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# New concept of Bioprostheses: a biosprothesis with discontinuation of the annular suport, the "Less Stented"

## *Novo conceito de Bioprótese: bioprótese com descontinuidade do anel de sustentação(Less Stented)®*

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*Abstract*

*Objective:* **To study a bioprosthesis with discontinuation of the annular support, named the "Less Stented ®" bioprosthesis. The Phase 1 objective was an "*in vitro*" study, during which the hemodynamic characteristics of the prosthesis were analyzed. Phase 2 of this study consisted of an initial clinical implant protocol.**

*Methods:* **The "Less Stented" bioprosthesis consists of a glutaraldehyde treated bovine pericardium prosthesis manufactured by Braile Biomedica Ltda, São José do Rio Preto, São Paulo, Brazil, using the same manufacturing protocols as the stented bioprostheses but with discontinuation of the annular support. Bioprostheses were tested in a pulse simulator system and analyzed in a cardiac simulator with respect to the transvalvular gradient, regurgitant fraction and leakage volume, discharge coefficient, performance and efficiency index. The two patients of the clinical protocol were analyzed according to the functional class (NYHA), an echocardiographic study and magnetic resonance, in both the pre- and postoperative periods.**

*Results:* **The transvalvular gradients ranged from 6.37 to 11.62 mmHg with a mean flow between 4.39 and 7.96 L/min, giving a good correlation (0.8291) on the regression curve with the increase in flow. The regurgitant fraction ranged between 10.95% and 17.94% and leakage volume between 4.49% and 7.87%. The discharge coefficient, performance and efficiency index showed favorable behavior with the increase in flow, with good coefficient correlations for all three variables (0.9385, 0.9332 and 0.9024, respectively). The two patients submitted to "Less Stented®" bioprostheses implant presented with good clinical evolutions.**

*Conclusions:* **"Less-Stented®" bioprostheses may represent a new alternative to aortic valve replacement.**

*Descriptors:* **Bioprostheses. Heat valve prosthesis. Aortic valve, surgery.**

***Resumo***

***Objetivo:* Estudar bioprótese com descontinuidade do anel de sustentação, a bioprótese "Less Stented®". O objetivo da fase 1 do trabalho foi o seu estudo "in vitro", onde foram avaliadas as características hemodinâmicas. O objetivo da fase 2 é relatar a experiência clínica inicial.**

***Método:* As biopróteses foram confeccionadas e avaliadas laboratorialmente na Braile Biomédica, em São José do Rio Preto, São Paulo. São próteses de pericárdio bovino, tratadas**

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**com glutaraldeído, segundo os mesmos padrões das próteses "stented". As próteses foram testadas no simulador de pulso e analisadas em simulador cardíaco. Foi realizada análise clínica e laboratorial (ecoDopplercardiografia e ressonância magnética) dos pacientes.**

***Resultados:*** **A análise do gradiente pressórico transvalvar mostrou que ao longo do fluxo médio, equivalente ao débito cardíaco e que variou de 4,39 a 7,96 l/min, o gradiente transvalvar se manteve dentro de níveis clinicamente aceitáveis (6,37 a 11,62 mmHg). A curva de regressão mostrou boa correlação com o aumento de débito cardíaco com $R^2$ = 0,8291. A fração regurgitante variou de 10,95 a 17,94%, sendo que a fração de vazamento variou de 4,49 a 7,87%. Quanto ao coeficiente de descarga, ao índice de performance e ao de eficiência, verificou-se que esses parâmetros mostraram comportamento favorável com aumento progressivo do débito cardíaco, com excelente correlação tanto para o coeficiente de descarga, quanto para o índice de performance e o índice de eficiência ($R^2$ respectivamente, 0,9385; 0,9332; 0,9024). Os dois pacientes submetidos ao implante da bioprótese "Less-Stented®" apresentaram evolução clínica satisfatória.**

***Conclusão:*** **A bioprótese "Less-Stented®" poderá representar uma nova alternativa de substituto valvar.**

***Descritores:*** **Bioprótese. Prótese das valvas cardíacas. Valva aórtica, cirurgia**

## INTRODUCTION

Biological tissue, both homologous and heterogeneous, has been utilized for more than 30 years for the preparation of replacement heart valves [1-5].

Currently the most commonly used tissues are heterogeneous, in particular bovine pericardium and porcine aortic valves, both of which are prepared in glutaraldehyde.

