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ORIGINAL RESEARCH

Acute Phase Pilot Evaluation of Small Diameter Long iBTA Induced Vascular Graft "Biotube" in a Goat Model

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WHAT THIS PAPER ADDS

Small diameter (4 mm), in body tissue architecture (iBTA) induced tissue engineered vascular grafts, "Biotubes" (length 10 cm [$n = 2$], 15 cm [$n = 2$], 22 cm [$n = 2$]), were used to bypass both carotid arteries of three goats. All six grafts showed no abnormal changes in vascular shape over the one month study period. Long, small diameter, tissue engineered Biotubes have the potential to be used as conduits in patients with chronic limb threatening ischaemia without available veins.

Objective: There is a need for small diameter vascular substitutes in the absence of available autologous material. A small diameter, long tissue engineered vascular graft was developed using a completely autologous approach called "in body tissue architecture technology (iBTA)". The aim of this pilot study was to evaluate "Biotubes", iBTA induced autologous collagenous tubes, for their potential use as small diameter vascular bypass conduits.

Methods: Biotubes (internal diameter 4 mm, length 50 cm, wall thickness 0.85 mm) were prepared by subcutaneous embedding of plastic moulds (Biotube Maker) in three goats for approximately two months. Allogenic Biotubes (length 10 cm [$n = 2$], 15 cm [$n = 2$], 22 cm [$n = 2$]) were bypassed to both carotid arteries by end to side anastomosis with their ligation between the anastomoses in another three goats. Residual Biotubes were examined for their mechanical properties. After four weeks, the harvested Biotubes were evaluated histologically.

Results: All Biotubes had sufficient pressure resistance, approximately 3000 mmHg. Although wall thickening occurred at two proximal anastomosis sites, all six grafts were patent without luminal thrombus formation, stenosis, or aneurysm deformation throughout the implantation period. Endothelial cells covered both anastomosis sites almost completely, with partial covering in the central portion of the grafts. Furthermore, α smooth muscle actin positive cells infiltrated the middle layer along almost the entire graft length.

Conclusion: This preliminary study showed that small diameter, long, tissue engineered Biotubes could function properly as arterial bypass conduits in a large animal for one month without any abnormal change in vascular shape. Thus, small diameter, long Biotubes are potentially viable conduits, which are biocompatible and labour non-intensive, and therefore, suitable for clinical practice. Additionally, Biotubes can start the regeneration process in a short period of time.

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INTRODUCTION

The quality of the autologous vein conduit is a key consideration during infrapopliteal bypass surgery because alternative conduits, such as expanded polytetrafluoroethylene (ePTFE) or polyethylene (PET) grafts, and cadaver saphenous vein, are not as readily available.[1–4] However, autologous vein conduits are limited because of coexisting diseases, such as varicose veins and narrowed veins, or a lack of useable veins after use during previous coronary and peripheral bypass procedures. Consequently, there is a considerable need for alternative materials for autologous venous tissues that could be used for vascular reconstructive procedures in lower limb bypass.

A clinically applicable long, small diameter, tissue engineered vascular graft (TEVG) was developed using a completely autologous approach called "in body tissue architecture technology (iBTA)".[5] The aim of this pilot study was to evaluate the potential use of "Biotubes", iBTA induced autologous collagenous tubes, as vascular bypass conduits in a goat model.

MATERIALS AND METHODS

Experiments on all six goats were performed in accordance with *the Guide for the Care and Use of Laboratory Animals* published by the United States National Institutes of Health (NIH Publication No. 85-23, 1996). All experiments were approved by the Tohoku University Ethics Committee (No. 2019AcA-041) and the Oita University Ethics Committee (No. 182201). The animals were raised in cages in the animal management room of Narita Animal Science (NAS) Laboratory Co., Ltd. (Chiba, Japan) at a temperature of 20—28 °C, humidity of 40—60%, and lighting time of 7 am—7 pm.

Preparation of long Biotube

In accordance with a previous report,[5] long Biotubes were prepared using spiral plastic moulds (Biotube Maker, Biotube Co., Ltd., Tokyo, Japan) (Fig. 1). Four Biotube Makers per goat were embedded subcutaneously into three goats. About one month after the embedding procedure, the Makers were harvested. Biotubes (50 cm in length, 4 mm in diameter) were extracted by removing the Makers. All Biotubes were immersed in a 70% ethanol solution for 30 minutes and stored in a 10% ethanol solution. Thereafter, the Biotubes were washed with physiological saline for at least 10 minutes immediately before implantation or burst strength measurement.

Mechanical evaluations

Storage Biotubes were cut to a width of 5 mm to obtain a total of 10 samples. Each sample was set on a uniaxial tensile tester (EZ-SX, Shimadzu, Kyoto, Japan) using two small pins (outer diameter 1.5 mm) and pulled at a speed of 10 mm/min until the sample broke.

