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Original Article

Values of osteoprotegerin in aortic valve tissue in patients with significant aortic stenosis depend on the existence of concomitant coronary artery disease

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ABSTRACT

Introduction: Calcific aortic valve stenosis (CAVS) is a serious clinical problem. The strongest predictor of CAVS progression is the amount of calcium in the aortic valve. The pathogenesis of CAVS is largely consistent with the pathogenesis of atherosclerosis; however, about 50% of patients with CAVS do not exhibit significant atherosclerosis. Cardiovascular calcification is currently considered an actively regulated process, in which the important role is attributed to the RANKL/RANK/OPG (receptor activator of nuclear factor κB ligand/RANK/osteoprotegerin) axis. We measured OPG levels in the tissue of calcified, stenotic aortic valves in relation to the presence or absence of coronary artery disease (CAD).

Materials and methods: Aortic valve samples were collected from 105 patients with calcified, mainly severe aortic stenosis, who were divided into two groups according to the presence of CAD. In Group A ($n=44$), there were normal coronary artery findings, while in Group B ($n=61$), there was angiographically demonstrated >50% stenosis of at least one coronary artery. The control Group C ($n=21$) consisted of patients without aortic stenosis and with normal angiographic findings on coronary arteries.

Results: The highest tissue concentrations of OPG [median (pmol/L), 25th–75th percentile] were found in Group A [6.95, 3.96–18.37], which was significantly different compared to the other two groups ($P=.026$ and .001, respectively). The levels of OPG in Group B [4.15, 2.47–9.16] and in Group C [2.25, 1.01–5.08] did not differ significantly ($P=.078$); however, the lowest concentrations of OPG were found in Group C. Neither age nor gender in our study had effect on tissue levels of OPG ($P=.994$ for gender; $P=.848$ for age).

Conclusion: Calcified and narrowed aortic valves, compared to the normal valves, were accompanied by a change in tissue concentrations of OPG, which is, in addition, dependent on the presence or absence of CAD. The highest tissue concentrations of OPG in our work were found in patients with significant aortic stenosis without concomitant CAD.

1. Introduction

Calcific aortic valve stenosis (CAVS) is a serious clinical problem. Of those over 65 years, some degree of aortic stenosis can be found in 2–3% of individuals and up to 25%, in the same age group, who present with nonobstructive aortic valve disease [1–4]. The strongest predictor of CAVS progression is the amount of calcium in the aortic valve [5]. Calcification of the aortic valve is only one form of cardiovascular calcification, which also includes calcification of the intimal layer of arteries in the case of classical atherosclerosis or calcification of the medial layer of arteries in Mönckeberg arteriosclerosis [6]. The pathogenesis of CAVS is largely consistent with the pathogenesis of atherosclerosis; however, about 50% of patients with CAVS do not exhibit significant atherosclerosis [7,8]. Cardiovascular calcification is currently considered an actively regulated process, which resembles bone tissue remodeling and involves a wide range of cells, cytokines, and signal molecules [9,10]. Among them, the important role is now being attributed to RANKL/RANK/OPG (receptor activator of nuclear factor κB ligand/RANK/osteoprotegerin) axis, which was first described in the process

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of bone remodeling. Measuring serum levels of RANKL and OPG were the subject of our previous work dealing with calcium deposition in stenotic aortic valves in relation to the presence or absence of coronary artery disease (CAD) [11]. Based on previous results, this work is devoted to measuring OPG levels in the tissue of calcified stenotic aortic valves in relation to the presence or absence of CAD.

2. Materials and methods

2.1. Patient groups

Aortic valve samples were collected during cardiac surgery from 105 patients with calcified, mainly severe aortic stenosis. The patients were divided into two groups according to the presence of CAD. In Group A ($n=44$), there were normal coronary artery findings, while in Group B ($n=61$), there was angiographically demonstrated >50% stenosis of at least one coronary artery. The control Group C ($n=21$) consisted of patients without aortic stenosis and with normal angiographic coronary artery findings who were heart transplant candidates (mainly due to dilated cardiomyopathy). Patients with bicuspid aortic valve and chronic kidney disease were excluded. Moreover, each patient was tested for renal function and glomerular filtration rate <60 ml/min/1.73 m^2 was also an exclusion criterion. All patients provided a signed informed consent and the study was approved by the ethics committee.

2.2. Tissue samples processing

Aortic valve samples were collected in the operating room immediately after surgical removal. The tissue samples were excised from aortic valve leaflets and deep frozen (−80°C) immediately after withdrawal. The frozen tissue was cut into small pieces and powdered by grinding with a prechilled abrasive material, with the occasional addition of liquid N_2 to prevent thawing. Once the tissue was ground into a fine powder, the extraction solution (1% TRITON-X 100, 1% IGEPAL, 0.03% aminocaproic acid, and 100 mM Tris pH 7.4) was added and the mixture was incubated at room temperature for 1 h. The mixture was then centrifuged at 10,000*g* and 4°C for 10 min and supernatant was immediately analyzed. The concentration of total protein was measured using the BCA method (Sigma-Aldrich) and the concentration of OPG was related to the concentration of total protein in the extract of homogenized tissue. OPG was determined by a commercial Human Osteoprotegerin ELISA kit from Biovendor — Laboratorni Medicina (Brno, Czech Republic) [12,13]. The kit has been validated and consequently used in more than 70 scientific publications. The assay measures total OPG (either free or bound to sRANKL) concentration. The antibodies used in this ELISA are specific for human OPG with no detectable cross-reactivities to human sRANKL and TRAIL (tumor necrosis factor-related apoptosis inducing ligand) at 120 pmol/L. Approximately 1% cross-reactivity with recombinant mouse OPG and less than 0.06% with recombinant human CD40 and recombinant human sTNF RI and sTNF RII have been observed. Determination of OPG does not interfere with hemoglobin (1.0 mg/ml), bilirubin (170 μmol/L), and triglycerides (5.0 mmol/L).

2.3. Statistical analysis

Data are expressed as mean ± standard deviation for continuous variables and as a percentage for categorical variables. OPG values are expressed as median with interquartile range (25th and 75th percentile). The Kruskal–Wallis test was used to compare the values of OPG between all groups (A, B, and control Group C) and the Mann–Whitney test was used to compare Group A and Group B. The analysis of variance applied to logarithmic data of OPG was used when comparing the values of OPG adjusted for other variables (age and gender).

3. Results

3.1. Baseline characteristics

Baseline characteristics of both groups (A and B) including distribution of age and gender in control Group C are summarized in Table 1. From the table, it is apparent that patients in Group B were significantly older with a higher incidence of hypertension and diabetes mellitus. Group A had a conversely higher proportion of patients with severe aortic stenosis (although the difference was not statistically significant), which corresponds to higher flow rates and pressure gradients on aortic valves. It should be noted that all patients in Group A and Group B had at least moderately severe aortic stenosis. In control Group C, patients were significantly younger with a higher proportion of men.

