CONFIDENTIAL

This document is intended only for surgeons that intend to use the Versaflex for clinical purposes.

VERSION II

BioIntegral No-React Versaflex (Semi- Stented and Versatile Valve): Monograph

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Introduction

The unique and patented design of the BioIntegral No-React Versaflex aortic valve is the result of careful evolution over many years. Stentless valves have been shown to have many advantages, including excellent hemodynamic characteristics[1-9] and reduced stress at the commissures.

The hemodynamic advantage over stented valves is demonstrated by the higher effective orifice area (EOA) of stentless valves.[10] Higher EOA is a result of the valve's advantageous ratio internal/external diameter, composite versus non-composite, its flexibility, and its ability to coapt well.

The commissures of a stentless valve are sutured to the aortic wall of the patient. This automatically reduces the stress in the commisures, as the elasticity and flexibility of the aortic wall contribute to the function of the valve. The reduction of commisure stress has also been demonstrated in studies of stented versus stentless homografts. The stentless homografts were found to have superior durability, when compared to homografts with a stent.[11]

The implantation of currently available standard stentless valves is time-consuming and demands high technical skills and expensive training. Slight malposition of the valve can lead to regurgitation or leaflet prolapsed. As a result, the risk of regurgitation in standard stentless valves (up to 35% of patients in some reports[12]) is sometimes countered by over-sizing. However, **over-sizing** can be detrimental because it actually **reduces the EOA!** The design of the Versaflex valve ensures correct placement, maximizes the EOA,and increases the effectivness of the valve, even if over-sized.

The prolonged cardiopulmonary by-pass cross-clamp times associated with standard stentless valves may lead to higher morbidity and mortality rates.[13-14] Some reports have associated standard stentless valves with prosthetic dehiscence, and added to an increased mortality rate.[15]

Background

The Shelhigh Stentless

The Shelhigh Stentless Aortic Heart Valve, Model NR-2000 was the first stentless valve designed by Shelhigh (Figure 1).

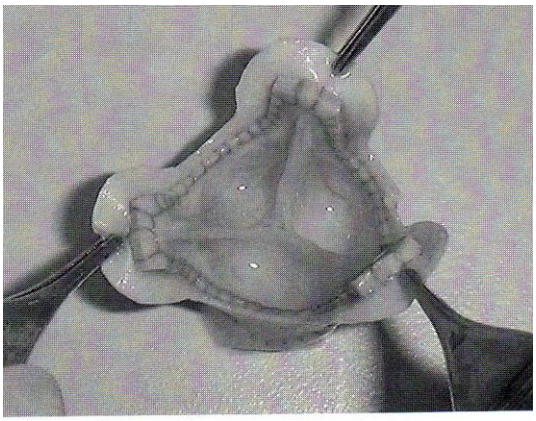

Figure 1

The Shelhigh Model *NR-2000* Stentless Valve

Dr. Van Geldorp and Dr. Brands of Breda, the Netherlands, showed in their study that implanting the No-React stentless valves was technically easier than implanting a homograft, with the same superior hemodynamic advantages. The event-free survival was 100% at four and a half years.[16]

Still the crossclamp time was relatively long like any other total stentless valve, for that reason the skeleton was added to the improve its function and simplify implantation.

Twelve years of follow-up with No-React valves has shown excellent hemodynamics.[17-19] Published data up to eight years shows that the valve is not only durable, but resists infection. [20, 21]

The BioIntegral No-React Versaflex Valve: The Concept of 'Skeletonization'

Although stentless valves have many advantages, these have not always been reproduced in the clinical setting. What was needed was a fresh look at the mechanics of the aortic root and a reconsideration of the disadvantages of the stentless concept. As a result, a stentless valve with a "skeleton" was developed to ensure a more accurate and anatomically appropriate implantation.

The "skeleton" of the valve, now known as the Versaflex, is a strong, flexible ring with short prongs that direct the commisures properly to the aortic wall, preventing possible distortion of the valve during implantation. 'Skeletonization' maintains the hemodynamic advantages of the stentless valve and

eliminates the uncertainty associated with its implantation. Using traditional surgical techniques, it is as easy as implanting a stented valve; no special training is needed.[22] More than twenty-five thousand No-React aortic valves have been implanted in the last twelve years in young and old patients and no calcification has been reported. [23]

The Future

The Versaflex

The BioIntegral No-React Versaflex applies the skeletonization construction to give it strength and flexibility. This No-React treated bioprothesis is a composite porcine valve, made of three leaflets and wrapped in porcine pericardium (Figure 2).

