BioIntegral Surgical

Implantation Monograph of the No-React® BioConduit™

A zero-porous valved aortic conduit with all-biological material

CONFIDENTIAL

This document is intended only for surgeons that intend to use the BioConduit™ Aortic Valve Conduit for implantation

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Introduction

Aortic valve conduits are used to provide a replacement for a combined disease of the ascending aorta and aortic valve. There are problems when replacing the valve in the ascending aorta with conventional valve conduits. These problems are caused by the conduit design, the material they are made from, the ability of the conduit material to prevent blood loss, hemodynamic effectiveness, risk of infection rates, and other factors.

Issues with traditional valve conduits

Valve conduits are available in three different designs/configurations:

1. Mechanical valves in woven polyester fabric conduits (collagen-coated and non-coated)
2. Homografts/autografts
3. Xenografts in woven polyester fabric conduits

The problem with each of these three alternatives is that:

1. Mechanical valves are associated with bleeding and infection (endocarditis); they also require the patient be on long-term anti-coagulation.

2. Homografts tend to dilate and slowly become insufficient. Homografts also calcify heavily (aortic wall), creating a "porcelain aorta" particularly in patients younger than age 65. Availability, transport, and storage also present problems.

3. The woven polyester fabric material in the bioprosthesis (e.g., Dacron™) reduces the hemodynamic efficiency of the valve, and increases the risk of infection. All woven polyester fabric conduits are prone to excessive bleeding through the pores or suture lines.

These options are not ideal because of the higher risks of infection, dilatation, calcification, stroke or hemolysis than via use of the BioConduit™.

Fabric or synthetic conduit disadvantages

Disadvantages of woven polyester fabric are that it compromises the hemodynamic properties of the conduit, and increases the risk of infection and hemolysis. This affects the long-term durability and, therefore, the long-term success rate of Dacron™ valve conduits.

Solution: The No-React® BioConduit™

The BioIntegral Surgical No-React® BioConduit™ porcine aortic valve and pericardial conduit gives surgeons a better alternative. The biological conduit is fitted with a stentless porcine valve, providing superior hemodynamics compared to mechanical valves. Since the BioConduit™ is made of only biological materials, the risk of infection is dramtically reduced[1].

Superior hemodynamics. The BioIntegral BioConduit™ is designed to be oversized. For example, for a 19 mm-diameter valve annulus, a conduit of 21-25 mm can be used to satisfy the hemodynamic requirements.

Reduced risk of infection. The risk of infection is markedly reduced as only natural materials are used, and No-React® valves have a long history of best-in-class infection protection[2,3,4,5]. .

No need for anti-coagulation or anti-rejection therapy. Clinical publications indicate that the No-React®-treated tissues are more biocompatible than homografts, and do not product anti-HLA antibodies[6].

No-React® BioConduit™: Ease and Availability

The BioIntegral No-React® BioConduit™ is readily available in six different sizes (21mm, 23mm, 25mm, 27mm, 29mm, and 31mm), and is immediately ready for implantation as rinsing is not required for any BioIntegral Surgical No-React® treated product. The stentless valve is covered and extended by a bovine pericardial conduit, 15 cm long (see Figure 1 below).

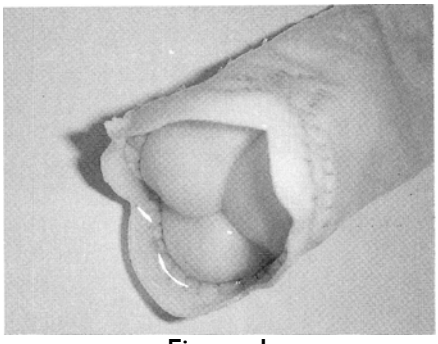

Figure 1

No-React® Advantages

The valves are treated with the No-React® anticalcification and anti-degenerative treatment making tissues non-reactive and highly biocompatible. These advantages have been proven with nearly 20 years of clinical data. This stentless valve satisfies the hemodynamic requirements for flexibility and strength for aortic valves, as well as having the durability necessary for the pericardial tube. The vascular durabilty is best-in-class for both synthetic and biological alternatives.

A major reason for this is the proprietary No-React(R) detoxification process. It eliminates residual glutaraldehyde and ensures stable tissue cross-linking. Based on clinical experience, results on eliminating long-term calcification and tissue deterioration issues have been definitive[1-3].

Long-Term Clinical Results

17 years of clinical experience with best-in-class infection protection and the best durability of any all-biological vascular product.

