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Faculteit Geneeskunde en Levenswetenschappen
School voor Levenswetenschappen
master in de biomedische wetenschappen

Masterthesis

Aortic valve replacement versus repair for aortic valve cusp prolapse

Youness Benyahya

Scriptie ingediend tot het behalen van de graad van master in de biomedische wetenschappen, afstudeerrichting klinische moleculaire wetenschappen

PROMOTOR :

Prof. Dr. Pieter VANDERVOORT

BEGELEIDER :

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Abstract

Introduction: Cusp prolapse of the aortic valve (AV) is defined as the visualization of an aortic cusp free margin below the normal coaptation height, resulting in backflow of blood into the left ventricle (LV) during diastole. Aortic valve replacement (AVR) remains the treatment of choice to treat this small anatomic defect. While short-term outcomes following AVR are excellent, long-term complications tend to cumulate during follow-up. AV repair techniques have the potential to avoid these complications, although the widespread implementation remains low.

Materials & methods: Between October 2007 and June 2017, 750 patients underwent an AV procedure at Ziekenhuis Oost-Limburg, Genk, Belgium (ZOL). Data were collected prospectively and analyzed retrospectively. Exclusion criteria were endocarditis, aortic stenosis (AS), secondary AR, or follow-up elsewhere.

Results: Among all patients in the surgical database, 79 (11%) patients had cusp prolapse, and 43 (6%) patients had prolapse of the right coronary cusp (RCC). Also, cusp prolapse has a different character compared to other causes of aortic regurgitation (AR) in terms of patient characteristics. Therefore, it is desirable that this group of patients have to be approached differently. Also, AV repair has better outcomes in terms of morbidity and mortality than AVR when treating cusp prolapse.

Conclusion: This study is the first to provide a head-to-head comparison between AVR and AV repair. Since AV repair is associated with better outcomes compared to AVR in the context of isolated cusp prolapse, further research, and a broader implementation of AV repair techniques are warranted.

Samenvatting

Introductie: Prolaps van de aortaklep wordt gedefinieerd als de visualisatie van een vrije marge van het aortaklepblad onder de normale coaptatiehoogte, resulterend in terugstroming van bloed in de linker hartkamer tijdens diastole. Aortaklepvervanging blijft de voorkeursbehandeling voor dit kleine anatomische defect. Hoewel de kortetermijnresultaten na een vervanging uitstekend zijn, hebben complicaties op lange termijn tijdens een follow-up de neiging om zich op te stapelen. Aortaklepherstel technieken kunnen deze complicatie voorkomen, hoewel de wijdverspreide implementatie nog steeds laag is.

Materialen & methode: Tussen oktober 2007 en juni 2017 hebben 750 patiënten een aortaklep ingreep in Ziekenhuis Oost-Limburg, Genk, België (ZOL). Gegevens werden prospectief verzameld en retrospectief geanalyseerd. Exclusiecriteria waren endocarditis, aortaklepstenose, secundaire aortakleplekken of follow-up elders.

Resultaten en discussie: Van alle patiënten in de chirurgische database hadden 79 (11%) patiënten een klep prolaps en 43 (6%) patiënten hadden een prolaps van de rechter coronaire slip. Klep prolaps heeft ook een verschillend karakter in vergelijking met andere oorzaken van aortakleplekken in termen van patiënten kenmerken. Daarom is het wenselijk dat deze groep patiënten anders wordt benaderd. Aortaklepherstel heeft ook betere resultaten, op het gebied van mortaliteit en morbiditeit, dan aortaklepvervanging bij de behandeling van klep prolaps.

Conclusie: Deze studie is de eerste die een directe vergelijking maakt tussen aortaklepvervanging en aortaklepherstel. Aangezien aortaklephestel gepaard gaat met betere resultaten in vergelijking met aortaklepvervanging in de context van geïsoleerde klep prolaps, is nader onderzoek en een bredere implementatie van hersteltechnieken gerechtvaardigd.

List of abbreviations

AF	Atrial fibrillation
AR	Aortic regurgitation
AS	Aortic stenosis
AVR	Aortic valve replacement
AV	Aortic valve
FAA	Functional aortic annulus
LCC	Left coronary cusp
LV	Left ventricle
MV	Mitral valve
NCC	Non coronary cusp
RCC	Right coronary cusp
STJ	Sinotubular junction
VAJ	Ventriculo-aortic junction

Table of contents

1. Introduction

Aortic regurgitation (AR) - defined as the diastolic backflow of blood from the aorta into the left ventricle (LV) - is caused by incompetent closure of the aortic valve (AV) (1). The prevalence of severe AR is rather low in the general population and is known to increase with age (2,3). Mechanistically, AR is induced by either primary intrinsic cusp disease or cusp-misalignment caused by an enlargement of the aortic root/ascending aorta or both (Table 1) (4,5). Cusp prolapse which is one of the causes of AR can be defined as the visualization of an aortic cusp free margin below the physiologic height of coaptation which often results in prolapsing of the cusp into the LV during diastole (6). Cusp prolapse can either be associated with dilatation of the aortic root/ascending aorta, which can be resolved by repairing the affected aortic root/ascending aorta. Cusp prolapse can also be isolated, with one or more of the cusps prolapsing despite a healthy aortic root. However, this type is more difficult to handle (7). Historically, aortic valve replacement (AVR) is the treatment of choice for most patients suffering from AR. While short-term outcomes following AVR are excellent, long-term complications including prosthetic valve dysfunction, thromboembolism and not to mention rapid degeneration of biological valves do occur regularly and tend to cumulate during follow-up. In the current era, multiple AV preservation and repair strategies have emerged as a feasible alternative for AVR in selected cases with isolated AR with or without associated aortic root pathology. These strategies eliminate those various prosthetic-related complications which reach an incidence of 4-5% per patient-year, as well as the need for life-long anticoagulation in mechanical valves (8). Nevertheless, unlike for the mitral valve (MV), the widespread implementation of AV repair strategies remains low (9). Also, in many cases, the heart team ordinarily opts for a radical approach using AVR even when small cusp deformities/defects like isolated cusp prolapse are to blame for AR (8). In other words, native valve disease is replaced by ‘prosthetic valve disease’ (10,11). Presumably, the cause of this statement is miscellaneous:

(i) Certain fundamental anatomic alterations and echocardiographic features are frequently missed intraoperatively in such a way that an accurate repair-oriented classification is not provided for the operator. In other words, cusp prolapse must be searched for (12). (ii) Currently, there is no standardization in techniques because most cases require a sophisticated individualized approach, which makes it more challenging to build-up surgical experience (8). (iii) Most repair strategies require a specific learning curve, plus surgical techniques are continually evolving. Studies describing older repair techniques should be interpreted cautiously. (iv) To the best of our knowledge, no randomized trials are comparing AV repair versus replacement in the management of AV-disease to date. Consequently, for some clinicians, the role of AV repair remains vague. (v) Long-term (>10years) outcome-data in terms of standardized definitions for morbidity and mortality after valve repair or preservation is scarce (6,13).

Therefore, we sought to determine how frequent AR finds its roots in isolated cusp prolapse. In order to do so, we retrospectively analyzed surgical data of a major tertiary heart center in Ziekenhuis Oost-Limburg, Belgium. Second, our group was very much intrigued by the question of how many of those cases the heart team had opted for AVR to treat such a small lesion and if there is a difference in outcome between AVR and AV repair. Also, the anatomy of a normal AV, as well as a repair-oriented classification of AR, are briefly mentioned.

