Early results with annular support in reconstruction of the bicuspid aortic valve

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Objective: Repair of the bicuspid aortic valve may be performed in aortic regurgitation and aneurysm. Dilatation of the atrioventricular junction has been identified as a risk factor for repair failure, and we have used suture annuloplasty to correct atrioventricular junction enlargement. The objective was to compare the early results of aortic repair with and without annuloplasty.

Methods: Between November 1995 and January 12, a total of 559 patients were treated with bicuspid aortic valve repair for predominant regurgitation ($n = 389$), aortic aneurysm ($n = 158$), or acute dissection ($n = 12$). Isolated valve repair (aortic valve repair) was performed for aortic valve regurgitation with preserved aortic dimensions ($n = 208$) and sinotubular junction remodeling plus valve repair for aortic aneurysm and preserved root size ($n = 116$). Root remodeling was used for dilatation involving the root ($n = 235$). In 193 patients, dilatation of the atrioventricular junction (>27 mm) was corrected with suture annuloplasty.

Results: Hospital mortality was 0.5% ($n = 3$); 2 patients required pacemaker implantation. Reoperation was necessary for recurrent regurgitation ($n = 54$) or stenosis ($n = 2$); 10-year freedom from reoperation was 82% but was inferior after isolated valve repair (70%, $P = .007$) compared with the 2 other techniques. Application of suture annuloplasty improved 3-year freedom from reoperation after isolated repair (84%) to 92% ($P = .07$). In all groups, the proportion of patients with no or trivial regurgitation was significantly higher with annuloplasty.

Conclusions: Preservation of the bicuspid aortic valve is feasible in many patients. Long-term stability of the repaired valves is good; the negative impact of a dilated atrioventricular junction can be reduced by suture annuloplasty. (*J Thorac Cardiovasc Surg* 2013;145:S30-4)

Bicuspid aortic valve (BAV) is the most frequent congenital cardiac anomaly.¹ A relevant proportion of those with BAV will require surgical treatment for aortic regurgitation (AR), even though hemodynamically normal function of BAVs has been observed in the seventh decade of life.² Aneurysmal aortic dilatation develops in more than 50% of individuals with BAV,^{3,4} either involving the root primarily or with predominant dilatation of the tubular ascending aorta.

Reconstruction of the regurgitant BAV was proposed as early as 1992 with excellent early results.⁵ It was shown that concomitant aortic dilatation could be treated simultaneously by root replacement or sinotubular junction remodeling.^{6,7} Subsequent studies showed a relevant proportion of repair failures in patients with BAV.^{8,9} Different predictors of repair failure were proposed, such as aortic dilatation⁸ or

triangular resection as part of the cusp repair.⁹ We found that symmetric postoperative prolapse was a relevant cause of failure that could be minimized reproducibly by systematically measuring and correcting effective cusp height.⁷ In a recent larger investigation, we found that anatomic denominators of the BAV, in particular marked dilatation of the atrioventricular junction (AVJ), remained a predictor of midterm repair failure.¹⁰ After valve-preserving root replacement including the tricuspid aortic valves, preoperative dilatation of the AVJ was a predictor of valve failure.¹¹

On the basis of these results, we modified the repair procedure in those with BAV by adding suture annuloplasty to correct dilatation of the AVJ. The current analysis compares the early results of our differential treatment of the valve and aortic pathology and analyzes the effect of the annuloplasty suture.

PATIENTS AND METHODS

Between November 1995 and January 2012, a total of 559 patients (485 male, aged 3-86 years; mean, 47.2 ± 14.1) were treated by valve preservation or repair of BAV at the Saarland University Medical Center.

The predominant pathology was AR ($n = 389$), aortic aneurysm ($n = 158$), or acute dissection ($n = 12$). The operations initially were performed without correcting dilatation of the AVJ. Since December 2008, dilatation of the AVJ (>27 mm) has been corrected with a circumferential annuloplasty suture. Thus, 366 patients were treated without an annuloplasty and 193 patients were treated with an annuloplasty. The early outcomes without and with annuloplasty were compared. The study was approved by the local ethics committee and approved for publication of the patient data in an anonymous fashion.