The breaking strength was defined as half of the maximum load (N) of the resulting load extension curve. The unit breaking force was defined as the breaking strength divided by the initial sample length. The estimated burst strength was calculated using the following formula:[6]

$$\mathrm{P} = F / (L_0\, D_i)$$

$$D_i = \frac{d_{pin}(\pi + 2) + 2\Delta s}{\pi}$$

$$\Delta s = \frac{\pi(d - d_{pin}) + d_{pin}}{2}$$

In these equations, P is the estimated internal burst pressure, F is the breaking strength, L_0 is the initial longitudinal length of the ring sample, D_i is the effective internal diameter, Δs is the distance between the pins, and d_{pin} is the diameter of the pin.

The sample thickness and width near the breaking position was measured using a 2D laser displacement sensor (LS-100CN, OPTEX FA, Kyoto, Japan). Young's modulus was calculated for the physiological pressure range according to a previously published method.[6]

Carotid artery bypass surgery

Biotubes with an internal diameter of 4 mm (except one which was tapering to 3 mm at one end) and three different lengths (10 cm [$n = 2$], 15 cm [$n = 2$], and 22 cm [$n = 2$]) were implanted into both the left and the right carotid arteries of three goats (weights: 37.5, 41.0, and 44.9 kg) in an allogenic fashion (Fig. 2). Longitudinal incisions (10 cm for a 10 cm graft or 5 cm each in the proximal and distal neck for 15 and 22 cm grafts) were made, and the carotid arteries were exposed. Grafts of 15 and 22 cm were buried under subcutaneous tunnels. Thereafter, three minutes after intravenous administration of heparin sodium (200 IU/kg), the carotid artery was cross clamped. One end of the Biotube was anastomosed side to end to the proximal carotid artery with a continuous 7-0 polypropylene suture. The other end of the Biotube was similarly anastomosed to the carotid artery distally. The carotid artery was ligated between the proximal and the distal anastomotic sites. After implantation, the animals received antiplatelet drugs (clopidogrel 75 mg/head, PO, SID) for one month. One month after implantation, patency, form, and blood flow were observed using 2D, pulsed wave Doppler echography (Viamo PLT-1204ST, Canon Medical System, Tokyo, Japan). Subsequently, the Biotubes, including the carotid artery anastomoses, were harvested. Finally, the goats were euthanised.