3.2. OPG levels

Levels of OPG in each group are shown in Fig. 1. The highest tissue concentrations of OPG [median (pmol/L), 25th–75th percentile] were found in Group A (6.95, 3.96–18.37). When using the Mann–Whitney test, the levels of OPG in Group B were significantly lower (4.15, 2.47–9.16, $P=.026$), even after adjustment for age and sex ($P=.025$). The lowest tissue concentrations of OPG were achieved in control Group C (2.25, 1.01–5.08), which according to the Kruskal–Wallis test was significantly different from Group A ($P=.001$); however, when compared to Group B, the difference did not reach statistical significance ($P=.078$). The tissue concentrations of OPG in the respective groups with regard to gender and age of the studied individuals are documented in Figs. 2 and 3. In our study, neither age nor gender had effect on tissue levels of OPG ($P=.994$ for gender; $P=.848$ for age).

4. Discussion

OPG is a member of the superfamily of tumor necrosis factors and is produced by various cells (endothelial cells, vascular smooth muscle cells, osteoblasts, etc.) and in different organs [14–16]. OPG acts as a decoy receptor for RANKL, thus inhibiting its interaction with RANK, a transmembrane receptor on the cell surface of cells in the monocyte–

Table 1
Baseline patient characteristics (Group A, Group B, and Group C)

	Group A ($n=44$)	Group B ($n=61$)	Group C ($n=21$)	*P* (A vs. B)
Age (years)	67.3 ± 10.7	71.4 ± 8.4	48.0 ± 13.6	.04
Sex (%, female)	43.2	36.1	19.0	n.s.
BMI (kg/m^2)	27.6	30.0		.02
Cardiovascular risk factors (%)				
Hyperlipidemia	50.0	34.4		n.s.
Hypertension	54.5	77.0		.02
Diabetes mellitus	25.0	45.9		.03
Cardiovascular conditions (%)				
Peripheral vascular disease	4.5	13.1		n.s.
Previous stroke/TIA	6.8	14.8		n.s.
Aortic stenosis severity				
Severe AS (%)	93.2	85.2		n.s.
AS peak velocity (m/s)	4.4 ± 0.8	3.8 ± 0.8		<.01
AS PGmax/mean (mmHg)	77.3 ± 32.7/ 51.3 ± 19.7	60.5 ± 23.6/ 37.5 ± 15.4		<.01
CAD (%)				
Normal angiogram	45.5			
Nonobstructive CAD	54.5			
1-Vessel disease		31.2		
2-Vessel disease		34.4		
3-Vessel disease		26.2		
Left main disease		8.2		

BMI, body mass index; TIA, transient ischemic attack; AS, aortic stenosis; PGmax/mean, peak pressure gradient/mean pressure gradient.

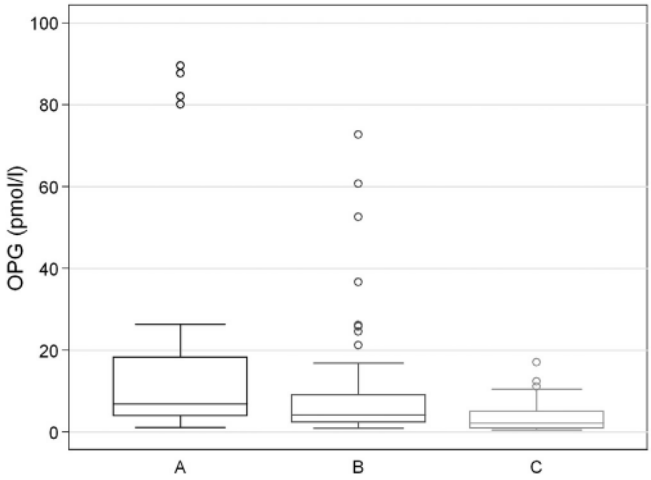

Fig. 1. Osteoprotegerin (OPG) levels in studied groups. Group A — patients with aortic stenosis and normal coronary artery findings; Group B — patients with aortic stenosis and concomitant CAD; Group C — patients without aortic stenosis and with normal coronary artery findings. The data are displayed by box-and-whisker plots. The bottom and top of the box are 25th and 75th percentiles, and the band inside the box is the median. Thus, 50% of observations lie inside the box. The "whiskers" go to the maximum/minimum with the exception of situations when outliers are present. Then the outlying points are displayed individually by the circles. Outliers are defined as the observations that are larger than 75th percentile by at least 1.5 times the interquartile range (IQR) or smaller than 25th percentile by at least 1.5 times the IQR. IQR is defined as 75th percentile minus 25th percentile.

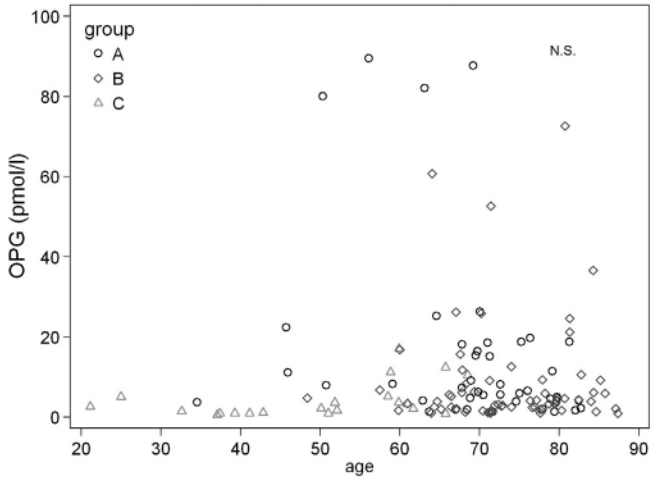

Fig. 3. Osteoprotegerin (OPG) levels in studied groups (A, B, and C) with respect to age. N.S., nonsignificant (P=.994).

macrophage system (e.g., dendritic cells, osteoclasts, and precursors). This affects their differentiation, function, and survival. In addition, OPG exhibits antiapoptotic effects through blockade of TRAIL [17]. OPG is a major regulator of bone remodeling, and more recently, it has been associated with cardiovascular calcification and atherosclerosis [18–22]. Its role in cardiovascular disease is controversial. Experimental data in animal models suggest that OPG is a vascular protective factor, which is capable of reducing atherosclerosis progression and calcium deposition [23,24]. In humans, there are two conflicting interpretations. Several studies have demonstrated a positive correlation between serum OPG levels and other variables such as age, hypertension, diabetes, renal insufficiency, the severity of CAD, and cardiovascular mortality [25–30]. The rise of OPG in the serum may be either causative for cardiovascular disease or it may be an adaptive response to reverse the harmful effects of RANKL, TRAIL, and other known ligands. The relationship between serum OPG levels and the severity of aortic stenosis is less obvious and is most likely influenced by the presence of atherosclerosis. In

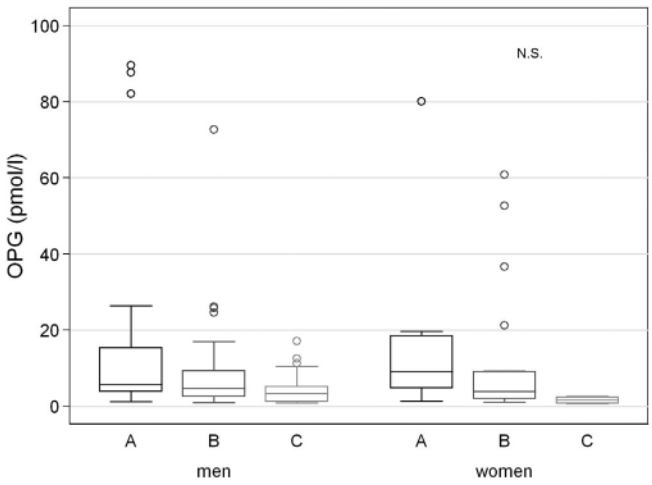

Fig. 2. Osteoprotegerin (OPG) levels in studied groups (A, B, and C) with respect to gender. The data are displayed by box-and-whisker plots. N.S., nonsignificant (P=.848).

