JGG 2017;65:192-197

Review

Calcific aortic stenosis: a peculiar feature of diastolic heart failure in the elderly

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Calcific aortic stenosis represents the most frequent valvular heart disease and one of the major cause of morbidity and mortality in the elderly. Aortic stenosis results from active biological events, characterized by lipid infiltration, inflammation, neoangiogenesis, endothelial dysfunction and bone deposition. The reduced mobility of aortic valve leaflets produces a fixed obstruction at the outflow, with a consequent remodelling of the left ventricle. The degree of left ventricle hypertrophy and fibrosis results in different degree of diastolic dysfunction and heart failure. Thus, the response of the left ventricle to the pressure overload guides the clinical status and the prognosis of patients with aortic stenosis. After aortic valve replacement hypertrophy and fibrosis partially regress, however the maladaptive LV remodelling strongly impacts the prognosis even after surgery. This review outlines the importance in the evaluation of the left ventricle in patients with severe aortic stenosis, exploring the pathophysiology of the transition from adaptive to maladaptive remodelling.

Key words: Aortic stenosis, Elderly, Diastolic dysfunction, Myocordial fibrosis, Left ventricular hypertrophy

AORTIC STENOSIS: EPIDEMIOLOGY AND PATHOPHYSIOLOGY

Aortic stenosis (AS) represents the most prevalent valve heart disease in Western countries [1]. In the elderly, severe AS is a major cause of morbidity and mortality, including sudden death, and its prevalence rises to 3% in patients over age of 80 years [2]. In developed countries, the degenerative aetiology is the most frequent (82%), followed by rheumatic (11%) and congenital (5%) [3]. Nevertheless, it is important to emphasize that calcification of aortic valve (AV) is not only a consequence of aging, but several pro-atherosclerotic factors may account for this degenerative process, such as arterial hypertension, hypercholesterolemia, smoking, etc. Therefore, in the initial phase of the disease, the degeneration of AV leaflets is a part of a diffuse atherosclerotic process [4]. Afterwards, a series of active biological events, such as lipid infiltration, inflammation, neoangiogenesis, endothelial dysfunction and bone deposition lead to a progressive AV calcification [5-9]. Hemodynamic stress and the consequent endothelial damage whit lipid infiltration are probably the first events in the AV calcification process. Microscopic observations in early stenotic valve show the presence of chronic inflammatory cells, lipids, disorganized collagen fibres, proteins of extracellular bone matrix, and bone minerals [10].

Increased levels of oxidized low-density lipoproteins promote inflammatory response and mineralization activity [11], inducing the transition of valvular fibroblasts to an osteoblastic phenotype [12 13]. Recent evidence suggests that low-grade inflammation, promoted by dysregulation of visceral adiposity, has an important role in the AV atherosclerotic process [14-17]. In this regard, we have recently demonstrated that increased echocardiographic thickness of epicardial adipose tissue, the visceral fat depot of the heart, is correlated with the presence of severe AS and is directly correlated with the secreted levels of inflammatory mediators [18].

Received: October 10, 2016 - Accepted: June 5, 2017

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Epicardial adipose tissue, being a source of both inflammatory mediators and cathecolamines [19] may also have an important role in cardiac dysfunction and heart failure (HF) progression.

THE LEFT VENTRICLE REMODELLING IN AORTIC STENOSIS

The presence of AS induces an abnormal and protract pressure overload upon the left ventricle, that results in systolic and diastolic dysfunction. These abnormalities exacerbate the well known adverse myocardial remodelling occurring with age [20]. In the early phase of AS the main compensatory mechanisms are represented by concentric left ventricular hypertrophy (LV) and elevation of end-diastolic pressure. The protracted pressure overload induces changes in the myocardial extracellular matrix leading to progressive myocardial fibrosis and decreasing LV compliance [21]. Thus, the initial adaptive remodelling becomes maladaptive with increased LV hypertrophy, myocardial fibrosis, heart failure [21], and worsening prognosis [22 23]. However, the degree of LV hypertrophy appears to be more closely associated to age, male sex, diabetes and obesity rather than severity of AS [24-27]. It is important to underline that in the elderly the presence of comorbidities [28], such as diabetes, hypertension, increased arterial stiffness, can influence cardiac overload and worse left ventricular response to AS. Myocyte apoptosis and fibrosis are supposed to mark the transition from hypertrophy to heart failure with the consequent onset of symptoms [29]. Interestingly, the degree of myocardial fibrosis secondary to AS seems to condition the presence and the progression of LV systolic dysfunction. Studies exploring the effects of longstanding pressure overload secondary to hypertensive heart disease [30] and AS [29] suggest that fibrosis is increased in patients with reduced LV ejection fraction. Fibrosis occurs after myocyte apoptosis [31], and areas of fibrosis are observed to co-localize with areas of myocyte loss. Of note, the presence of mid-wall fibrosis is associated with a significant increase in mortality [31 32]. It is reasonable to hypothesize that fibrosis is associated to adverse prognosis not only because it increases LV stiffness but also because it is associated to an increased risk of cardiac arrhythmias [32 33].
Furthermore, the magnitude and chronicity of the increased LV filling pressure are associated with an increase in left atrial size [34 35], which has been shown to predict postoperative symptomatic improvement [36] and subsequent prognosis in AS patients [37].