The first generations of these bioprostheses were mounted on stainless steel support annuli known as stents. The evolution to polyacetal or polypropylene plastic annuli was fast and justified by their flexibility, which diminished the tension on the biological cusps of the bioprostheses. These are thus, stented bioprostheses that are utilized to replace both the aortic and mitral valves and are easy and fast to implant.

At the end of the 1980s, stentless bioprostheses mounted without support annuli appeared for aortic valve replacement [6-8]. These were developed to reduce the hemodynamic disadvantages of the conventional stented bioprostheses, as the transvalvar gradient was reduced when no annulus was employed.

However some problems emerged: positioning of stentless bioprostheses is more difficult when compared to the conventional stented prostheses and more time is required. So, for these reasons they are still little used.

Considering these difficulties, we developed the 'Less stented' bioprosthesis (Figure 1), of bovine pericardium treated in glutaraldehyde aiming at summing the advantages of the two existing concepts. In 'Less stented' bioprostheses these is an interruption in the support annulus giving more flexibility to the bioprosthesis and reducing the gradient, and it is mounted in such a way that its implantation technique is the same as the conventional stented bioprostheses. Thus, as in stented bioprostheses, these new 'Less stented' prostheses employ sutures that are passed through the annulus of the aortic valve and through the Teflon annulus of the bioprosthesis and tied. This work aimed at analyzing the *in vitro* hemodynamic characteristics of this new concept of bioprostheses and reporting on the initial clinical experience.

Fig. 1 – "Less Stented" Bioprosthesis

## METHOD

### 1. Manufacture of the 'Less stented' bovine pericardium bioprosthesis

The 'Less stented' prosthesis is made from bovine pericardium pre-treated with glutaraldehyde and submitted to rigorous quality control.

The bovine pericardium is obtained from an abattoir, immediately after slaughter, from animal whose ages range from 30 to 60 months and which had previously been inspected by the Government Animal Health Inspectors. Pericardium rich in collagen fibers and free from fat is utilized. Subsequently it is treated with sodium chloride and buffered magnesium chloride.

In the laboratory, the pericardium if mounted on a support and then submitted to tanning by immersion, without pressure, in a solution of purified, buffered 0.5% glutaraldehyde. The entire procedure aims at tanning the pericardium, whilst maintaining the alignment or parallelism on the collagen bands, in such a way that they do not suffer stretching or alteration of its natural undulations.

Thus, the pericardium will retain its natural mechanical elasticity necessary for the correct functioning of the bioprosthesis.

After tanning, the tissue is submitted to a treatment with an oxidant solution, which removes the antigenic pericardium substances and impurities, cellular remnants as well as increasing the resistance of the tissue. After completing the tanning period, the pericardium is placed in a 4% formaldehyde conserving solution. After this phase, the prostheses are submitted to quality control, and are only released when they fill the rigid pre-established control criteria [9].

During the prostheses preparation procedure there are several tests:

- SHRINKING TEST

This test measures the effect of the fixing substance on the structures of the bovine pericardium, in particular on the collagen fibers, that is, if the biological tissue was effectively fixed by the glutaraldehyde. Samples from all the bovine pericardia are tested and those that do not reach the specified standards are rejected.

Fresh pericardium shrinks at 60 ºC, while fixed pericardium resists higher temperatures. A temperature of 83 ºC is considered the minimum to guarantee adequate fixation of the collagen fibers by the glutaraldehyde.

- MECHANICAL RESISTANCE TEST – TRACTION TRIAL

This test is performed on the fixed bovine pericardium in random directions.

An apparatus is employed that enables reliability tests to be performed. As a load is applied to a sample it is automatically compared with a proven stretching of the material, thereby producing a load-stretch diagram. From this diagram, values of tension, rupture, stretching and tenacity indexes can be calculated directly. The minimum acceptable value for traction is 1.5 kg/mm$^2$.

- HISTOLOGICAL AND HISTOCHEMICAL ANALYSIS

This analysis is performed on all pericardium samples, with the minimum histologic standards being: prominent undulation of the collagen fiber structure, preservation of the elastic fibers, a small quantity of fundamental amorphic substances and reduced space between the different extracts intercrossing of collagen bands and absence of degeneration.

- MICROBIOLOGICAL TEST

This control includes cultures to identify aerobic bacteria and fungi. To identify bacteria, a culture medium of glycosylated broth (BHI – Brain Heart infusion) is used and for fungi sabouraud agar is utilized. The material is incubated for 72 hours and 15 days respectively in a bacteriological incubator at 37 ºC. The bioprostheses are only released for use after the results of all the cultures are known.