1.1. The anatomy of the aortic root and annulus

Specific fundamental knowledge of the normal anatomy of the AV not only leads to a better understanding of the pathological conditions concerning the AV but also to the development of innovative surgical techniques. The aortic root is a complex structure forming the bridge between the LV and the ascending aorta. It is a unit consisting of different components with a

well-coordinated dynamic behavior: the AV leaflets, the leaflet attachments, the sinuses of Valsalva, the interleaflet triangles, the sinotubular junction (STJ) and the annulus (Figure 1). Each component of the aortic root contributes to the function of the aortic root as a whole: the intermittent unidirectional channeling of blood while maintaining laminar flow, minimal resistance, and minimal tissue stress and damage, during different hemodynamic conditions and demands. This well-coordinated dynamic behavior is of importance for specific flow characteristics, coronary perfusion, and left ventricular function (14,15). In order to report anatomical inconsistencies and more importantly, mechanisms of AV disease, profound knowledge of the aortic root and its various components is crucial.

The aortic root forms the bridge between the LV and ascending aorta, situated right posteriorly relative to the subpulmonary infundibulum. This cylindrical interpart extends from the basal attachments of the three leaflets in the muscular wall of the LV towards the STJ, a demarcated transition between the sinuses of Valsalva and the tubular portion of the ascending aorta, more distally. Inside, its central part consists of the interleaflet triangles, besides the three leaflets housed in supporting arterial sinuses of Valsalva. The three embedded semilunar leaflets are supported in a crown-like fashion with parabolic lines of attachment in the valvar sinus and hinges extending from their basal attachment in the subvalvular outflow tract towards its uppermost peripheral part at the STJ where a true anatomic ring is formed (Figure 2). More proximally, it is essential to point out that the anatomical boundary between LV and aorta, does not coincide with but instead is crossed by its hemodynamic sibling (e.g., the borders of crown-like leaflet attachment). This circular ventricular-arterial junction (VAJ, ‘annulus in the eyes of the biologist’) marks the demarcation point where ventricular tissue progresses in fibroelastic tissue of the arterial trunk, near the base of the coronary sinuses. The other fibrous portion of VAJ-circumference lies beneath the non-coronary sinus and half of the left coronary sinus (LCC) in the aorto-mitral valvar continuity. The normal point of leaflet coaptation falls

symmetrical at the center of the AV-orifice, just in between the VAJ and the STJ and thus at the level of the valvar sinuses. Because of the semilunar nature of these leaflets, three small inter-leaflet triangular-shaped extensions (containing fibrous tissue) reach the level of the STJ. The parabolic hinge-lines of the leaflets themselves (crown-like points of attachment, generally called 'surgical annulus') cross the VAJ and form the hemodynamic junction between LV and aorta (whereas all structures distal from this point are subject to arterial pressure contrary to proximal structures subject to ventricular pressure). Unlike its distal counterparts, the aortic annulus itself is not a distinct anatomic structure but instead a virtual ring defined by the plane formed by joining the basal anchor points or nadirs of the hinge lines. This functional aortic annulus (FAA, 'echocardiographic annulus') accounts for the narrowest non-circular part of the aortic root and represents a major component vital for normal valve function. Any alteration in the above-mentioned components can provoke AR and more importantly disturb normal behavior of the other component which may further enhance AR (16–20).

Much like in MV repair, all possible lesions and especially the mechanism of disease should be clearly addressed at the time of valve repair. Hence an in-depth repair-oriented classification of AV disease is possible (Figure 3) (21).

1.2. Cusp prolapse

1.2.1. Cusp prolapse - definition and prevalence

AR can be defined as the diastolic backflow of blood from the aorta into the LV owing to incompetent sealing of the AV. Mechanistically, AR is induced by either primary intrinsic cusp disease or cusp-misalignment caused by an enlargement of the aortic root/ascending aorta or both. Most cases of primary AR are due to degenerative valve disease (often combined aortic stenosis (AS) and AR). The minority is attributable to leaflet/cusp prolapse.

Cusp mobility can be seen as the ratio of free margin length over the length of basal cusp insertion. Therefore, traditionally, cusp prolapse is defined as an excess in free margin length against the length of the base of cusp insertion which leads to a decrease in coaptation height as well as increased mobility of this diseased cusp during diastole (22). Generally, this type of cusp prolapse is the result of the commissural disruption caused by overly stretch in root disease or either excessive tissue. Contrariwise, after annuloplasty or root replacement procedures, prolapse may also emerge, as a consequence of overly lowering the length of basal cusp insertion.

The prevalence of isolated AV cusp prolapse in the general population is low, even more, when bicuspid valves are excluded. Presumably, pre –and intraoperative failure of recognition of this tiny lesion is partly to blame (23). Several reasons explain the low prevalence of AV cusp prolapse as an isolated lesion in the general population. First, no clear consensus exists over the definition of cusp prolapse. Another reason is that it is not easily recognized, especially when it is not explicitly looked for (24,25). Cusp prolapse can usually be detected echocardiographically (Figure 4) but requires confirmation and quantification during the surgical inspection (Figure 5). Echocardiographic findings, such as an eccentric AR, are highly sensitive and specific (92% and 96%) for the diagnosis of cusp prolapse. Also, the presence of a fibrous band, on echocardiography and intraoperative examination, is very specific (92%) and can help to localize the prolapsing cusp (6,26). Furthermore, cusp prolapse most frequently involves the right coronary cusp (RCC), followed by the non-coronary (NCC) and then the LCC, which is infrequently involved in isolated cusp disease. However, the etiology and pathophysiology of isolated cusp prolapse, and the RCC, which are mostly involved, is not clear (6).

1.2.2. Possible causes for isolated cusp prolapse

Unlike for cusp prolapse associated with ventricular septal defects (Ventouri-effect exposed on RCC caused by outlet-VSD), the etiology and pathophysiology of isolated cusp prolapse are often unknown. Besides well-known causes as rheumatic valve disease or traumatic disruption, some literature states isolated cusp prolapse may be the result of longstanding cusp stress as caused by hypertension. On the other side of the spectrum, intrinsic cusp tissue abnormalities could be a possible cause, considering the fact that some patients also express MV disease. This was the case for three patients without root dilation in the study performed by Shapiro et al., whereas in the study of Boodhwani et al. 12 out of 50 patients (24%) required concomitant MV repair. Microscopically, the three aortic leaflets are covered by a continuous endothelial lining on both ventricular and aortic side (not in line but across the direction of flow) (Figure 6). Between both surfaces, there are three layers of connective tissue, composed of differential amounts of elastic and collagen fibers coupled in a sponge-like structure. It was previously suggested that this arrangement is crucial to withstand external forces. This becomes clear as collagen fibrils can only be strained about one or two percent before fracture, while the aortic cusps themselves can be elongated up to 40%. It is believed that the surrounding highly-extensible elastin matrix interconnects collagen fibers and allows them to return to their undeformed state, maintaining rest geometry.

Furthermore, the RCC is more prone to prolapse than the other cusps. This predominance of RCC prolapse can be explained in part by the variation in size and dimension of the different AV cusps (27). Kunzelman et al. (28) reported that the RCC tends to have a shorter height than the LCC and NCC (1.33 cm vs. 1.39 and 1.37 cm, respectively), thereby predisposing the RCC to prolapse. It was also found that the length of the free margin of the right cusp is higher than that of the other two cusps (3.3 cm vs. 3.15 and 3.27 cm, respectively) (Table 2). The NCC tends to be the largest of the three leaflets, and the right tends to be the smallest (28).

1.2.3. Treatment strategies for cusp prolapse

Possible repair strategies are summarized in figure 3. The success of AV repair highly depends on cusp tissue morphology (meaning rheumatic, calcified, destructed valves are not amenable for repair). Usually, a combination of both techniques targeting the ascending aorta/aortic root (remodeling/reimplantation) and repair techniques acting on annulus/aortic leaflets are needed. Since cusp prolapse is the result of an increase in free margin length, the current strategies are aimed at a reduction of this length and possible adjacent tissue (to eliminate tissue redundancy and restore normal cusp geometry). Different cusp repair strategies have been described of which the 'central plication' (Figure 7), 'free margin cusp resuspension' (Figure 8), 'triangular resection' and 'extension with an autologous pericardial patch' (Figure 9) are most applied. The chosen surgical repair technique is matched to the macroscopic presentation of the diseased cusp. In trileaflet aortic valves, the cusp tissue is generally thin and pliable, which results in central free margin plication or cusp resuspension or both combined being the preferable technique.

