

# Pathology of Transcatheter Valve Therapy

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**Objectives** This study sought to report on the pathology of transcatheter aortic valves explanted at early and late time points after transcatheter aortic valve implantation.

**Background** Information on pathological findings following transcatheter aortic valve implantation is scarce, particularly late after transcatheter aortic valve implantation.

**Methods** This study included 20 patients (13 men, median age 80 years [interquartile range: 72 to 84] years) with previous transcatheter aortic valve implantation with a valve explanted at autopsy (n = 17) or surgery (n = 3) up to 30 months after implantation (10 transapical and 10 transfemoral procedures).

**Results** Structural valve degeneration was not seen, although fibrous tissue ingrowth was observed at later time points with minimal effects on cusp mobility in 1 case. Minor alterations in valve configuration or placement were observed in up to 50% of cases, but they were not accompanied by substantial changes in valve function or reliably associated with chest compressions. Vascular or myocardial injury was common, especially within 30 days of transcatheter aortic valve implantation (about 69%), with the latter associated with left coronary ostial occlusion by calcified native aortic valve tissue in 2 cases. Mild to severe myocardial amyloidosis was present in nearly 33% of cases and likely played a role in the poor outcome of 3 patients. Endocarditis, migration of the valve, and embolization during the procedure led to surgical valve removal.

**Conclusions** Structural degeneration was not seen and minor alterations of valve configuration or placement did not affect valve function and were not reliably caused by chest compressions. Vascular or myocardial injury is very common early after transcatheter aortic valve implantation and myocardial amyloidosis represents a relatively frequent potentially significant comorbid condition.  
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Transcatheter aortic valve implantation (TAVI) has been established as an effective treatment for patients with severe aortic valve stenosis who are not suitable for open-heart surgery (1) or as an alternative treatment to open-heart surgery in high-risk patients (2).

Mortality occurring <30 days after TAVI reflects mostly procedure-related mortality (3,4), whereas later mortality occurring from 30 days to 1 year after TAVI is mostly caused by either progression of heart failure or the natural course of comorbid conditions (3,5,6). Procedure-related mortality decreases with increasing operator and center experience (3). Later mortality, by contrast, decreases by performing the procedure in lower-risk populations with fewer comorbid conditions (5).

Very little information is currently available on the pathological findings following TAVI (7). Post-mortem studies in humans consist of 2 case reports (8,9) and a single series of 7 post-mortem cases (10). These prior reports primarily demonstrate findings early after valve implantation with only 1 reported case with late follow-up at 425 days (9). In this report, we describe pathological findings in 20 valves explanted at early, intermediate, and late time points following TAVI.

## Methods

**Patients.** All patients with prior TAVI who died and underwent a post-mortem examination or who had a valve surgically explanted at our institution were reviewed. Written permission for pathological examination was obtained in each case.

**Valves and procedural approach.** The Cribier-Edwards valve (Edwards Lifesciences, Irvine, California), the prototypic balloon-expandable prosthetic implant (11), is constructed of a stainless steel frame with attached equine pericardial leaflets and a fabric-sealing cuff. This was subsequently replaced with the Edwards Sapien valve (Edwards Lifesciences) with bovine pericardial leaflets and a longer fabric sealing cuff (12). The prosthetic valve is crimped onto a balloon catheter and introduced through a large sheath in the femoral artery (transarterial) (13) or directly through the left ventricular apex using an intercostal incision (transapical) (14). The prosthesis is placed inside the diseased native aortic valve and the balloon expanded, displacing the native cusps.

**Pathological analysis.** Entire hearts (in case of an autopsy) or the explanted transcatheter valves (in case of surgical removal) were fixed in 10% buffered formalin and examined by a cardiovascular pathologist (M.F.A.). Autopsy hearts were examined by a stepwise approach to identify and evaluate structural and nonstructural changes in the prosthesis, changes associated with the prosthesis or the procedure, and other cardiac or vascular findings, in accordance with accepted approaches for traditional prosthetic valves

(15) or recommendations for transcatheter valves (16). Surgically excised transcatheter valves were examined in a similar fashion.

For microscopic analysis, paraffin-embedded myocardium was sectioned at 4  $\mu\text{m}$  and stained with hematoxylin and eosin, Masson trichrome (to identify fibrosis) (Ventana Medical Systems, Tucson, Arizona), Prussian blue (to identify iron) (Ventana Medical Systems), and Congo red (Ventana Medical Systems) and sulfated Alcian blue (to identify amyloid) (Acros Organics, Geel, Belgium, Fisher Scientific, Ottawa, Ontario, Canada). In selected patients with relevant rhythm disturbances and/or unexplained death, the region of the atrioventricular node and the bundle branches within the interventricular septum were microscopically examined. Valve cusps, when examined, were sectioned at 4  $\mu\text{m}$  and stained with hematoxylin and eosin, Movat pentachrome (Fisher Scientific; Sigma-Aldrich, Oakville, Ontario, Canada; Acros Organics), and microbiological stains, if appropriate.

