Development of a Microporous Compliant Small Bore Vascular Graft

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ABSTRACT: Purpose: To produce biodurable small diameter microporous vascular grafts with self-sealing properties for vascular access, for peripheral vascular and potentially for coronary artery bypass. The prosthesis should retain compliance and pulsatile flow in situ using a unique modus operandi permitting wall compression which accommodates changes in volume.

Method: We have utilised efficient low temperature coagulation technology to develop a unique range of small diameter microporous vascular grafts using ChronoFlex, a biodurable polycarbonate urethane.

Results: Grafts have been subjected to a range of in vitro and in vivo testing, demonstrating excellent physical and mechanical characteristics, self-sealing, maintenance of compliance and pulsatile flow in situ and patency up to twenty-two weeks.

INTRODUCTION

The purpose of this communication is to describe our approach to the design, development and production of a self-sealing vascular
access graft, and the continuing development of a compliant small diameter vascular prosthesis for peripheral vascular and potentially for coronary artery bypass using a unique patented fabrication process and a new generation of biodurable poly carbonate urethanes.

STATUS OF POLYURETHANE GRAFT DEVELOPMENT

Polyurethanes have been recognized for some time as an extremely attractive and readily available range of materials for the advancement and fabrication of small diameter vascular prostheses. The elastic properties of the material, coupled with low thrombogenicity and very attractive physical and mechanical properties that can be generated from a wide variety of processing methods, has led to considerable research effort and expenditure over the last twenty years, aimed at the development of polyurethane vascular grafts.

A search of the patent data base and scientific literature will disclose a very wide array of fabrication methods and variations of polyurethane materials used by research groups and commercial companies around the world, who have sought to advance the science of vascular graft design with the aim of improving the performance of small diameter grafts to achieve clinical results closer to those of reversed saphenous vein.

Two principal difficulties have hampered the clinical use and subsequent commercialisation of virtually all polyurethane vascular graft developments:

1. The bio-durability of polyurethane.
2. The inability of laboratory processing methods to produce a consistent high quality product efficiently and economically.

DEVELOPMENT HISTORY

From 1988 to 1992, our laboratories worked on methods for the fabrication of a small diameter compliant vascular prosthesis to a design concept originated by Underwood et al. [1]. In common with many polyurethane developments, doubts about the long-term stability of the material (a poly-ether-urethane), arose from in vivo experimental implants, bringing that particular project to a close.

However, several important factors were demonstrated during the development program:

1. Processing technology [2]—that can manufacture high quality and consistent product to very tight tolerances.
2. A product design that allowed the maintenance of compliance [3]
and the transmission of pulsatile flow and energy in vivo; allowing smaller diameter grafts with increased velocity of flow.

3. Elimination of suture hole bleeding and greatly improved handling characteristics.

4. Significantly improved twelve months patency over e.P.T.F.E. when implanted as an aorta-iliac bypass graft in dogs [3].

5. Attractive surface for endothelial cell seeding [4,5].

**POLYURETHANE DEGRADATION**

Poly-ether-based segmented polyurethanes were considered to be the state of the art in terms of biocompatibility and biostability. However, vascular grafts fabricated from ether urethanes exhibited degrees of polymer degradation when implanted into living systems.

In 1983, Szycher [6] first proposed that poly-ether-polyurethanes were susceptible to in vivo oxygennation of the polyether chain. The most susceptible group is the methyl group in the alpha position to the ether oxygen, which undergoes oxidation, causing eventual chain cleavage, leading to a significant reduction in molecular weight at the surface and eventual surface fissuring.

Whilst it is not normally supposed that enzymes catalyse the degradation of synthetic polymers, the possibility exists that ether-based polyurethanes are degraded by enzymes in vivo. Williams [7] remarked that since enzymes have the ability to reduce the activation energy of chemical reactions, a degradation reaction that may normally only occur at elevated temperatures or in the presence of actinic radiation may conceivably take place under physiological conditions in the presence of the correct enzymes.

In a landmark study, Phua and Anderson [8] tested the biodegradation of polyurethanes by in vitro exposure to enzymes. Ultra-thin samples were exposed to two proteolytic enzymes, papain and urinase, at 37°C for one to six months. Both enzymes were found to be capable of degrading poly-ether-urethane.

As papain is closely related to cathepsin B, a thiol endopeptidase which is released by cells of the inflammatory response, the authors concluded that segmented poly-ether-urethanes can be degraded by enzymes which are present during the inflammatory response.