The use of synthetic / composite valved grafts are considered acceptable, but the 10 year results are not highly desired[7,8]. Complications such as infection which require graft removal and in turn, a higher rate of mortality for the patient[9,10]. Therefore, in the presence of infection the use of an all-biological conduit is imperative[10,11].

In the presence of infection, the BioConduit has a uniquely positive record. Studies conducted in the UK and Germany indicate infection and reinfection rates of the BioConduit matching those of homografts[1,2,3,4,5]. And given the lack of availability of homografts, patient/prosthesis mismatch, and other unique considertions, the BioConduit is a more reliable and predictable option.

Durability of the BioConduit is best-in-class, even as compared to homografts and autografts. No-React® tissues have a track record of tissue durability regardless of patient age. After 5,000 implants and 17 years of experience, the all-adverse event rate is 0.4%. Calcification and degeneration have not been observed.

And while biological alternatives to composites are preferred, the durability of cryopreserved allografts is limited at the 10 year mark, raising the lifetime risk of their use[12]. Pulmonary autografts used during the Ross procedure have their own specific durability issues, such as dilatation (in 75-90% of cases studied[13]) and pulmonary insufficiency[14]. Pasquale and others discovered that this degenerative process begins only after three years post-implant. While these changes to the collagen stucture of the autografts post reimplantation is not well understood, the effects of negative remodeling have been observed[15].

Aortic valve replacement

The aortic annulus should be sized using the standard sizers. A conduit one or two sizes larger than the annulus may be selected. The BioIntegral No-React® BioConduit™ is designed for implantation with one suture line at the base. The distal portion is then attached to the distal ascending aorta (see Figure 1).

For the BioConduit™, the surgeon can tailor the outflow of the valve according to the patient's needs. The long pericardial conduit allows the surgeon either to use the device as a mini root or as a total aortic root replacement.

The Bentall Procedure

Introduced in 1968 and commonly performed today, the Bentall Procedure involves removing the entire ascending aortic root and valve. A valved conduit is then implanted. The coronary ostia are re-implanted into the side of the conduit.

(Please see the instructions in the next section on how to implant the BioIntegral Surgical No-React® BioConduit™).

Implantation of the BioConduit™

Below are step-by-step diagrams and descriptions of how to implant the BioIntegral No-React® BioConduit™:

1. After aortic cannulation and starting extracorporeal circulation, crossclamp the distal aorta (See Figure 1 below).

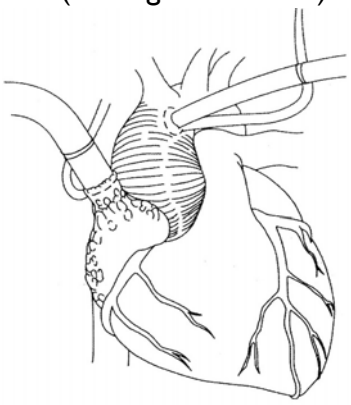

Figure 1

2. The aorta is partially or completely transected (see Figure 2).

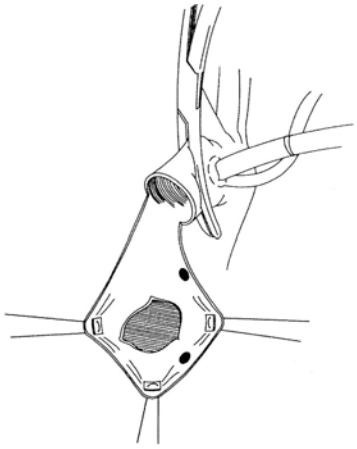

Figure 2

3. A BioIntegral No-React® BioConduit™ is secured with a single, continuous suture using preferably 3-0 monofilament sutures (interrupted sutures with pledget when there is no infection may also be done (See Figure 3).