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Abbreviations and Acronyms

AR = aortic regurgitation
AVJ = atrioventricular junction
BAV = bicuspid aortic valve

The patients were treated with a consistent technique,⁷ although slight modifications were made over time. Isolated valve repair was performed for AR with preserved aortic dimensions (<42–45 mm; *n* = 208). Sinotubular junction remodeling plus valve repair was chosen for aortic aneurysm (>45–50 mm) and preserved root size (*n* = 116); root remodeling was used for dilatation involving the root (*n* = 235).

The degree of AR ranged from trivial (0) to severe (4), with a mean of 2.6 ± 1.1 . There was no significant difference between mean severity of regurgitation between the initial cohort (2.5 ± 1.1) and the 193 patients with annuloplasty (2.8 ± 0.9 ; *P* = .07). The mean diameter of the AVJ was 27.8 ± 2 mm in those without annuloplasty (*n* = 366) and 31.9 ± 3 mm in those with annuloplasty (*P* < .0001). Cardiac comorbidity requiring additional treatment included mitral regurgitation (*n* = 20), tricuspid regurgitation (*n* = 5), coronary artery disease (*n* = 42), and atrial fibrillation (*n* = 20).

Cusp Repair Technique

The principles of cusp repair have been reported.^{7,10} Repair was pursued if the nonfused cusp did not exhibit calcifications. First, any prolapse of the nonfused cusp (commonly noncoronary) was eliminated using plicating sutures. The redundancy of the fused cusps was reduced primarily using plicating sutures on the free margin. Triangular resection with suture adaptation was performed if fibrosis or limited calcifications in the raphe made plication difficult. In the presence of more extensive calcifications, a pericardial patch was inserted to bridge the defect in the fused cusps. The diagnosis of prolapse initially was made by visual inspection. Since December 2004, an effective height of the nonfused cusp of less than 9 mm was considered as prolapse and corrected¹²; the fused cusp was always adjusted to a height identical to the free margin. Plication of redundant cusp tissue was performed in 454 instances, and triangular resection of cusp tissue was performed in 181 cases. A pericardial patch was inserted for partial cusp replacement in 181 valves.

Choice of Procedure

Isolated aortic cusp repair was performed if the ascending aorta was normal (<40 mm). Sinotubular junction remodeling was used if the sinotubular diameter determined by transesophageal echocardiography exceeded 35 mm and the maximum sinus diameter was less than 42 (body surface area <2 m²) to 45 mm.¹³ Since November 2004, the graft was first sutured to the sinotubular junction, and then cusp repair was performed only to detect and eliminate any prolapse induced by reduction of sinotubular junction.⁷ Root remodeling was performed as described previously.⁶ Graft size was generally chosen according to the body surface area of the patient (<1.8 m²: 24 mm; 1.8–2.2 m²: 26 mm; >2.2 m²: 28 mm).

Annuloplasty

A suture annuloplasty similar to procedures described by others^{14,15} was performed whenever the atrioventricular diameter exceeded 27 mm. In the initial 89 instances, a number 2 braided polyester suture (Ethibond, Ethicon, Hamburg, Germany) was used; in the subsequent 104 cases, a polytetrafluoroethylene suture was used (Gore-Tex CV-0; WL Gore and Associates, München, Germany).

For isolated aortic valve repair, a suture was started from the inside of the outflow tract 4 to 7 mm deep through septal muscle in a horizontal plane 2

mm below the nadir of cusp insertion, from the center of the right cusp to the center of the left cusp. The posterior arm was then passed from the inside to the outside close to the left fibrous trigone and fixed tangentially outside the nadir of the noncoronary sinus. The anterior arm was passed from the inside to the outside to the left of the membranous septum, leaving sufficient tissue between suture and septum (Figure 1). It was similarly fixed tangentially outside the nadir of the noncoronary sinus. In conjunction with root remodeling, the suture was passed only from the outside, passing through myocardial tissue outside the right coronary cusp and just outside the nadir of the sinuses. The suture was tied around a Hegar dilator, thus effectively reducing the atrioventricular diameter; the size of the dilator was chosen according to the body surface area of the patient (≥ 1.8 m²: 25 mm, <1.8 m²: 23 mm). All patients were followed clinically and echocardiographically; follow-up was complete in 98% of patients (cumulative, 2559 years; mean, 4.6 ± 3.6 years).

