla et al. mentioned the important difference of prosthetic endothelialisation between animal models and humans. The trans-anastomotic endothelialisation (TAE) is seen mostly in animal models when using short prostheses [4]. Animal species, senescence, anatomical dimensions and graft surface determines TAE in TEVGs [4]. Pre-clinical experimentation with longer prostheses in larger animals is needed to better reflect the conditions in human subjects. This may answer the more rapid endothelialisation seen in the rat carotid position compared to the abdominal aortic model.

Intimal hyperplasia coverage was 6–8% up to 24 weeks in the carotid model compared to 26–67% in our abdominal aortic series [8,10]. The main factor affecting IH is the shear forces inside the prostheses. This is determined by the cross-sectional area quotient Q_c in between the prosthesis and the distal run off vessel [4]. The values for most of the studies were $Q_c > 0.5$ (cross-sectional area of the prosthesis less than half of the size of the distal vessel). Whereas the value for clinical anastomosis is nomally $Q_c < 0.5$ (graft cross-sectional area twice that of the run off vessel). This means that the shear forces are higher than the threshold for the formation of intimal hyperplasia [4]. Compliance mismatch also greatly contributes to the formation of IH. The flow condition is also different in experimental studies. This is the possible explanation why the observed IH were low. This may not reflect the true condition of anastomoses in human patients.

4.4. Cellular infiltration

Cellular infiltration in the carotid grafts varied between 85% and 95% throughout the implantation period. Macrophages and myofibroblasts were clearly seen infiltrating into the fibres of the graft and with some GCs at the adventitial layer, but there was no fibrous capsule at the outer layer of the graft. This is higher than the abdominal aortic prostheses series which varied between 24% at 3 weeks and 40% at 6 months ($p < 0.05$) [8,10].

Cellular infiltration and proliferation is greatly affected by the pore size in between the fibres of the synthetic material [4,6]. The open dodecahedron shape has the potential of allowing cellular infiltration and orientation in different directions and biomechanical strain determines cellular orientation [4]. ECM proteins, cyclic strain and growth factors affect cellular proliferation and differentiation in differing ways [6,16]. Ingrowth of capillaries is essential in tissue-engineered constructs to foster cell ingrowth and remodelling of the degrading scaffold. This was clearly seen in our grafts in both the carotid and abdominal positions although there is a higher vascular density in the abdominal aortic position compared to the carotid position at 6 and 24 weeks ($p < 0.05$) (Figs. 5 and 6).

4.5. Calcification

Calcification in areas of IH appeared earlier (at 3 weeks) in the carotid position compared to the abdominal aortic series (12 weeks onward) [10]. IH has been the bane of the vascular reseacher and a factor that contributed to early graft failure [3,4]. The amount of IH seen in animal research models may be not representive of the true picture in human patients due to the different cross-sectional area quotient Q_c [4].

5. Conclusion

PCL has proven to be a good material for the creation of TEVGs. The

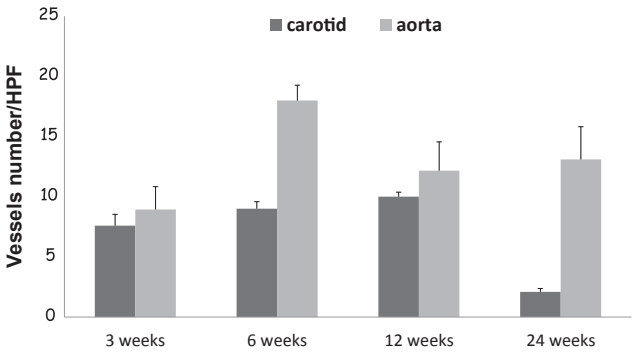

Fig. 5. Compares the vessel density as assessed by vessel numbers per high power field between carotid and aortic PCL grafts up to 24 weeks implantation.

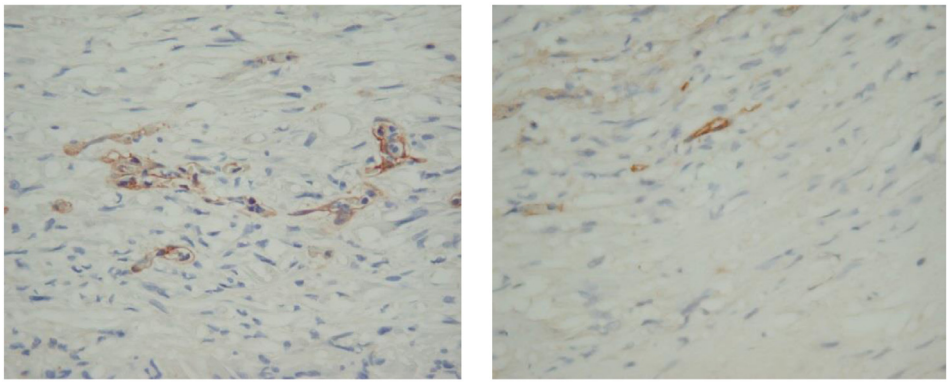

Fig. 6. Vascular density in the carotid PCL graft after 3 and 24 weeks of implantation (CD34 immuno-histologic staining staining).

requisites of an optimum TEVG will be one that is biodegradable and biocompatible, non-infective, non-toxic, non-thrombogenic with good handling and mechanical properties. Such synthetic, degradable polymers may represent an ideal scaffold for cellular infiltration and proliferation. Good ECM formation is needed to overcome polymer degradation. Tissue regeneration and remodelling with resorbtion of the synthetic scaffold will lead to the formation of a neo-vessel with similar compliance and physical properties as the native artery. In the rat carotid model our graft showed good endothelialisation and cellular infiltration as early as 3 weeks and compliance was also higher than the aortic series. IH and calcification were lower than in the aortic series. However, patency was only 65% as compared to 100% in the abdominal aortic position which may be explained by compliance and shear stress differences. The overall morphologic and functional performance of our PCL graft is better in the carotid position as compared to the abdominal aortic position except for the patency rate.

Declaration of interests

None.

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