**NEW GENERATION POLYURETHANES**

It has been reported by both Capone and Szycher that polycarbonate-urea-urethane is resistant to biological oxidation (surface fissuring) for periods of up to six months [9,10].
Polycarbonate elastomers were fabricated as tubing stretched to 300% over mandrels and implanted subcutaneously in experimental animals. The tubing was retrieved at three and six months, evaluated by S.E.M. and F.T.I.R. analysis, with no evidence of degradation.

Stokes [11] compared ChronoFlex to Pellethane in vivo using the “Stokes Test” which is designed to accelerate environmental stress cracking, using strain as the accelerant. Extruded tubing was stretched over mandrels to 400% elongation. ChronoFlex showed no evidence of environmental stress cracking at eighteen months post-implantation.

ChronoFlex is a second generation segmented polycarbonate-based polyurethane which exhibits good mechanical properties and low modulus of elasticity. This allows strength, but remains relatively soft and compliant, allowing us to tailor-make a ChronoFlex formulation to give the desired physical and mechanical properties required for the successful development of a small diameter vascular prosthesis.

PROCESSING METHOD—VASCULAR GRAFTS

Our patented process involves what we term “low temperature cast coagulation.” In this system, we gently extrude polymer solution onto the smooth surface of a mandrel. The mandrel and extrusion head rotate in synchronization, minimizing shear and residual stress, whilst a pair of 2.5 metre long mandrels are drawn through the twin extrusion heads into a coagulant maintained at 40°C.

Mandrel rotation and transverse speed, extrusion head rotation speed and polymer pump pressure are all electronically controlled and coordinated to give the desired structure and geometry to the graft wall.

By controlling the process conditions, grafts can be produced with a wide range of physical and mechanical characteristics; an example would be a very porous graft allowing rapid cellular ingrowth which could be suited to venous applications.

The polymer solution comprises a solution grade ChronoFlex [12], a water soluble filler of between 10 and 60% by weight and a surfactant in an amount between 1 and 10% by weight. During phased coagulation the fillers prevent collapse of the structure as the solvent disperses and the filler dissolves into the coagulant, resulting in a single layer uniform microporous structure shown in Figure 1. A single layer structure avoids the danger of delamination and subsequent loss of strength, maintains cross section and allows the surgeon to cut the graft evenly and cleanly.
Porosity and permeability are controlled by the process conditions. The open pore structure which forms the mid-portion of the wall is created as part of the product design to allow wall compression. This unique technology is proven to produce products economically and efficiently which meet our exacting design specifications which are far in excess of international standards for synthetic vascular grafts.

 QUALITY CONTROL

We employ a combination of internal inspection and independent external testing. Testing is performed to the appropriate standard; we are currently following the Draft European Standard [13] and the revised A.A.M.I. Standard [14] which is much closer to publication as a Standard then any of the other three Draft Vascular Graft Standards that have unfortunately been in preparation for some years.

 QUALITY CONTROL INSPECTION

Performed on every graft— in house
Surface Properties:  Internal and direct illumination
Internal diameter:  Calibrated taper gauge
Length:  Calibrated rule
Wall thickness:  Measured at four points on each end with calibrated constant force gauge
Concentricity:  Calculated from wall thickness data
Porosity:  Calculated by a gravimetric method

**BATCH TESTING**

Performed on every production batch by external laboratories

Physical:  Longitudinal and Radial Tensile Strength, Permeability and Suture Retention
Residuals:  Assess process conditions
Microbiology:  Bio-Burden
Pyrogen:  EP/USP Pyrogenicity Test

**VASCULAR ACCESS GRAFT—CHRONOFLEX**

Like peripheral grafts—Vascular Access Grafts need special design characteristics; they are used in a demanding application where patients rely upon them for routine access to life-preserving dialysis.

A Vascular Access Graft ought to be:

- Biostable and biocompatible
- Available for early puncture if required
- Technically easy to implant and puncture without the need for special preparation or techniques
- Self-sealing to minimise puncture site bleeding and prevent haematoma formation
- Able to retain mechanical strength with puncture over time
- Kink and compression resistant

It is generally accepted that at twelve months post implant, only 60% of e.P.T.F.E. vascular access grafts will remain patent and that 60% of grafts will have had at least one major revision to restore or maintain patency.

E.P.T.F.E. remains, however, the current choice for secondary vascular access, although it suffers from two limiting major drawbacks, namely post-operative healing time, three to four weeks are recommended before puncturing, and time to achieve haemostasis following dialysis
needle withdrawal of between five and twenty minutes [15].

The ChronoFlex Vascular Access Graft can overcome the fundamental disadvantages of Teflon in secondary vascular access because it does not rely upon tissue invasion for puncture site healing (Figure 2). The inherent elasticity of ChronoFlex gives the ability to “self-seal” which provides for minimal blood loss at puncture sites, enabling dialysis to commerce much earlier, if required, improving the quality and convenience of haemodialysis (Figure 3).