- MANUFACTURE AND LINING OF THE "LESS STENTED" ANNULUS

The Delrin annulus used on the bovine pericardium valve is divided into three equal parts duly manufactured so that it stays without slots. These braces will give support to the 'Less Stented' valve. The size of the annulus is shown in Figure 2.

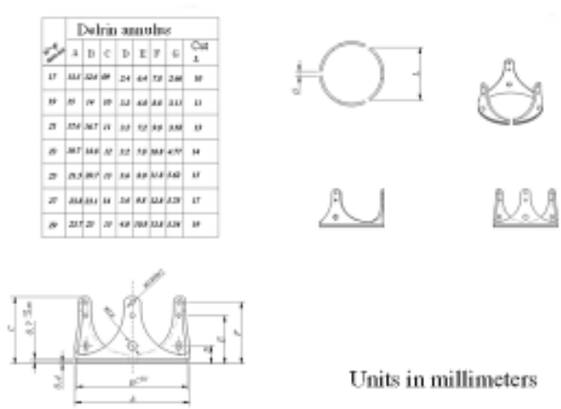


Fig. 2 – Diagram of bioprostheses with its dimensions.

The braces are individually lined with bovine pericardium using running sutures.

• Lining of the support annulus of the valve

The bovine pericardial membranes utilized to line the rings are selected according to the diameter and thickness of the pericardium, that is, the size and the thickness depend on the diameter of the prosthesis to be mounted.

The previously selected bovine pericardium is cut in a rectangular shape, the size of the diameter if the Delrin rings.

The reverse sides of the lateral edges of the bovine pericardium patch are brought together and a continuous suture is performed.

The pericardium tube is introduced inside the ring and folded in a manner that the lining exceeds ± 3 mm for future finishing of the valve. A continuous suture is made around the entire ring.

The external layer of bovine pericardium (first layer) is carefully trimmed around and between the braces.

The second layer of bovine pericardium is then trimmed around and between the braces of the ring, leaving a border of pericardium, which will be utilized in the finishing of the ring.

**Mounting the 'Less Stented' bioprosthesis**

The bovine pericardium is cut according to the size of

the ring of the bioprosthesis to be manufactured.

The sides of the bovine pericardium are joined with three single sutures. Starting from the third suture, continuous running sutures are used. Subsequently, after alignment of the center of the cuspids the pericardium is fixed on the braces.

**Finishing**

The bovine pericardium of the valve is fixed to the bovine pericardium of the stent removing the suture threads of the support ring.

The annulus is delicately removed from the ring that was utilized to mount the valve.

The already lined Delrin braces are inserted in the pre-molded valve.

The excess pericardium is trimmed from around the valve and the remaining pericardium lining of the annulus is sutured using running sutures to the pericardium of the valve and the braces.

Following this the valve is placed inside a Dacron tube to construct the flange.

**2 Study phases**

**2.1 First phase – *in vitro* study**

The bioprostheses were made and evaluated in the laboratory in Braile Biomedica, São José do Rio Preto, Brazil.

The prostheses were evaluated in a pulse simulator using a mean systolic volume of 80 mL (79.3 ± 1.0). Nº 25 bioprostheses were used and 5 measurements were made for 60, 70, 80, 90 and 100 pulses per minute. Thus, a total of 25 measurements were recorded.

The characteristics assessed were:

1. Transvalvar pressure gradients at the mean and maximum flow rates;
2. Regurgitation and escape fractions;
3. Discharge coefficient, performance index and efficiency index.

**2.2 Second phase – clinical study**

The protocol was approved by the Research Ethics Committee of the Heart Institute and by the Ethics Committee for the Analysis of Research Projects of the Clinical Directorate of the Hospital das Clinicas and the Medicine School of the University of São Paulo. The protocol included the implantation of 'Less Stented' Bioprostheses to replace the aortic valve. Two Less Stented bioprostheses were implanted in the Heart institute after the patients signed an informed consent form.

RESULTS

**1- In vitro studies**

**Analysis of the transvalvar pressure gradient**

With a mean flow it was observed that the transvalvar gradient maintained within clinically acceptable limits (6.37 to 11.62 mmHg) and the cardiac outflow rate varied between 4.39 and 7.96 L/min. The regression curve presented with a good correlation when the cardiac outflow was increased giving an $R^2$ of 0.8291. At the maximum flow rate, a clinically significant gradient occurs with high outflows (> 7 L/min), also giving a good correlation (R2 = 0.9284), as is demonstrated in Figure 3.

