

# Traumatic leaflet injury during the use of percutaneous valves: a comparative study of balloon- and self-expandable valved stents

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## Abstract

**OBJECTIVES:** No comparison of balloon- or self-expandable valved stents (VSs) regarding tissue injury (if any) has been reported yet. The objective was to evaluate the occurrence and compare the severity of traumatic injury to leaflets from balloon- or self-expandable VSs.

**METHODS:** Twelve homemade VSs were used for this experiment. These three-leaflet bovine pericardial bioprostheses had either a stainless steel (Group A) or a nitinol stent (Group B). After a 30-min period of compression (external diameter of VS reduced to 7 mm), the prostheses were deployed by balloon inflation (Group A) or by unsheathing (Group B). After H&E staining, pericardial leaflets were subsequently analyzed qualitatively and quantitatively for microscopic lesions. Non-crimped pericardial leaflets were used as a control group (Group C).

**RESULTS:** All deployed VSs had microscopic lesions evocating traumatic injury to pericardial leaflets. Transverse fractures and longitudinal cleavages were the two main lesions encountered. Transverse fractures (no. per field) were significantly more frequent in the VS in comparison with the control group: 5 (range: 0–13), 4 (range: 0–9) and 0 (range: 0–1) in Groups A, B and C, respectively ( $P < 0.001$ ). Cleavages (no. per field) were also more frequent with balloon-expandable VSs compared with self-expandable VSs [3 (range: 0–7) vs 1 (range: 0–8);  $P = 0.03$ ].

**CONCLUSIONS:** Traumatic injury to the pericardial leaflets does occur during crimping and deployment of balloon- or self-expandable VSs. Injury may be more severe with the balloon-expandable VSs. The impact of such an injury on prosthesis durability requires a further investigation.

**Keywords:** Pericardium • Leaflets • Percutaneous valves • Injury

## INTRODUCTION

Transcatheter aortic valve implantation (TAVI) has been shown to be feasible and effective in patients with severe aortic valve stenosis through either a retrograde transarterial or an antegrade transapical access [1, 2]. This new technology is currently under clinical investigation, and there is a wide consensus to restrict its use to high-risk surgical candidates [3].

Within a few years, the question of extending the indications of TAVI to medium- or low-surgical-risk patients will be asked. The answer to this question will certainly depend on valve durability. Up to now, medium-term results (e.g. 5-year results) have not been reported.

The procedural handling of percutaneous valves differs from that of surgically implanted bioprosthesis where crimping and balloon inflation of prostheses is not required. Transcatheter

implantation of valved stents (VSs) may be responsible for the traumatic injury to their leaflets that might secondarily alter prosthesis durability. Tissue dislocation, fractures of collagen bundles and areas of plasmatic insudation have been recently documented in the leaflets of four balloon-expandable Sapien-Edwards bioprostheses (Edwards Lifesciences, Irvine, CA, USA) shortly after their deployment [4]. To the best of our knowledge, no such reports exist with the Corevalve (Medtronic Inc., MN, USA), a self-expandable VS frequently used during TAVI. Tissue trauma (if any) might be less frequent in the latter since crushing of the pericardium during valve expansion does not occur as is the case with balloon-expandable VSs.

The purpose of the present experimental study was, therefore, to evaluate the occurrence and compare the severity of traumatic injury to leaflets from balloon- or self-expandable VSs.