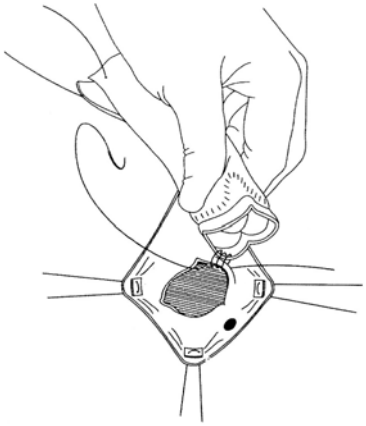

Figure 3

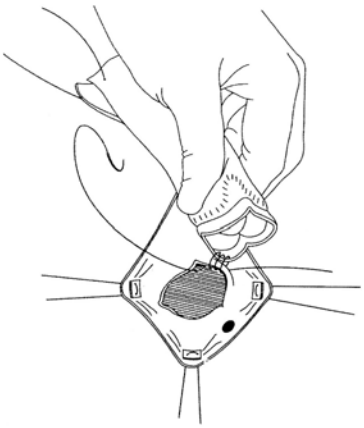

Figure 3

4. The conduit is totally biological; no woven polyester fabric is present (See Figure 4).

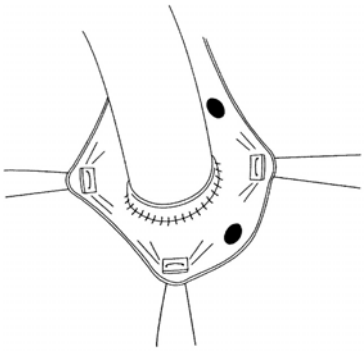

Figure 4

Warning: the suture line of the tube of the conduit should face the middle of the non-coronary cusp. Otherwise, the surgeon may find himself perforating the suture line to anastamos the right or left coronary artery

Any aortic conduit, biological or synthetic, must be sutured with non-absorbable suture material, because we are dealing with No-React tissue, which causes no foreign body reaction, blood oozing is completely impermissible, if such oozing or

leaking of blood is present, we suggest to stop the oozing with 5-0 continuous or interrupted sutures.

If the surgeon permits mild bleeding or oozing, the surgeon cannot rely on the oozing to stop and in rare cases, hematoma can result. Experience of 5,000 implantations have shown that people that follow this technique unique to No-React® tissue never experience hematoma. Again, this is not a Dacron conduit, and scar formation cannot be expected.

After reversing the heparin, look carefully at all the anastomoses to make sure there is no oozing. If there is any evidence of oozing, use Prolene 6-0 sutures to correct the issue.

5. An opening is made in the conduit adjacent to the left coronary ostium for implantation of the left coronary artery. (See Figure 5).

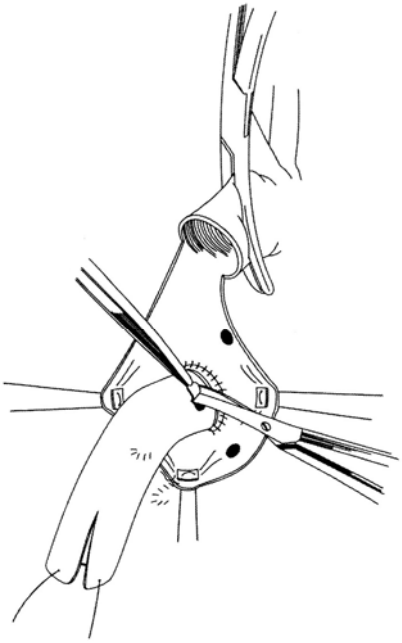

Figure 5

6. Anastamosis is made between the conduit and the right coronary ostias using the two buttons you have dissected from the aortic wall, preferably with 6-0 Prolene (see Figure 6 and Figure 7). **Make sure bleeding and oozing have been taken care of with careful suturing as per all anastomoses with the device. Do not close the sternum if any oozing is present.**

