

Transcatheter Heart Valve Crimping and Expansion: Commentary

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Abstract

Bovine pericardium represents the material of choice to serve as leaflets but this material is fragile and mishandling might lead to dramatic consequences. The complete innocuousness of handling at implantation has not been reached as crimping and balloon inflation cause various degrees of injury. These can impair the physical characteristics and aggravate the thrombogenicity. The design of the device must promote the long-term durability of the pericardium. The role and selection of polyester fabrics as buffer between the metallic frame and the pericardium is likely to prevent major abrasion at implantation and *in situ*.

Commentary

Transcatheter valve deployments represent the most fascinating and disruptive technology of the last few decades [1]. Should the long-term durability of percutaneous valves approach or surpass that of conventional devices, open-heart surgery might become obsolete. The ultimate goal will be the total valve replacement not only for aortic valves but mitral and pulmonary valves as well, as it becomes possible to accommodate the specific requirements of every patient [2-3]. We are enthusiastic participants in the worldwide efforts to achieve the long-term durability of the percutaneous devices. Bovine pericardium represents the material of choice to serve as leaflets but this material is fragile and mishandling might lead to dramatic consequences. The complete innocuousness of handling at implantation has not been reached as crimping and balloon inflation cause various degrees of injury [4]. These can impair the physical characteristics and aggravate the thrombogenicity. The design of the device must promote the long-term durability of the pericardium. The role and selection of polyester fabrics as buffer between the metallic frame and the pericardium is likely to prevent major abrasion at implantation and *in situ* [5].

We hereby propose to highlight the outstanding achievements related to this disruptive technology and to point out the weaknesses that should be satisfactorily addressed. The clinical results so far attained fully justify the continuous implantation of the percutaneous valves. After focusing on the adverse events related to injuries to the devices, we hereby demonstrate how the bovine pericardium is the most appropriate material. This material has stood the test of time and has become fully entrenched so that alternative materials will therefore have great difficulties in being adopted in the foreseeable future.

Descriptive Clinical Achievements

As a result of the remarkable development of minimally invasive techniques in cardiovascular medicine during the last decades, procedures using these techniques have gained rapid and broad

acceptability especially as healthcare is becoming prioritized worldwide [6]. Being less invasive, the patients recover much faster and can return home soon after the procedure. The plethora of innovative devices available is the result of physician-driven initiatives and start-up companies that rapidly merged with major manufacturers [7]. The clinicians continue to require increasingly sophisticated devices to restore various heart functionalities, to make the valve replacement a common treatment for aortic valve diseases [8], to extend the indications for pulmonary valve replacement [9] and propose new avenues for the treatment of the mitral valve [10]. The biofunctionality is the first key issue addressed by the clinicians. Most attention is paid to the ease of use of deployment systems and to the early and mid-term clinical performance [11]. The literature is abundant with reports of single centre experiences and multicentre trials. Ultimately the multiplicity of registries generates new ideas that contribute to further development of new generations of devices [12]. The long-term durability still raises some question marks about the complexity of the device design, the handling during delivery (crimping, sheath loading and expansion) and the *in-vivo* aging [13]. The biocompatibility of the implantable devices remains an ill-defined concept. There are formidable gaps between the various options in selecting the most appropriate foreign surface to interface with blood. The biocompatibility of the cardiovascular devices is rarely adequately addressed because it integrates numerous phenomena related to the continuous interactions between the host and the foreign materials. As a result of these interactions, the implants and their environments are continuously remodelled by a process that transforms a foreign body alien to the patients into a composite device incorporating various biological and biotissue components. Myriads of scientists give priority to the flow surface being totally nonthrombogenic. This first option might be reasonable for catheters that are used for a short period of time but the biofilm that forms on the surface can be rapidly colonized with bacteria. A second option is bioencapsulation of the foreign material but the capsules are too frequently made of a stiff collagenous tissue with collagen fibres that are devoid of any waviness. Such

straight and stretched fibres show neither motility nor softness. With time, they are likely to break and then calcify. The third option is the use of materials that permit the conductance of fluids through the thickness of the wall such as the bovine pericardium [14]. As the design requirements for any cardiovascular implant are not completely quantified, it is of paramount importance to continuously reassess their risks and benefits during their life-time. An ideal implant should have two characteristics: first, its potential durability should exceed the life-expectancy of the patient; second, it should not cause side-effects likely to compromise the patient's health.