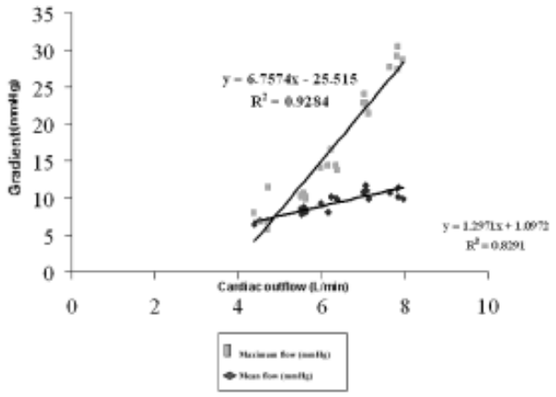


Fig. 3 – Analysis of the transvalvar pressure gradient

**Analysis of the regurgitation fraction and the escape fraction**

The regurgitant volume is calculated from the sum of the closing volume (volume necessary to close the prosthesis) and the escape volume (the volume that is lost through leakage in the prosthesis during the closing process). The regurgitant fraction ranged between 10.95% and 17.94% and the leakage volume varied from 4.49% and 7.87%. These values are considered low, but the most relevant aspect is that there is a tendency of regurgitant fractions to reduce with the increase of cardiac outflow ($R^2$ of 0.3544) and, in particular, there is no increase in the leakage volume with progressively higher outflows ($R^2$ of 0.0033) demonstrating a good capacity of closure of the prosthesis in studies (Figure 4).

**Analysis of the discharge coefficient, performance index and efficiency index**

These parameters measure the hydrodynamic functioning of the prosthesis and theoretically should be stable as the cardiac outflow increases, or better still, increase. With the prosthesis under study, it was confirmed that these parameters demonstrated a favorable behavior with a gradual increase of cardiac outflow, with excellent correlation for the discharge coefficient and for the performance and efficiency indexes ($R^2$ of 0.9385, 0.9332 and 0.9024 respectively) as shown in Figure 5.

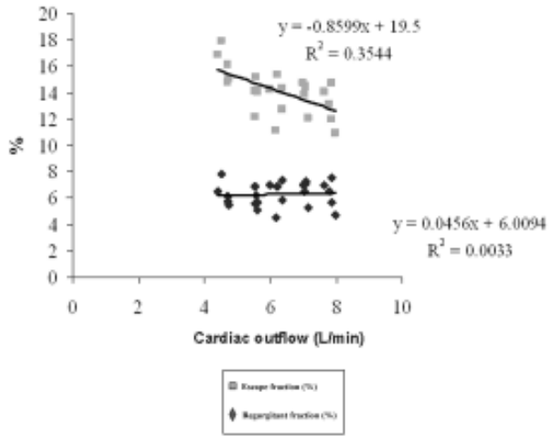


Fig. 4 – Analysis of regurgitant fraction and the escape fraction

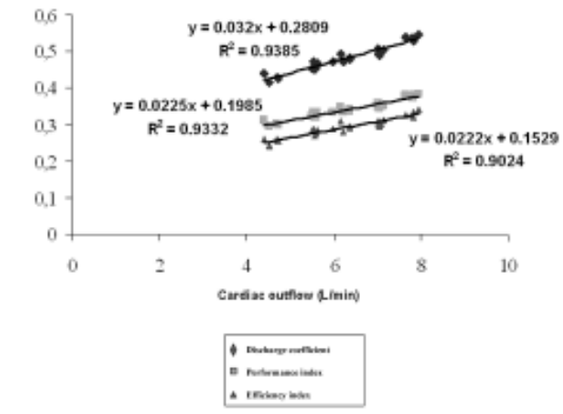


Fig. 5 – Analysis of the discharge coefficient, performance index and efficiency index

**2 – Initial clinical experience**

**Case 1:**

A 44-year-old Caucasian male patient, N.E.R, with 1.75 m of height and 76.2 kg with a history of murmurs over 2 years, fainted one year previous to surgery and had suffered progressive dyspnea and precordial pain since the incident. In the physical examination, the arterial blood pressure of the right upper limb was 110 x 70 mmHg, the pulse was 62 beats per minute, and the patient was "parvus tardus, acyanotic, hydrated, anicteric with normal color. The lungs had vesicular murmurs without adventitious noises and palpable fremitis with aortic, mitral and cervical region focuses. On cardiac auscultation, a systolic murmur was evidenced at an aortic focus ++++/6+ with irradiation to all the precordium and carotids.