## MATERIALS AND METHODS

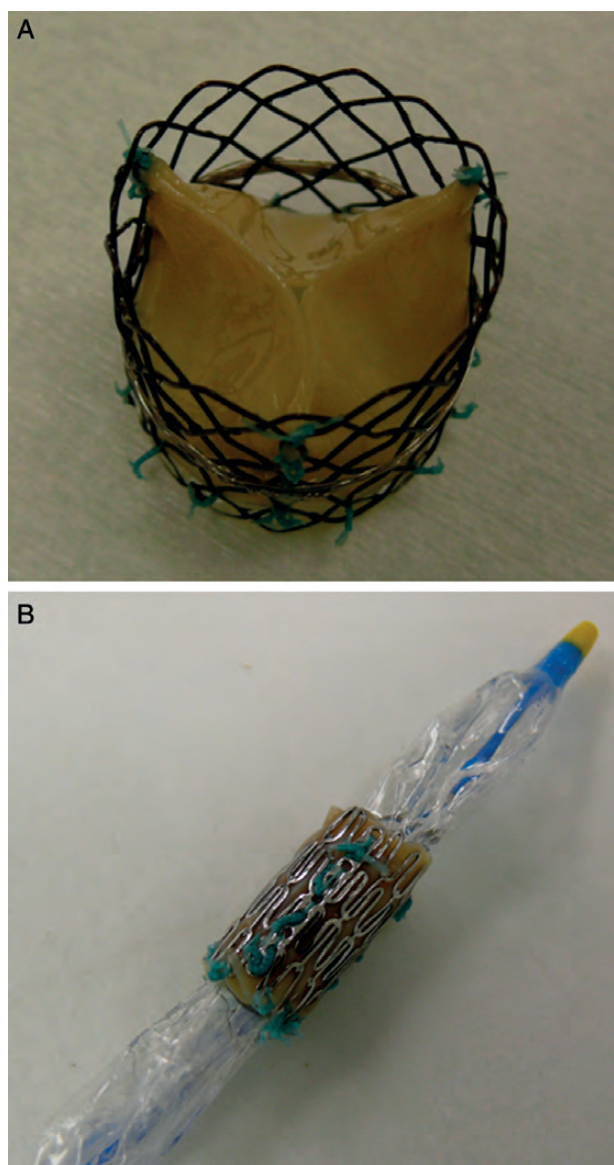
### Valved stents construction

Twelve VSs were used in this study. Each prosthesis consisted of three bovine pericardial leaflets mounted onto a metallic stent (Fig. 1).

A fresh bovine pericardium was obtained from a slaughterhouse. Fat was first removed and samples were immersed and stored in a 0.625% glutaraldehyde solution. Samples selected from the anterior part of the pericardium were used for valve construction.

Valve leaflets were designed with a rectangular shape (16-mm height and 26-mm length). All leaflets had a thickness ranging from 0.35 to 0.45 mm as determined with a Mitutoyo micrometer.

Two types of stent were used. The first was a self-expandable stent made of braided nitinol (Cormove, Ivry le Temple, France).



**Figure 1:** (A) A self-expandable valved stent consisting of three bovine pericardial leaflets sutured into a braided nitinol stent. (B) A view of a crimped balloon-expandable valved stent made of a stainless steel stent and three bovine pericardial leaflets.

The second was a stainless steel stent used in manufacturing of the balloon-expandable Sapien-Edwards bioprosthesis (Edwards Lifesciences). All these stents have been designed for construction of 23-mm VS.

Three rectangular pericardial leaflets were sutured onto each stent. Leaflets were directly attached to the inner side of the stents with interrupted 5/0 braided sutures (Ethicon, Issy-les-Moulineaux, France). No tissue skirt was incorporated into the prosthesis (Fig. 1).

After construction, the VSs were stored in a 0.625% glutaraldehyde solution until use.

### Experimental protocol

Three experimental groups were compared.

Group A consisted of six balloon-expandable VSs. They were slowly crimped onto a 23-mm balloon (Edwards Lifesciences) with a specifically designed crimper (Edwards Lifesciences) (Fig. 1). Crimped prostheses were regularly immersed in a saline solution to prevent valve desiccation. After 30 min, VSs were re-expanded by balloon inflation. Complete deployment was achieved within 3–4 s.