our previous study, we observed significantly higher serum OPG levels in patients with aortic stenosis and concomitant coronary atherosclerosis [11]. A different situation arises regarding OPG expression in the tissue of narrowed, calcified aortic valve. OPG expression is common in normal, unaltered valves; however, the observations of authors dealing with this issue in the case of calcified, stenotic valves differ. Most authors observed decreased or even absent OPG production in calcified aortic valves [31,32], while Pohjolainen showed an increased production of OPG in connection with increased severity of aortic stenosis [33]. In our study, we demonstrated that the highest tissue concentrations of OPG were in the group of patients with significant aortic stenosis without concomitant CAD. This group consisted of patients with the most severe degrees of aortic stenosis and the highest load of calcium in aortic valves. Our findings support the hypothesis that worsening of CAVS is accompanied by inhibition of osteoclastogenesis. OPG is upregulated early in disease progression in valve tissue and favors inhibition of osteoclast resorptive activities so mineral is not removed from calcified lesions [34,35]. The question remains whether the rise in tissue concentration of OPG is not an adaptive response and OPG is actually a protective factor. When measuring the tissue levels of OPG, it has to be understood that, besides local production, the circulation is another source from which it can be extracted [36]. The involvement of the same molecules (OPG, RANKL, RANK, and other cytokines) and their extraction from circulation could partially explain the link between CAD and CAVS. It appears that the RANKL/OPG ratio is more important than the level of OPG [17,20]. RANKL and RANK are often not expressed in healthy tissue, but their production increases in valves and blood vessels affected by calcification; thus, the RANKL/OPG ratio increases [31,37–41]. The situation is even more complicated because tissue levels of RANKL do not correlate with serum levels [20]. Thus, in the case of cardiovascular calcification, the rise in serum OPG levels is not accompanied by simultaneous rise in serum RANKL levels.

5. Conclusion

The RANKL/RANK/OPG axis plays an important role in bone remodeling and pathological cardiovascular calcification. CAVS, as the epitome of valvular calcification, is accompanied by a change in the production of individual members of this axis. Besides valvular disease, many other factors, especially the simultaneous presence of atherosclerosis, age, gender, and various comorbidities, can play a significant role. In our study, we demonstrated that the highest tissue concentrations of OPG were in patients with significant aortic stenosis, but without concomitant CAD. These patients showed the most severe degrees of aortic stenosis and the highest load of calcium in aortic valves.