Statistical Methods

All continuous data are presented as mean $\pm$ standard deviation. Group differences were tested by chi-square test for categorical variables and Student *t* test for continuous variables. Kaplan–Meier curves were calculated for survival, freedom from reoperation, and freedom from valve replacement (Prism, GraphPad Inc, San Diego, Calif). Group differences in the Kaplan–Meier analysis were tested by log-rank test.

RESULTS

Three patients died in hospital, for a hospital mortality of 0.5%. These 3 deaths occurred in the 366 operations without annuloplasty (0.8%); none were in patients with annuloplasty. Twelve patients died late; survival at 10 years was 96% after valve repair, 97% after sinotubular junction remodeling and 89% after root remodeling (*P* = .99). The incidence of atrioventricular block requiring pacemaker implantation was 0 of 356 in the initial group and 2 of 193 (1%) in the annuloplasty group.

The addition of annuloplasty to the procedure significantly increased the proportion of aortic valves completely competent or with only trivial regurgitation. This was seen early after isolated repair (*P* = .01) and 12 months postoperatively (*P* = .038; Figure 2) and after root remodeling, both early (*P* = .00018) and at 1 year (*P* = .001; Figure 3). After sinotubular junction remodeling, there was a trend at discharge (*P* = .07) and significant improvement at 12 months (*P* < .001; Figure 4).

Reoperation was necessary for recurrent regurgitation (*n* = 54) or stenosis (*n* = 2). Ten-year freedom from reoperation was significantly inferior after isolated valve repair (70%) compared with sinotubular junction remodeling (93%) or root remodeling (89%; *P* = .0007). Stabilization of the AVJ with suture annuloplasty led to a trend in improved 3-year freedom from reoperation after isolated valve repair from 84% to 92% (*P* = .07; Figure 5). The aortic valve suture had no effect on 3-year freedom from reoperation for the complete cohort or sinotubular junction remodeling and root remodeling.

Complications of the annuloplasty occurred in 5 individuals (2.6%). Four complications occurred in the first 89 individuals; 1 complication was observed in the more recent 104 individuals. Obstruction or distortion of the proximal circumflex artery was observed in 2 patients after isolated

FIGURE 1. Annuloplasty suture as applied in isolated aortic valve repair.

cusp repair, which was treated by removal of the annuloplasty suture. Erosion of the membranous septum occurred in 3 individuals. In 2 patients, a braided polyester suture was used; in 1 patient, a polytetrafluoroethylene suture was used. The patients were treated by patch closure of the septum, in 2 with concomitant aortic valve replacement.

DISCUSSION

Bicuspid anatomy of the aortic valve is not only the most frequent cardiovascular anomaly but also of clinical relevance. Many affected individuals will require aortic valve surgery; treatment of regurgitation or aneurysmal dilatation commonly is necessary at a younger age. The traditional treatment of valve regurgitation has been aortic valve

FIGURE 2. Postoperative degree of AR at discharge and 12 months after isolated aortic valve repair (- annular suture: without annuloplasty, + annular suture: with annuloplasty). AR, Aortic regurgitation.

FIGURE 3. Postoperative degree of AR at discharge and 12 months after sinotubular junction remodeling plus cusp repair (- annular suture: without annuloplasty, + annular suture: with annuloplasty). ST, Sinotubular.

replacement. For concomitant aortic dilatation involving the root, composite replacement of the valve and aorta has been the standard treatment for several decades.¹⁶ Both mechanical and biologic prostheses have been found to carry the risk of valve-related complications of 4% to 5% per patient year.¹⁷ The long-term risk of composite replacement of valve and root with a mechanical prosthesis is more difficult to determine on the basis of published data. It is noteworthy that this seemingly durable solution seems to carry a yearly risk of reoperation of 1%.^{18,19}

Reconstructive surgery has become an attractive alternative to aortic valve replacement because of the absence of anticoagulation and the decreased incidence of valve-related complications.^{5-11,13,15,18-21} BAV repair has evolved over the past 20 years.⁵⁻⁹ Isolated repair of the prolapsing fused cusp initially was performed⁵; later, valve-preserving root replacement⁶ and sinotubular junction remodeling^{7,13} were added to correct concomitant aortic dilatation.