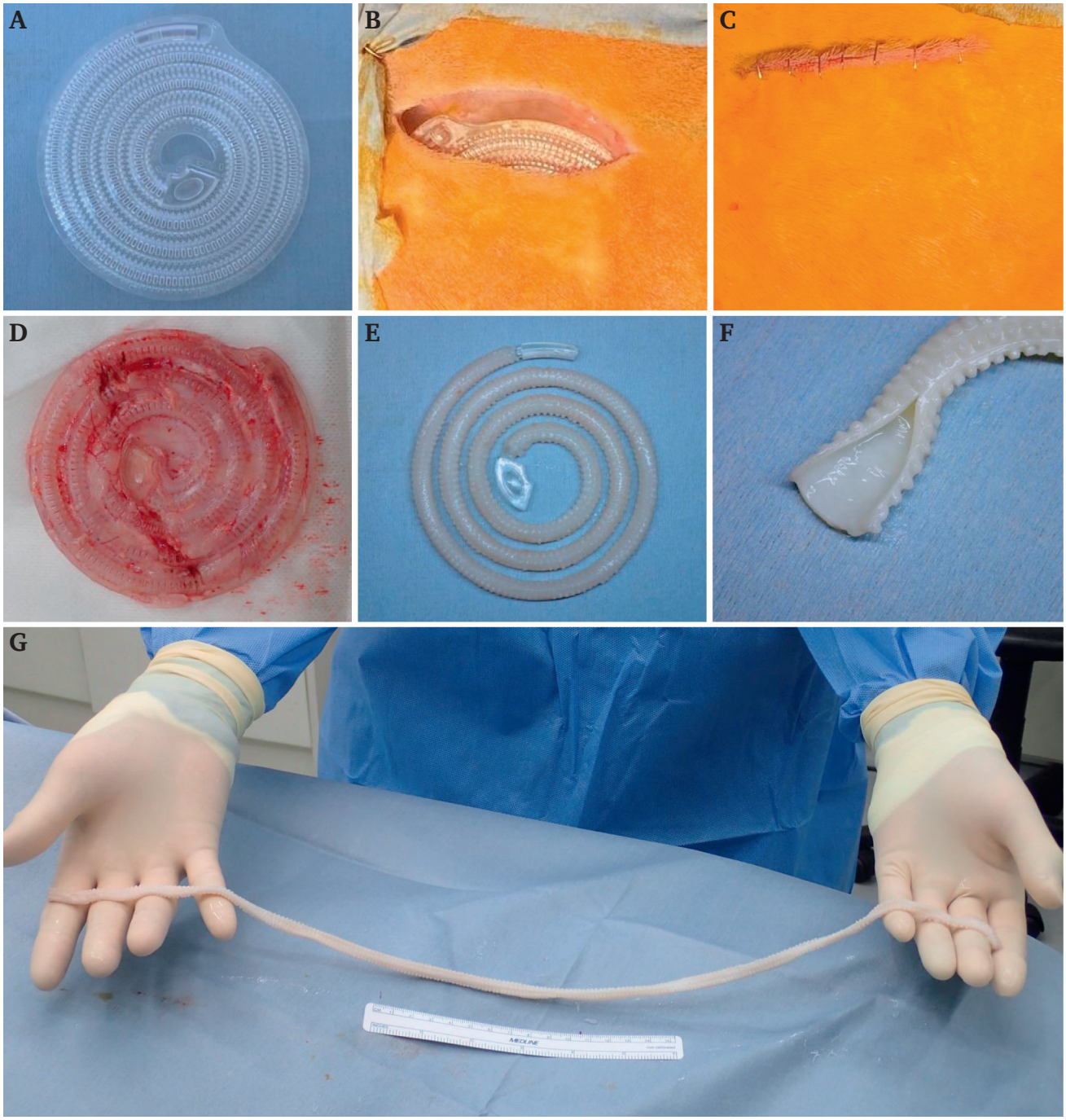

Figure 1. Preparation of Biotube by in body tissue architecture. (A) Biotube Maker as a plastic mould. (B, C) Subcutaneous embedding of a Biotube Maker in a goat. (D) Biotube Maker harvested with surrounding subcutaneous connective tissues. (E) Biotube formed around the spiral rod in the Biotube Maker. (F) Smooth luminal and protruded outer surfaces of Biotube. (G) Biotube (over 50 cm long) obtained by extraction from the spiral rod.

Histological examinations

Biotubes were fixed in 4% paraformaldehyde saline solution (FUJIFILM Wako Pure Chemical Co., Osaka, Japan) and embedded in paraffin before 5 μm sections were obtained. For histochemical analysis, the sections were stained with haematoxylin and eosin (HE). For immunohistochemical analysis, sections were deparaffinised and incubated with anti-α-smooth muscle actin (α SMA) mouse monoclonal antibodies (1:200; ab7817, Abcam, Cambridge, UK) and CD31 rabbit polyclonal antibodies (1:100; ab28364, Abcam) overnight at 4°C. Thereafter, sections were incubated at room temperature for one hour with rabbit secondary antibodies to mouse IgG (Alexa Fluor 594) (1:1000; ab150128) and goat secondary antibodies to rabbit IgG (Alexa Fluor 488) (1:1000; ab150077), respectively. DAPI (ProLong Gold Antifade Mountant with DAPI, Thermo Fisher Scientific, Inc., MA, USA) was used as a nuclear counterstain. The sections