However, though it is an imminently repairable lesion, many remain reluctant to repair AR caused by cusp prolapse. This is due to the low incidence of cusp prolapse, the lack of preoperative and intraoperative recognition of the lesion, insufficient experience with surgical repair techniques, no standardization of repair techniques opposed to a broad scale of techniques to treat prolapse of the MV and the lack of long-term data on outcome after repair (6,9,26).

AVR or root replacement with either a mechanical or biological valve substitute remains the gold standard for surgical treatment of AR. AVR may be performed with either a mechanical or biological valve prosthesis (Figure 10). Ideally, a prosthetic valve should sustain excellent hemodynamics at rest and exercise, have minimal transaortic pressure gradients, should be durable in the long-term, resist thrombus formation without the need for anticoagulation, and be simple to the implant. These complications (Table 2-3) that reach an incidence of 3% to 5%

per year force us to consider AV repair as an alternative which avoids the complications (11,29). As such, some authors state that native valve disease is replaced by prosthetic valve disease.

2. Study objectives

The first objective was to determine the actual prevalence of cusp prolapse in a surgical database. Second, we were intrigued how often the RCC is affected, as it is believed the RCC is more prone to prolapsing disease. The third objective was to compare the baseline characteristics of patients who underwent AV surgery for degenerative valve disease and cusp prolapse as it is believed both subgroups are different in terms of baseline characteristics despite receiving identical treatment (i.e., mostly AVR remains the golden standard treatment for both groups). Ultimately, outcomes after AVR opposed to AV repair to treat isolated cusp prolapse were compared.

3. Material and methods

3.1. Study design and population

Between October 2007 and June 2017, 750 patients were surgically treated for AV disease at Ziekenhuis Oost-Limburg, Genk, Belgium (ZOL). Data were collected prospectively and analyzed retrospectively after checking each patient's medical file separately.

Among all the patients, 602 (80%) patients were identified as having AR while 148 (20%) patients had AS. From the group of AR patients, 529 (88%) patients suffered from primary AR, as opposed to 73 (12%) cases of secondary AR. In the group of primary AR patients, degenerative valve disease was the leading cause in 419 (89%) cases, and isolated cusp prolapse was identified in 79 (15%) patients. This study population is summarized in table 5.

In order to compare patient characteristics between all patients with primary AR (degenerative AR opposed to cusp prolapse), AS and all causes of secondary AR (root dilatation, aortic dissection) were excluded. This resulted in a study cohort of 498 patients.

For the final study objective (comparison of outcomes after AVR vs. AV repair to treat isolated cusp prolapse) the resulting subcohort of isolated cusp prolapse consisted of 60 patients after exclusion of patients with follow-up elsewhere. In this subgroup, 36 subjects underwent AVR, and 24 patients were treated with AV repair techniques.

3.2. Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPPS) (IBM Corporation, New York, USA). Normality was assessed using the Shapiro–Wilk statistic. Categorical variables were presented as absolute numbers and percentages. Continuous variables were reported by mean ± standard deviations for normally distributed data, and by median(interquartile range) when not normally distributed. Differences between the study groups were analyzed using standard t-tests if normally distributed, and Mann-Whitney test if otherwise. Categorical variables were compared using the Chi-square test. Comparative survival and freedom from recurrent AR were calculated using the Kaplan–Meier method (time-to-event analysis). Statistical significance was set at a p-value below 0.05.

3.3. Outcomes

Each patient's medical file was searched for possible bleeding owing to antithrombotic therapy (especially in the context of mechanical prosthetic heart valves). Furthermore, mortality was assessed for all patients. Cardiac death is defined as death resulting from an acute myocardial infarction (AMI), sudden cardiac death, death due to heart failure (HF), and death due to cardiovascular (CV) procedures. Recurrence of moderate-to-severe AR was handled as a categorical variable. Moderate to severe AR was defined as 2 or more, while minor was defined as less than 2, scored visually during echocardiography of which the latest results were used. Patients were defined symptomatic when having an NYHA greater than two. Stroke refers to a previous cerebrovascular accident (CVA) or transient ischemic attack (TIA).

4. Results

4.1. Prevalence of isolated cusp prolapse.

Among all patients in the surgical database, 79 patients or 11 percent suffered from isolated cusp prolapse. In 43 patients or 6 percent of all patients, the RCC was affected by cusp prolapse.

4.2. Isolated cusp prolapse vs. degenerative valve disease

4.2.1. Baseline characteristics

Baseline characteristics are summarized in table 6. Age was significantly lower ($p < 0.001$) in patients with isolated cusp prolapse. Patients with degenerative valve disease are significantly more limited in terms of the New York Heart Association class (NYHA) ($p = 0.001$). Hypertension between both groups was not significantly different ($p = 0.231$). Patients with isolated cusp prolapse had significantly less risk factors and comorbidities opposed to degenerative valve disease cases: previous acute myocardial infarct (AMI) ($p = 0.02$), previous percutaneous coronary intervention (PCI) ($p = 0.053$), dyslipidemia ($p < 0.001$), diabetes mellitus (DM) ($p < 0.001$), peripheral artery disease (PAD) ($p = 0.001$), and angor ($p = 0.049$).

4.2.2. Preoperative echocardiographic and catheterization data

Preoperative echocardiographic and catheterization data are summarized in table 7. Left ventricular ejection fraction (LVEF) was comparable for both groups (52 ± 15 vs. 57 ± 6, $p = 0.454$). Cardiac index (CI) was significantly higher in the group of patients who underwent surgery for degenerative valve disease ($p < 0.001$). Systolic pulmonary artery pressure (SPAP) was significantly higher for the group with degenerative valve disease ($p = 0.034$).

4.2.3. Peri-operative data

Peri-operative data are summarized in table 8. Aortic cross-clamp time (ACC) and extracorporeal circulation time (ECC) were significantly different for both groups (119±48 vs. 224±67, $p < 0.001$) and (157(103-190) vs. 248(219-304), $p = 0.001$). More patients with degenerative valve disease underwent a concomitant procedure like mitral valve annuloplasty (MVP) ($p = 0.004$). Length of stay in the hospital for both groups was comparable (15±11 vs. 15±7, $p = 0.625$). During their postoperative course, patients who underwent surgery for degenerative valve disease experienced more frequently postoperative atrial fibrillation (AF) ($p = 0.014$). Postoperative mortality was comparable for both groups. Postoperative AR was trivial for all subjects.

4.3. Isolated cusp prolapse: aortic valve replacement vs. aortic valve repair

The outcome in terms of mortality and morbidity are compared and summarized in table 9 and figures 11-13. For the group of patients who underwent AVR, overall survival in the first year was 97%, 89% at year 4, and 78% at 8 years. Freedom from cardiac death in the first year was 97%, 92% in year 4, and 78% in year 8. Freedom from moderate-to-severe recurrent AR was 100% at year one, year 4, and year 8. In contrast to the patients who underwent AV repair, overall survival was 96% at year one, 83% in year 4, and 67% in year 8. Freedom from cardiac death was 96% at year one, 83% in year 4, and 67% in year 8. Freedom from recurrent AR was 96% at year one, 75% in year 4, and 58% in year 8. In short, all-cause mortality, and cardiac death, and redo surgeries were higher after an AVR compared to AV repair.

5. Discussion

This is the first study to perform a head-to-head comparison between AVR and AV repair strategies to treat isolated cusp prolapse of the AV. Furthermore, the prevalence of isolated cusp prolapse in a surgical database of a tertiary referral center was investigated. The key findings of this study are: (1) As expected, the prevalence of isolated cusp prolapse in the surgical database is substantial (11%). (2) The RCC was most frequently diseased (6%). (3) Though isolated cusp prolapse is most commonly treated with AVR, indeed these subjects have significantly different baseline characteristics compared to patients with degenerative AV disease. (4) Outcomes after AV repair as opposed to AVR to treat isolated cusp prolapse are superior in terms of mortality and redo surgery.