**Statistics.** Statistical analyses were done using R Statistical Computing for Mac OS (The R Foundation for Statistical Computing, Vienna, Austria). Data are presented as medians and interquartile ranges, unless otherwise indicated. For each valve and cardiac findings groups (structural and nonstructural changes/dysfunction; prosthesis/procedure-related changes; and other cardiac changes), group comparison was performed using Kruskal-Willis test. Significance was taken at  $p = 0.05$  level for all analyses.

## Abbreviations and Acronyms

**CPR** = cardiopulmonary resuscitation

**TAVI** = transcatheter aortic valve implantation

## Results

**Patient characteristics.** A total of 17 valves were examined at autopsy (median age: 78 years, 10 men), including 6 Cribier-Edwards valves and 11 Edwards Sapien valves. Access for implantation was nearly equivalent, either apical ( $n = 9$ ) or transarterial ( $n = 8$ ), for the entire group. Three valves were removed from patients at the time of open-heart surgery (median age: 82 years, all men).

**Time after implantation and cause of death.** Of the 17 autopsy patients, median post-procedural survival was 5 days (interquartile range: 2 to 25 days, range: 0 to 943 days). Patients were stratified into 3 temporal categories (16,17): immediate-early (<7 days); intermediate (7 to 29 days); and late ( $\geq 30$  days). Death occurred in 9 patients <7 days after implantation and was due to: cardiac causes (heart failure, major arrhythmia, rupture of adjacent structures, left main occlusion) in 5; cerebrovascular accident in 1; major bleeding in 2; and sepsis in 1. In the intermediate group, cause of death was cardiac in 3 and sepsis in 1. After 30 days, 1 patient died because of an intracerebral bleed (on warfarin for atrial fibrillation) and 3 because of progressive heart and

**Table 1. Patient Characteristics and Pathological Findings of Autopsy Cases**

| Age (Yrs)    | Time to Death After Implantation | Pathological Findings  | Access Route |
|--------------|----------------------------------|--|--------------|
| <b>Men</b>   |                                  |  |              |
| 78           | 3 days                           | Recent myocardial injury<br>Recent brain injury                | Apical       |
| 87           | 5 days                           | Coronary ostial occlusion<br>Recent myocardial injury          | Arterial     |
| 57           | 5 days                           | Heavily calcified bicuspid aortic valve<br>Recent brain injury | Apical       |
| 65           | 5 days                           | Cuspal thrombosis<br>Recent myocardial injury                  | Arterial     |
| 80           | 6 days                           | Recent myocardial injury<br>Recent brain injury                | Apical       |
| 76           | 2 weeks                          | Amyloidosis  | Arterial     |
| 77           | 28 days                          | Possible hypertrophic cardiomyopathy                           | Apical       |
| 73           | 1 month                          |  | Arterial     |
| 89           | 20 months                        | Fibrous tissue ingrowth<br>Amyloidosis                         | Arterial     |
| 85           | 24 months                        | Fibrous tissue ingrowth<br>Recent brain injury                 | Arterial     |
| <b>Women</b> |                                  |  |              |
| 84           | <1 day                           | Vascular injury<br>Recent myocardial injury                    | Apical       |
| 58           | <1 day                           | Vascular injury<br>Recent myocardial injury                    | Apical       |
| 81           | <1 day                           | Partial coronary ostial occlusion<br>Recent myocardial injury  | Apical       |
| 80           | 5 days                           | Recent myocardial injury<br>Amyloidosis                        | Apical       |
| 71           | 10 days                          | Recent myocardial injury<br>Ischemic bowel                     | Apical       |
| 81           | 6 weeks                          | Amyloidosis  | Apical       |
| 99           | 30 months                        | Fibrous tissue ingrowth<br>Amyloidosis                         | Arterial     |

16 cases showed some degree of coronary artery disease (mild to severe); 13 cases had mitral annular calcification; all 17 cases showed myocardial hypertrophy.

renal failure. All 3 surgically excised transcatheter valves were removed more than 30 days after implantation, ranging from 108 to 336 days after implantation (Table 1).