FIGURE 4. Postoperative degree of AR at discharge and 12 months after root remodeling (- annular suture: without annuloplasty, + annular suture: with annuloplasty). AR, Aortic regurgitation.

FIGURE 5. Freedom from reoperation after isolated aortic valve repair (- annular suture: without annuloplasty, + annular suture: with annuloplasty). IA, Isolated aortic valve repair.

After initial enthusiasm over the technical simplicity of repair (1 coaptation line), it was soon realized that the durability of valve repair was limited in a proportion of patients.^{8,9} Different predictors of failure were proposed, and surgical techniques evolved to accommodate or eliminate these risk factors. Nevertheless, some have argued that any repair of BAVs would ultimately be bound to fail because of degeneration into relevant stenosis.²² Our current data do not support this hypothesis in general; up to 16 years postoperatively, stenosis requiring repeat surgical treatment has been rare. Reoperation has mostly been required for recurrent regurgitation.

It was found that prolapse of the nonfused cusp also may be present and require additional correction⁷; the concept of effective height became a helpful addition in our experience.¹² More recently, anatomic characteristics of the valve, such as the diameter of the AVJ or orientation of the 2 normal commissures, predicted valve stability.¹⁰ In particular, marked dilatation of the AVJ, which is frequent in AR, led to a high probability of late repair failure.¹⁰ We have also identified a large AVJ as a risk factor for failure in valve-preserving aortic surgery.¹¹ These findings prompted us to change the operative strategy to explore whether additional stabilization of the AVJ would improve the results of BAV repair further in analogy to the results of ring annuloplasty in mitral repair.

The concept of treating dilatation of the AVJ in aortic valve repair is not new.¹⁴ David and Feindel²¹ created an operation that specifically addressed this aspect. It has been argued that valve reimplantation within a vascular graft would minimize valve failure; in our experience, this did not eliminate the dilated AVJ as a predictor for reoperation.¹¹ The implantation of an external annular support has been propagated as an alternative solution.²³ The results were promising, but the application lacked a well-defined control group.²³ In addition, these 2 approaches may have some drawbacks. Valve reimplantation is an aggressive operation and has been shown to result in abnormal cusp motion.²⁴ This procedure may be difficult to perform if the basal

ring is widely apart from the AVJ,²⁵ which we observe in the right sinus in approximately 20% to 30% of our operations. In these instances, fixation of the valve within the graft is bound to lead to a certain degree of anatomic distortion or would require incising the right ventricle to achieve adequate graft placement. Implantation of an external ring has some advantages over the reimplantation procedure in terms of technical ease; the same anatomic limitations regarding AVJ and basal ring anatomy apply. In addition, many aspects of optimal material and placement are still unclear.²⁶ This was the reason for us to apply a technique of annular support similar to that proposed by Taylor and colleagues¹⁴ and Svensson.¹⁵

Our follow-up data confirmed the hypothesis that suture annuloplasty could reduce and stabilize the AVJ diameter without distortion of the aortic root. For valve-preserving root replacement and sinotubular junction remodeling, our current results do not yet clearly confirm the need for an additional support. Nevertheless, the early results showed a significantly higher proportion of completely competent aortic valves despite significantly larger AVJs. Up to 3 years, this did not translate into a clinical advantage, that is, decreased risk of reoperation. This may be related to some complications as part of the early learning curve in applying the annular suture. Alternatively, one might argue that the durability of valve function in this context was already good, and a longer follow-up would be required to detect a clinical advantage.