The prevalence of isolated cusp prolapse of our surgical database is more substantial (11%) than described in current literature. Also, the cusp most affected by prolapse remains the RCC. Shapiro et al. prospectively investigated the prevalence and clinical significance of AV prolapse in 2000 consecutive patients undergoing routine echocardiography. Twenty-four cases of AV prolapse (1.2%) were identified, irrespective of the degree of regurgitation severity. This percentage was even lower for isolated AV prolapse. Also, patients with trileaflet aortic valves, the right coronary cusp (RCC) was most frequently affected (ten out of 24 patients) (23). Boodhwani et al. retrospectively reviewed prospectively collected surgical data of 428 patients who had undergone AV repair. Bicuspid valves were excluded. All pre –and intraoperative echocardiograms were reviewed by a trained echocardiographer blinded to the used surgical technique. Forty-six percent (n=195) were treated for cusp prolapse and of these 111 patients had trileaflet valves and therefore defined the cohort of interest. In 50 patients, isolated cusp prolapse was present (isolated group) whereas both cusp disease and root dilatation accounted for regurgitation in 61 patients (associated group). Once again, in both groups, the RCC most commonly needed surgical repair (irrespective of the number of repaired cusps) (24).

The mean age of patients with isolated cusp prolapse in our surgical database was 73 years, which was significantly lower compared to the group of patients who underwent surgery for degenerative valve disease. Also, the young age of patients with isolated cusp prolapse stays consistent with the age described in the literature. Also, in the same study described by Boodhwani et al., the mean age of the 50 patients with isolated cusp prolapse was relatively young at 57 years. Given the young age of this patient cohort, many of these patients would undergo mechanical AV replacement (24).

Our study demonstrated that AV repair showed lower mortality rates compared to AVR. This is consistent with the results described by the current literature. The group of Ottawa Heart Institute performed a systematic review of 17 observational studies, including 2891 selected patients in which aortic repair strategies were applied. Aortic root reconstruction using a reimplantation or remodeling technique was required in 12 studies. Pooled analysis of all 17 studies showed a relatively low operative risk despite complex valve preservation and repair techniques, admittedly in specialized centers. Early in-hospital mortality was acceptable at a rate of 2,6% (95% CI: 1,4-4,4%). This may also partly stem from good patient selection and relatively young age (11).

Unfortunately, there was no significant difference in recurrent AR and valve-related complications (bleeding, thrombosis, stroke, AF, endocarditis) between AVR and AV repair. However, there were more redo surgeries in the AVR group. This could be explained in part by the small sample size. These results are inconsistent with the current literature. The incidence of valve-related events was rather low described by the group of Ottawa Heart Institute Eight studies reporting on endocarditis in operated valves, noted a median event rate 0,23% per patient-year, whereas nine studies reported modest rates (0,52% per patient-year) concerning the composite outcome of thromboembolism and late neurological events (patient-years is the product of patient numbers with the mean follow-up time). Five-year freedom from recurrent

AI>2+ and late AV re-intervention were respectively estimated at a median of 88% and 92% (11). Boodhwani et al. also demonstrated that AV repair is feasible in this patient population and can be performed safely with low rates of AV reoperation, acceptable rates of recurrent AR and low valve-related complications (24). Another study performed by Price et al. studied outcomes in terms of valve-related events in 475 consecutive patients and drew identical conclusions (30). Specifically for AV prolapse, the group of Brussels reported good outcomes in 146 patients who underwent elective AV repair for leaflet prolapse between 1996 and 2006. Both patients with and without associated root dilation or aortic aneurysm were included. There was no in-hospital mortality, and only two patients required redo-surgery for early AR recurrence. Three patients required reoperation for late AR recurrence. Overall survival and freedom from severe AR recurrence (>2) were estimated at 99+-1% and 91+-7% at four years, respectively. (24).

6. Limitations

Besides the inherent limitations related to the retrospective design of this study. Surgical techniques and experience may have changed over time. Thus, the results of this study may differ from those of future studies using the same procedures. Also, the small sample size could lead to insignificant results.

7. Conclusion

To this day, AV repair has gone a long way to become an attractive alternative for valve replacement in patients with isolated AR. Multiple studies revealed lower rates of valve-related events opposed to prosthetic valves which carry a substantial higher cumulative risk and do not offer lifelong durability in these typically, younger patients. However, unlike for the MV, there is no clear consensus concerning various repair strategies in current guidelines, let alone worldwide dissemination of repair strategies. As a result, even for tiny lesions like partial cusp prolapse, AV replacement often remains the therapy of choice despite the emergence of a repair-oriented classification system and various repair techniques with comparable, good mid-term outcome. Multiple possible explanations were provided in this paper. Of these presumably, the lack of long-term multicenter outcome data and head to head comparison of this data with outcome after AV replacement is at the forefront.

This study is the first to provide a head-to-head comparison between AVR and AV repair to treat isolated cusp prolapse. Novel repair approaches using longlasting materials are needed to become the true 'golden standard' for isolated AR. Especially in this era where three-dimensional processing and patient-tailored computerized modeling of heart valves is re-invented on a daily basis, the road is entirely open for the development of 'patient-tailored valve repair strategies 2.0 with pre-intervention simulation of the possible outcome.

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9. Appendix

9.1. Figures

Figure 1: Illustration of the aortic root components (25).

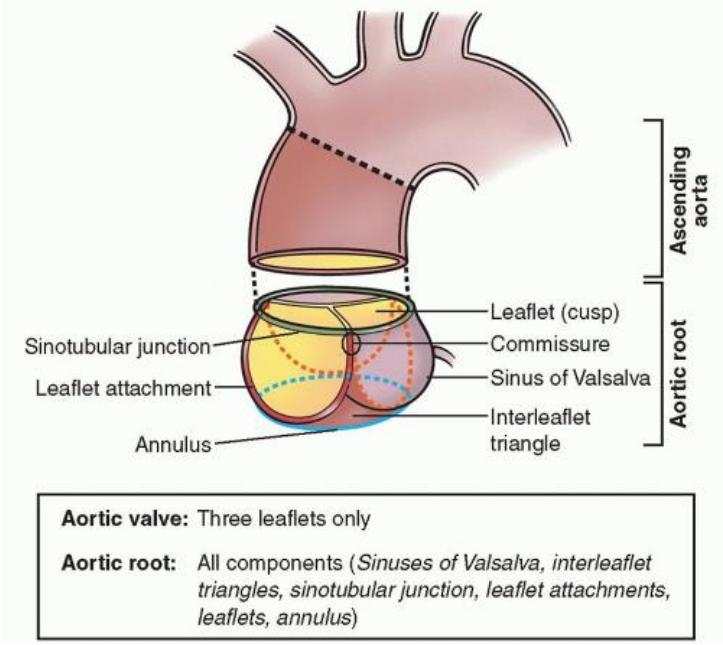


Figure 2: Three-dimensional representation of the aortic root and annulus. Coronet-shaped surgical annulus (yellow lines), the ventriculo-aortic junction (VAJ) (blue lines), the echocardiographic annulus (red lines). Nadirs (green circles), commissures (blue circles), the sinotubular junction (STJ) (green lines) (17).