References

[1] NM R, RO B, SH R. Calcific aortic stenosis: an update. Nat Clin Pract Cardiovasc Med 2007;4:254–62.
[2] VT N, JM G, TN S, JS G, CG S, M. E-S. Burden of valvular heart disease: a population-based study. Lancet 2006;368:1005–11.
[3] RO B, BA C, K C, AC dL, DP F, MD F, et al. 2008 focused update incorporated into the ass/aha 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (writing committee to revise the 1998 guidelines for the management of patients with valvular heart disease): endorsed by the Society of Cardiovascular Anesthesiologists, Society of Thoracic Surgeons. Circulation 2008; 118:e523–661.
[4] E B, JB G, R S, P P, G. F. Insights into the use of biomarkers in calcific aortic valve disease. J Heart Valve Dis 2010;19:441–52.
[5] R R, T B, G P, I L, G C, M. S, et al. Predictors of outcome in severe, asymptomatic aortic stenosis. N Engl J Med 2000;343:611–7.
[6] K. A. Media calcification and intima calcification are distinct entities in chronic kidney disease. Clin J Am Soc Nephrol 2008;3:1599–605.
[7] J Q, Z C, J G, J M, S C, B F, et al. Relationship between aortic valve calcification and the severity of coronary atherosclerotic disease. J Heart Valve Dis 2010;19:466–70.
[8] A M, L V, S B. Aortic valve stenosis and coronary artery disease: pathophysiological and clinical links. J Cardiovasc Med (Hagerstown) 2007;8:983–9.
[9] JD M, RM W, DD H. Calcific aortic valve stenosis: methods, models and mechanisms. Circ Res 2011;108:1392–412.
[10] KI B, NM R, DA T. The regulation of valvular and vascular sclerosis by osteogenic morphogens. Circ Res 2011;109:564–77.
[11] Motovska Z, Vichova T, Doktorova M, Labos M, Maly M, Widimsky P. Serum dickkopf-1 signalling and calcium deposition in aortic valve are significantly related to the presence of concomitant coronary atherosclerosis in patients with symptomatic calcified aortic stenosis. J Transl Med 2015;13:63.
[12] Clancy P, Oliver L, Jayalath R, Buttner P, Golledge J. Assessment of a serum assay for quantification of abdominal aortic calcification. Arterioscler Thromb Vasc Biol 2006; 26:2574–6.
[13] Rogers A, Eastell R. REVIEW: circulating osteoprotegerin and receptor activator for nuclear factor κB ligand: clinical utility in metabolic bone disease assessment. J Clin Endocrinol Metab 2005;90:6323–31.
[14] Malyankar UM, Scatena M, Suchland KL, Yun TJ, Clark EA, Giachelli CM. Osteoprotegerin is an alpha vbeta 3-induced. NF-kappa B-dependent survival factor for endothelial cells J Biol Chem 2000;275:20959–62.
[15] Hofbauer LC, Shui C, Riggs BL, Dunstan CR, Spelsberg TC, O'Brien T, et al. Effects of immunosuppressants on receptor activator of NF-kappaB ligand and osteoprotegerin production by human osteoblastic and coronary artery smooth muscle cells. Biochem Biophys Res Commun 2001;280:334–9.
[16] Galeone A, Paparella D, Colucci S, Grano M, Brunetti G. The role of TNF-alpha and TNF superfamily members in the pathogenesis of calcific aortic valvular disease. ScientificWorldJournal 2013;2013:875363.
[17] Collin-Osdoby P. Regulation of vascular calcification by osteoclast regulatory factors RANKL and osteoprotegerin. Circ Res 2004;95:1046–57.
[18] Simonet WS, Lacey DL, Dunstan CR, Kelley M, Chang MS, Lüthy R. Osteoprotegerin: a novel secreted protein involved in the regulation of bone density. Cell 1997;89: 309–19.
[19] Akat K, Kaden JJ, Schmitz F, Ewering S, Anton A, Klomfass S, et al. Calcium metabolism in adults with severe aortic valve stenosis and preserved renal function. Am J Cardiol 2010;105:862–4.
[20] Panizo S, Cardus A, Encinas M, Parisi E, Valcheva P, López-Ongil S, et al. RANKL increases vascular smooth muscle cell calcification through a RANK-BMP4-dependent pathway. Circ Res 2009;104:1041–8.
[21] Adamczyk T, Mizia-Stec K, Mizia M, Haberka M, Chmiel A, Chudek J, et al. Biomarkers of calcification and atherosclerosis in patients with degenerative aortic stenosis in relation to concomitant coronary artery disease. Pol Arch Med Wewn 2012;122: 14–21.
[22] Jono S, Ikari Y, Shioi A, Mori K, Miki T, Hara K, et al. Serum osteoprotegerin levels are associated with the presence and severity of coronary artery disease. Circulation 2002;106:1192–4.
[23] Callegari A, Coons ML, Ricks JL, Yang HL, Gross TS, Huber P, et al. Bone marrow- or vessel wall-derived osteoprotegerin is sufficient to reduce atherosclerotic lesion size and vascular calcification. Arterioscler Thromb Vasc Biol 2013;33:2491–500.
[24] Callegari A, Coons ML, Ricks JL, Rosenfeld ME, Scatena M. Increased calcification in osteoprotegerin deficient smooth muscle cells: dependence on receptor activator of NF-κB ligand and interleukin-6. J Vasc Res 2014;51:118–31.
[25] Browner WS, Lui LY, Cummings SROV. Associations of serum osteoprotegerin levels with diabetes, stroke, bone density, fractures, and mortality in elderly women. J Clin Endocrinol Metab 2001;86:631–7.
[26] Yano K, Tsuda E, Washida N, Kobayashi F, Goto M, Harada A, et al. Immunological characterization of circulating osteoprotegerin/osteoclastogenesis inhibitory factor: increased serum concentrations in postmenopausal women with osteoporosis. J Bone Miner Res 1999;14:518–27.
[27] Fahrleitner-Pammer A, Dobnig H, Piswanger-Soelkner C, Bonelli C, Dimai HP, Leb G, et al. Osteoprotegerin serum levels in women: correlation with age, bone mass, bone turnover and fracture status. Wien Klin Wochenschr 2003;115:291–7.
[28] Avbersek-Luznik I, Malesic I, Rus I, Marc J. Increased levels of osteoprotegerin in hemodialysis patients. Clin Chem Lab Med 2002;40:1019–23.
[29] Knudsen S, Foss C, Poulsen P, Anderson N, Mogensen C, Rasmussen L. Increased plasma concentrations of osteoprotegerin in type 2 diabetic patients with microvascular complications. Eur J Endocrinol 2003;149:39–42.
[30] Kazama JJ, Shigematsu T, Yano K, Tsuda E, Miura M, Iwasaki Y, et al. Increased circulating levels of osteoclastogenesis inhibitory factor (osteoprotegerin) in patients with chronic renal failure. Am J Kidney Dis 2002;39:525–32.
[31] Kaden JJ, Bickelhaupt S, Grobholz R, Haase KK, Sarikoç A, Kiliç R, et al. Receptor activator of nuclear factor kappaB ligand and osteoprotegerin regulate aortic valve calcification. J Mol Cell Cardiol 2004;36:57–66.
[32] Shetty R, Pepin A, Charest A, Perron J, Doyle D, Voisine P, et al. Expression of bone-regulatory proteins in human valve allografts. Heart 2006;92:1303–8.
[33] Pohjolainen V, Taskinen P, Soini Y, Rysä J, Ilves M, Juvonen T, et al. Noncollagenous bone matrix proteins as a part of calcific aortic valve disease regulation. Hum Pathol 2008;39:1695–701.
[34] Otto CM, Kuusisto J, Reichenbach DD, Gown AM, O'Brien KD. Characterization of the early lesion of "degenerative" valvular aortic stenosis. Histological and immunohistochemical studies. Circulation 1994;90:844–53.
[35] Ueland T, Aukrust P, Dahl CP, Husebye T, Solberg OG, Tonnessen T, et al. Osteoprotegerin levels predict mortality in patients with symptomatic aortic stenosis. J Intern Med 2011;270:452–60.
[36] Weiss RM, Lund DD, Chu Y, Brooks RM, Zimmerman KA, El Accaoui R, et al. Osteoprotegerin inhibits aortic valve calcification and preserves valve function in hypercholesterolemic mice. PLoS One 2013;8:e65201.
[37] Dhore CR, Cleutjens JP, Lutgens E, Cleutjens KB, Geusens PP, Kitslaar PJ, et al. Differential expression of bone matrix regulatory proteins in human atherosclerotic plaques. Arterioscler Thromb Vasc Biol 2001;21:1998–2003.
[38] Min H, Morony S, Sarosi I, Dunstan CR, Capparelli C, Scully S, et al. Osteoprotegerin reverses osteoporosis by inhibiting endosteal osteoclasts and prevents vascular calcification by blocking a process resembling osteoclastogenesis. J Exp Med 2000;192:463–74.
[39] Schoppet M, Al-Fakhri N, Franke FE, Katz N, Barth PJ, Maisch B, et al. Localization of osteoprotegerin, tumor necrosis factor-related apoptosis-inducing ligand, and receptor activator of nuclear factor-κB in Monckeberg's sclerosis and atherosclerosis. J Clin Endocrinol Metab 2004;89:4104–12.
[40] Collin-Osdoby P, Rothe L, Anderson F, Nelson M, Maloney W, Osdoby P. Receptor activator of NF-kB ligand and osteoprotegerin expression by human microvascular endothelial cells, regulation by inflammatory cytokines, and role in human osteoclastogenesis. J Biol Chem 2001;276:20659–72.
[41] Tyson K, Reynolds J, McNair R, Zhang Q, Weissberg P, Shanahan C. Osteo/chondrocytic transcription factors and their target genes exhibit distinct patterns of expression in human arterial calcification. Arterioscler Thromb Vasc Biol 2003; 23:489–94.

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Prognostic impact and change of concomitant mitral regurgitation after surgical or transcatheter aortic valve replacement for aortic stenosis

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ABSTRACT

Background: Significant aortic stenosis (AS) is frequently associated with mitral regurgitation (MR) of varying degrees. We sought to assess the change in MR grade after the aortic valve procedure, to find predictors of MR improvement and finally to determine the prognostic impact of persistent MR.
Methods: We retrospectively analyzed a group of 101 AS patients who underwent aortic valve replacement (AVR) or transcatheter aortic valve implantation (TAVI) at our institution between January 2007 and March 2014 and who presented with MR grade 2 or higher on preoperative echocardiogram – 35 patients underwent an isolated AVR, 18 underwent TAVI, and the rest underwent a combined procedure, which included coronary artery bypass grafting. The mean follow-up was 28.5 ± 21 months.
Results: MR improved significantly after the procedures (2.4 ± 0.5 vs. 1.9 ± 0.9, $p < 0.001$) and a decline in the severity of MR was observed regardless of etiology (degenerative/post-rheumatic, functional/ischemic, combined) without significant changes between groups ($p = 0.667$). Downgrading of MR severity was associated with improvement in ejection fraction ($p = 0.021$) and reduction in the size of cardiac chambers, especially the left atrium (left atrial diameter, $p < 0.001$). None of the preoperatively evaluated factors (severity of AS, MR etiology, ejection fraction, cardiac chamber dimensions, coronary artery disease, and New York Heart Association functional class) was a significant predictor of MR improvement. Persistence of higher degrees of MR was associated with a more frequent need for cardiovascular hospitalization, while the survival rate 3 years after procedure was not affected ($p = 0.146$).
Conclusions: In the majority of AS patients, an aortic valve procedure leads to reduction in coexistent MR. A significant decrease in the severity of MR in our study was observed regardless of etiology and preoperative grade of MR. Persistence of higher degrees of MR was associated with increased patient morbidity.