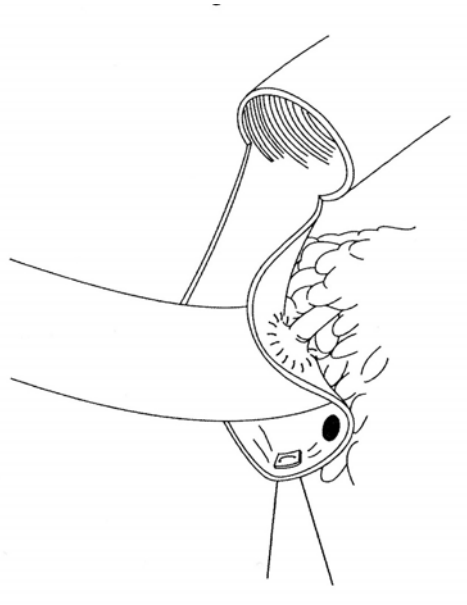

Figure 6

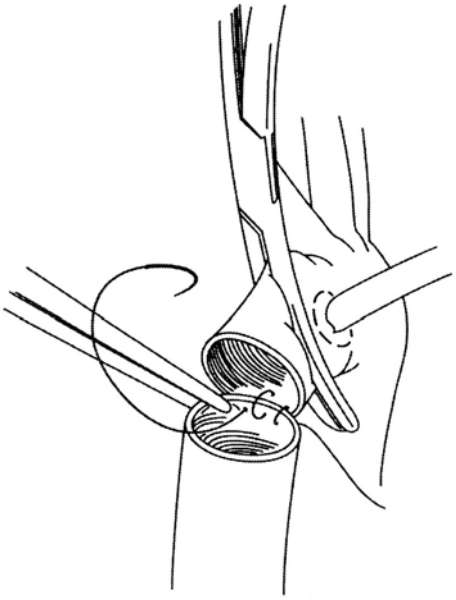

Figure 8

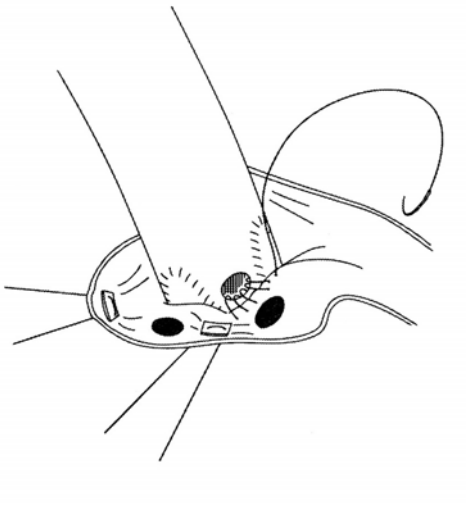

Figure 7

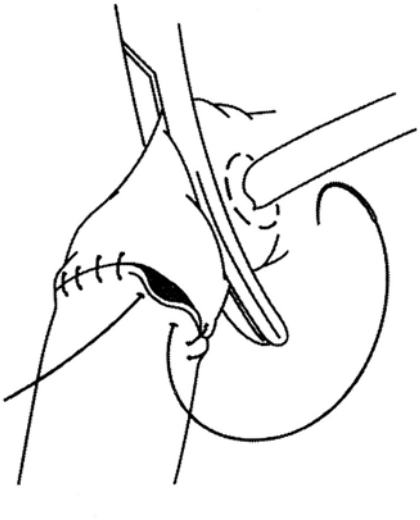

Figure 9

7. The distal anastomosis is completed. **The same care to prevent oozing should be made with the distal anastomosis.** When no infection is present, we recommend putting a Teflon pledget on the anastamosis (see Figure 8 and Figure 9).

8. After air is aspirated from the graft, the cannulae are removed from the right atrium and the aortic arch (See Figure 10).

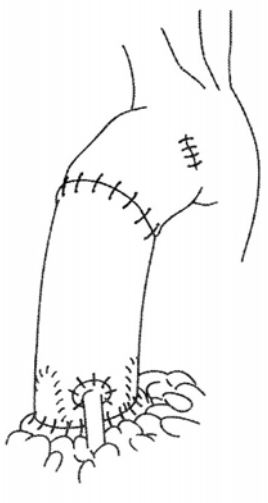

Figure 10

9. If the diameter of the aorta is significantly larger than that of the conduit, the anastomosis is completed as far as possible and the remaining defect is closed with a No-React® pericardial patch. Usually the piece of pericardium--trimmed from the distal end from the conduit--is sufficient for this purpose (See Figure 11).

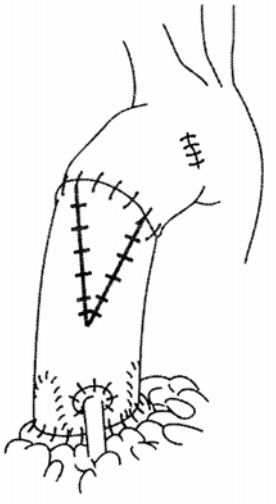

Figure 11

Conclusion

In many situations, the BioIntegral No-React BioConduit™ offers benefits over conventional mechanical valves, xenografts, allografts, and homografts. Besides offering superior hemodynamics, strength, flexibility and availability of a variety of sizes, the conduit has demonstrated a low risk of infection or bleeding.

In addition, the proprietary No-React® tissue detoxification process has been shown to be effective by the absence of calcification in a large series of pulmonic conduits implanted in children[6]. Also, after more than 5,000 implants and 17 years follow-up, no dilatation has ever been reported. This is a confirmation that the No-React® tissue is non-reactive and does not degenerate. **Furthermore, human endothelial studies of the very few explants that we have received have been shown to have a monolayer endothelial cell lining.**

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