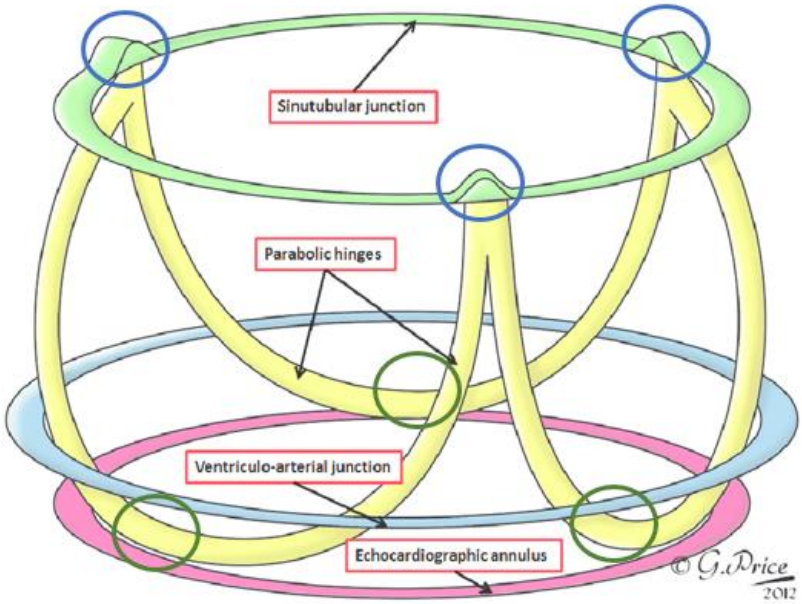


Figure 3: Repair-oriented functional classification of aortic regurgitation (AR) with a description of disease mechanisms and repair techniques used. FAA: functional aortic annulus, STJ: sinotubular junction, SCA: subcommisural annuloplasty (21).

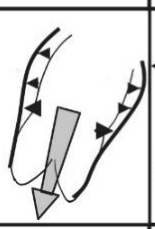
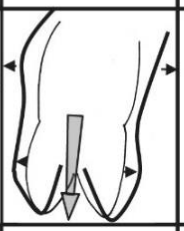
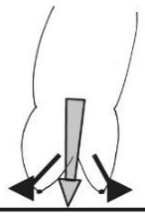
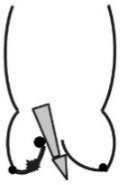
AI Class	Type I Normal cusp motion with FAA dilatation or cusp perforation				Type II Cusp Prolapse	Type III Cusp Restriction
	Ia	Ib	Ic	Id		
Mechanism						
Repair Techniques (Primary)	STJ remodeling *Ascending aortic graft*	Aortic Valve sparing: *Reimplantation or Remodeling with SCA*	SCA	Patch Repair *Autologous or bovine pericardium*	Prolapse Repair *Plication* *Triangular resection* *Free margin Resuspension* *Patch*	Leaflet Repair *Shaving* *Decalcificatio* *Patch*
(Secondary)	SCA		STJ Annuloplasty	SCA	SCA	SCA

Figure 4: Transesophageal echocardiographic views of the aortic valve in the long axis (A), demonstrating an eccentric aortic insufficiency jet. (B), cusp prolapse with coaptation below the level of the aortic annulus and fibrous band (white arrow). (C), a short-axis view of the aortic valve confirms the presence of the fibrous band (white arrow) (6).

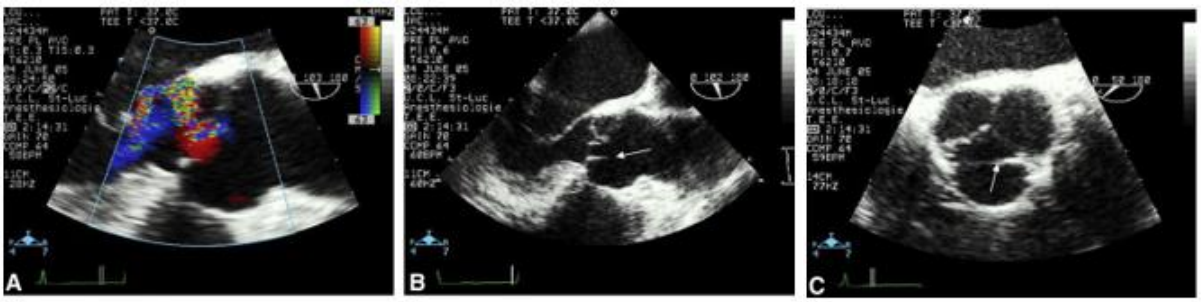


Figure 5: After a transverse aortotomy, cusp inspection reveals a transverse fibrous band on the prolapsing cusp indicated by the black arrow. Right coronary cusp (A and B) and non coronary cusp (C) (6).

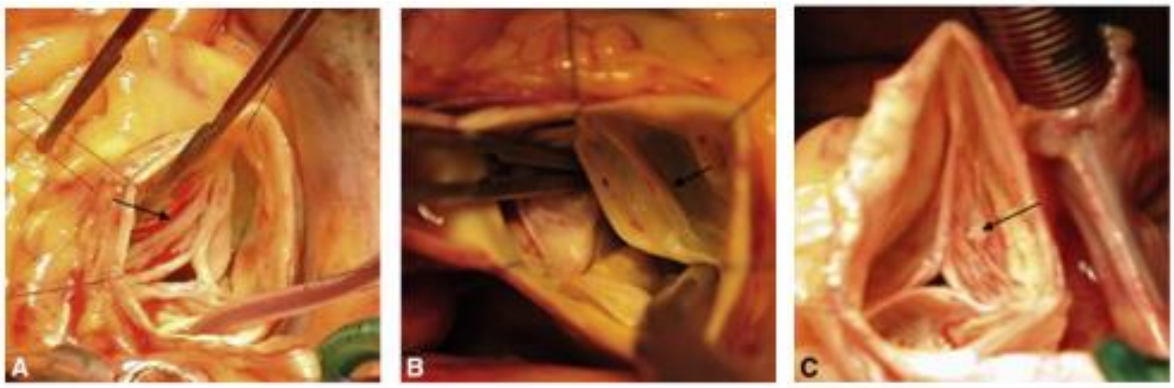


Figure 6: Microstructure of aortic valve cusps showing the characteristic trilaminar architecture (31).

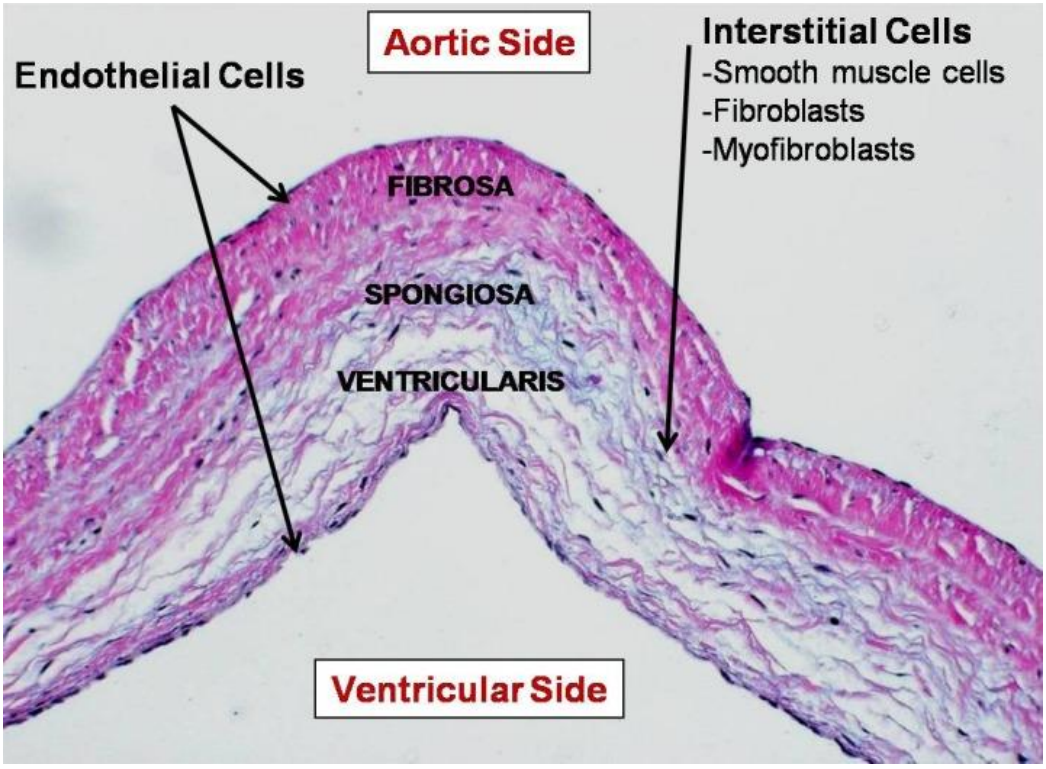


Figure 7: Step by step illustration of LP repair with central plication (24).