THE LEFT VENTRICLE: BIOMARKERS OF DECOMPENSATION

The progressive LV decompensation in AS is driven primarily by two processes: myocyte death and myocardial fibrosis [38]. Therefore, biomarkers of LV stress/damage could be helpful in the identification of those patients with more advanced disease. The increased LV wall stress determines an elevation of the circulating levels of brain natriuretic peptide (BNP) and the related N-terminal fragment of proBNP (NT-proBNP) which are widely used in the diagnosis and management of heart failure [39-42]. In particular, several studies in AS patients, demonstrated that BNP levels increase along with the transition from LV hypertrophy to heart failure [43-47], thus suggesting an important role for natriuretic peptides in the evaluation of patients with severe AS and equivocal symptoms. Myocardial ischemia due to inadequate microcirculation [48 49] promotes myocardial loss. Myocyte death is believed to be one of the key factors driving LV decompensation in AS, thus high-sensitivity troponin T is indicated as a valuable marker of myocardial damage. Some studies [50 51] suggested that troponin levels are correlated with LV mass, myocardial fibrosis, severity of AS, and are predictive of adverse outcome. Furthermore, neurohormonal activation represents a putative additional mechanism of cell death [52-57] and may offer important prognostic indications in heart failure [58].
It is widely established that the presence and the extent of fibrosis are absolutely relevant in the transition from hypertrophy to heart failure. Unfortunately, biomarkers of fibrosis have not an established role in AS patients. Recently, Galectin-3, a member of the lectin family and important mediator of myocardial fibrosis, emerged as a potentially useful prognostic marker in patients with heart failure [59-61].

EVALUATION OF SYMPTOMS

Echocardiography is the key tool for the diagnosis and evaluation of AV disease and clinical decision-making is based on echocardiographic evaluation of AS severity [62].
Once the diagnosis of severe AS is achieved, a careful evaluation of symptoms becomes mandatory. Guidelines clearly establish that the onset of symptoms represents the indication to valve replacement, although, especially in elderly patients, there is often a reluctance to recommend valve replacement due to the supposed high surgical risk. The prognosis of AS dramatically changes with the onset of symptoms such as angina, syncope and dyspnoea [63]. However, clinical manifestation is frequently insidious at the onset and can be

highly variable among patients with similar degrees of valve stenosis. In many patients, the first and subtle symptom is represented by a reduced exercise tolerance [64] and consequently symptoms evaluation is particularly challenging because in this population the daily life activity is strongly conditioned by the presence of comorbidities [65-67].

Exercise testing may add important information in 'supposed' asymptomatic patients allowing to recognize exercise-related symptoms due to AS and unmask the reduced exercise capacity. In particular, in old sedentary patients, exercise-induced angina, early excessive dyspnea, dizziness or syncope are compatible with symptoms of AS. It is important to underline that the risk of exercise testing is low in asymptomatic patients with AS as reported in numerous prospective and retrospective studies. Exercise testing should not be performed in symptomatic patients with AS when the aortic mean pressure gradient ≥ 40 mmHg, due to high risk of complications, comprising syncope, ventricular tachycardia, and death [68 69].