Group B consisted of six self-expandable 23-mm VSs. These prostheses were also slowly compressed (with the same crimper used in Group A) and introduced into a 21-Fr Teflon tube (to prevent spontaneous stent re-expansion). The compressed prostheses were regularly flushed with a saline solution. After 30 min of compression, VSs were unsheathed and allowed to freely re-expand.

After prostheses deployment, the leaflets were meticulously taken from the VSs and stored in a 0.625% glutaraldehyde solution until histological processing.

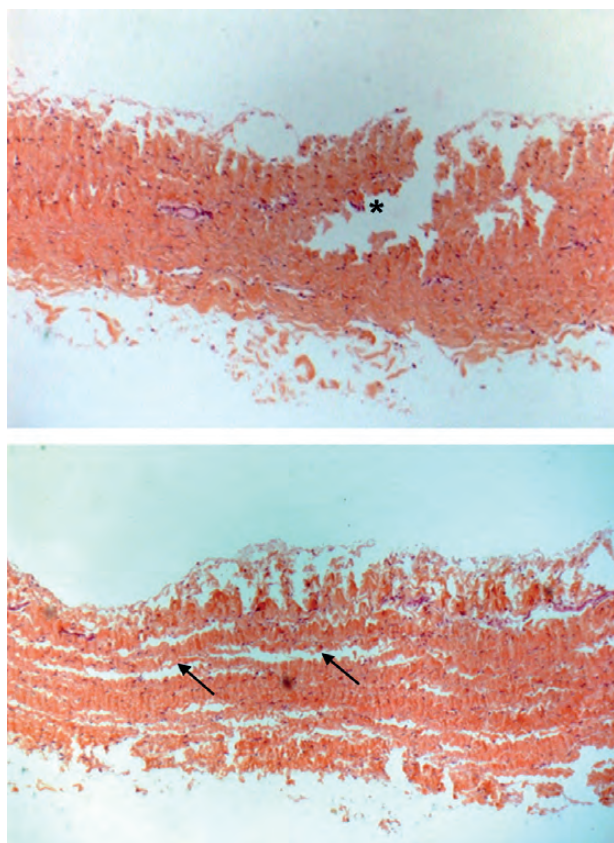
Group C (control group) included 18 pericardial leaflets randomly taken from the samples intended to be used for VS construction. These 'unmounted' leaflets were processed for histological analysis the same way as were the 'mounted' leaflets from Groups A and B.

### Histological analysis

After paraffin embedding, pericardial leaflets sections were cut at 5  $\mu$ m of thickness and stained with H&E. The samples were analyzed and digitalized pictures were obtained at  $\times 5$  and  $\times 20$  magnifications in three random microscopic fields for each leaflet at each magnification.

Transverse tissue fracture and longitudinal tissue cleavage were two basic lesions frequently found in the VS leaflets (Fig. 2). Transverse fractures usually originated from one surface of the pericardium and extended more or less deeply inside the leaflets. Longitudinal cleavages originated inside the pericardium and extended parallel to its long axis. For quantification, only significant lesions (i.e. of 'sufficient' size) were taken into account. Transverse fractures were arbitrarily considered as significant when their length exceeded 15% of the pericardium's thickness. Longitudinal cleavages were also considered as significant when their length exceeded 15% of the length of the pericardium (within the microscopic field). The number of fractures and cleavages per field was determined at  $\times 5$  magnification. Regarding fractures quantification, bias (limits of agreement), as determined by the Bland–Altman method, was 0.2 (–1.5; 1.9) and 0.3 (–1.6;





**Figure 2:** A typical aspect of transverse fracture (asterisks) and longitudinal cleavage of the bovine pericardium (arrow) (H&E staining;  $\times 5$  magnification) in a balloon-expandable valved stent.

2.2) for intra and interobserver variability, respectively. Regarding cleavages quantification, bias (limits of agreement) was  $-0.2$  ( $-1.1$ ;  $0.7$ ) and  $-0.1$  ( $-1$ ;  $0.8$ ) for intra and interobserver variability, respectively.