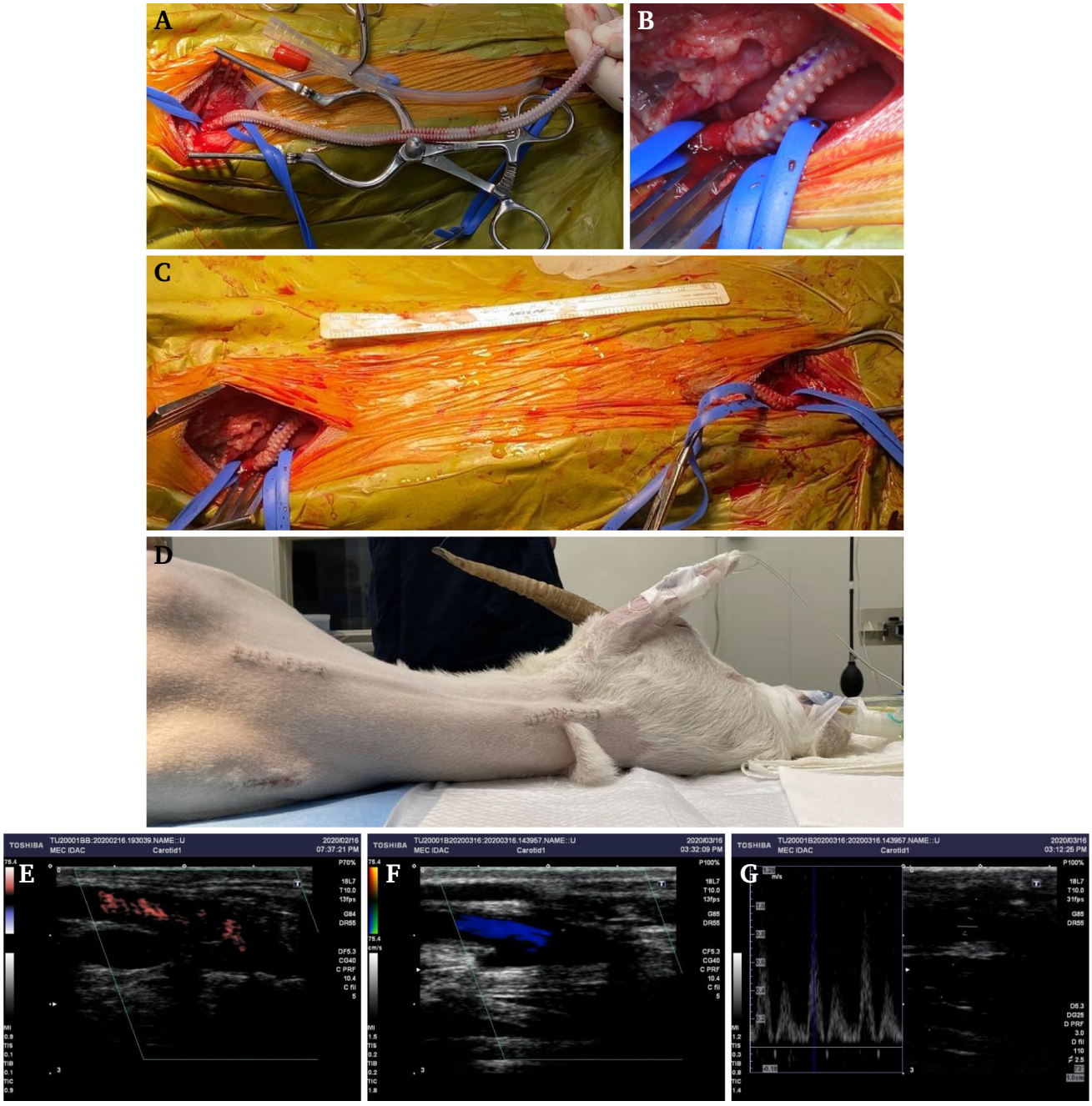

Figure 2. Bypass surgery. (A, B) Just after proximal anastomosis, neither bleeding nor leakage were seen. (C) Bypass surgery was completed with a 22 cm long Biotube. (D) One month post-operatively, no aneurysm formation was seen. (E) Colour Doppler ultrasound shows smooth blood flow. (F) 2D ultrasound shows neither stenosis nor thrombus formation. (G) Blood flow velocity was measured to be about 0.8—1.0 m/s using pulsed wave Doppler ultrasound.

were analysed using fluorescence microscopy (ECLIPSE-Ti, Nikon Corporation, Tokyo, Japan).

RESULTS

Preparation of long tissue engineered Biotubes

Long tissue engineered Biotubes were prepared using spiral plastic Biotube Makers that were embedded subcutaneously in goats for about one month. The adhesion between the Maker and surrounding tissue was mild and they could be pulled apart easily. After removing the connective tissues covering the Maker and subsequently removing its shell, Biotubes were found to form around the spiral mandrel (Fig. 1E). Twelve Biotubes were obtained from 12 moulds (four Makers per goat). However, two Biotubes had walls that were thinner on one side, while 10 Biotubes were formed over the entire length without defects and had a smooth luminal surface (Fig. 1F and G). The minimum estimated burst pressure was 1891 mmHg, the maximum was 4582 mmHg, and the average and standard deviation

were 3355 ± 930 mmHg. Young's modulus of the Biotubes in the physiological pressure range was 3.70 ± 0.95 MPa, which was between that of goat carotid arteries (1.67 ± 0.52 MPa) and ePTFE grafts (5.69 ± 1.40 MPa).

Carotid artery bypass surgery

The Biotubes were very smooth, during the bypass procedure resembling a saphenous vein, and there was neither bleeding from the needle holes at the anastomosis site nor any haemorrhage from the Biotubes (Fig. 2A—C). All six grafts were palpated, and patency was retained during the one month study period. No dilation or rupture of the grafts was observed (Fig. 2D). Ultrasound showed that all grafts had a smooth blood flow pattern without mosaic flow (Fig. 2E), and there was no stenosis or thrombus formation in the graft (Fig. 2F). The blood flow velocity was maintained at about 0.8—1.0 m/s during the observation period (Fig. 2G). The estimated blood flow was approximately 460 mL/min.