**Structural and nonstructural prosthesis changes.** The most common structural change observed was a less than round configuration that ranged from slightly oval to almost D-shaped (Figs. 1 and 2). This finding occurred across all temporal categories and, in some instances, was accompanied by an apparent malalignment or malapposition of valve cusps (cuspal tautness, laxity, and/or poor coaptation). There were no macroscopic signs of cuspal degeneration (calcifications or cuspal tears), or any evidence of fracture or disruption of the metallic stent in any valve.

Fibrous tissue ingrowth was found in valves from patients dying late after TAVI (Fig. 3) and ranged from minimal to extensive where a thin layer of filmy fibrous tissue covered approximately 80% to 90% of the inner aspect of the

metallic stent (Fig. 4). Localized fibrous tissue ingrowth onto the basal aspects of the cusps mildly reduced cuspal mobility in 1 case (Fig. 1).

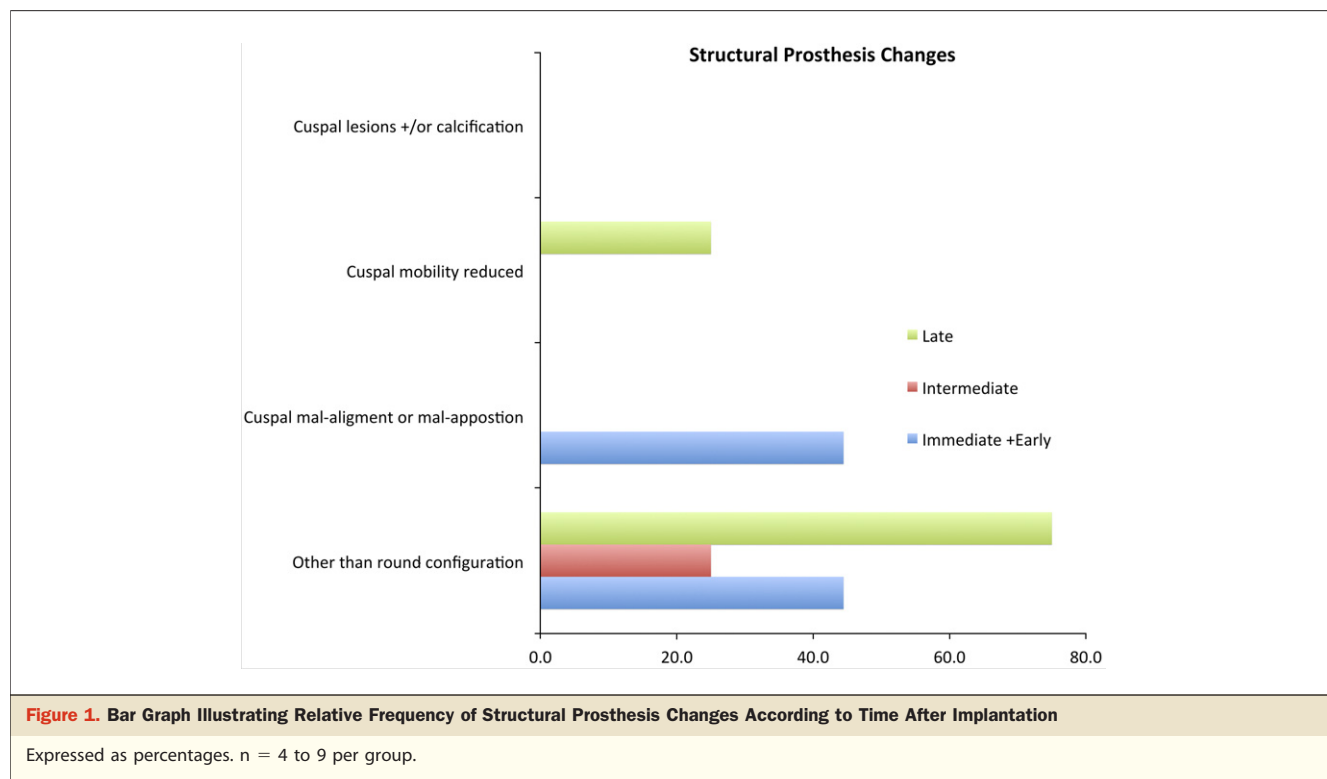
A probe-patent paravalvular defect was another relatively frequent observation that spanned all temporal categories (Fig. 3). Minor degrees of prosthesis malposition, using relation of the inferior aspect of the prosthesis stent frame to the insertion of the anterior leaflet of the mitral valve as a guide, were also observed in several cases.