In a previous study, spaces between collagen bundles were found excessively increased in the pericardial leaflets from four deployed Sapien-Edwards bioprostheses [4]. These 'gaps' might reflect increased shearing stress on the tissue. This pathological aspect was quantitatively assessed by the disruption index. This index measures the contribution of the gaps between collagen bundles relatively to the pericardium thickness. For each leaflet, the disruption index was determined on two random fields at  $\times 20$  magnification. The distance between collagen bundles was measured along 10 equally interspaced lines perpendicular to the long axis of the sample. On each line, the measured distances were summed and normalized to the length of the line. For each field, the mean value of the 10 normalized distances was defined as the disruption index (expressed in percentages). Bias (limits of agreement) was  $1.3\%$  ( $-3.6\%$ ;  $6.2\%$ ) for intraobserver variability and  $-1.9\%$  ( $-6\%$ ;  $2.2\%$ ) for interobserver variability as determined by the Bland-Altman method.

### Statistical study

Results were expressed as median (range). Comparison between quantitative variables was performed with the Kruskal-Wallis or the Mann-Whitney's tests where appropriate. Significance was defined as a  $P$ -value  $< 0.05$ .

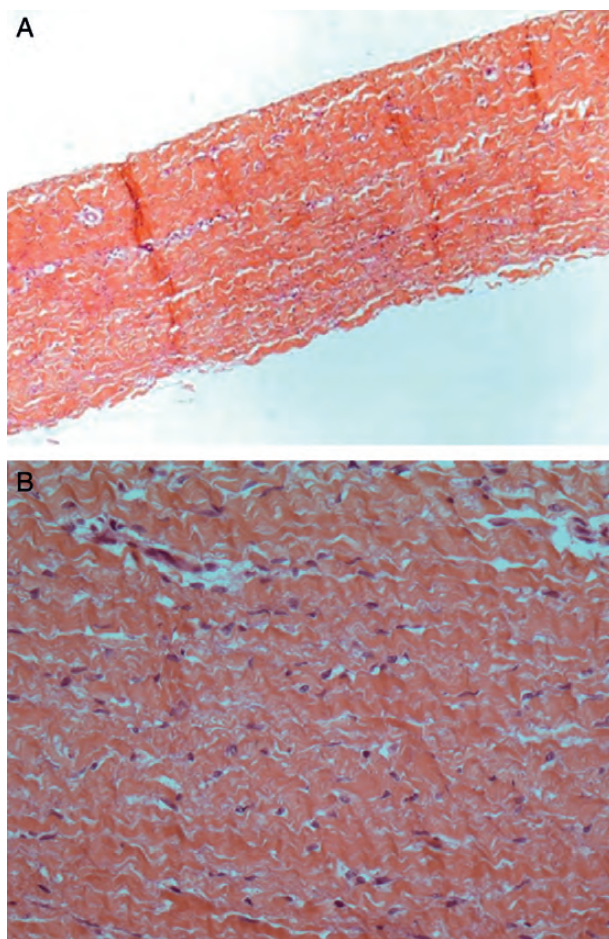
## RESULTS

Immediately after valve deployment, the leaflets had a crumpled aspect that rapidly disappeared after immersion in a saline solution. There was, however, no other macroscopic evidence of traumatic injury to the pericardial leaflets such as laceration, dehiscence or tears.

At microscopic analysis, the tissue appearance was well-preserved in the control group (Fig. 3). Wavy collagen bundles were clearly seen. Fractures of collagen fibres were occasionally noticed.

Conversely, microscopic lesions were found in all leaflets from the deployed VSs. These lesions mainly consisted in tissue fractures and longitudinal cleavages of the pericardium (Fig. 2). These lesions had a heterogeneous distribution. Areas of non- or mildly affected tissue were adjacent to areas of severely damaged tissue. The entire thickness of the leaflets might be involved. The severity of the lesions also differed among the leaflets within the same prosthesis.