Introduction

Significant aortic stenosis (AS) is frequently associated with mitral regurgitation (MR) of varying degrees. The prevalence of MR is reported in up to 75% of patients undergoing aortic valve replacement (AVR) [1]. Similarly, coexisting moderate to severe MR is frequent in patients undergoing transcatheter aortic valve implantation (TAVI) and the occurrence is reported in 22–48% of patients [2–4]. Severe MR usually requires surgical intervention at the time of AVR; however, in the setting of either moderate degree of MR or excessively high risk of double valve surgery, the mitral valve is often left untreated. A number of factors have to be taken into account when making a decision regarding the extent of surgery. The persistence of moderate to severe MR after an aortic valve procedure is associated with a worse outcome and higher morbidity [5–7]. Double valve surgery is burdened by higher operating and in-hospital mortality compared to isolated AVR [8,9]. Most studies have demonstrated a significant improvement in MR after isolated AVR or TAVI, although only the functional etiology of MR was examined in most of them [10–13]. However,

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not all patients experience a reduction in MR severity and the degree of reduction is not exactly known. For these reasons, we decided to retrospectively analyze group of AS patients that preoperatively presented with MR grade 2 or higher and underwent aortic valve surgery or intervention without mitral valve procedure. Our aims were to (1) assess the change in MR grade after aortic valve procedures, (2) to identify predictors of MR improvement, and (3) finally to determine the prognostic impact of persistent MR with respect to survival and morbidity.

Methods

We retrospectively reviewed 101 AS patients who underwent an aortic valve procedure between January 2007 and March 2014 in our Cardiocenter. All of these patients presented with MR grade 2 or higher on preoperative echocardiogram. In all cases, the indications for surgery or intervention as well as the extent of surgery were discussed during the heart team session. The decision not to intervene on the mitral valve was based either on the degree of MR or unacceptably high risk of double valve surgery. Thirty-five patients underwent isolated AVR, 18 underwent TAVI, and the rest underwent a combined procedure, which included surgical myocardial revascularization (Fig. 1). The mean follow-up was 28.5 ± 21 months and the median follow-up was 24 months. All patients underwent a standard preoperative examination including transthoracic echocardiography and selective coronarography. Most patients also had preoperative transesophageal echocardiography with a more accurate assessment of the etiology and severity of MR. The severity of MR was determined according to current guidelines integrating structural, Doppler, and quantitative parameters (regurgitation jet evaluation in color flow mapping, pulse wave, and continuous wave Doppler examination, width of vena contracta, and regurgitant orifice area measurement – PISA method). MR severity was graded as follows: 0 = none, 1 = mild, 2 = mild to moderate, 2.5 = moderate, 3 = moderate to severe, and 4 = severe. The etiology of MR was based on the presence of morphological changes of the mitral valve apparatus considered typical for degenerative or post-rheumatic disease. The determination of a functional or ischemic etiology of MR was based on the absence of structural changes. The combined etiology of MR was considered in the case of coexistence of functional and morphological changes. Linear dimensions of cardiac chambers (internal dimension of the left ventricle and anteroposterior dimension of the left atrium) were measured in the parasternal long-axis view using two-dimensional echocardiography. Left ventricle ejection fraction (EF) was assessed using the biplane method of disks (modified Simpson's rule) where feasible. In rare cases with a poorly visible endocardium, the EF was estimated. In patients with AVR, a bioprosthesis or mechanical prosthesis was inserted at the discretion of the surgeon and patient preference. The subgroup of patients, whose operative risk was too high, underwent TAVI with a CoreValve ReValving (Medtronic, Dublin, Ireland) system implantation. After surgery or intervention, all patient follow-ups were monitored by our institution's specialized ambulatory department. Post-procedure echocardiography examination was performed in 94% of patients (5 patients died before examination, 1 patient was a no-show) during the first year after procedure, not earlier than one month after the procedure (the median was 2 months). We also monitored all post-procedure hospitalizations at our institution. Mortality data were obtained from a database maintained by the Institute of Health Information and Statistics of the Czech Republic.

The research was carried out according to the principles of the Declaration of Helsinki. Patients gave informed consent and the ethics committee of University Hospital Kralovske Vinohrady in Prague (Czech Rep.) approved the study.

Statistical analysis

Data are expressed as mean ± standard deviation for continuous variables and as a percentage for categorical variables. Continuous variables (EF, cardiac chamber dimensions) were compared using the paired *t*-test with a significance level (*p*-value) < 0.05. The change in MR grade was tested using Bowker and Wilcoxon paired tests. Relationships between changes in the degree of MR and changes in specific parameters (EF, cardiac chamber dimensions) as well as the influence of preoperative factors on changes in MR grade were tested using a robust variant of linear regression and multiple linear regression. The prognostic value of procedural-related MR changes was tested using logistic regression; survival rates were estimated, and graphed, using the Kaplan–Meier method. Survival rates were compared using the log-rank test.

Results

Baseline characteristics, including echocardiographic data, are summarized in Table 1. As shown, the predominance of patients in our cohort had mild to moderate (grade 2) MR pre-procedurally and the most frequent etiology was degenerative followed by combined etiology. The majority of patients with degenerative etiology of MR had various extent of annular calcification with leaflet thickening and only the minority (8 patients) had anterior or posterior leaflet prolapse. Table 2 summarizes the echocardiographic variables that were compared before and after procedures. This comparison was made only in those patients ($n = 95$) whose echocardiographic data were available both before and after procedure. As shown, EF, left ventricular end-diastolic diameter (LVEDD), and left atrial diameter (LAD) did not differ significantly, although there was a trend toward reduced size, particularly, in left atrial dimensions ($p = 0.052$ for indexed value).

Change in MR

Quantitative changes in MR are shown graphically in Fig. 2. The majority of patients (59%) experienced an improvement in MR post-procedure. MR remained unchanged in 24% of patients, worsened in 12% of patients, and 5% of patients died before their scheduled postoperative echocardiographic examination. Overall, there was a statistically significant reduction in the degree of MR

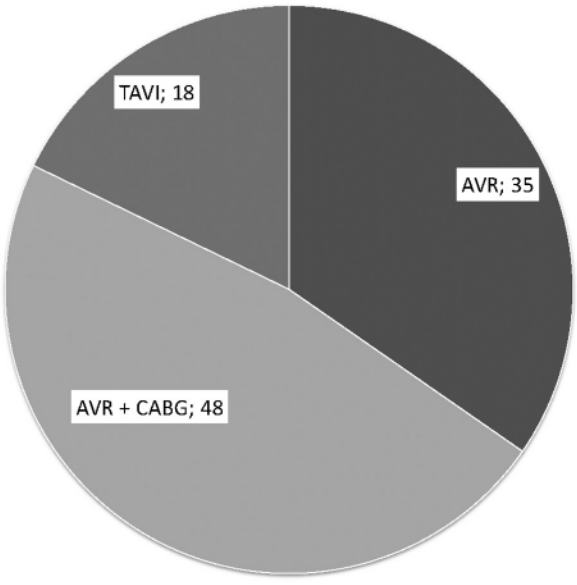

Fig. 1. Procedures. Thirty-five patients underwent isolated aortic valve replacement (AVR), 18 transcatheter aortic valve implantation (TAVI), and the rest (48) combined procedure – AVR + coronary artery bypass grafting (AVR + CABG).