A different picture was observed for isolated aortic valve repair. In this subgroup, the proportion of completely competent valves was significantly higher with the annuloplasty. In addition, up to 3 years postoperatively there was a trend toward improved durability, that is, freedom from reoperation. At this time, this trend is not significant, and further follow-up will be necessary to confirm the observations. However, the clinical observations were impressive in that complete stability of aortic valve function and dimensions have been found in the majority of patients.

We have indeed seen complications related to the addition of the annular suture, even though the overall incidence was low. The risk of atrioventricular block was 0.5% and thus similar to aortic valve replacement; it is conceivable that the incidence could be reduced further by completely external placement, thus keeping the annuloplasty further away from the bundle of His. Of greater concern was the erosion of the membranous septum, which occurred in 1.5% of the patients. The mechanism was most likely related to the size of the suture, which will lead to more unfavorable stress distribution compared with a wider annuloplasty device. In addition, the braided polyester has the advantage of tissue ingrowth, but also the known traumatic effect on tissue.

Obstruction of the circumflex artery was related to the suture passed around the circumflex in 1 patient and distortion of the epicardial tissue in 1 patient. The incidence is similar to that of coronary obstruction in mitral repair.²⁷ Although this complication (if recognized early enough) can be treated by removal of the suture, the approach has to be modified to avoid it. If technically feasible, completely external placement with blunt dissection of an external tunnel inferior to the left coronary artery should be able to minimize the risk. We have not observed this complication after root remodeling, for which the suture was always applied externally. In addition, the first such complication has increased our awareness of the problem, which can be detected by paying more attention to ventricular function during intraoperative transesophageal echocardiography. We have developed a low threshold for removing the annuloplasty whenever there were concerns over coronary supply to the lateral wall.

Study Limitations

Limitations are related to the retrospective nature of the current study. A prospective randomized investigation seems justified on the basis of the current results. In addition, the current follow-up and cohort size are limited. Longer follow-up and experience with more patients will be necessary to confirm the current findings.

CONCLUSIONS

This is the first report indicating that suture annuloplasty may be used in conjunction with BAV repair to correct dilatation of the AVJ. The early results indicate a positive effect on the proportion of almost or completely competent aortic valves; there is a trend toward improved valve stability after isolated repair of the aortic cusps. Further research will be necessary to define the best material and best mode of placement for such an annuloplasty to make it a safe routine component of aortic valve repair.