Transverse fractures were rarely found in the control group and were always of small size. This was not the case for Groups A and B. In both of them, deep fractures could be seen (Fig. 4). The occurrence of significant fractures within the pericardium was (no. per field): 5 (range: 0–13), 4 (range: 0–9) and 0 (range: 0–1) in Groups A, B and C. The incidence of fractures was



**Figure 3:** A microscopic appearance of the control bovine pericardium. The architecture is well-preserved. Note the wavy aspect of the collagen bundles [H&E staining; (A)  $\times 5$  magnification and (B)  $\times 20$  magnification].



significantly higher between the VS groups and the control group (Group A vs C:  $P < 0.001$ ; Group B vs C:  $P < 0.001$ ). This was not the case between both types of VSs (Group A vs B;  $P = 0.75$ ).

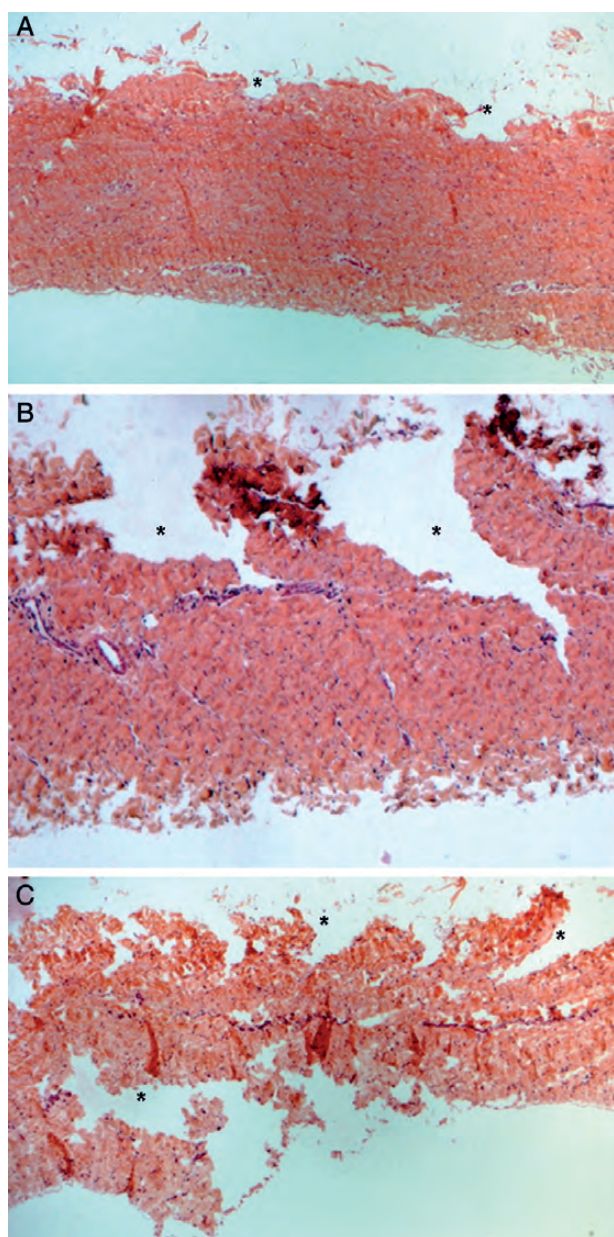
Longitudinal cleavages were found in the three groups of pericardial samples. In the control group, these cleavages were usually thin and short (Fig. 5). In the two other groups, however, important (large and long) cleavages were seen. In some cases, cleavages were so large that leaflets appeared split into two parts (Figs 5 and 6). The occurrence of significant cleavages within the pericardium was (no. per field): 3 (mean: 2.9–range: 0–7) in Group A, 1 (mean: 1.75–range: 0–8) in Group B and 1 (mean: 1–range: 0–5) in Group C. This incidence was

significantly higher in Group A compared with Group B ( $P = 0.03$ ) and Group C ( $P < 0.01$  in both cases).