Histological examination

At harvest, the Biotubes could be easily peeled off with little adhesion to the surrounding subcutaneous tissue and showed a native vascular like appearance (Fig. 3A). All Biotubes were patent without any abnormal changes in the vascular shape. Slight wall thickening occurred around the proximal anastomotic site of the 22 cm Biotubes (Fig. 3B), but the other anastomotic sites were white, very smooth, and continuously integrated with the end of the native carotid artery (Fig. 3B1, 2). At the proximal anastomotic site, there was little inflammation around the implanted Biotubes, and they were covered with native tissues (Fig. 3C). The walls of the Biotubes became thinner than 100 μm with increasing distance from the anastomotic site, indicating their degradation. Vascular tissues derived from the native artery extended gradually on the luminal surface of the Biotube wall. Native tissues also adhered to the outside of the Biotube wall, and the total thickness of the implant was 1 mm, not significantly different from that of the original Biotube.

To investigate the condition of the entire length of the implant region, tissues near the site of anastomosis (*1 and *3 in Fig. 3A) and around the centre of the Biotube (*2 in Fig. 3A) were observed (Fig. 4). Although all three implants had almost the same thickness (approximately 1 mm) and smooth, white luminal surfaces with no remarkable macroscopic change (Fig. 4A and B), fibrinoid derived blood components that thinly covered almost all luminal surfaces of the central part were observed on histological examination (Fig. 4C2). As shown in Fig. 3, the luminal surfaces of the Biotubes near both anastomotic regions were completely covered with an endothelial lining, similar to that of the anastomotic regions themselves (Fig. 4D1 and D3). On the other hand, there seemed to be no endothelial coverage in the central parts (Fig. 4D2). However, further magnification of the centre part of the Biotubes revealed round, CD31 positive, endothelial like cells lightly deposited on the surface of the fibrinoid layer (Fig. 5A1, B1). In addition, a CD31 positive endothelial layer was partially observed in the central part without a fibrinoid layer (Fig. 5A2, B2). The wall of the implant region occupied the α SMA positive smooth muscle cell layer (Fig. 4E1 — E3).

DISCUSSION

This preliminary study has confirmed that "Biotubes", iBTA induced small diameter long collagenous tubes, worked well as bypass graft conduits over the short term. Although vascular replacement with an autogenous vein offers the best mid and long term patency and limb salvage outcomes, particularly for patients with below knee arterial lesions and chronic limb threatening ischaemia, they are limited as mentioned above. Therefore, the development of innovative technologies targeting the fabrication of small calibre grafts instead of veins is essential. Such ideal grafts may be achieved by developing a TEVG; however, it is very challenging to achieve immune acceptance, the requisite tissue mechanics, low thrombogenicity, and immediate availability. Numerous approaches for the development of TEVGs have been described and reviewed extensively.[7] Most techniques tend to involve scaffold based methods, using decellularised natural matrices, or tissue engineering by self assembly. These approaches need complex *in vitro* preparation steps, including cell culture, decellularised constructs, or the incorporation of synthetic materials.

Previously, autologous prosthetic tissues were developed using the iBTA technique.[5,8] iBTA is a cell free tissue engineering technology that can be used to produce autologous implantable tissues with the desired shape by simple subcutaneous embedding of a specially designed mould. The iBTA technique does not require complex steps or large scale plants, because the body itself works as a bioreactor.

Fundamentally, TEVGs should satisfy the criteria for serving as a conduit to support blood flow; therefore, they must withstand the pressures exerted by the blood flow without bursting or permanently deforming through aneurysm formation. Biotubes in this *in vitro* study showed pressure resistance of approximately 3000 (1891—4582) mmHg comparable with the previously reported burst pressure (approximately 1700 mmHg) of the human saphenous vein.[9] Additionally, in this *in vivo* study, one month after being implanted as arterial bypass grafts, none of the Biotubes experienced bursting or bleeding events. Macroscopically and microscopically, no arterial deformation was observed in any graft over four weeks, which may be because the Young's modulus of Biotubes was close to that of carotid arteries.

For over four decades, almost all *in vitro* TEVGs have been developed only to lengths of <10 cm; however, longer vascular grafts are needed for clinical use. This study examined the *in vivo* performance of long Biotubes (10—22 cm) in animal implantation experiments, using 50 cm Biotubes. The performance of the Biotubes during the operation was excellent, as evidenced by smooth handling and their short term durability without bleeding, dilatation, or thrombotic occlusion over one month. Histological examination of the Biotubes one month after implantation as arterial bypass