External reinforcement by spirals or individual rings to prevent kinking has enhanced the use of e.P.T.F.E. as a looped graft for forearm implants. PolyGraft has designed a looped version of the ChronoFlex V.A.G. The loop with a 15 mm radius is permanently formed by an additional processing step. This does away with the need for external reinforcement which can erode through the overlying skin can also and restrict thrombectomy access.

The material, elasticity, and single layer structure of the graft combine to eliminate suture hole bleeding, minimise puncture site blood loss, maintain circular cross section, enhance kink and twist resistance, and allow the graft to be cut evenly.

Through in vivo studies, we plan to demonstrate that a self-sealing access graft will reduce the overall complication rate associated with

Figure 2. Illustration of ChronoFlex Vascular Access Graft straight and pre-looped.
haemodialysis access, have a positive economic impact on its maintenance, and improve the quality of life for dialysis patients.

**SPECIFICATION OF CHRONOFLEX VASCULAR ACCESS GRAFT**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Specification</th>
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<tbody>
<tr>
<td>Structure</td>
<td>Single layer, Microporous</td>
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<tr>
<td>Internal diameter</td>
<td>5 or 6 mm ± 0.1 mm</td>
</tr>
<tr>
<td>Wall thickness</td>
<td>0.9 mm ± 0.05 mm</td>
</tr>
<tr>
<td>Eccentricity</td>
<td>Less than 0.15 mm</td>
</tr>
<tr>
<td>Ultimate longitudinal strength</td>
<td>Greater than 25 N</td>
</tr>
<tr>
<td>Ultimate radial tensile strength</td>
<td>Greater than 1.0 N/mm</td>
</tr>
<tr>
<td>Water permeability</td>
<td>Less than 5 cm³ cm⁻² min⁻¹</td>
</tr>
<tr>
<td>Suture retention</td>
<td>Greater than 2.5 N</td>
</tr>
<tr>
<td>Porosity</td>
<td>Approximately 70% void to solid ratio</td>
</tr>
<tr>
<td>Volume compliance</td>
<td>Between 5 and 10%</td>
</tr>
<tr>
<td>Sterility</td>
<td>Sterile</td>
</tr>
<tr>
<td>Pyrogenicity</td>
<td>Non-Pyrogenic</td>
</tr>
</tbody>
</table>
GENERAL SAFETY TESTING

Biological Tests
U.S.P. Class Six
Haemolysis
AMES
Cytotoxicity

V.A.G.
Pass
Pass
Pass
Pass

SELF-SEALING

To initially assess the self-sealing characteristic of the material, we use an artificial circuit working at a pressure of 120 mm Hg, circulating water at 37°C. The grafts are punctured with a 16 g dialysis needle and the needle is withdrawn. The puncture site is photographed immediately after needle withdrawal (Figure 4). Because of the minimal leakage, we have not attempted to measure water loss.

STRENGTH AFTER REPEATED PUNCTURE

Following the method given in ANSI/AAMIVP20-1994, 8.3.4., we have simulated dialysis use and determined the radial tensile strength after repeated puncture to be

<table>
<thead>
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<th>Punctures per square centimetre</th>
<th>0</th>
<th>8</th>
<th>16</th>
<th>24</th>
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<tr>
<td>To simulate months of use</td>
<td>0</td>
<td>6</td>
<td>12</td>
<td>18</td>
</tr>
<tr>
<td>Radial Tensile Strength (Mean N/mm)</td>
<td>2.14</td>
<td>2.05</td>
<td>2.01</td>
<td>1.81</td>
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</tbody>
</table>

demonstrating that the retained strength after eighteen months of simulated dialysis use remains greater than the product release specification. The actual reduction in radial tensile strength is 15%.

EXPERIMENTAL IMPLANTS–VASCULAR ACCESS

To assess initial biological response, we have implanted four 5 mm ID grafts into two dogs as Carotid Artery interposition grafts. The implants were prospectively assigned to be explanted at six weeks and have shown no unexpected events. All grafts were patent at explant. Light microscopy shows (Figure 5) a well-developed neointima lining the anastomotic region of the graft without apparent lumenal reduction. The surrounding capsule is composed of tissue macrophages and foreign body type giant cells.