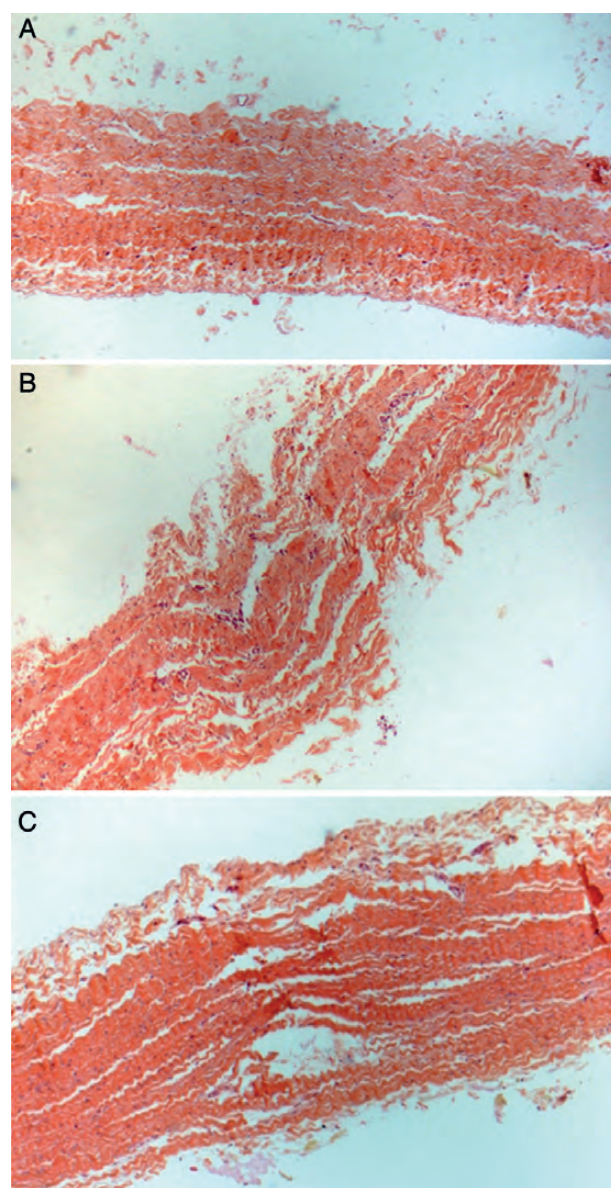
The disruption index was significantly higher in Groups A and B in comparison with the control group: 24.2 (range 14–61.3), 27.5 (range 12.1–53.6) and 16.4 (range 7.4–31), respectively ( $P < 0.001$ ). There was no statistically significant difference in the severity of tissue damage (as reflected by the disruption index) between the leaflets from the two different types of VSs ( $P = 0.87$ ).

## DISCUSSION

Traumatic injury to the leaflets of percutaneous valves has been considered as a potential concern regarding valve durability [5]. The present study has clearly demonstrated that such a traumatic