Small amounts of recent thrombotic material on the ventricular and aortic aspects of the cusps (preferentially near the commissural regions) and metallic stent were found in 1 case in the immediate-early group. Histologically, the thrombotic material was composed largely of fibrin and platelets. Notably, echocardiography at the time of valve implantation suggested thrombus on the guidewire and possibly on the valve despite heparinization. There was no evidence of thromboembolism at the time of autopsy, however. Vegetations were not seen in any of the prostheses from cases examined at autopsy.

**Functional consequences of structural and nonstructural prosthesis changes.** Most patients demonstrated paravalvular aortic regurgitation, as assessed by echocardiography, ranging from trivial to moderate in severity. Structural and nonstructural prosthesis changes do not readily explain the paravalvular regurgitation observed. Transvalvular aortic regurgitation was not seen in the valve with fibrous tissue ingrowth that mildly reduced cuspal mobility. Based on cases with well-documented use of chest compressions during cardiopulmonary resuscitation (CPR) (n = 8), an equal number of cases with chest compressions were found to be associated with altered valve shape (n = 4) as compared to those that were not (n = 4). However, dramatic changes in shape that were accompanied by tautness of 1 valve cusp and laxity of others (Fig. 2B) did not demonstrate significant alterations in valve function during life.

**Prosthesis- or procedure-associated changes.** Most of these findings occurred primarily in immediate-early or intermediate periods after implantation with a more frequent occurrence in the immediate-early time frame (Fig. 5) (p = 0.03). Myocardial injury in the form of contraction band change in isolated or clusters of cardiac myocytes or areas of coagulative necrosis of myocardium was observed in more than 50% of all cases with the greatest frequency of occurrence seen in patients dying in the immediate-early period (Fig. 5). In select cases, acute injury of the conducting myocardium, especially the left bundle branch, was observed with evidence that both ischemic and direct traumatic injury played a role. Most likely, any injuries observed arose from the valve or delivery system rather than from the guidewire.

Sections of healing transapical access sites showed evidence of injured myocytes, accumulation of mesenchymal



cellular elements, hemorrhage, and small amounts of fibrous connective tissue deposition.

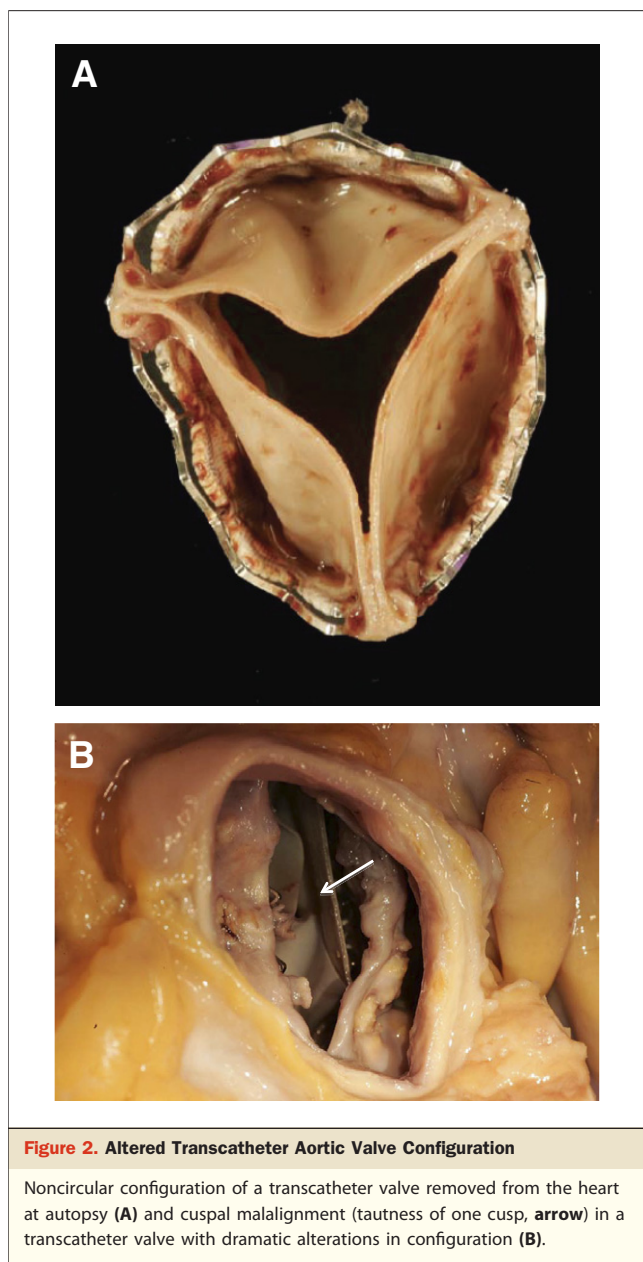
Apparent obstruction of coronary ostia was observed relatively frequently at autopsy examination, providing an explanation for some of the myocardial injury observed (Fig. 5). The most severe obstruction was observed in 2 cases in which a calcified and thickened native aortic valve cusp caused complete or near complete obstruction of the left coronary ostium. This was accompanied by hypotension and showed significant ischemic myocardial injury in both. The distance from the aortic annulus to the left coronary ostium was relatively short in both patients: 8.5 and 9.5 mm, respectively. The left sinuses of Valsalva were of normal size and not particularly shallow.