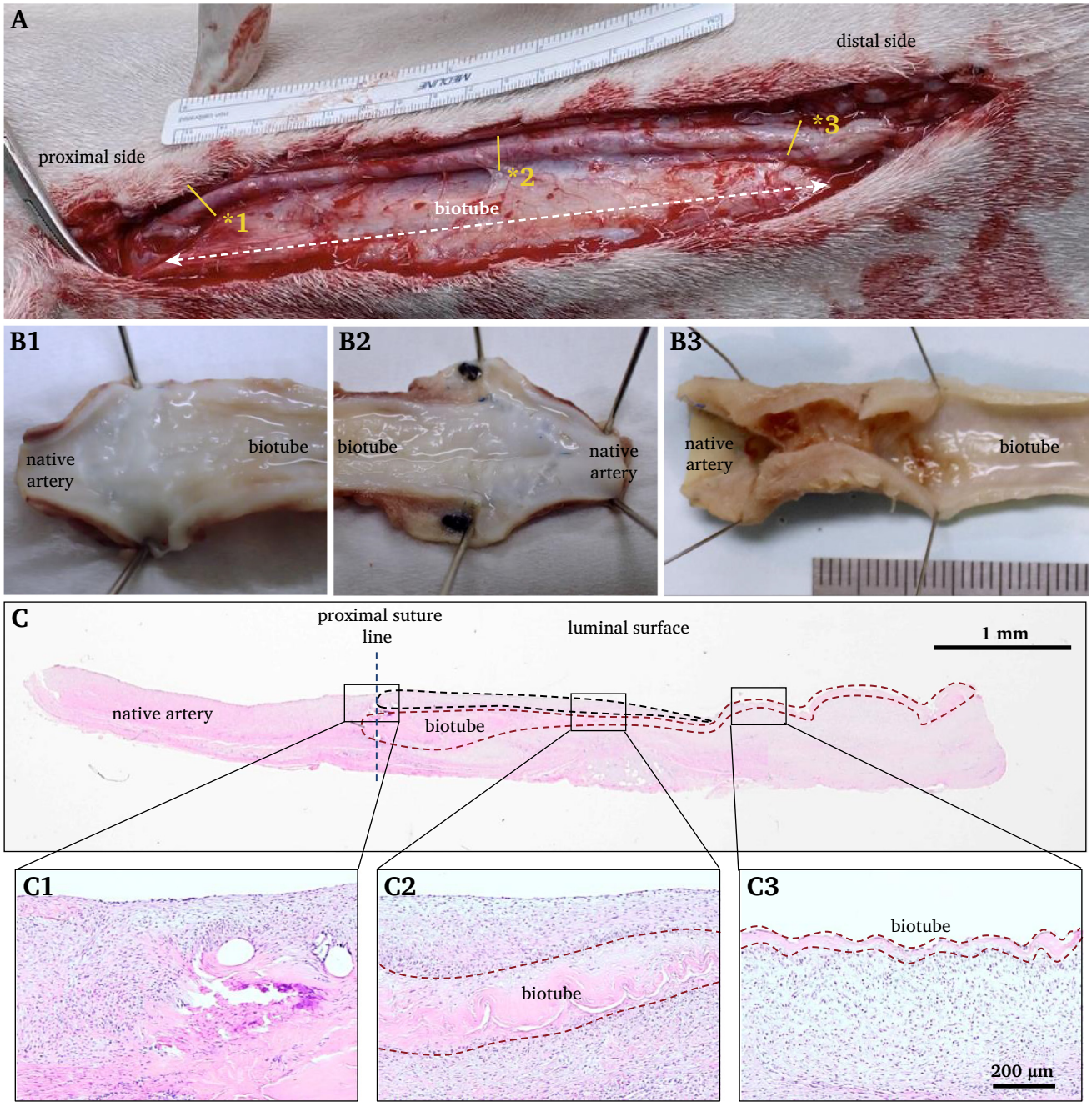

Figure 3. Macroscopic and microscopic histological evaluation. (A) Biotube was peeled off with little adhesion and showed native vascular like appearance. (B) Typical examples of the inside appearance of the anastomotic site: B1; one graft's proximal site, B2; distal site of the same graft, B3; another graft's proximal site. (C) Microscopic findings of one of the proximal anastomotic sites. The Biotube was left inside the red dotted line. C1, C2, C3; the Biotube became thinner than 100 μm as the distance from the anastomosis increased.

grafts showed that their luminal surfaces were macroscopically very smooth, and there were no thrombi attached to the tissues at all. Previous histopathological evaluation of explanted vascular grafts demonstrated that the host cellular inflammatory response causes mechanical degradation because of inappropriate remodelling.[10–12]

In addition, in the absence of autologous veins, biological grafts can also be used in infected fields, or in patients with a high risk of infection.[13] Recently, Lawson's group reported in their study of haemodialysis conduits in patients with end stage renal failure that most infiltrating host cells appeared to be non-immune and non-inflammatory in the fluorescence immunostaining of their explanted bioengineered vessels.[14,15] Compared with the *in vitro* tissue engineered grafts reported by Lawson's group, Biotubes have about 1/3 of the production time, the same usage, less than 1/10 of the cost, and the same qualities. In addition, Biotubes are apparently labour non-intensive and have an advantage in terms of safety, as they are autologous tissues. When iBTA induced short vascular grafts were used as vascular access