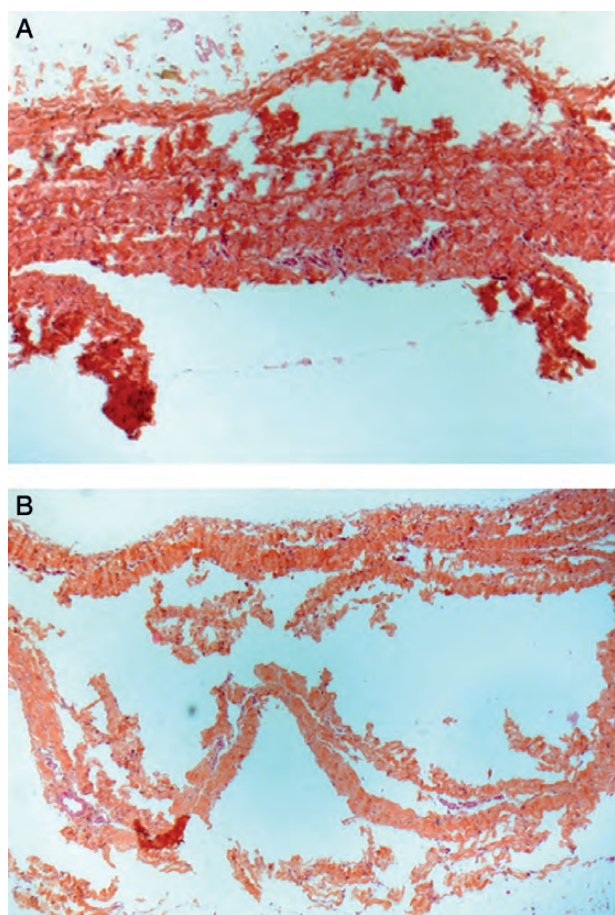


**Figure 4:** Transverse fracture in the bovine pericardium from a control (A), a self-expandable (B) and a balloon-expandable valved stent (C). Note the small (non-significant) aspect of the fracture in the control pericardium and the large (significant) one in both VSs (asterisks). (H&E staining;  $\times 5$  magnification.)



**Figure 5:** Longitudinal cleavages in the bovine pericardium from a control (A), a self-expandable (B) and a balloon-expandable valved stent (C). Note the thin aspect (when present) of the cleavages in the control pericardium and the large one in both VSs. (H&E staining;  $\times 5$  magnification.)





**Figure 6:** A microscopic view of a bovine pericardial leaflet from a self-expandable (A) and a balloon-expandable VSs (B). Both leaflets are split into two parts by large longitudinal cleavages (H&E staining;  $\times 5$  magnification).

injury occurs during crimping and deployment of balloon- or self-expandable VSs. Another important finding is that one type of lesions (longitudinal cleavage of the pericardium) was more frequently observed with the balloon-expandable VSs.

In the current clinical practice, two types of VSs are used during TAVI, the Sapien-Edwards (Edwards Lifesciences) and the Corevalve (Medtronic Inc.) prostheses. These two prostheses consist of the three-leaflet pericardial VSs that are necessarily compressed before implantation. Several thousands of patients benefited from TAVI since the first human case. Despite this, it seems that the preservation of the pericardium structural integrity after VS deployment has not been investigated in control studies yet.

In a previous study, we have reported that lesions (fracture of collagen bundles, tissue dislocation) were present in all the leaflets taken from four Sapien-Edwards prostheses [4]. These lesions were considered to be of traumatic injuries. In that study, however, the pericardium from the Sapien-Edwards prosthesis was compared with the pericardium obtained from a slaughterhouse. To confirm (or reject) the occurrence of a traumatic injury in the pericardial leaflets from a deployed VS, a bovine pericardium from a unique source was used in the present experimental study.

Undoubtedly, VS crimping and deployment are associated with tissue injury, as shown in the results section. The presence of tissue trauma was recently confirmed by another team [6]. De

Buhr *et al.* observed areas of broken collagen fibres within the bovine pericardial leaflets of deployed homemade balloon-expandable VS. Tissue injury may be induced during the crimping and/or the deployment step. Injury does occur during crimping since traumatic lesions were seen in both types of VSs. The fact that longitudinal cleavages were more frequent in the balloon-expandable VS suggests that balloon inflation, *per se*, may contribute to the injury. Crushing and shearing of the pericardium between the stent on one side and the balloon on the other are two potential mechanisms of this balloon-related tissue injury.