Procedural-related injuries to vascular or other cardiac structures were seen in a small number of cases (Fig. 5) that when present resulted in catastrophic effects and rapidly led to very poor outcomes. Traumatic disruption of the annular region of the aorta occurred in 1 patient in whom the smallest available prosthesis (23-mm diameter) was significantly larger than the relatively small (18 mm) and heavily calcified annulus. In a second patient with severe mitral annular calcification and substantially reduced leaflet mobility, a 2-cm tear involving the basal aspects of the anterior mitral leaflet and adjacent outflow tract (Fig. 6) was created during the procedure that resulted in communication between the left ventricle and atrium and hemodynamic collapse. Transapical access was associated with massive

bleeding followed by death due to multiorgan failure at day 5 in another patient.

**Other cardiac and vascular findings.** All patients had evidence of increased cardiac mass or hypertrophy. Many patients also had coronary atherosclerosis and its manifestations, including healed myocardial infarction and procedures such as coronary artery bypass surgery and/or percutaneous coronary intervention. Mitral annular calcification was also a common finding whose severity potentially played a role in some of the deleterious outcomes described previously. Myocardial amyloidosis was present in nearly one-third of all autopsy cases (5 cases, age 60 to 99 years) and ranged in severity from relatively mild to extensive and severe. Less severe involvement by amyloid was likely an incidental finding in 2 patients, but where it was severe, it may have contributed to death due to progressive heart failure leading to death at 40, 608, and 943 days after surgery.

**Findings in surgically excised transcatheter valves.** Reasons for surgical valve explantation were: embolization at the time of the procedure with the valve deployment in the aortic arch and definitive surgical open-heart aortic valve replacement with explantation of the embolized valve (at day 108); low implantation with gradual migration to the left ventricular outflow tract resulting in severe aortic regurgitation (at day 109); and endocarditis (at 336 days). In the latter case, the patient developed *Streptococcus angiosus* endocarditis of mitral and transcatheter aortic valves 6



weeks after a dental procedure that took place without endocarditis prophylaxis. The endocarditis spread to the mitral valve at the contact point of the aortic valve prosthesis with the anterior mitral leaflet leading to a perforation and regurgitation.

## Discussion

As a relatively new interventional procedure, detailed pathological examination of autopsy or surgical material from patients undergoing transcatheter implantation is critical to the ongoing evolution and improvement of this approach to treatment of aortic valve disease. Results of the present investigation provide important insights into the changes in

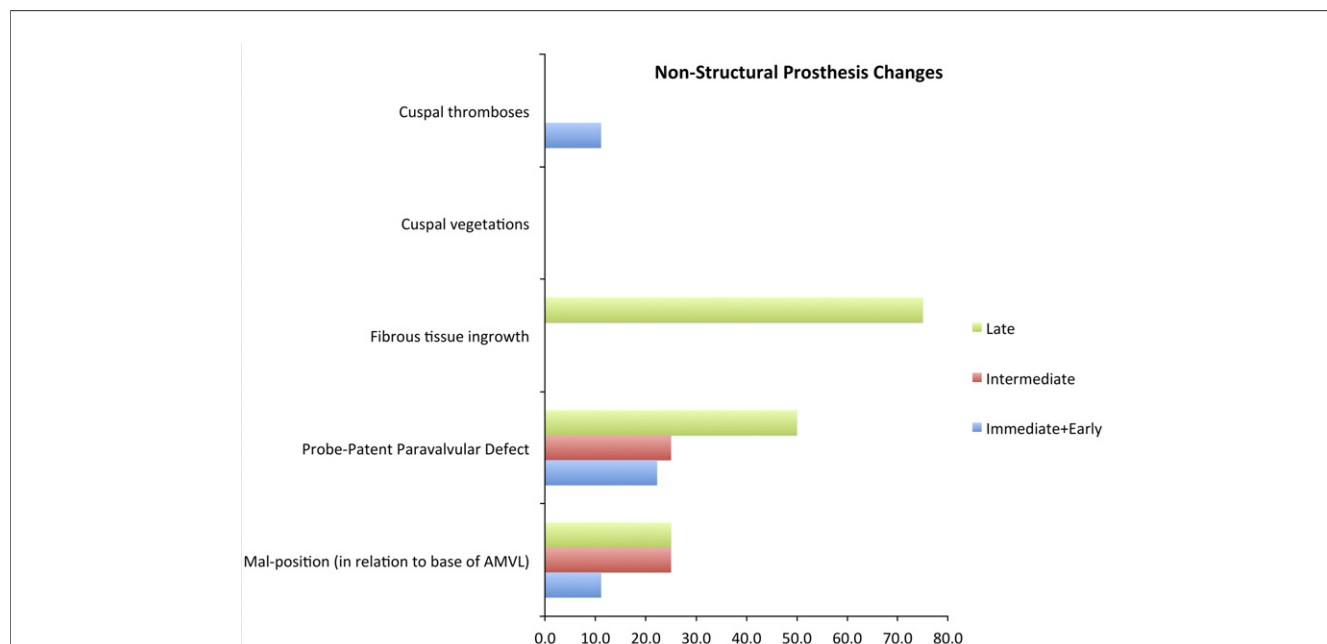
the transcatheter valves, mechanisms, and functional consequences of changes observed in the prostheses; emphasize key pathologies related to the transcatheter valve implantation procedure; and serve to highlight the potential significance of comorbidities in this patient population.