LEFT VENTRICULAR REMODELLING AFTER SURGERY

AV replacement (AVR) is followed by immediate hemodynamic improvement due to afterload reduction and improved active myocardial relaxation. However the regression of hypertrophy and the amelioration of diastolic function require more time [70]. The hypertophy regression is more precocious and a marked reduction in LV mass usually occurs within 18 months from AVR [71-73]. However, some authors described that a regression of muscular tissue was observed after surgery while fibrous tissue remained unchanged [74]. Consequently, after surgery, there is a relative increase in fibrous content and some authors described a deterioration of LV diastolic function early after AVR. In accordance, it has been described a development of moderate to severe diastolic dysfunction late after AVR, despite a reduction in the LV mass index [70 74]. A late and progressive reduction of LV fibrosis has been described after some years from surgery [74 75]. Of note, the fibrosis regression is predominantly related to the reduction of interstitial fibrosis, while the replacement fibrosis seems to remain unchanged [71-74 77]. Overall, presence of higher grades of myocardial fibrosis increases the risk of congestive heart failure and death [78] while patients with mild diastolic dysfunction have a better prognosis after AVR [79].

As regard the systolic function, a rapid recovery has been described after both surgical and percutaneous AVR [80 81]. Speckle-tracking echocardiography [82] demonstrated improvements in LV systolic function 6 months after AVR. Of interest, there is a significant better recovery of circumferential and radial strain with respect to the longitudinal. Longitudinal strain is particularly affected by the presence of fibrosis, thus its impaired recovery after AVR may reflect the presence of higher degree of fibrosis. Several clinical factors can influence the extent and the duration of LV remodelling after AVR. First of all, the presence of patient-prosthesis mismatch can contribute to the persistence of LV pressure overload and consequently to the persistence of hypertrophy and diastolic dysfunction [83]. Indeed in patients with patient-prosthesis mismatch and hypertension after AVR, an attenuated LV remodelling has been described [84 85].

CONCLUSIONS

Aortic stenosis, the most diffuse valve disease in the elderly, is a disease of the valve and the myocardium. After an initial phase of adaptive remodelling, a maladaptive LV remodelling occurs in the advanced stages of the disease. Progressive myocyte death and myocardial fibrosis result in the transition from hypertrophy to heart failure. Markers of left ventricular (LV) decompensation, such as BNP and troponins, may help in the identification of patients who may benefit from early surgery. Preoperative myocardial remodelling conditions survival after surgery and continues after surgery.

References

1 Iung B, Baron G, Butchart EG, et al. *A prospective survey ofpatients with valvular heart disease in Europe: the Euro Heart Survey on Valvular Heart Disease*. Eur Heart J 2003;24:1231-43.

2 Osnabrugge RL, Mylotte D, Head SJ, et al. *Aortic stenosis in the elderly: disease prevalence and number of candidates for transcatheter aortic valve replacement: a meta-analysis and modeling study*. J Am Coll Cardiol 2013;62:1002-12.

3 Eveborn GW, Schimmer H, Heggelund G, et al. *The evolving epidemiology of valvular aortic stenosis: the Tronso study.* Heart 2013;99:396-400.

4 Losi MA, Brevetti G, Schiano V, et al. *Aortic valve sclerosis in patients with peripheral and/or coronaryarterialdisease.* Echocardiography 2010;27:608-12.

5 Parisi V, Leosco D, Ferro G et al. *The lipid theory in the pathogenesis of calcific aortic stenosis.* Nutr Metab Cardiovasc Dis 2015;25:519-25.

6 Rajamannan NM. *Calcific aortic stenosis: a disease ready for prime time*. Circulation 2006;114:2007e9.

7 Rajamannan NM, Subramaniam M, Rickard D, et al. *Human aortic valve calcification is associated with an osteoblast phenotype*. Circulation 2003;107:2181e4.

[8] Del Puente A, Esposito A, Savastano S, et al. *Dietary calcium intake and vitamin D are major determinants of bone mass variation in women*. Aging Clin Exp Res 2002;14:382-8

[9] Conti V, Corbi G, Simeon V, et al. *Aging-related changes in oxidative stress response of human endothelial cells.* Aging Clin Exp Res 2015;27:547-53.

[10] Otto CM, Burwash IG, Legget ME, et al. *Prospective study ofasymptomatic valvular aortic stenosis: clinical, echocardiographic, and exercise predictors of outcome.* Circulation 1997;95:2262-70.

[11] Rajamannan NM. *Oxidative-mechanical stress signals stem cell niche mediated Lrp5 osteogenesis in eNOS(-/-) null mice*. J Cell Biochem 2012;113:1623e34.