The durability of any implanted bioprosthesis is crucial for its indications. To date, the medium (5 years) and long-term (10–15 years) durability of percutaneous valves remain unknown. From a theoretical viewpoint, structural alterations of the pericardium may lead to an accelerated deterioration through several mechanisms. First, fractures of collagen bundles may create new sites for calcium deposition. Calcification has been associated with areas of collagen deterioration in some experimental studies [7]. Secondly, collagen network disorganization of the injured pericardium may also alter the tissue elasticity which may lead to increased stress on the leaflets. Increased stress on leaflets has been associated with valve calcification [7, 8]. Finally, traumatic injury may increase leaflet permeability to plasmatic proteins. Areas of plasma insudation have been described in deteriorated Ionescu-Shiley's bioprosthesis. These areas were associated with calcification [9]. It should be noted that such a lesion has recently been reported in an explanted Sapien-Edwards prosthesis [4].

In the present experiment, lesions seen in crimped and deployed VS were more pronounced than those observed in a previous study with the Sapien-Edwards prosthesis [4]. Such differences may be related to the magnitude of the compression (21 Fr instead of 22 Fr), the duration of the compression (30 min against usually 15–20 min), the selection of the pericardium (tissue elasticity was not used as a selection criterion) and the origin of the pericardium (physical properties are likely dependent on the bovine species). Despite those differences, however, traumatic lesions were also seen with the Sapien-Edwards bioprosthesis [4].

In the present study, furthermore, the deployment of the VSs was performed in an '*ex vivo*' experiment. It is likely that traumatic lesions to the leaflets might have been more severe in case of an '*in vivo*' study. In that case, increased balloon inflation is required to 'force' the resistance of the poorly compliant native aortic valve or annulus. Leaflet laceration by calcific excrescences originating from the ventricular side of the aortic leaflets may be another mechanism of tissue injury during valve deployment.

We did not study the behaviour of porcine pericardium subjected to stent compression. This is the subject of an ongoing study. Although crimping might be deleterious to the porcine pericardium (acute compressive stress), the results of our study should not be extrapolated to the Corevalve prosthesis.

Because of the potential impact of tissue injury on long-term valve durability, efforts to understand the underlying mechanisms should be made. A better comprehension of this phenomenon might lead to an effective preventive strategy. In the meantime, one should be very cautious in extending the indications of TAVI to lower surgical risk patients.

In conclusion, traumatic injury to pericardial leaflets did occur during crimping and deployment of balloon- or self-expandable VSs. Injury might be more severe with balloon-expandable VSs.

The impact of such an injury on prosthesis durability requires a further investigation.

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**Conflict of interest:** Rachid Zegdi is a stockowner of Cormove, a company that is developing a new percutaneous valve.

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## EDITORIAL COMMENT

# Pericardial traumatic injury in transcatheter aortic valve implantation

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**Keywords:** Pathology • Transcatheter aortic valve implantation • Pericardium • Aortic stenosis • Valve disease

Transcatheter aortic valve implantation (TAVI) is a very promising new treatment for native aortic stenosis or failed bioprostheses [1].

Glutaraldehyde xenograft tissue is employed because of its pliability for folding during implantation and minimizing its size in order to reach its final position in the aortic root. In the CoreValve® system, the stent is self-expanding, whereas in the Edwards Sapien, the valve has to be dilated by balloon inflation to approximate the stent to the aortic annulus without suturing, so as to prevent escape of the prosthesis and paravalvular leakage. In the latter procedure the pericardium is crushed against the stent.

Since the operation is relatively easily accomplished with early success, the question arises of whether it might also be

indicated in low-risk patients, thus avoiding sternotomy, general anaesthesia, cardio-pulmonary bypass and cardiac arrest.

However, in contrast to the traditional surgical implant, TAVI requires cusp crimping and, in the case of the Edwards Sapien, balloon inflation. Both manoeuvres may be responsible for tissue injury. Previous observations by Zegdi *et al.* have shown evidence of cusp injury following percutaneous aortic valve deployment of the Edwards Sapien [2]. To confirm these preliminary findings, the same group made an experimental study, comparing the severity of traumatic cusp injury in home-made balloon- vs self-expanding valved stents (VS); a non-crimped pericardium was used as a control [3].