**Structural and nonstructural prosthesis changes.** Current surgical bioprostheses are relatively durable, although structural degeneration and failure can be anticipated to occur 5 to 20 years after implantation (18,19) with minimal histological degeneration seen up to 6 years after implantation (20). In surgical bioprostheses, the major cause of failure is related to calcification and tears of valve cusps, resulting in regurgitation or stenosis (15,21). It is reassuring that we did not observe significant structural valve failure in any case, even up to 943 days after implantation. Variable degrees of fibrous tissue ingrowth were observed late after implantation with some localized involvement of valve cusps resulting in a mild reduction in cuspal mobility but had no impact on measurable valve function. Given its well-recognized occurrence in surgical bioprosthesis (15), it is highly likely that more extensive fibrous tissue ingrowth will occur over time in some prostheses and lead to prosthesis dysfunction, which most likely can be treated by valve-in-valve implantation (22).

A less than round configuration of the stent frame was a relatively common observation, and the degree of noncircular configuration varied substantially. We cannot speculate on the reason for stent eccentricity, except for CPR with chest compressions as a possible explanation in patients dying after transcatheter valve implantation. However, a consistent and significant relationship between a noncircular configuration of the stent frame and CPR with chest compressions was not observed. This does not rule out the possibility that CPR with chest compressions may cause deformation in selected patients. The finding of deformed stent frames in this post-mortem study stands in contrast to our finding on computed tomography scans, on which circular stents were found, 3 years or more after transcatheter valve implantation (23). Chest compressions during CPR might explain this discrepancy in part but only in selected cases. Whether such deformed stent frames, even when mild, increase shear stress, thereby accelerating structural valve degeneration needs further investigation (24,25).

Thrombosis and thromboembolic complications occur less often in association with bioprostheses as compared to mechanical valves (26). Thrombus was uncommon in our series, with significant thrombus evident in only 1 patient in whom intraprocedural heparinization may have been subtherapeutic. Nevertheless, post-procedural thromboembolic stroke remains a concern, and most groups use long-term aspirin and clopidogrel for 1 to 6 months (27). The ideal antithrombotic regimen is yet to be determined (28).

Surgical bioprostheses are said to be associated with a 4% 10-year risk for endocarditis (29). Mechanical valves are most



**Figure 3. Bar Graph Illustrating Relative Frequency of Nonstructural Prosthesis Changes According to Time After Implantation**

Expressed as percentages. n = 4 to 9 per group. AMVL = anterior mitral valve leaflet.

often associated with localization of infection at the sewing ring, whereas infection of bioprosthetic valves is more often localized on the valve cusps (15). Infection of our single transcatheter valve was rather diffuse, involving the sewing skirt as well as the valve cusps and was accompanied by infection and perforation of the mitral leaflet (30). Piazza et al. (31) reported a similar case in a low implanted CoreValve prosthesis (Medtronic, Inc., Minneapolis, Minnesota).