[12] O'Brien K, Reichenbach D, Marcovina S, et al. *Apolipoproteins B,(a), and E accumulate in the morphologically early lesion of degenerative valvular aortic stenosis.* Arterioscler Thromb Vasc Biol 1996;16:523e32.

[13] Nadlonek NA, Lee JH, Weyant MJ, et al. *Ox-LDL induces PiT-1 expression in human aortic valve interstitial cells.* J Surg Res 2013;184:6e9.

[14] Iacobellis, G. *Epicardial and pericardial fat: close, but very different.* Obesity 2009;17:625.

[15] Sacks, HS, Fain JN. *Human epicardial adipose tissue: a review*. Am Heart J 2007;153:907-17.

[16] Rabkin, RW. *Epicardial fat: properties, function and relation ship to obesity*. Obes Rev 2007;8:253-61.

[17] Mazurek T, Zhang L, Zalewski A, et al. *Human epicardial adipose tissue is a source of inflammatory mediators.* Circulation 2003;108:2460-6.

[18] Parisi V, Rengo G, Pagano G, et al. *Epicardial adipose tissue has an increased thickness and is a source of inflammatory mediators in patients with calcific aortic stenosis*. Int J Cardiol 2015;186:167-9.

[19] Parisi V, Rengo G, Perrone-Filardi P, et al. *Increased epicardial adipose tissue volume correlates with cardiac sympathetic denervation in patients with heart failure*. Circ Res 2016;118:1244-53.

[20] Rengo G, Parisi V, Femminella GD, et al. *Molecular aspects of the cardioprotective effect of exercise in the elderly*. Aging Clin Exp Res 2013;25:487-97.

[21] Levy D, Garrison RJ, Savage DD, et al. *Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study*. N Engl J Med 1990;322:1561-6.

[22] Spirito P, Bellone P, Harris KM, et al. *Magnitude of left ventricular hypertrophy and risk of sudden death in hypertrophic cardiomyopathy*. N Engl J Med 2000;342:1778-85.

[23] Schillaci G, Verdecchia P, Porcellati C, et al. *Continuous relation between left ventricular mass and cardiovascular risk in essential hypertension.* Hypertension 2000;35:580-6.

[24] Salcedo EE, Korzick DH, Currie PJ, et al. *Determinants of left ventricular hypertrophy in patients with aortic stenosis.* Cleve Clin J Med 1989;56:590-6.

[25] Lavie CJ, Milani RV, Patel D, et al. *Disparate effects of obesity and left ventricular geometry on mortality in 8088 elderly patients with preserved systolic function*. Postgrad Med 2009;121:119-25.

[26] Orlowska-Baranowska E, Placha G, Gaciong Z, et al. *Influence of ACE I/D genotypes on left ventricular hypertrophy in aortic stenosis: gender-related differences*. J Heart Valve Dis 2004;13:574-81.

[27] Hein S, Arnon E, Kostin S, et al. *Progression from compensated hypertrophy to failure in the pressure-overloaded human heart structural deterioration and compensatory mechanisms.* Circulation 2003;107:984-91.

[28] Maio S, Baldacci S, Simoni M, et al. *Impact of asthma and comorbid allergic rhinitis on quality of life and control in patients of Italian general practitioners*. J Asthma 2012;49:854-61.

[29] Querejeta R, Lopez B, Gonzalez A, et al. *Increased collagen type I synthesis in patients with heartfailure of hypertensive origin: Relation to myocardial fibrosis.* Circulation 2004;110:1263-8.

[30] Bing OH, Ngo HQ, Humphries DE, et al. *Localization of alpha1(I)collagen mRNA in myocardium from the spontaneously hypertensive rat during the transition from compensated hypertrophy to failure.* J Mol Cell Cardiol 1997;29:2335-44.

[31] Dweck MR, Joshi S, Murigu T, et al. *Midwall fibrosis is anindependent predictor of mortality in patients with aortic stenosis.* J Am Coll Cardiol 2011;58:1271-9.

[32] Nazarian S. *Is ventricular arrhythmia a possible mediator of theassociation between aortic stenosis-related midwall fibrosis and mortality?* J Am Coll Cardiol 2011;58:1280-2.

[33] Assomull RG, Prasad SK, Lyne J, et al. *Cardiovascular magnetic resonance, fibrosis, and prognosis in dilated cardiomyopathy.* J Am Coll Cardiol 2006;48:1977-85.

[34] Pritchett AM, Jacobsen SJ, Mahoney DW, et al. *Left atrial volume as an index of left atrial size: a population based study*. J Am Coll Cardiol 2003;41:103-43.