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Table 1
Baseline patient characteristics.

Age (y) (n = 101)	76.1 ± 8.2
Sex – male, n (%)	60 (59.4)
BSA (m^2) (n = 101)	1.9 ± 0.2
BMI (kg/m^2) (n = 101)	28.1 ± 5.3
Cardiovascular risk factors, n (%)	
Hyperlipidemia	39 (38.6)
Hypertension	76 (75.2)
Diabetes mellitus	35 (34.7)
Cardiovascular conditions, n (%)	
Previous MI	24 (23.8)
Previous PCI	5 (5.0)
Previous CABG	6 (5.9)
Peripheral vascular disease	10 (9.9)
Previous stroke/TIA	5 (5.0)
NYHA class I	14 (13.9)
NYHA class II	24 (23.7)
NYHA class III	49 (48.5)
NYHA class IV	14 (13.9)
Noncardiac conditions, n (%)	
Renal insufficiency	15 (14.9)
Echocardiographic parameters	
Peak AV velocity (m/s) (n = 101)	4.0 ± 0.8
Peak AV gradient (mmHg) (n = 101)	66.5 ± 25.5
Mean AV gradient (mmHg) (n = 101)	42.4 ± 17.2
MR grade 2, n (%)	55 (54.4)
MR grade >2, n (%)	46 (45.6)
MR degenerative, n (%)	47 (46.5)
MR ischemic/functional, n (%)	20 (19.8)
MR post-rheumatic, n (%)	3 (3.0)
MR combined, n (%)	31 (30.7)

BSA, body surface area; BMI, body mass index; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; TIA, transient ischemic attack; NYHA, New York Heart Association; AV, aortic valve; MR, mitral regurgitation.

Table 2
Comparison of echocardiographic parameters.

Echocardiographic parameter	Pre-procedure	Post-procedure	Difference	P value
EF (%) (n = 95)	51.3 ± 13.4	52.6 ± 10.7	1.4 ± 8.6	0.126
LVEDD (mm) (n = 95)	51.9 ± 7.3	51.0 ± 6.6	−0.9 ± 5.4	0.115
LVEDDi (mm/m^2) (n = 95)	27.4 ± 3.5	27.0 ± 3.7	−0.4 ± 3.0	0.195
LAD (mm) (n = 95)	46.6 ± 6.0	45.7 ± 5.5	−0.9 ± 5.4	0.107
LADi (mm/m^2) (n = 95)	24.8 ± 4.0	24.2 ± 3.2	−0.6 ± 2.8	0.052
MR grade (n = 95)	2.4 ± 0.5	1.9 ± 0.9	−0.5 ± 0.8	<0.001

EF, ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVEDDi, left ventricular end-diastolic diameter – indexed value; LAD, left atrial diameter; LADi, left atrial diameter – indexed value, MR, mitral regurgitation.

post-procedure (2.4 ± 0.5 vs. 1.9 ± 0.9, $p < 0.001$). Preoperatively, 45.6% of patients had an MR grade >2, while after the procedure, the value had fallen to 27% of patients. When we focused on patients (a total of 14 patients) with higher degrees of MR (≥ 3), we found that 8 patients experienced improvement in MR, no change was observed in 5 patients, and MR worsened in 1 case. This shows that even in those with more severe MR, there was significant improvement after aortic valve procedures (3.3 ± 0.4 vs. 2.6 ± 0.9, $p = 0.020$). With regard to the etiology of MR, we observed a significant decrease in the degree of MR across all etiologies without significant changes between groups ($p = 0.667$) (Table 3). It can be assumed that a change in MR severity, after an aortic valve procedure, will be accompanied by a change in EF and dimensions of the heart cavities. Using a linear regression method, we observed a significant association between the reduction of MR and improvement in EF ($p = 0.021$) as well as a reduction in the size of the cardiac chambers

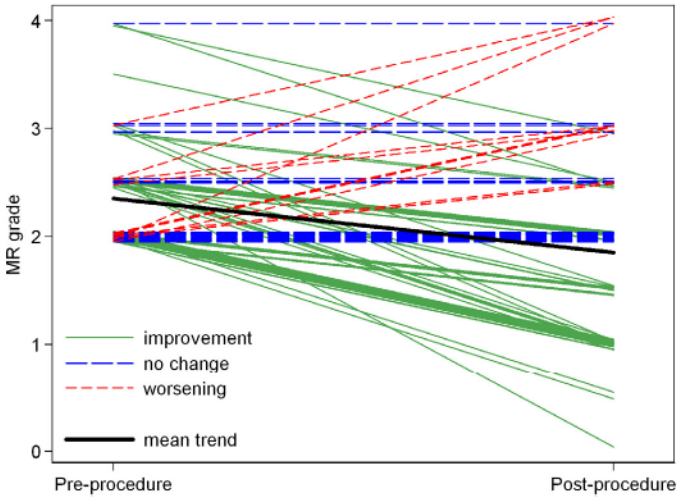

Fig. 2. Change of mitral regurgitation (MR) in patients undergoing aortic valve procedure. The pre-procedural and post-procedural grades of MR for individual patients undergoing aortic valve procedure were plotted.

(LVEDD, $p = 0.014$; LVEDD indexed, $p = 0.019$; LAD, $p < 0.001$; LAD indexed, $p = 0.001$). The most significant association was found in the size of the left atrium, which alone remained significant when multiple regression analysis was used (LAD, $p = 0.006$; LAD indexed, $p = 0.008$).

Predictors of improvement in MR

The aim was also to identify factors that predict improvement in MR after an aortic valve procedure. We studied quantitative indicators of AS severity (peak aortic velocity and pressure gradients), the etiology of MR, heart chamber dimensions, EF, pre-procedural New York Heart Association functional class, and the extent of coronary artery disease. Our analysis was unable to confirm that any of these variables could be used as predictors of improvement in MR after aortic valve procedures. The association between the average change in MR, the number of affected coronary arteries, and the type of procedure is shown in Table 4. As shown, three-vessel disease and the TAVI procedure were associated with lesser degrees of MR change, but it was not statistically significant.

Prognostic impact of MR

We reviewed all cardiovascular hospitalizations at our institution and particularly hospitalizations for heart failure in our cohort of patients. As shown in Table 5, we found higher morbidity (more hospital admissions) for patients, whose MR did not improve after their aortic valve procedure. From the table, it is obvious that in the group of patients who were hospitalized after the procedure, virtually no improvement in MR had occurred compared to

Table 3
Change in MR according to etiology.

Etiology of MR	n	MR grade pre-procedure	MR grade post-procedure	Difference	P value
Degenerative/ post-rheumatic	48	2.36	1.88	−0.48	<0.001
Ischemic/ functional	19	2.29	1.66	−0.63	0.001
Combined	28	2.36	1.91	−0.45	<0.05

MR, mitral regurgitation.