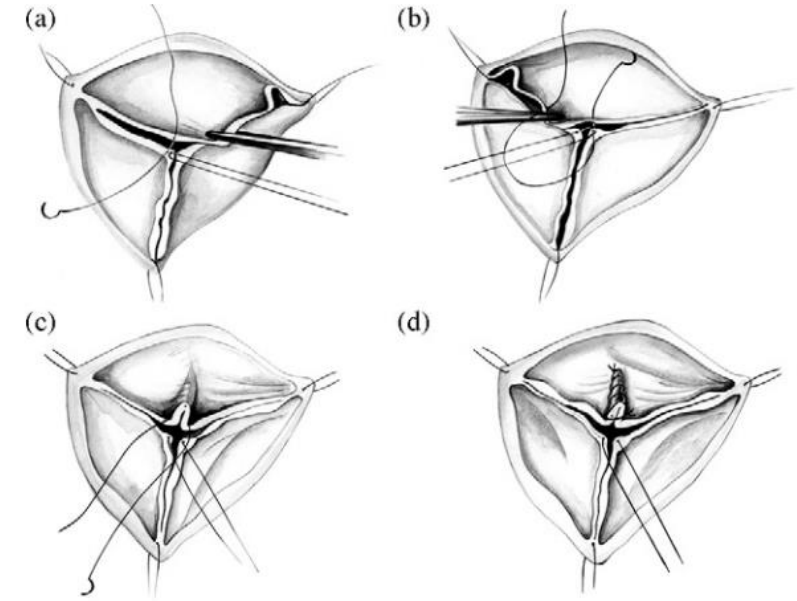


Figure 8: Illustration step by step of resuspension with a running suture of GoreTex 7/0 (24).

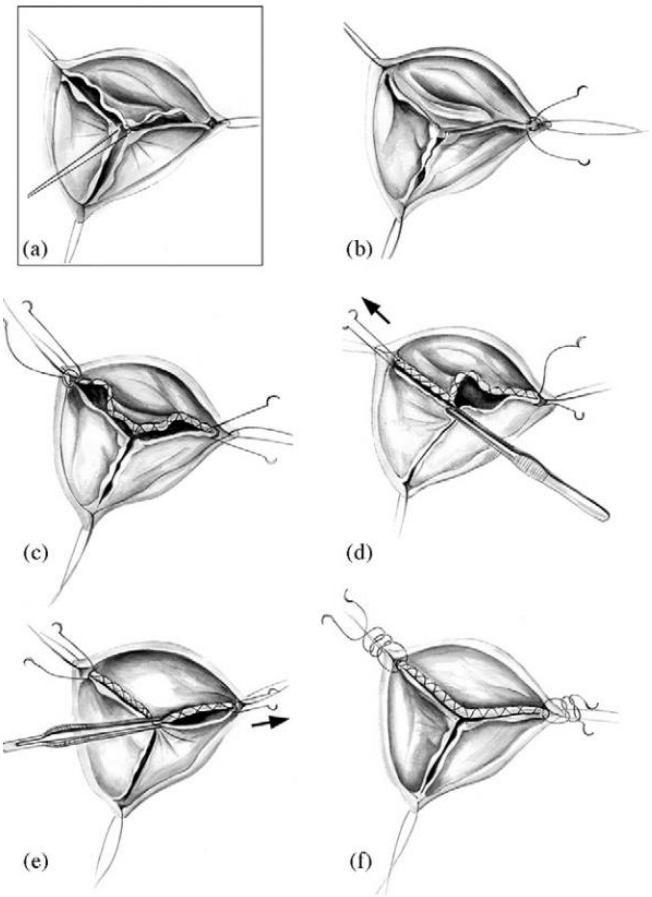


Figure 9: A) Tricuspid triangular resection. (B) Resection of the leaflet in a case of bacterial endocarditis. (C) The gap is restored by using an autologous pericardium patch (32).

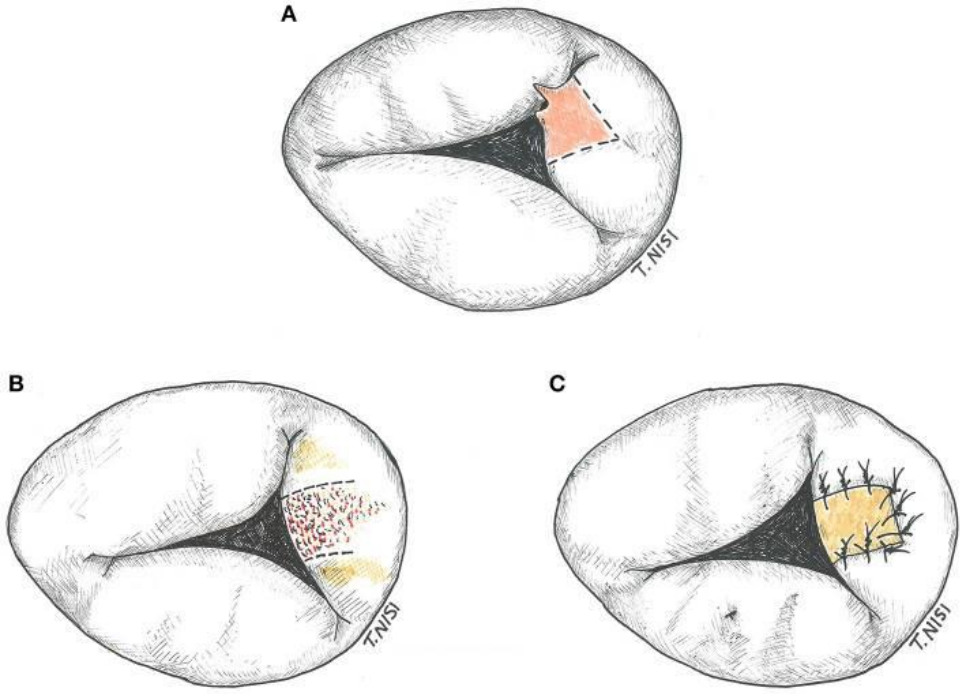


Figure 10: Types of the valve prosthesis. A: Mechanical valve; B: Biological valve (10)

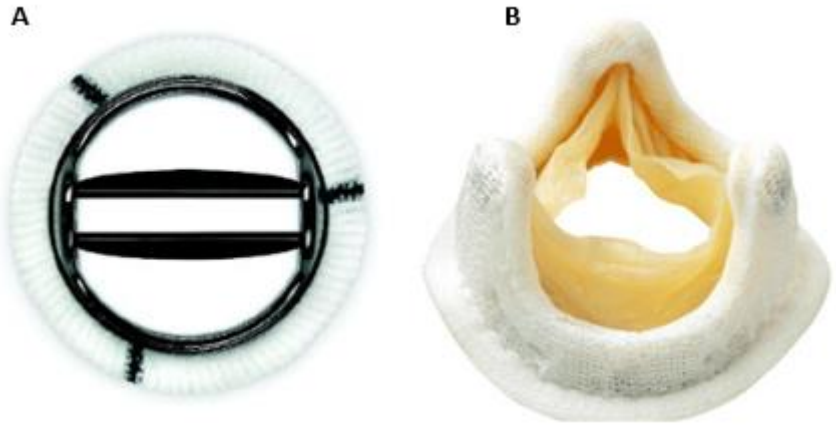


Figure 11: Overall survival for cusp prolapse between AVR and AV repair.