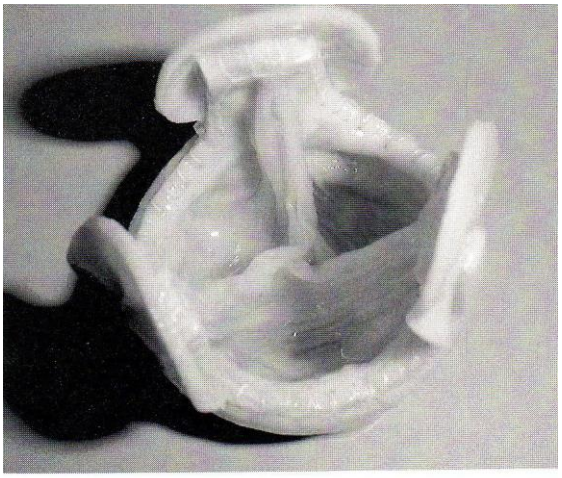

Figure 2
The BioIntegral No-React Versaflex

The Versaflex is correctly defined as a stentless valve, as the skeleton does not support the commisures – its commisures must be sutured to the aortic wall for proper function. The hemodynamic performance equals or exceeds that of standard stentless valves. The valve has no fabric; it is only made from biological tissue.

European Clinical Experience

The BioIntegral No-React Versaflex received the CE Mark in 2009 . In its first year, many surgeons implanted the valve successfully without previous experience with stentless valves, , without special training.[17]

The Versaflex is undergoing a post-marketing clinical study in centres throughout Europe, The Versaflex is very flexible. It can be distended up to a 30° angle and the cusps continue to coapt well (Figure 3).

Figure 3

Shelhigh Stentless vs. BioIntegral Versaflex

Recent testing at BioIntegral compared the hemodynamic performace of the BioIntegral No-React Versaflex with the identical design, but without the skeletonization.

Tests were performed in fresh aortic roots specially mounted on a pulse duplicator. At all flow rates tested, the Versaflex has uniformly higher EOAs (Figure 4).

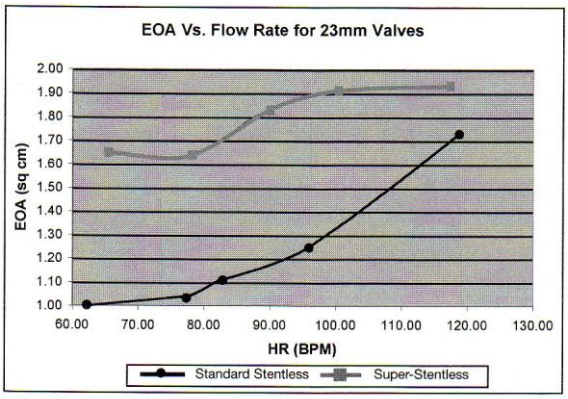

Figure 4

This in-vitro study has shown that adding a skeleton to the stentless valve enhances the hemodynamics of an identical valve.

In the clinical study done in Parma, Italy, comparing the echocardiogram of the Versaflex with one of the

standard stentless valves, the 2D echo evaluation of the size 21mm revealed a higher EOA (1.7cm^2) than a standard stentless valve of the same size (1.1 cm^2).[17]

Validation Through Fatigue Testing

The Versaflex has been fatigue tested to validate its strength and durability up to 400 million cycles, using the Shelhigh FTS-300 Fatigue Tester consistent with ISO guidelines.

Accelerated fatigue testing is done at a rate of 1400 beats per minute and at a closing pressure of 150 mmHg. Pressures are measured weekly and visual inspections are performed daily using a variable speed stroboscope. This has been confirmed by 12 years follow-up of clinical studies with no report of tissue failure.

Tissue Calcification

Calcification and tissue deterioration have been widely recognized problems in conventionally treated glutaraldehyde bioprostheses, especially in younger patients, and residual glutaraldehyde has been indicated as a cause of or major contributor to the problem.

No-React Treatment

The unique, No-React tissue detoxification treatment from BioIntegral is not a replacement of glutaraldehyde; it is an enhancement. The No-React treatment detoxifies the tissue, eliminates residual glutaraldehyde and ensures stable tissue cross-linking.

Clinical reports have shown promising results in mitigating early or late calcification and tissue deterioration.[18-19] In a study of over 200 Porcine Pulmonic Valve Conduits, it has been shown that, even in young children, in the absence of infection, the No-React treatment protects against calcification to a remarkable degree.[20] No calcification has been seen so far (up to 12 years).

In the Operating Room

Presentation

The valve is stored in benzyl alcohol and contains no free glutaraldehyde. As a result, it requires no rinsing, although, like any bioprosthesis, it must be kept moist during implantation. It is supplied mounted on a plastic holder, secured by a single suture. The valve may be removed from the jar with forceps by grasping the plastic holder and then attaching it to the valve handle. The holder has a female screw thread, which accepts the valve handle supplied with the sizers (Figure 5).