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Table 4
Predictors of Improvement in MR.

Predictor	Change in MR per patient (n=95)	P value
Number of diseased coronary arteries		
0	−0.53	0.409
1	−0.60	
2	−0.73	
3	−0.25	
Procedure		
AVR	−0.56	0.557
AVR+CABG	−0.55	
TAVI	−0.26	

MR, mitral regurgitation; AVR, aortic valve replacement; CABG, coronary artery bypass grafting; TAVI, transcatheter aortic valve implantation.

Table 5
Prognostic Impact of MR.

	Change in MR per patient (n=95)	P value
Cardiovascular hospitalization		
+	−0.05	0.007
−	−0.62	
Heart failure hospitalization		
+	+0.29	0.001
−	−0.61	

MR, mitral regurgitation.

hospitalization-free patients, who had MR reduced by 0.6 degrees, on average. Additionally, in patients hospitalized for congestive heart failure, MR was seen to have worsened, with an average change of 0.3 degrees per patient. In summary, compared to patients with MR improvement, those with worse MR had a higher hospitalization rate. Three-year survival rates are shown in Fig. 3. Thirty-day all-cause mortality in our cohort was 6.93%, and one-year mortality was 14.61%. When survival of patients based on improved MR vs. not improved MR was compared, statistically significant differences during the 3 years were not achieved (p = 0.146) (Fig. 4). It can be concluded that persistent MR had a negative effect on morbidity but its effect on mortality was not significant.

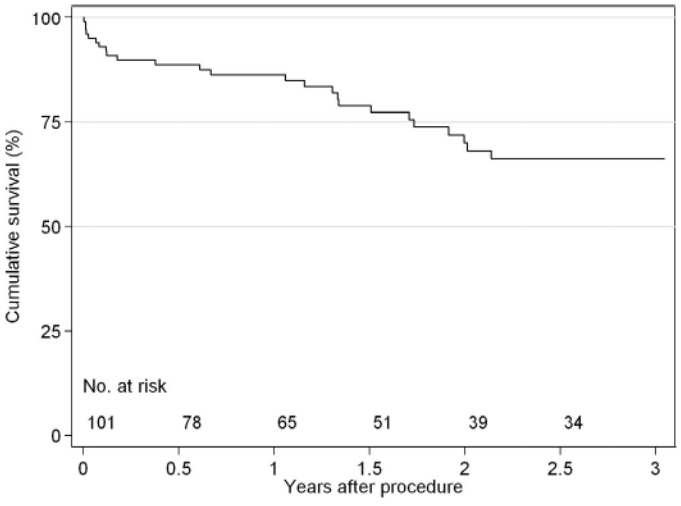

Fig. 3. Kaplan–Meier curve for survival in patients after aortic valve procedure.

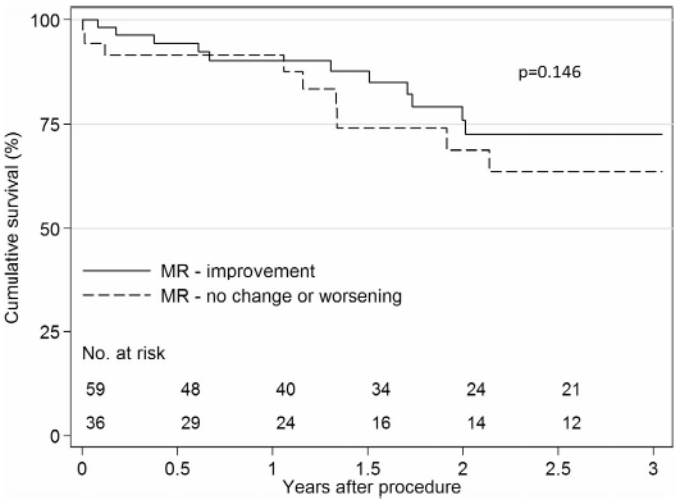

Fig. 4. Kaplan–Meier curves for survival in patients according to the change in mitral regurgitation (MR).

Discussion

Our study confirmed, like previous studies, a significant reduction in MR grade after aortic valve procedures. MR was improved in 59% of patients, and the average decrease in MR severity was 0.5 degrees. Kaczorowski et al. [14] found virtually the same reduction in MR severity after AVR (0.54 degrees). Barbanti et al. [15] observed improvement in MR after AVR in 69.4% of patients and after TAVI in 57.7% of patients. Waisbren et al. [16] found improvement in MR after AVR in 66% of patients. Clearly to the contrary, Wyler et al. [17] found improvement in MR, after AVR, in only 23% of patients. Most of the studies dealing with this issue included only patients with functional MR, in which the severity of regurgitation is more affected by hemodynamic situation. In everyday clinical practice, the combination of degenerative and functional changes of mitral valve is more frequent, but the recommendation how to manage these patients is lacking. In our study with the predominance of degenerative MR, the improvement in MR severity was observed regardless of etiology. This could be particularly important in polymorbid elderly patients with degenerative AS and MR, where double valve surgery can be burdened by an unacceptably high risk. On the other hand, it should be anticipated that the decrease in MR after isolated AVR will be only slight. Our results could also be helpful in deciding whether to address moderate degrees of MR in the presence of significant AS. Of course, many factors (age, coronary artery disease, comorbidities, patient's preference, etc.) all contribute to the final decision; however, our opinion based on the presented results, is to not intervene in MR grade 2/4 cases. It should be mentioned that only a minority of our patients had mitral valve prolapse; therefore, the results are not applicable to all types of degenerative mitral valve disease.

Several studies have identified factors that appear to predict improvement or worsening of MR after an aortic valve procedure. Ruel et al. [6] identified preoperative variables (larger size of the left atrium, the presence of permanent atrial fibrillation, and lower aortic valve pressure gradients) that were often associated with higher grades of MR postoperatively and which, in combination with MR, contributed to a worse prognosis. Many other works dealing with this issue have identified other factors, which in turn predicted MR improvement after surgery. These were mainly the absence of pulmonary hypertension [10,13], functional or ischemic etiology of MR [13,18], the absence of atrial fibrillation [13,19], the absence of calcification of the mitral valve [10], and a higher mean

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aortic valve pressure gradient [13]. In our setting, we tested quantitative parameters of aortic stenosis severity, MR etiology, preoperative heart chamber dimensions, EF, preoperative New York Heart Association functional class, and the extent of coronary artery disease, but none of these factors was found to be a statistically significant predictor of changes in the degree of MR post-procedure. The fact that we failed to identify factors that predict a change in the degree of MR is one of the major limitations of our study. Although we know that, on average, there was a decline in the degree of MR, we were not able to identify patients in whom this change would occur. Generally, previous studies on this subject have agreed that the presence of moderate or higher MR in AS patients before an aortic valve procedure carries a worse prognosis during the postoperative period, which manifested as either higher mortality [5,7,15,19–21] or higher morbidity [6]. Khawaja et al. [7] observed lower mortality rates in patients who experienced improvement in MR compared to those, who did not. In our group of patients, we observed a higher frequency of cardiovascular hospitalization and particularly, hospitalization for heart failure, in patients in whom higher degrees of MR persisted post-procedure. We also compared survival rates relative to procedure-related changes in MR; however, statistically significant differences were not found.