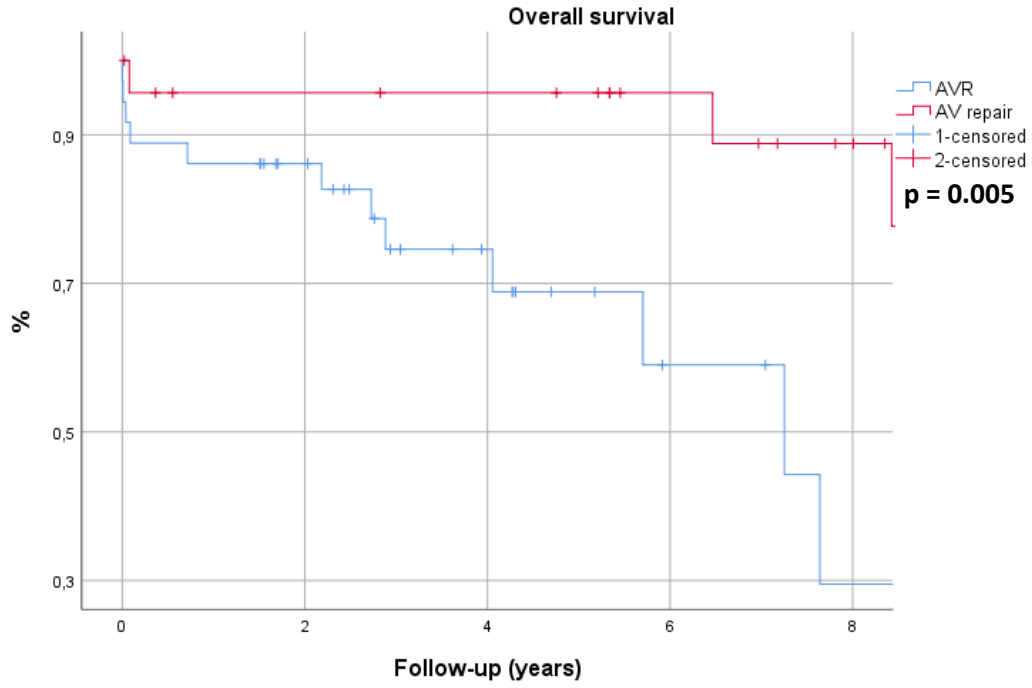


Figure 12: Freedom from cardiac death for cusp prolapse between AVR and AV repair.

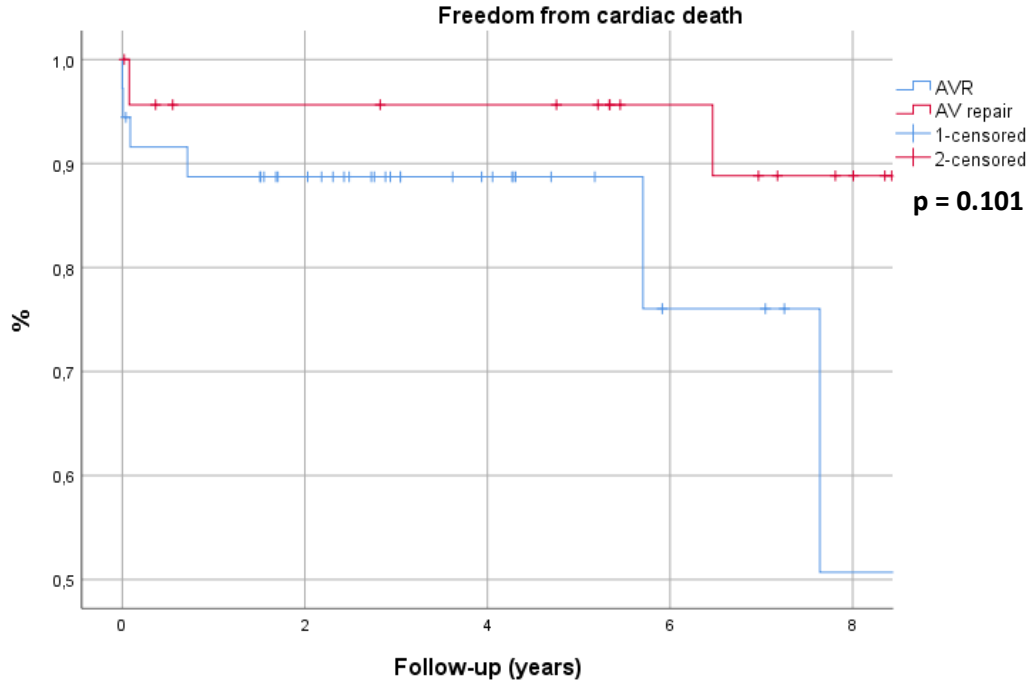
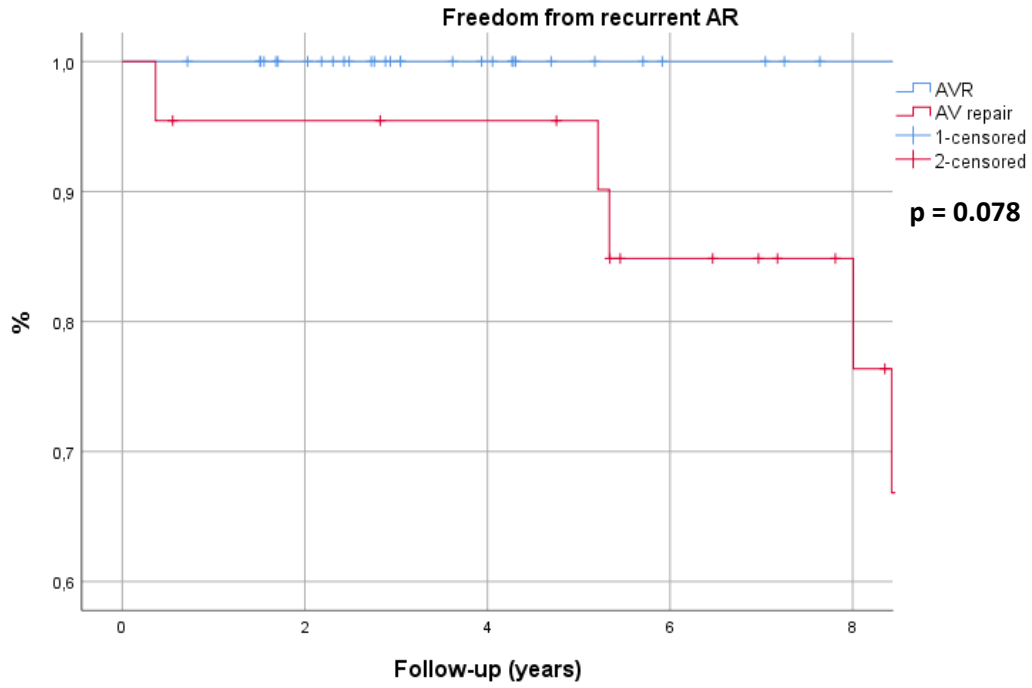


Figure 13: Freedom from recurrent AR for cusp prolapse between AVR and AVR repair.



9.2. Tables

Table 1: The leading causes of aortic regurgitation (AR) (33).

Primary valve disease	
Rheumatic	
Congenital:	Bicuspid aortic valve
	Outlet supracristal VSD
	Discrete subaortic stenosis
Endocarditis*	
Other inflammatory disorders	
Degenerative	
Traumatic leaflet rupture*	
Secondary AR	
Aortic root dilatation	
Aortic dissection*	Damage to aortic annulus
	Prolapsing intimal flap with intact leaflets and annulus

*Disorders leading to acute AR.
VSD, ventricular septal defect.

Table 2: Human aortic leaflet dimensions (28).