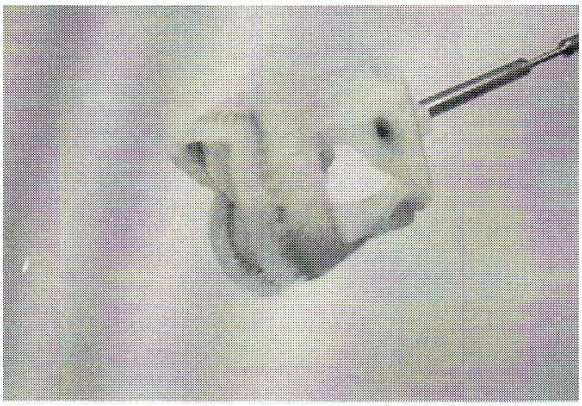

Figure 5
The BioIntegral No-React Versaflex in the BioIntegral Valve Holder

A single suture attaches the (3) three 1cm circular pledgets. This should be cut with small scissors inserted inside the plastic tag.

Surgical Technique 1

Aortotomy

A transverse aortotomy is generally preferred. It is important to make sure the transverse aortotomy is high enough above the right coronary ostia, typically 2-3 cm,from the base of the aorta, to ensure that the aorta is not distorted after closure. The surgeon will be guided by the anatomy of the valve and root, especially the position of the coronary ostia with respect to the annulus, in deciding whether annular, supra-annular or infra-annular implantation is appropriate. For best hemodynamic results, we recommend the sub-annular implantation using **self-plegeted** technique. The annulus of the valve will become the plegets for the sutures, after suture trading the annulus is pushed inside the ventricle, and the suture pulled up and tied down on the aortic side.

Since the valve is deformable it is easy to push the valve inside the ventricle even though the valve was over-sized by at least one size.

Surgical Technique 2

Sizing

The internal diameter of the annulus should be measured with the sizers provided. The sizers accurately measure the supra-annular diameter and the corresponding size of valve should be chosen. The valve should normally be positioned in subannular or supra-annular position. Because of the excellent hemodynamic performance of the valve, over-sizing is not required but, provided the usual care is taken to guard the coronary ostia, a size 21mm can be routinely implanted in infra- or supra-annular position in a measured 19mm annulus with good results.

Please note that because of the presence of the "skeleton" over-sizing of the Versaflex valve, it achieves a real hemodynamic benefit – unlike standard stentless valves. The most important factor is that the level of cusps is well maintained even though the skeleton is soft (the skeleton is deformable but it is difficult to twist the ring).

The BioIntegral No-React Versaflex stentless bioprosthesis is available in sizes 21mm, 23mm, 25mm, 27mm and 29mm.

Surgical Technique 3

Suturing the Annulus

It is recommended to implant the valve in infra-annular position to achieve the best hemodynamic results and to obtain a totally clean and smooth outflow of the left ventricle.

The self- pledgeted technique better retains sutures and avoids the risk of embolization of individual pledgets. This technique will also assure a low position of the valve, and will leave the aortic sinuses completely free.

Please review the video for the self-plegeted technique implantation.

Most surgeons prefer to implant the valve, starting at one commisure and follow-up by interrupted sutures from the right or left side of the commissural sutures until all of the annulus has been completely threaded with mattress sutures.

Alternatively a continuous technique using 3-0 or 4-0 Prolene™ may be used starting at one commissure and passing the needle from the ventricle out, and through the valve annulus.

Versaflex is a universal annulus and is versatile enough to be implanted in any technique a surgeon chooses.

With the sutures in place, the valve is slid into position. Care must be taken to prevent any leaflet damage by using surgical instuments. The valve skeleton and the holder enable surgeons to use the 'no-touch' technique; this means not touching the valve directly with fingers or instruments. The valve holder is removed by making a single cut in the circumferential suture, then pulling the holder free.

The most important advantage of this skeleton (semi-stent) is even if you have very pathologic and deformed aorta the valve will always be symmetric.

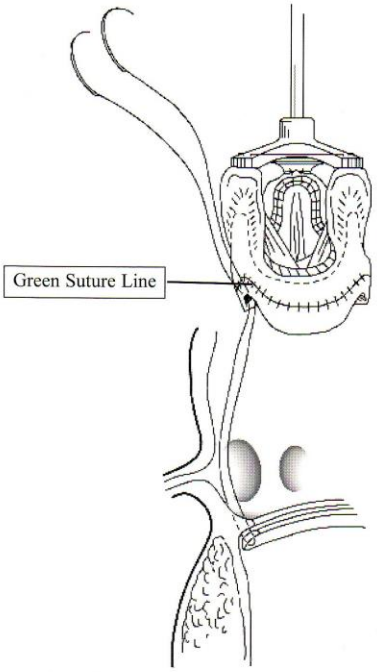

Figure 8

It is important to note that the Versaflex is now a universal lateral annulus and not a vertical annulus as depicted in figure 8.