Cardiac catheterism demonstrated coronary circulation without obstructive lesions, a double aortic lesion with predominant stenosis. The left ventricle had a hypertrophic aspect and normal contraction. The left ventricle-aorta gradient was 120 mmHg. A preoperative Doppler echocardiogram diagnosed slight aorta insufficiency and significant aorta stenosis with an aortic transvalvar gradient of 144 mmHg (peak) and 91 mmHg (mean) and concentric-type myocardial hypertrophy with the left ventricle adapted, ejection fraction of 69% and final diastolic volume of 40 mL. Magnetic resonance demonstrated significant concentric-type left ventricular hypertrophy with the ventricular function globally preserved, with several small areas of myocardial fibrosis focalized in specific segments, inferior-lateral-basal and septal-basal of the left ventricle.

On 13th June 2003, the patient was submitted to aortic valve replacement using an A-27 'Less Stented' bioprosthesis. The intra-operative transesophageal Doppler echocardiogram revealed a transvalvar gradient pre-cardiopulmonary bypass of 84 mmHg (peak) and 44 mmHg (mean), a valve area of 0.8 $cm^2$ and an ejection fraction of 40%. In the post-cardiopulmonary bypass period, after the implantation of the bioprosthesis, the transvalvar gradient was 33 mmHg (peak) and 13 mmHg (mean) with a valve area of 1.7 $cm^2$ and an ejection fraction of 45%.

The anatomicopathological result of the aortic valve study demonstrated chronic valvulitis with calcification and neo-vascularization, fibrin thrombus in a small area of the valve surface and a morphologic aspect compatible with the sequel of rheumatic disease.

The patient presented with a good evolution, and was released from hospital on the sixth postoperative day. A Doppler echocardiogram performed on the sixth postoperative day demonstrated an aortic transvalvar gradient of 28 mmHg (peak) and 13 mmHg (mean, slight concentric-type myocardial hypertrophy, an ejection fraction of 76% and a final diastolic volume of 166 mL.

**Case 2:**

The case of a 43-year-old male Caucasian patient, R.B.C, with 1.66 m of height and 60 kg with a 1-year history of precordial pain triggered by effort is reported. Over this period the patient presented with progressive dyspnea. The physical examination evidenced an arterial blood pressure in the right upper limb of 130 x 70 mmHg and a pulse of 80 beats per minute. The patient was acyanotic, hydrated, anicteric and with normal color. On auscultation, a regular cardiac rhythm was heard with a hypo phonetic second sound, with systolic murmur with an aortic focus of ++++++/6+ with cervical irradiation and a diastolic murmur with an aortic focus ++++/6+.

Cardiac catheterization demonstrated coronary circulation without obstructive lesions, double aortic lesion with predominant stenosis. The left ventricle had a hypertrophic aspect with slightly diffuse hypokinesia. The left ventricle-aorta gradient was 110 mmHg. A preoperative Doppler echocardiogram diagnosed significant aortic insufficiency and significant aortic stenosis, with an aortic transvalvar gradient of 165 mmHg (peak) and significant concentric-type myocardial hypertrophy, an ejection fraction of 68% and final diastolic volume of 85 mL. Magnetic resonance demonstrated significant concentric-type left ventricular hypertrophy with a preserved global left ventricle function, double aortic lesion with predominant stenosis and a late intensification focalized in the antero-medial portion.

On 1st December 2003, the patient was submitted to aortic valve replacement using an A-27 'Less Stented' bioprosthesis. The intraoperative transesophageal Doppler echocardiogram revealed a pre-cardiopulmonary bypass gradient of 139 mmHg (peak) and 78 mmHg (mean), with an ejection fraction of 68%. In the post-cardiopulmonary bypass period after implantation of the bioprosthesis, the transvalvar gradient was 23 mmHg (mean) with an ejection fraction of 65% (Figure 6).