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References

1. Ward C. Clinical significance of the bicuspid aortic valve. *Heart*. 2000;83:81-5.
2. Fenoglio JJ Jr, McAllister HA Jr, DeCastro CM, Davia JE, Cheitlin MD. Congenital bicuspid aortic valve after age 20. *Am J Cardiol*. 1977;39:164-9.
3. Nistri S, Sorbo MD, Marin M, Palisi M, Scognamiglio R, Thiene G. Aortic root dilatation in young men with normally functioning bicuspid aortic valves. *Heart*. 1999;82:19-22.
4. Nkomo VT, Enriquez-Sarano M, Ammass NM, Melton LJ III, Bailey KR, Desjardins V, et al. Bicuspid aortic valve associated with aortic dilatation: a community-based study. *Arterioscler Thromb Vasc Biol*. 2003;23:351-6.
5. Cosgrove DM, Rosenkranz ER, Hendren WG, Bartlett JC, Stewart WJ. Valvuloplasty for aortic insufficiency. *J Thorac Cardiovasc Surg*. 1991;102:571-6.
6. Schäfers HJ, Langer F, Aicher D, Graeter TP, Wendler O. Remodeling of the aortic root and reconstruction of the bicuspid aortic valve. *Ann Thorac Surg*. 2000;70:542-6.
7. Schäfers HJ, Aicher D, Langer F, Lausberg HF. Preservation of the bicuspid aortic valve. *Ann Thorac Surg*. 2007;83:S740-5.
8. Moidl R, Moritz A, Simon P, Kupilik N, Wolner E, Mohl W. Echocardiographic results after repair of incompetent bicuspid aortic valves. *Ann Thorac Surg*. 1995;60:669-72.
9. Casselman FP, Gillinov AM, Akhrass R, Kasirajan V, Blackstone EH, Cosgrove DM. Intermediate-term durability of bicuspid aortic valve repair for prolapsing leaflet. *Eur J Cardiothorac Surg*. 1999;15:302-8.
10. Aicher D, Kuniyara T, Abou Issa O, Brittner B, Gräber S, Schäfers HJ. Valve configuration determines long-term results after repair of the bicuspid aortic valve. *Circulation*. 2011;123:178-85.
11. Kuniyara T, Aicher D, Rodionicheva S, Groesdonk HV, Langer F, Sata F, et al. Preoperative aortic root geometry and postoperative cusp configuration primarily determine long-term outcome after valve-preserving aortic root repair. *J Thorac Cardiovasc Surg*. 2012;143:1389-95.
12. Schäfers HJ, Bierbach B, Aicher D. A new approach to the assessment of aortic cusp geometry. *J Thorac Cardiovasc Surg*. 2006;132:436-8.
13. Asano M, Kuniyara T, Aicher D, El Beyrouti H, Rodionicheva S, Schäfers HJ. Mid-term results after sinotubular junction remodelling with aortic cusp repair. *Eur J Cardiothorac Surg*. 2012;42:1010-5.
14. Taylor WJ, Thrower WB, Black H, Harken DE. The surgical correction of aortic insufficiency by circumcission. *J Thorac Cardiovasc Surg*. 1958;35:192-231.
15. Svensson LG. Sizing for modified David's reimplantation procedure. *Ann Thorac Surg*. 2003;76:1751-3.
16. Bentall H, De Bono A. A technique for complete replacement of the ascending aorta. *Thorax*. 1968;23:338-9.
17. Hammermeister K, Sethi GK, Henderson WG, Grover FL, Oprian C, Rahimtoola SH. Outcomes 15 years after valve replacement with a mechanical versus a bioprosthetic valve: final report of the Veterans Affairs randomized trial. *J Am Coll Cardiol*. 2000;36:1152-8.
18. Karck M, Kallenbach K, Hagl C, Rhein C, Leyh R, Haverich A. Aortic root surgery in Marfan syndrome: comparison of aortic valve-sparing reimplantation versus composite grafting. *J Thorac Cardiovasc Surg*. 2004;127:391-8.
19. Etz CD, Bischoff MS, Bodian C, Roder F, Brenner R, Griep RB, et al. The Bentall procedure: is it the gold standard? A series of 597 consecutive cases. *J Thorac Cardiovasc Surg*. 2010;140:S64-70.
20. Aicher D, Fries R, Rodionicheva S, Schmidt K, Langer F, Schäfers HJ. Aortic valve repair leads to a low incidence of valve-related complications. *Eur J Cardiothorac Surg*. 2010;37:127-32.
21. David TE, Feindel CM. An aortic valve-sparing operation for patients with aortic incompetence and aneurysm of the ascending aorta. *J Thorac Cardiovasc Surg*. 1992;103:617-21.
22. Robicsek F, Thubrikar MJ, Cook JW, Fowler B. The congenitally bicuspid aortic valve: how does it function? Why does it fail? *Ann Thorac Surg*. 2004;77:177-85.
23. Lansac E, Di Centa I, Bonnet N, Leprince P, Rama A, Acar C, et al. Aortic prosthetic ring annuloplasty: a useful adjunct to a standardized aortic valve-sparing procedure? *Eur J Cardiothorac Surg*. 2006;29:537-44.
24. Fries R, Graeter T, Aicher D, Reul H, Schmitz C, Böhm M, et al. In vitro comparison of aortic valve movement after valve-preserving aortic replacement. *J Thorac Cardiovasc Surg*. 2006;132:32-7.
25. Anderson RH. Clinical anatomy of the aortic root. *Heart*. 2000;84:670-3.
26. Schäfers HJ. Aortic annuloplasty—a new aspect of aortic valve repair. *Eur J Cardiothorac Surg*. 2012;41:1124-5.
27. Obarski TP, Loop FD, Cosgrove DM, Lytle BW, Stewart WJ. Frequency of acute myocardial infarction in valve repairs versus valve replacement for pure mitral regurgitation. *Am J Cardiol*. 1990;65:887-90.