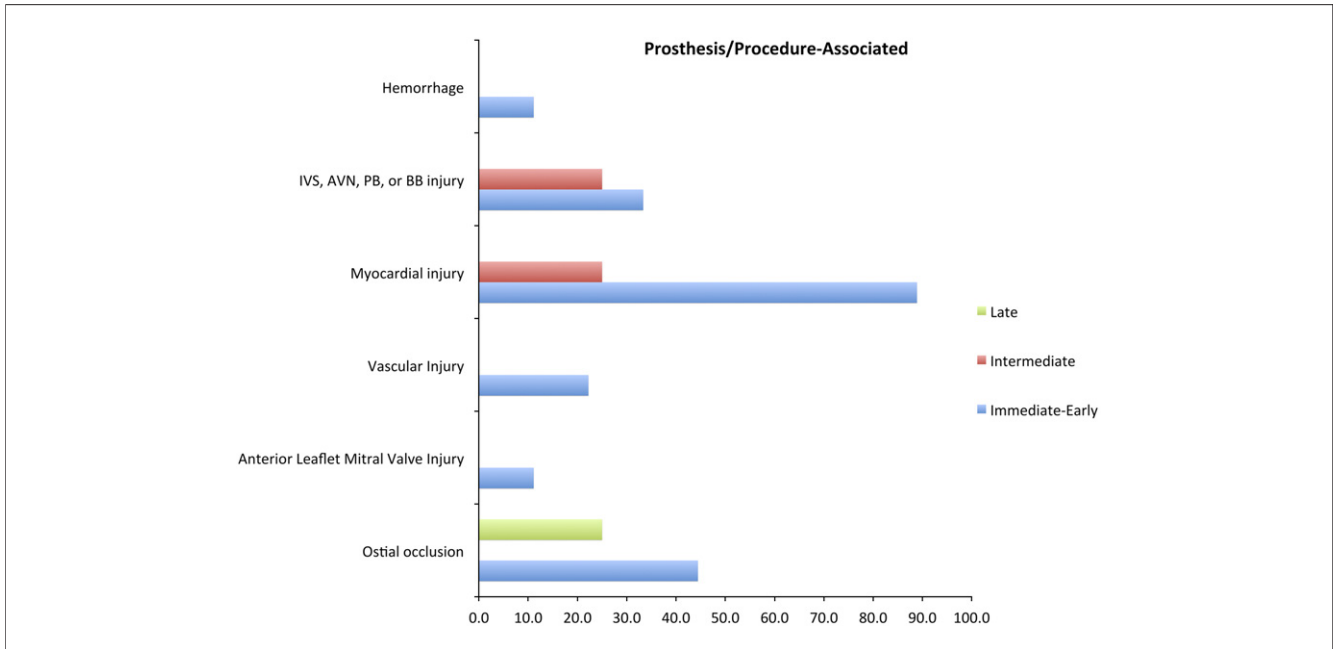
**Figure 4. Fibrous Tissue Ingrowth**

Photograph showing fibrous tissue ingrowth on the stent frame of a transcatheter valve (arrow).

**Functional consequence of prosthesis changes.** Mild to moderate paravalvular aortic regurgitation after TAVI is common, as was observed in patients in our study, although the clinical relevance of this degree of paravalvular regurgitation is uncertain (32–34). Despite a significantly higher incidence of trivial to moderate paravalvular leaks in patients after transcatheter valve implantation as compared to surgical patients, transcatheter valve patients have significantly better hemodynamics and improvement of left ventricular function (35–37). Whether paravalvular leaks after TAVI result in (clinically relevant) hemolysis (as described from surgical collectives (38)) needs further investigation.

Of interest is the finding that the presence of a noncircular shape of the stent frame, mild degrees of malalignment or malposition of the transcatheter valve, or presence of a probe patent paravalvular defect had no significant or consistent association with severity of transvalvular or paravalvular aortic regurgitation during life. Thus, mild alterations in configuration or placement of transcatheter prosthetic aortic valves, as observed at autopsy, do not appear to adversely affect function.

**Prosthesis- and procedure-associated findings.** Recent myocardial injury was a relatively frequent observation in our series of patients, especially in those dying in the immediate-early time period after implantation. Left coronary ostial obstruction was likely causative in 2 patients and was associated with low origins of the left coronary artery and bulky, calcified native cusps in both