The feasibility of percutaneous valve deployment was pioneered by Manolopoulos who developed innovative delivery systems [15]. Despite the low visibility achieved by this disruptive undertaking, the experimental research continued through the 1970 and 1980. Andersen's experimental investigations [16] paved the way to the first clinical deployment by Cribier in 2001 (Figure 1) [17]. Today, probably more than 100,000 patients worldwide have received an implanted aortic valve through either a retrograde transarterial or an antegrade transapical access. Compared to aortic revalving, the number of pulmonary valve implantation has remained insignificant. Over the past decade, the increasing number of reports about the clinical efficacy and the safety of this emerging minimally invasive technique was a clear-cut demonstration of the broad acceptability of this rapidly maturing technique [18].

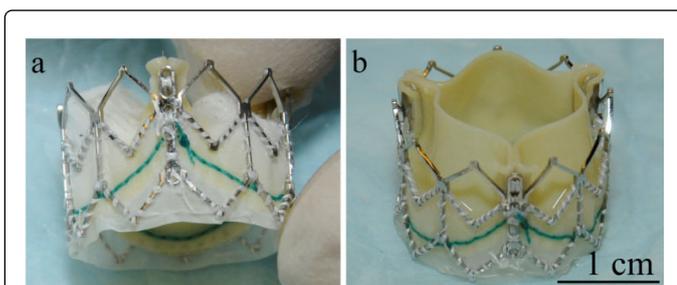


Figure 1: The third generation Sapien XT percutaneous heart valve. The stainless steel frame exhibits a high radial strength to ensure circularity after deployment and optimal hemodynamics. Its low frame height conforms well to the cardiac anatomy. The bovine pericardium leaflets are sutured to the frame. The polyester fabric serves as a buffer to prevent abrasion the leaflet, promotes a good anchorage and minimize paravalvular leak.

However, the percutaneous mitral valve deployment is still in its infancy. Although it has been restricted to frail and elderly patients, this is now being extended to less risky patients as this technique is highly effective and it is anticipated that this procedure may soon exceed the number of open surgical cases [19]. The risks associated with the patients' condition were stratified and thus, the pressure to treat a broader range of patients percutaneously is pushing the medical community to extend the indications. This exacerbates the issue of long-term biodurability of the devices and the prevention of adverse events that are due to or caused by the device. The adherence to the 3Bs' rule, biofunctionality, biodurability, and biocompatibility must be further enhanced to anticipate further developments and acceptability and open the door to making percutaneous valve replacements the primary treatment for valve disease. Whilst the technology and clinical applications of percutaneous aortic valve deployment has become

fully-fledged, there are still uncertainties concerning pulmonary valves while the mitral valve represents a new challenge.

The initial clinical successes of implantations performed by daredevil clinicians have opened the way for more patients who are not suitable for open surgery to be treated by minimally invasive means. The technique of percutaneous deployment of aortic and pulmonary heart valves has gained considerable maturation within a couple of decades and the treatment of the mitral valve by the same method is now at hand. Regrettably, the physicians pay more attention to the technique itself and to short term follow-ups. The medical literature is inundated with statistical data on the performance through a multiplicity of registries. The adverse events must be addressed as well and be analysed in term of technical weaknesses, either patient-and/or device-related. Our teams of scientists have been actively working closely with clinicians for several decades. The retrieval programs of vascular grafts and heart valves harvested at reoperation or autopsy were instrumental in contributing to the improvements of devices for open surgery [20-22]. Consequently, our teams became involved with cardiovascular devices for percutaneous surgery, initially stent-grafts. More recently, our research programs were extended to percutaneous heart valves.

Injuries at Crimping and Deployment that cannot be Repaired *In Vivo*

As clinicians are intending to treat a broader range of patients percutaneously, it is essential to continually reassess the performances of the devices.

The injuries caused to the bovine pericardium leaflets were documented by several teams worldwide. Zegdi and Amazhounne illustrated the traumatic leaflet injuries at the implantation of percutaneous aortic valves [23,24]. These injuries leading to collagen bundle fragmentation and disruption were the result of crimping and balloon expansion. The entire thickness of the valve leaflets was involved. The bovine pericardium as processed is not a living tissue and holds no healing capacity. The biological origin of the material cannot mask the feature of the material, single leather

For Khoffi and Heim, the degradation of the tissue was aggravated in small diameter valves (19 and 21 mm) with a loss of mechanical characteristics of up to 50% [25]. Coupling sophisticated morphological examination (scanning electron microscopy and second harmonic generation microscopy) and mechanical measurements, Alavi et al. were meritorious in focusing on crimping only [26]. Damages were observed on the flow surface with all crimping sizes and the deeper layers of the pericardium were affected more extensively in the 14F than in the 16F and 18F sizes.

In addition, the crimping itself impairs the pericardial leaflet structure. During crimping, according to de Buhr et al. a displacement of the stent on the catheter during the balloon inflation was observed with a high speed camera. Stents slipped distally on the balloon 13.8 mm while imprinting stent struts onto the pericardial tissues that penetrated deeply through the entire thickness [27]. In the meantime, it is important to be aware of the deformations of the stents during crimping and ballooning. Such deformations are likely to be aggravated *in vivo* (Figures 2 and 3) [28,29].