Conclusions

Surgical or transcatheter aortic valve procedures in AS patients lead, in most cases, to a reduction in coexistent MR. Based on our results, one can expect a reduction in the severity of MR of about one-half of a degree, on average. In contrast with other studies, we included patients not only with functional but also with other etiologies of MR (degenerative, combined, and post-rheumatic) and found significant decrease in the severity of MR regardless of etiology. Factors that can preoperatively identify patients who will experience an improvement in MR remain elusive and certainly need to be the subject of future research. Persistence of higher degrees of MR post-procedure is associated with increased morbidity, which was seen in our study as a higher frequency of cardiovascular hospitalizations.

Authors contributions

RF carried out substantial contribution to the study conception and design, analysis and interpretation the data, and drafting of manuscript; ZM carried out substantial contribution to the study conception and design, and analysis and interpretation of the data; PB participated in acquisition of data; MM performed the statistical analysis; ZS revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Disclosures

The authors declare that there is no conflict of interest.

References

[1] Moazami N, Diodato MD, Moon MR, Lawton JS, Pasque MK, Herren RL, Guthrie TJ, Damiano RJ. Does functional mitral regurgitation improve with isolated aortic valve replacement? J Card Surg 2004;19:444–8.
[2] Gurvitch R, Wood DA, Tay EL, Leipsic J, Ye J, Lichtenstein SV, Thompson CR, Carere RG, Wijesinghe N, Nietlispach F, Boone RH, Lauck S, Cheung A, Webb JG. Transcatheter aortic valve implantation: durability of clinical and hemodynamic outcomes beyond 3 years in a large patient cohort. Circulation 2010;122:1319–27.
[3] Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Brown DL, Block PC, Guyton RA, Pichard AD, Bavaria JE, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 2010;363:1597–607.
[4] Webb JG, Pasupati S, Humphries K, Thompson C, Altwegg L, Moss R, Sinhal A, Carere RG, Munt B, Ricci D, Ye J, Cheung A, Lichtenstein SV. Percutaneous transarterial aortic valve replacement in selected high-risk patients with aortic stenosis. Circulation 2007;116:755–63.
[5] Barreiro CJ, Patel ND, Fitton TP, Williams JA, Bonde PN, Chan V, Alejo DE, Gott VL, Baumgartner WA. Aortic valve replacement and concomitant mitral valve regurgitation in the elderly: impact on survival and functional outcome. Circulation 2005;112:1443–7.
[6] Ruel M, Kapila V, Price J, Kulik A, Burwash IG, Mesana TG. Natural history and predictors of outcome in patients with concomitant functional mitral regurgitation at the time of aortic valve replacement. Circulation 2006;114:I-I541.
[7] Khawaja MZ, Williams R, Hung J, Arri S, Asrress KN, Bolter K, Wilson K, Young CP, Bapat V, Hancock J, Thomas M, Redwood S. Impact of preprocedural mitral regurgitation upon mortality after transcatheter aortic valve implantation (TAVI) for severe aortic stenosis. Heart 2014;100:1799–803.
[8] Galloway AC, Grossi EA, Baumann FG, LaMendola CL, Crooke GA, Harris LJ, Colvin SB, Spencer FC. Multiple valve operation for advanced valvular heart disease: results and risk factors in 513 patients. J Am Coll Cardiol 1992;19:725–32.
[9] Mueller XM, Tevaearai HT, Stumpe F, Fischer AP, Hurni M, Ruchat P, von Segesser LK. Long-term results of mitral-aortic valve operations. J Thorac Cardiovasc Surg 1998;115:1298–309.
[10] Tassan-Mangina S, Metz D, Nazeyllas P, Torossian F, Pop C, Bertrand J, Baehrel B, Elaerts J. Factors determining early improvement in mitral regurgitation after aortic valve replacement for aortic valve stenosis: a transthoracic and transesophageal prospective study. Clin Cardiol 2003;26:127–31.
[11] Harris KM, Malenka DJ, Haney MF, Jayne JE, Hettleman B, Plehn JF, Griffin BP. Improvement in mitral regurgitation after aortic valve replacement. Am J Cardiol 1997;80:741–5.
[12] Tunick PA, Gindea A, Kronzon I. Effect of aortic valve replacement for aortic stenosis on severity of mitral regurgitation. Am J Cardiol 1990;65:1219–21.
[13] Toggweiler S, Boone RH, Rodés-Cabau J, Humphries KH, Lee M, Nombela-Franco L, Bagur R, Willson AB, Binder RK, Gurvitch R, Grewal J, Moss R, Munt B, Thompson CR, Freeman M, et al. Transcathether aortic valve replacement: outcomes of patients with moderate or severe mitral regurgitation. J Am Coll Cardiol 2012;59:2068–74.
[14] Kaczorowski DJ, MacArthur JW, Howard J, Kobrin D, Fairman A, Woo YJ. Quantitative evaluation of change in co-existent mitral regurgitation after aortic valve replacement. J Thorac Cardiovasc Surg 2013;145:341–8.
[15] Barbanti M, Webb JG, Hahn RT, Feldman T, Boone RH, Smith CR, Kodali S, Zajarias A, Thompson CR, Green P, Babaliaros V, Makkar RR, Szeto WY, Douglas PS, McAndrew T, et al. Impact of preoperative moderate/severe mitral regurgitation on 2-year outcome after transcatheter and surgical aortic valve replacement. Insight from the Placement of Aortic Transcatheter Valve (PARTNER) Trial Cohort A. Circulation 2013;128:2776–84.
[16] Waisbren EC, Stevens LM, Avery EG, Picard MH, Vlahakes GJ, Agnihotri AK. Changes in mitral regurgitation after replacement of the stenotic aortic valve. Ann Thorac Surg 2008;86:56–62.
[17] Wyler S, Emmert MY, Biaggi P, Seifert B, Grünenfelder J, Falk V, Salzberg S. What happens to functional mitral regurgitation after aortic valve replacement for aortic stenosis? Heart Surg Forum 2013;16:E238–42.
[18] Vanden Eynden F, Bouchard D, El-Hamamsy I, Butnaru A, Demers P, Carrier M, Perrault LP, Tardif JC, Pellerin M. Effects of aortic valve replacement for aortic stenosis on severity of mitral regurgitation. Ann Thorac Surg 2007;83:1279–84.
[19] Jeong DS, Park PW, Sung K, Kim WS, Yang JH, Jun TG, Lee YT. Long-term clinical impact of functional mitral regurgitation after aortic valve replacement. Ann Thorac Surg 2011;92:1339–45.
[20] Harling L, Saso S, Jarral OA, Kourliouros A, Kidher E, Athanasiou T. Aortic valve replacement for aortic stenosis in patients with concomitant mitral regurgitation: should the mitral valve be dealt with? Eur J Cardiothorac Surg 2011;40:1087–96.
[21] Hutter A, Bleiziffer S, Richter V, Opitz A, Hettich I, Mazzitelli D, Ruge H, Lange R. Transcatheter aortic valve implantation in patients with concomitant mitral and tricuspid regurgitation. Ann Thorac Surg 2013;95:77–84.

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