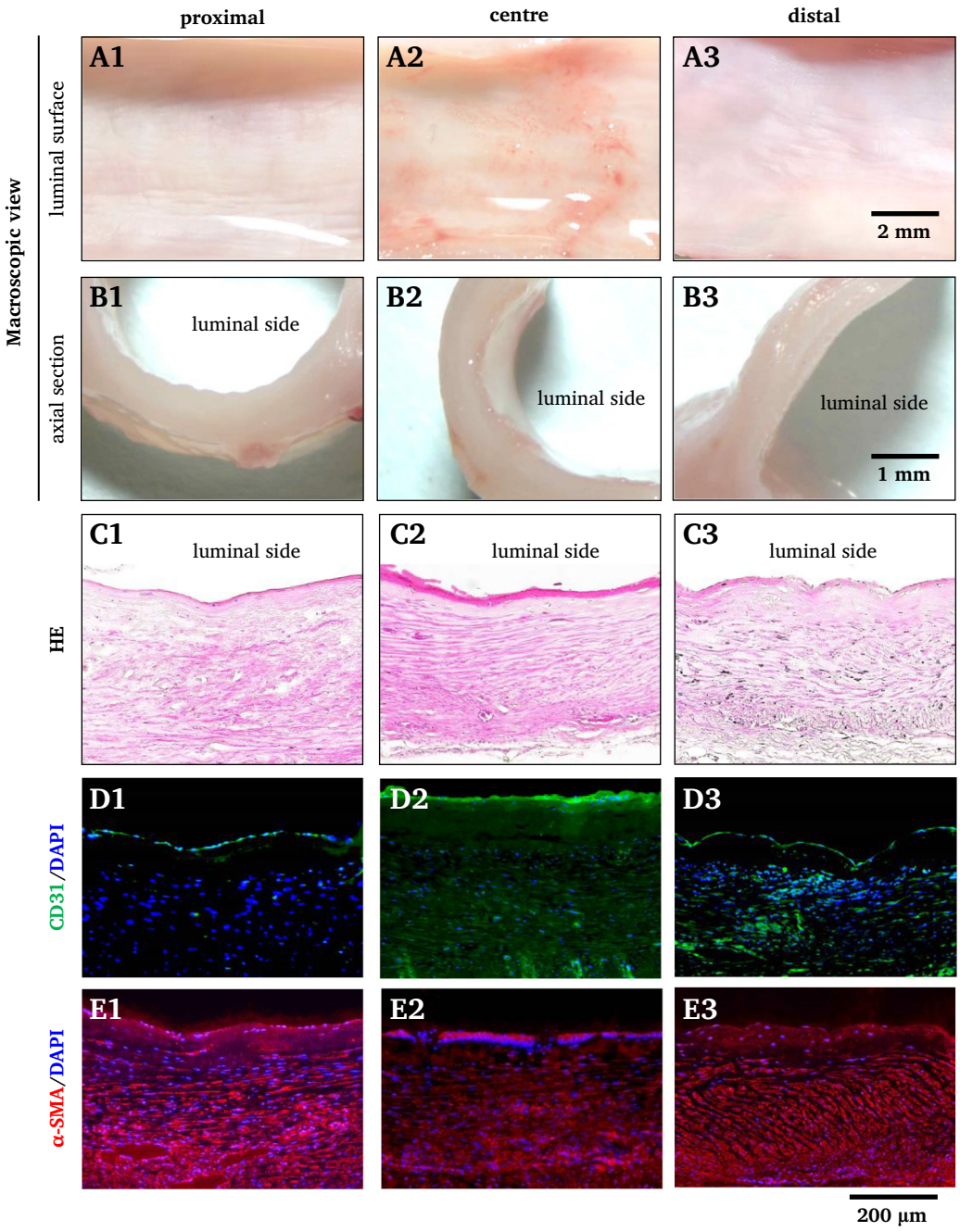

Figure 4. Histological evaluation of cross section of the bilateral anastomotic sites (*1 proximal, *3 distal parts in Fig. 3A Biotube) and at the central parts (*2 in Fig. 3A Biotube). A1 — 3, B1 — 3: White and smooth luminal surfaces were observed in all three parts. C1, 3 and D1, 3: Luminal surface near both anastomotic sites was covered with endothelial lining. C2: A fibrinoid layer derived from blood components covered the luminal surface of the central parts. D2: There seemed to be no endothelial coverage on the centre parts. E1 — 3: α SMA positive smooth muscle cell layer occupied all parts of the Biotubes.

grafts in haemodialysis patients, completely autogenetic Biotubes were biocompatible, eliciting no immune or inflammatory response.[16] Even though Biotubes were heterogeneously implanted in this study, no inflammatory reactions were observed. In addition to the α SMA positive cells that infiltrated the middle layer of almost the entire length of the grafts, endothelial cell coverage was observed not only at both anastomotic sites, but also at the centre of the grafts. This was indicative of vascular wall reconstruction.