How to Improve the Durability of the Bioprostheses to make Open-Heart Surgery Obsolete

The design of the valves is of considerable importance in ensuring their innocuousness so that their durability will surpass the patient life expectancy. Abrasion of the leaflets represents a continuous risk of damage to the flow surface of the leaflets. This is why we proposed to insert a polyester fabric to prevent abrasion. However, we must select a thin and smooth calendered woven fabric to reduce the thickness (Figures 4 and 5) [5].

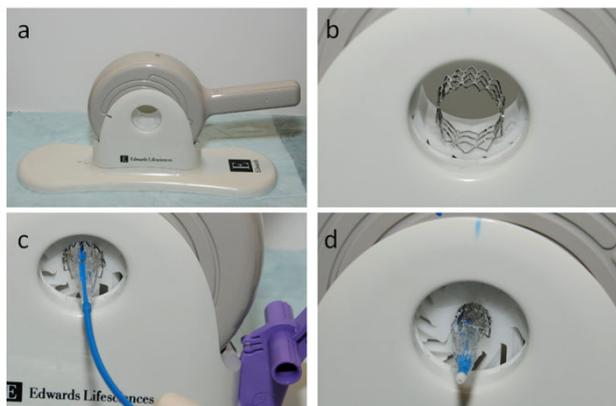


Figure 2: Disposable crimping tool holding a compression mechanism used to crimp a stent from an explanted valve Sapien XT. The stent was fitted over a balloon and was exposed to radial compression to permit its insertion within a sheath. After the crimping is completed, the mechanism is released and the stent fitted over with the balloon is pulled out.

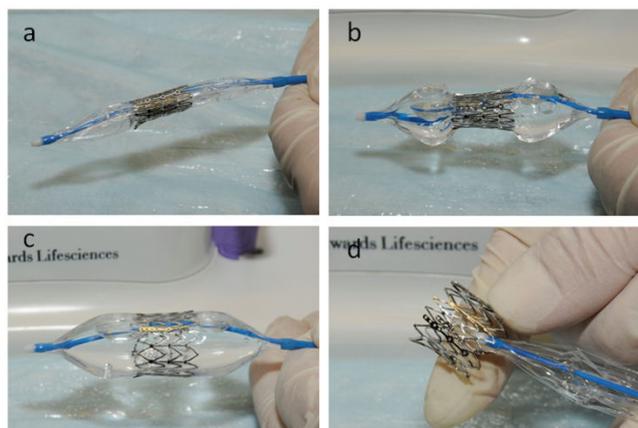


Figure 3: Expansion of the same stent with the inflating balloon. The expansion was associated with some deformation of the stent that eventually slipped distally. The use of the stent from an explanted device probably contributed to aggravate these observations.

Beside the issue of durability of bovine pericardium after crimping and expansion, the increased acute thrombogenicity must be examined in depth. This is why we have undertaken this series of *in vitro* testing regarding the platelet uptake [4]. The thrombi, generally exophytic but occasionally endophytic must be eliminated to prevent any calcification. The fibrinolytic mechanisms of the patient might be sufficient to eliminate the mural thrombi onto an intact flow surface in an aortic valve. A blood thinner is required in case of injured pericardium leaflets as in the case of any pulmonary valve or mitral valve. With the help of multicentre trials, a consensus which does not currently exist could in future be attained on this issue [30].

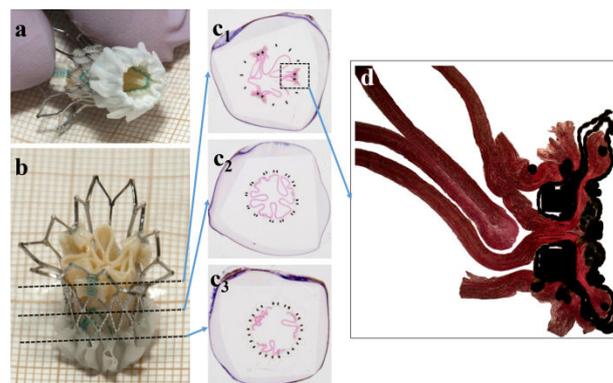


Figure 4: Crimped Sapien 3 percutaneous heart valve. The polyester fabric prevents paravalvular leak after deployment. The bovine pericardium leaflets are irregularly pleated over the length of the device. The leaflets are sutured to the frame in a meticulous way which may have a favorable impact on the potential longer term durability.