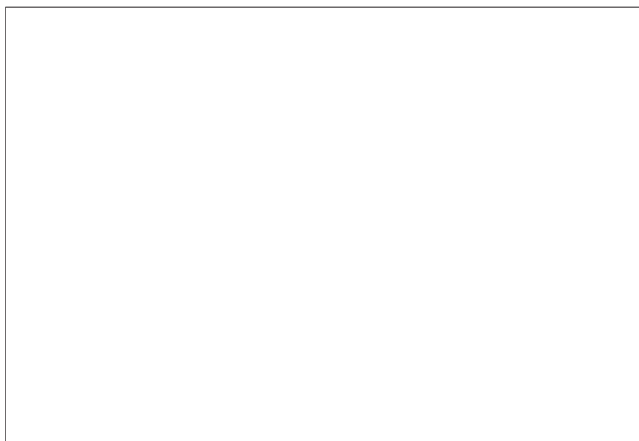
**Figure 5. Bar Graph Illustrating Relative Frequency of Procedure-Associated Changes According to Time After Implantation**

Expressed as percentages. n = 4 to 9 per group. AVN = atrioventricular node; BB = bundle branch; IVS = interventricular septum; PB = penetrating bundle.

cases (Fig. 7). Another known risk factor for coronary ostial obstruction is a narrow aortic root with shallow aortic sinuses (39). This complication has been described in 0.6% of cases in a recent large registry (27), suggesting that multimodality screening (40) may be important. Obstruction of coronary arteries can be predicted during balloon valvuloplasty with aortography during balloon inflation. If coronary obstruction occurs during implantation, early clinical signs include hypotension and severe hypokinesis on echocardiography (41). Management in-

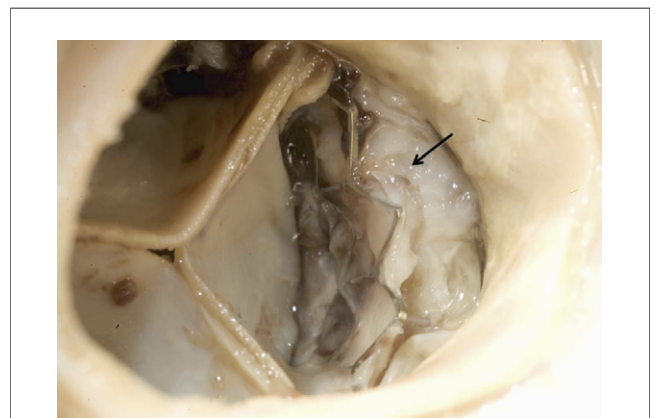
cludes prompt cardiopulmonary support, coronary angiography, and, in most cases, urgent coronary revascularization (39,42,43).

New onset of heart block can occur following transcatheter valve implantation. The incidence of heart block is reportedly lower with the balloon-expandable Edwards valve, used in this series, as compared to the self-expanding CoreValve (3,27,44). Based on findings in select cases where the conduction system was examined, it appears that a combination of direct traumatic effects to the bundle branch



**Figure 6. Mitral Valve Injury With Left Ventricle and Left Atrial Communication**

Defect (arrow) in the anterior leaflet of a mitral valve with severe calcification of its annulus (double arrow) that led to a communication between the left ventricle and the left atrium.



**Figure 7. Left Coronary Ostial Obstruction**

Photograph showing a bulky, calcified native valve cusp filling the sinus region of the aorta (arrow) to cause obstruction of the left coronary ostium.

system and ischemic injury occurring because of pressure-induced alterations of flow in coronary septal arteries in the interventricular septum are potential contributing factors.

**Other cardiac and vascular findings.** One accompanying finding that warrants special mention is myocardial amyloidosis, which occurred in nearly one-third of all cases studied. Senile systemic amyloidosis is very common in elderly people, reportedly present in 25% of individuals over the age of 80 years, and often goes unrecognized (45). Whereas patients with cardiac amyloidosis can successfully undergo surgical procedures, operative and post-operative problems associated with anesthesia are well described (46-48). As such, recognition of the possible presence of the condition and involvement of anesthetists familiar with cardiac anesthesia in this setting are important. Moreover, the transcatheter valve approach, as compared to open-heart valvular replacement with cardiopulmonary bypass, may be the technique of choice in this patient population.

## Conclusions

Significant structural degeneration of transcatheter valves does not occur up to 30 months after implantation, and minor alterations in valve configuration or placement do not appear to be associated with substantial changes in function of the valves during life when assessed by echocardiography. Chest compressions during CPR may cause alterations in configuration of valves but only in a minority of cases. Myocardial injury is common early after the implantation procedure with coronary ostial obstruction by a thick, calcified native aortic valve cusp in the setting of a shallow coronary sinus, narrow aortic root, and/or low origin of the ostium likely a causative factor in some. Finally, myocardial amyloidosis is common in this patient population and warrants recognition because of its potential to have deleterious effects.

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**Key Words:** autopsy ■ long-term follow-up ■ pathology ■ stent deformation ■ tissue overgrowth ■ transcatheter aortic valve replacement.