Limitation and future studies

In this study, the implanted period was short and the number of grafts was limited. Currently, longer term physicochemical and biological safety studies are also being conducted in parallel.[8]

Because autologous iBTA induced TEVG basically is an issue for emergency use, limited patients with chronic limb threatening ischaemia may be available; however, it could

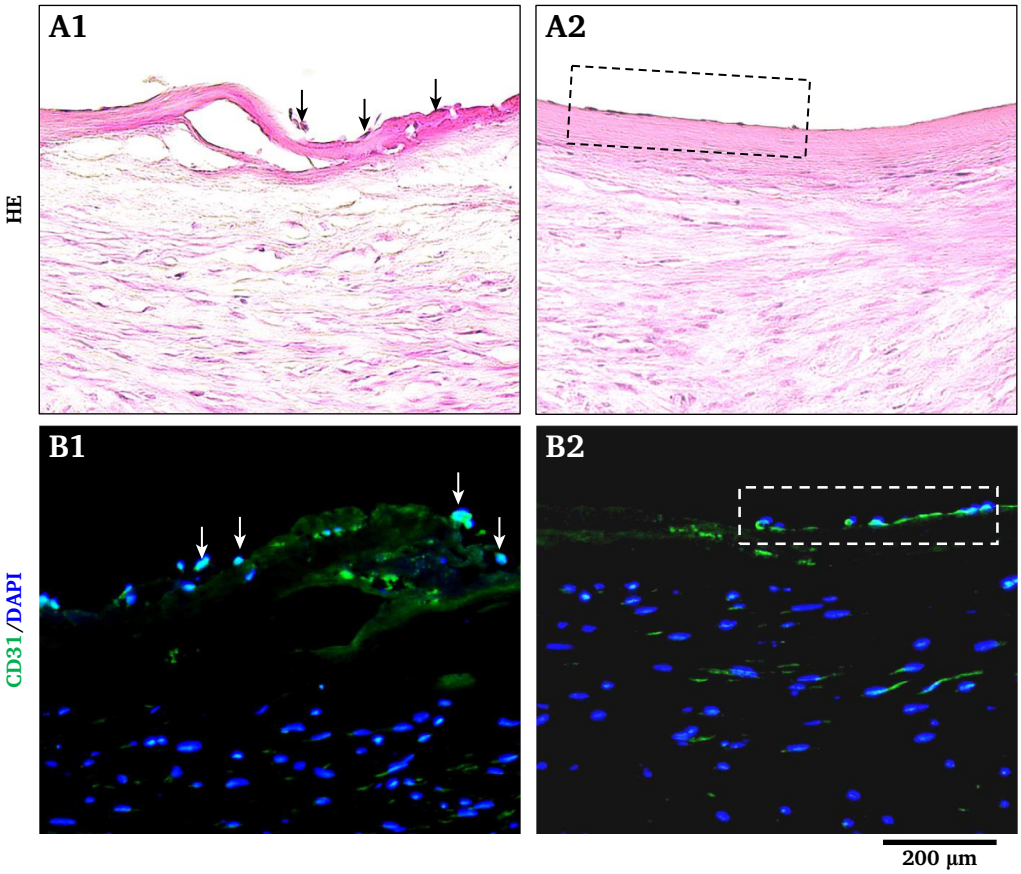

Figure 5. Further magnified histological evaluation of the central part of the Biotube. A1 and B1: Round, CD31 positive endothelial like cells (arrows) were slightly deposited on the surface of the fibrinoid layer. A2 and B2: Partial CD31 positive endothelial layer was seen in the central part without a fibrinoid layer.

be desirable for patients without available autologous veins. Biotubes, used heterogeneously in this study, could be stored for several months. This means that patients at the pre-critical stage of peripheral artery disease may be candidates for revascularisation with Biotubes.

Conclusion

The results of this study indicate that long, small diameter, tissue engineered Biotubes are potentially viable conduits as they are biocompatible and labour non-intensive, and do not require *in vitro* cell processing, therefore, they can be used in clinical practice.

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CONFLICT OF INTEREST

Yasuhide Nakayama, Ryuji Higashita, and Tomonori Oie are directors and stockholders of Biotube Co., Ltd. The other authors declare no conflicts of interest.

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