To assess short-term patency, we implanted 5 mm ID ChronoFlex
Figure 4. Illustration of puncture site leakage evaluation test: (a) dialysis needle *in situ*; (b) dialysis needle withdrawn.
Figure 5. Light micrograph (x) of ChronoFlex graft sectioned in the coronal plane in the anastomotic zone, removed at six weeks after Carotid artery interposition grafting. There is a well-formed neointima arising from the adjacent artery which extends into the graft. Despite the diameter mismatch (ChronoFlex 5 mm I.D., Canine Carotid 3 mm), there is no lumenal reduction within the anastomotic zone suggesting architectural remodelling has occurred to the cell matrix of the larger graft.
grafts into two adult beagle dogs. Each animal received bilateral Aorta-Femoral bypasses with the iliac arteries tied off. Patency is monitored monthly by colour-coded Duplex examination. Two grafts remain patent at twenty-four weeks in one animal, in the other animal, both grafts failed at eighteen and sixteen weeks, respectively, caused by proximal anastomotic stenosis.

An additional two animals received bilateral Carotid Artery interposition grafts; two of these grafts remain patent at twenty-two weeks, the other two at fifteen weeks.

COMPLIANT ARTERIAL PROSTHESIS DESIGN

Traditionally, vascular grafts have come from technology transfer, mostly taking a material with industrial applications and fabricating a tube which, by virtue of the material characteristics, had some of the required properties of a bypass graft. Design has not figured highly in graft development beyond material characteristics.

The ideal characteristics of a vascular graft described by James C. Stanley [16] are: biocompatible, non-thrombogenic, physically durable, elastic properties of the saphenous vein, resistance to infection, and technically easy to implant.

It is also logical that a vascular prosthesis should mimic the characteristics of a natural artery. After all, we are producing an arterial substitute which, from a physical and mechanical view, ought to become part of the overall cardiovascular system rather than functioning in isolation.

Compliance [17,18] is seen by many as the vital attribute in matching prostheses to the arterial tree and could be an important contributor to improving the clinical performance of small diameter grafts, particularly in low flow situations such as below knee arterial bypass. Obtaining long-term compliance has been an elusive goal because most grafts rely upon overall external dilation which is rapidly prevented by perivascular ingrowth resulting in loss of compliance.

The design approach is to build a prosthesis which, amongst other features, will maintain compliance and pulsatile flow in vivo, enabling the transmission of energy and a better quality of flow. This is achieved through a mechanism of wall compression which accommodates increases in volume without the need for external dilation (Figure 6).

We have assessed dynamic compliance by a calibrated, highly accurate positive displacement mechanism provided by Dynatek Laboratories, Missouri, in a series of ChronoFlex grafts over a pressure excursion of 80 mm Hg to 120 mm Hg at a cycle rate of seventy-two beats per
Figure 6. Illustration of unique modus operandi allowing luminal expansion by wall compression without external dilation.
minute. The results ranging from 2.75–10.5% radial compliance demonstrated our ability to vary compliance by control of processing conditions and ChronoFlex formulation (Figures 7 and 8). This will allow us to custom-produce artificial blood vessels with site-specific characteristics.

By Duplex follow-up of implanted ChronoFlex grafts with a radial compliance of 6%, we are able to demonstrate compliance and pulsatile flow in situ (Figure 9). The scan shows pulsatile flow in the mid portion of a ChronoFlex graft at one month post-op (Dog Aorta-Fem), validating the design feature that enables pulsatility to be maintained.

By a novel technique of blood flow and compliance measurement using digital subtraction angiography, Seifalian et al. [19] confirmed that ChronoFlex grafts are more compliant than e.P.T.F.E., the current choice of smaller diameter vascular grafts for lower limb arterial bypass.

**ChronoFlex Vascular Graft Compliance v Pressure Excursion**

![Graph](image)

*Figure 7. Chart of % radial compliance v pressure excursion of different ChronoFlex grafts.*
ChronoFlex Vascular Grafts

Radius v Pressure

Figure 8. Chart of radius v pressure of different ChronoFlex grafts.

Figure 9. Duplex Scan Dog Aorta—Femoral Bypass thirty days.
A clinically successful small diameter vascular prosthesis which will give results closer to those of a saphenous vein in demanding applications such as distal and coronary artery bypass will come from a combination of technologies. Whilst compliance will be a very important feature in our development program, we are also investigating and evaluating other potential methods of enhancing performance; for example, bonding platelet inhibitory drugs onto the inner surface giving pharmacological support, utilising advanced surface analysis and engineering techniques to provide a surface suitable for endothelial cell attachment, addressing the issue of tapered grafts in combination with kink and compression resistance.

CONCLUSION

We have presented our methods and materials used to fabricate a self-sealing vascular access graft and given details of our programme to develop a small diameter compliant vascular prosthesis for lower limb arterial and coronary artery bypass. We expect that a combination of proven technology, product design and the use of ChronoFlex, a second generation polycarbonate biodurable urethane, will lead to clinically successful compliant polyurethane vascular grafts becoming available.

REFERENCES