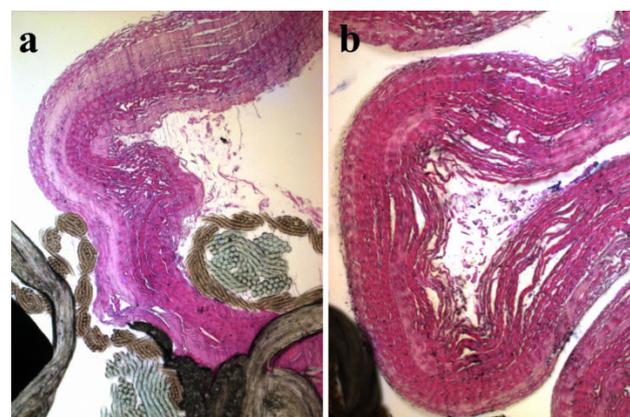


Figure 5: The structure of the leaflet at the site of suture is modified because of compression and pleating causing delamination and cavitation. These observations which are present at manufacture are aggravated with handling at deployment, more specifically during crimping and ballooning.

The pericardium leaflets are in no way living tissues. They are leathers that become adapted to the living environment. There is still a considerable gap between basic research and the clinical applications. Endothelialisation of the flow surfaces and utilization of induced human pluripotent stem cells (iPSCs) necessitate more research while

patients deserve immediate treatments [31]. Currently, the durability is mostly attained with preservation of the geometry of the valves with pericardium of young animals [32]. Hemodynamic deficits must be avoided. Porcine cusps might be better than bovine pericardium leaflets but the manufacture is more complex and they are more fragile [33]. In addition, aortic annulus deformations of percutaneous valves were observed both *in vitro* and *in vivo* [34]. The radial forces to inflate crimped valves are 30 to 40% higher than those crimped at room temperature [35].

The outstanding technical success of the percutaneous heart valve technology and its further developments will continue to extend the indications for treatment to more and more patients regardless of age. A reassessment of the concept cannot be ignored. As the brainstorming of myriads of physicians and engineers is still very active, it is very difficult and risky to favour any specific avenues of research. At this stage, bovine pericardium from young calves appears as a key-component for the devices. Donkey pericardium that shows the same structure but is much thinner might also be recommended [36]. Animals from the wild cannot be selected based upon the uncertainties about procurement and the absence sanitary controls and they will remain as laboratory curiosity. The search for the ideal stent is still debated: self-expandable *vs.* balloon deployable. Fabric cuffs can be incorporated, but the site still raises question marks. The selection of the sutures remains unanswered. Beside the multiplicity of try and see initiatives, an independent retrieval program appears as fully justified and necessary. Adverse events beside undisputable clinical successes are the fate of modern implantology. Any of them must be investigated to discriminate between those that are patient related, device related or technique related. In addition, the accessibility to the actual data of the public agencies must be improved [37]. A better balance between trade secrets from the company and public access to information must be reached.

We do believe that the young bovine pericardium will keep its pole position for the predictable future. Alternative tissues from farmed animals such as pigs might still be acceptable. The safety and regular supply are mandatory issues. Valves with polymer leaflets involve polyurethane (PU) and polyester. All the more recent PU polymers selected for percutaneous devices might display the same weaknesses as the devices of the early 1970s: thrombosis, calcification, degradation [38]. The valves with leaflets made of woven polyester fabrics show an interesting durability so long as the risk of fraying at their edges is kept under control [39]. However, the *in vivo* healing of polyester fabric is unpredictable with sequences of encapsulation, fibrinolysis, thrombotic accumulation and possibly embolization [40]. For these reasons, the polyester fabric will probably be history very soon. Leaflets manufactured with decellularised tissues have not demonstrated any superiority compared to bovine pericardium. The perspective of eliminating the cells is an interesting avenue but the collagen bundles might be partially degraded during the process. Is the banding of the collagen fibres well preserved? The decellularised tissue performance will need to be demonstrated more convincingly before they can reach clinical acceptability [41,42]. Finally, the hopes associated with tissue engineering represent the future. Despite intensive research worldwide, the results achieved to date are still not sufficient for a successful clinical implantation of tissue engineered valves [43,44].

Conclusion

The lifetime of the devices fitted with young bovine pericardium for percutaneous valve surgery will be prolonged for years thanks to the

attention paid to every step in the surgical procedure and in the manufacturing and deploying of the device. Our contribution regarding the analysis of crimping at implantation draws attention to the importance of handling of the devices with care. We consider that each part of the 3Bs rule must be reassessed continuously. New generations of devices are introduced regularly with particular emphasis on deployment and the possibility of repositionability, prevention of leak and good fitting. The importance of these features cannot be overlooked but more attention must also be paid to assembling the different materials, the design of the devices and the most appropriate handling at deployment [45,46].

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