	Right	Left	Noncoronary	Average
Height (cm)	1.33 ± 0.06	1.39 ± 0.08	1.37 ± 0.04	1.36 ± 0.06
Free margin length (cm)	3.30 ± 0.14	3.15 ± 0.14*	3.27 ± 0.13	3.24 ± 0.13
Attached edge length (cm)	4.64 ± 0.20	4.76 ± 0.22	4.81 ± 0.16	4.74 ± 0.19
Perimeter (cm)	7.94 ± 0.33	7.91 ± 0.35	8.08 ± 0.28	7.98 ± 0.31
Area (cm2)	2.97 ± 0.17	3.09 ± 0.27	3.17 ± 0.18	3.07 ± 0.21

*$p < 0.05$, left < right, left < noncoronary, one-way ANOVA.

Values given as mean plus or minus standard error of the mean.

Table 3: Mechanical vs. biological valves (34).

Type of prosthetic valve	Mechanical valves	Biological valves
Indications	• Aortic valvular disease • < 65 years	• Aortic valvular disease • ≥65 years
Advantages	• Durability (20–30 years)	• Lower thrombotic risk • No lifelong anticoagulation therapy • Decreased risk of bleeding • Limited impact on activity level
Disadvantages	• Thrombosis • Lifelong anticoagulation • Bleeding risks • Lifestyle modifications (to reduce bleeding)	• Durability (10-15 years) • Structural valve deterioration
Outcomes	• Lower reoperation rates • Lower mortality	• Higher reoperation rates • Higher mortality

Table 4: Surgical options for the treatment of AR: advantages and disadvantages (34). AR: aortic regurgitation.

Aortic valve prostheses	Mechanical prostheses	Biological prostheses	Valve repair/ preservation
Specific surgical expertise requiered	-	-	++
Durability	Excellent	Limited	Limited
AC required	Yes	No	No
Valve sound	Yes	No	No
Hemodynamics	Adequate	Adequate	Excellent

Table 5: Study population.

Total sample size	750
AV procedure n(%)	
AVR	654 (87)
AV repair	96 (13)
Etiology n(%)	
AS	148 (20)
AR	602 (80)
Primary AR	529 (88)
• Degenerative	419 (79)
• Isolated cusp prolapse	79 (15)
• RCC	43 (54)
• NCC	33 (42)
• LCC	17 (22)
• Endocarditis	31 (6)
Secondary AR	73 (12)
• Root dilatation	46 (64)
• Dissection	26 (36)
Cusp anatomy	
• Unicuspid	3 (0.4)
• Bicuspid	125 (17)
• Tricuspid	620 (83)
• Quadricuspid	1 (0.1)
AVR: aortic valve replacement, AV: aortic valve, AS: aortic stenosis AR: aortic regurgitation, RCC: right coronary cusp, NCC: non coronary cusp, LCC: left coronary cusp.	

Table 6: Baseline characteristics.

	Degenerative valve disease n = 419	Isolated cusp prolapse n = 79	P-value
Demographics			
Age (years)	80±12	73±15	**<0.001**
Male gender	239(57)	57(72)	**0.012**
BMI (kg/m^2)	27(24-30)	34(29-39)	0.907
NYHA class			**0.001**
I	9(2)	9(11)	
II	101(24)	18(23)	
III	287(69)	50(63)	
IV	22(5)	2(3)	
Creatinine (mg/dl)	1.27±0.82	0.84±0.13	0.603
FEV1	1.9(1.4-2.6)	3.0(2.4-3.3)	**0.001**
Euroscore II	0.04±0.03	0.011±0.004	**<0.001**
Risk factors n(%)			
Previous cardiac surgery	47(11)	7(9)	0.537
Previous AMI	46(11)	2(3)	**0.020**
Previous PCI	60(14)	5(6)	**0.053**
Hypertension	479(78)	57(72)	0.231
Dislipidemia	274(65)	35(44)	**<0.001**
Smoking	59(14)	19(24)	0.082
Comorbidities n(%)			
COPD	60(14)	11(14)	0.926
DM	83(20)	3(4)	**<0.001**
Stroke	37(9)	2(3)	0.056
PAD	126(30)	9(11)	**0.001**
Obesity	100(24)	17(22)	0.449
AF	89(21)	16(20)	0.972
Angor	76(18)	8(10)	**0.049**

BMI: body mass index, NYHA: New York Heart Association, AMI: acute myocardial infarct, PCI: percutaneous coronary intervention, COPD: chronic obstructive pulmonary disease, DM: diabetes mellitus, PAD: peripheral artery disease, AF: atrial fibrillation.

Table 7: Preoperative echocardiographic and catheterization characteristics.

	Degenerative disease n = 419	Cusp prolapse n = 79	P-value
Echocardiography			
AR grade			**<0.001**
≤1	143(41)	9(12)	
2	113(32)	13(18)	
3	77(22)	37(50)	
4	20(6)	15(20)	
LVEF, %	52±15	57±6	0.454
Catheterization			
Ao diastole (mmHg)	65(59-72)	72(62-73)	0.951
Ao systole (mmHg)	149(130-160)	144(134-149)	0.404
CI (l/min/m^2)	160±148	111±142	**<0.001**
DPAP (mmHg)	18(14-21)	22(21-23)	0.482
SPAP (mmHg)	43(36-47)	40(37-48)	**0.034**
PAWP (mmHg)	20±7	30±10	0.521

n: sample size, AR: aortic regurgitation, LVEF: left ventricular ejection fraction, Ao: aorta, CI: cardiac index, DPAP: diastolic pulmonary artery pressure, SPAP: systolic pulmonary artery pressure, PAWP: pulmonary artery wedge pressure.

Table 8: Peri-operative data.

	Degenerative disease n = 419	Cusp prolapse n = 79	p-value
ACC (min)	119±48	224±67	**<0.001**
ECC (min)	157(103-190)	248(219-304)	**0.001**
CABG	143(34)	21(27)	0.190
MVR	28(7)	1(1)	0.059
MVP	42(10)	17(22)	**0.004**
TVP	31(7)	8(10)	0.408
AF	125(30)	10(13)	**0.014**
Pacemaker	8(0.02)	0(0)	0.464
Stroke	7(2)	0(0)	0.716
Mortality	26(6)	6(8)	0.062
Hospital length (days)	15±11	15±7	0.625
AR grade			**<0.001**
≤1	287(100)	63(96)	
2	1(0.3)	3(5)	
3	0(0)	0(0)	
4	0(0)	0(0)	
Maximum AV gradient, mmHg	18(15-26)	13(10-19)	**0.002**
Miminim AV gradient, mmHg	9(8-14)	7(5-12)	**0.011**

n: sample size, ACC: aortic cross-clamp time, ECC: extracorporeal circulation time, CABG: coronary artery bypass grafting, MVR: mitral valve replacement, MVP: mitral valve plasty, TVP: tricuspid valve plasty, AF: atrial fibrillation, AR: aortic regurgitation, AV: aortic valve.

Table 9: Follow-up data: AVR vs. AV repair for cusp prolapse.

	AVR n = 36	AV repair n = 24	P-value
AR grade			**<0.001**
<1	32(89)	15(62)	
2	0(0)	4(7)	
3	0(0)	3(13)	
4	0(0)	0(0)	
NYHA			0.098
I	8(28)	16(67)	
II	9(25)	5(21)	
III	6(17)	0(0)	
IV	4(11)	1(4)	
Redo surgery	3(8)	1(4)	0.701
Endocarditis	3(8)	0(0)	0.309
Stroke	2(6)	3(13)	0.614
Bleeding	2(6)	0(0)	0.458
HF	5(14)	3(13)	0.575
AF	12(33)	7(27)	0.559
Pacemaker	1(3)	5(21)	0.073
n: sample size, AR: aortic regurgitation, LVEF: left ventricular ejection fraction, NYHA: New York Heart Association, HF: heart failure, AF: atrial fibrillation.			

Acknowledgments

Over the last eight months, I was honored to be allowed working on such an exciting and beneficial study at Hospital Ziekenhuis Oost-Limburg at the Department of Cardiology. Looking back at these eight months, it was a fantastic experience with many enjoyable, fun, and educational moments.

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Youness Benyahya