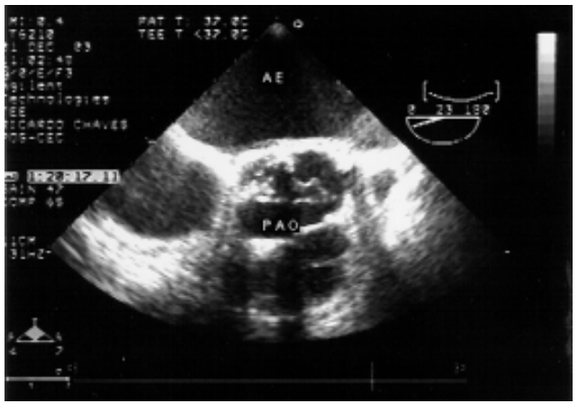


Fig. 6 – Intraoperative transesophageal Doppler echocardiogram of case 2 - The 'Less Stented' prosthesis with normal opening and functioning

The patient presented with a good evolution and was released from hospital on the 11th postoperative day. A transthoracic Doppler echocardiogram preformed on the 22nd March 2004 in the fourth postoperative month demonstrated the biological 'Less Stented' prosthesis in the normal aortic position. The aortic transvalvar gradients were 14 mmHg (peak) and of 7 mmHg (mean) and significant concentric-type myocardial hypertrophy, an ejection fraction of 70% and final diastolic volume of 91 mL were evidenced. Magnetic resonance showed a preserved ventricular function, significant left ventricular hypertrophy, the existence of late intensification focalized in the antero-medial portion. The opening of the prosthesis to the limit of its braces and absence of reflux were easily observed.

## COMMENTS

At the end of the 1980s, the stentless bioprosthesis mounted without a support ring emerged, to replace the aortic valve [6]. They were developed to reduce the hemodynamic disadvantages of the conventional bioprostheses (stented) as the absence of the ring reduces the transvalvar gradient and consequently the 'stress' on the tissue. This diminishes the problems of functional dysfunction and reduces the volume of the left ventricle mass [8], improving the left ventricular function and the late survival rate of the patients. However, the implantation technique is more complex than conventional prostheses, and is associated with higher rates of mortality and early reoperations for prosthetic insufficiency.

The mid-term clinical results with the utilization of the stentless prosthesis are satisfactory. GOLDMAN et al. [10] published the 8-year evolution of Toronto Stentless prostheses implanted to replace the aortic valve in 447 patients. The authors observed a low adverse event rate and a structural dysfunction free survival rate of 97.4%, with low mean transvalvar gradients (4.4 mmHg) and good effective valve area (2.4 $cm^2$). However, nearly 20% of the patients presented with moderate or significant aortic insufficiency in the late postoperative period, with five patients undergoing reoperations (0.3% patients/year), which was attributed, by the authors, to aortic dilation.

Another commonly employed stentless prosthesis is the Cryolife O'Brien. In a 7-year follow-up, GELSOMINO et al. [11] published an actuarial survival rate of 93.6% and a structural dysfunction free rate of 98.1%, as well as significant reductions of the left ventricle mass index, the mean and peak transvalvar gradients and improvement of the left ventricular function. According to the authors, these prostheses are indicated for aortic valve replacement in patients with small aortic annuli. LUCIANI et al. [12] published similar results with the Biocor PSB Stentless prostheses, with a 92% structural dysfunction free rate over 8 years.

According to PEPPER et al. [13], the most common situation is that the sinotubular junction presents with a diameter smaller than the aortic valve. This may cause problems, with, for example, the implantation of a large valve compared to the annulus would excessively increase the coaptation of the leaflets, resulting in an excessive gradient. Also, according to the authors, when the sinotubular junction is larger than the annulus, the coaptation may easily be insufficient when using stentless bioprostheses, causing regurgitation.

In the initial experience of O'BRIEN et al. [14], the authors highlighted several technical problems related to the implantation of stentless prostheses: not to utilize the oblique anatomy, to preserve the geometry of the aortic root; not to leave remnant tissue of the native aortic valve, in particular calcium residues; not to utilize intra-annular sutures, as they lead to a reduction of the effective valvar orifice; supra-annular sutures on the margin of the bioprosthesis do not leave space underneath, fixing the wall of the prosthesis adequately to the aortic wall.

VRANDECIC et al. [7], in a work reporting on the first 100 implantations in the Biocor institute, reported that in the majority of cases it is necessary to utilize a heterologous pericardial patch to close the aorta, in order to avoid distortion in the implanted stentless bioprosthesis.

As we have seen, the majority of authors report great technical difficulties in implanting stentless bioprostheses in comparison to the conventional bioprostheses. In these first two cases reported, the implantation technique of the Less Stented bioprosthesis was the normal technique, that is, the same manner of implantation of the stented bioprosthesis.

As has been previously described, the transvalvar gradient progressively diminishes in the postoperative period with stentless bioprostheses [15,16], a situation that also occurred in our patients.

## CONCLUSION

The Less Stented ® bioprosthesis may represent a new alternative for valve replacement.

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