Surgical Technique 4

Suturing the Commissural Flanges

The valve is supplied with three (3) 1cm circular patches, made from No-React treated pericardium, which may be optionally used to strengthen the sutures holding the flanges to the aortic wall (Figure 9).

Figure 9
3 Small Pericardial Circular Pledgets

A double-ended 4-0 Prolene™ mattress suture is passed though the pericardium flange above the commisure from inside the aorta and through the circular pledget. If the upper, horizontal suture is passed first, it may be tied immediately to facilitate placement of the second and third vertical sutures (Figure 10).

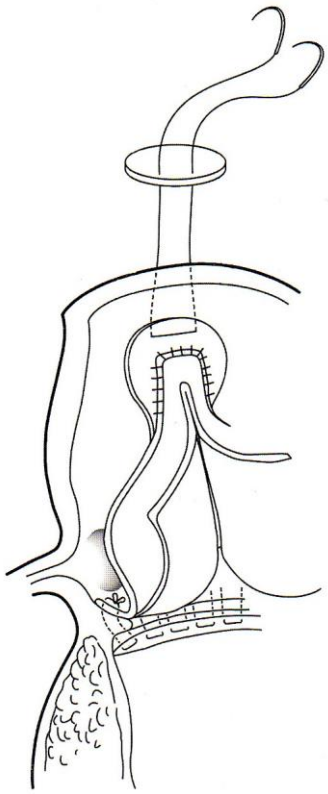

Figure 10

Alternatively, a continuous technique may be employed using three 4-0 Prolene™ sutures, starting with a mattress suture on the outside of the aorta. The sutures can then be run continuously, from the outside in, following the commisures and then ending with a knot on the outside (Figure11).

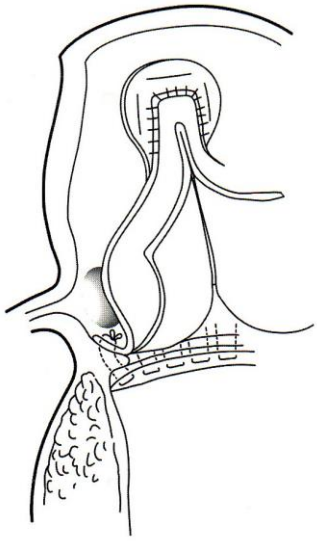

Figure 11

An outside view of the valve at the end of the procedure with the circular pledgets forming a buttress for the suture holding the flanges of the BioIntegral No-React Versaflex is shown in Figure 12.

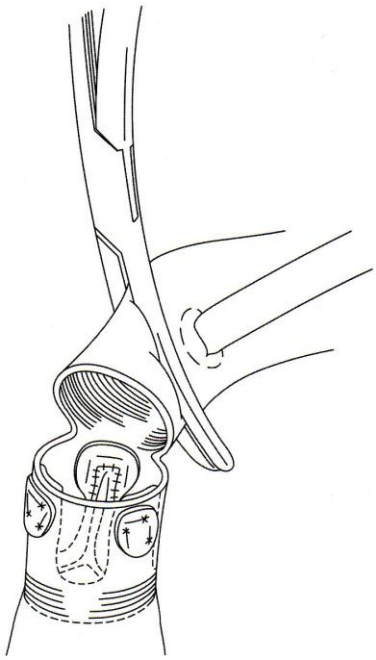

Figure 12

The aorta is then closed using the surgeon's preferred technique, and the procedure is completed in the customary manner. If the surgeon has elected to make an oblique opening of the aorta, the corresponding flanges can be included in the suture line.

Surgical Considerations and Pitfalls

Coronary Ostia

The sawing ring of the Versaflex is universal and generally , the left coronary ostium is free. If the left coronary ostium is rather low, BioIntegra strongly recommend the subannular

Bicuspid Valve

When implanting the Versaflex to replace a bicuspid valve, the implantation may be difficult if the coronary ostia face each other (180°). In this circumstance one of the commissural posts may obstruct one of the coronary ostia. (In this case, a mini-root replacement can be a good option, using the BioIntegral No-React BioConduit).Or again the sun annular implantation will keepgenerally the flange below the right coronary ostia.

The surgeon must measure the distance between the annulus and the right coronary ostia. It should be at least 2cm.

Note

A videotape demonstrating the surgical technique of the BioIntegral No-React Versaflex is available. We recommend viewing the video before implanting this valve.

Conclusion

BioIntegral's No-React Versaflex has the excellent hemodynamics expected from a stentless valve but is as easy to implant as a stented valve, because of its strong yet flexible ring. The No-React tissue detoxification treatment has been shown to mitigate calcification. The treatment also keeps tissue soft and pliable.

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