[35] Rossi A, Tomaino M, Golia G, et al. *Usefulness of left atrial size in predicting postoperative symptomatic improvement in patients with aortic stenosis*. Am J Cardiol 2000;86:567-70.

[36] Lancelloti P, Donal E, Magne J, et al. *Risk stratification in asymptomatic moderate to severe aortic stenosis: the importance of the valvular, arterial and ventricular interplay*. Heart 2010;96:134-71.

[37] Nishimura RA, Otto CM, Bonow RO, et al. *American College of Cardiology; American College of Cardiology/ American Heart Association; American Heart Association. 2014 AHA/ACC guideline 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.* J Thorac Cardiovasc Surg 2014;148:e1-e132.

[38] Hein S, Arnon E, Kostin S, et al. *Progression from compensated hypertrophy to failure in the pressure-overloaded human heart structural deterioration and compensatory mechanisms.* Circulation 2003;107:984-91.

[39] Coats CJ, Parisi V, Ramos M, et al. *Role of serum N-terminal pro-brain natriuretic peptide measurement in diagnosis*

of cardiac involvement in patients with anderson-fabry disease. Am J Cardiol 2013;111:111-7.

40 Seino Y, Ogawa A, Yamashita T, et al. *Application of NT pro-BNP and BNP measurements in cardiac care: a more discerning marker for the detection and evaluation of heart failure.* Eur J Heart Fail 2004;6:295-300.

41 Yamamoto K, Burnett JC Jr, Jougasaki M, et al. *Superiority of brain natriuretic peptide as a hormonal marker of ventricular systolic and diastolic dysfunction and ventricular hypertrophy.* Hypertension 1996; 28:988-94.

42 Rengo G, Pagano G, Parisi V, et al. *Changes of plasma norepinephrine and serum N-terminal pro-brain natriuretic peptide after exercise training predict survival in patients with heart failure.* Int J Cardiol 2014;171:384-9.

43 Gerber IL, Stewart RAH, Legget ME, et al. *Increased plasma natriuretic peptide levels reflect symptom onset in aortic stenosis.* Circulation 2003;107:1884-90.

44 Nessmith MG, Fukuta H, Brucks S, et al. *Usefulness of an elevated B-type natriuretic peptide in predicting survival in patients with aortic stenosis treated without surgery*. Am J Cardiol 2005;96:1445-8.

45 Ben-Dor I, Minha S, Barbash IM, et al. *Correlation of brain natriuretic peptide levels in patients with severe aortic stenosis undergoing operative valve replacement or percutaneous transcatheter intervention with clinical, echocardiographic, and hemodynamic factors and prognosis*. Am J Cardiol 2013;112:574-91.

46 Bergler-Klein J, Klaar U, Heger M, et al. *Natriuretic peptides predict symptom-free survival and postoperative outcome in severe aortic stenosis*. Circulation 2004;109: 2302-8.

47 Weber M, Arnold R, Rau M, et al. *Relation of N-terminal pro-B-type natriuretic peptide to severity of valvular aortic stenosis.* Am J Cardiol 2004;94:740-5.

48 Marcus ML, Koyanagi S, Harrison DG, et al. *Abnormalities in the coronary circulation that occur as a consequence of cardiac hypertrophy*. Am J Med 1983;75:62-6.

49 Galiuto L, Lotrionte M, Crea F, et al. *Impaired coronary and myocardial flow in severe aortic stenosis is associated with increased apoptosis: a transthoracic Doppler and myocardial contrast echocardiography study.* Heart 2006;92:208-12.

50 Røsjø H, Andreassen J, Edvardsen T, et al. *Prognostic usefulness of circulating high-sensitivity troponin T in aortic stenosis and relation to echocardiographic indexes of cardiac function and anatomy.* Am J Cardiol 2011;108:88-91.

51 Chin CW, Shah AS, McAllister DA, et al. *High-sensitivity troponin I concentrations are a marker of an advanced hypertrophic response and adverse outcomes in patients with aortic stenosis.* Eur Heart J 2014;35:2312-21.

52 Leosco D, Rengo G, Iaccarino G, et al. *Exercise promotes angiogenesis and improves beta-adrenergic receptor signalling in the post-ischaemic failing rat heart*. Cardiovasc Res. 2008;78:385-94.

53 Leosco D, Rengo G, Iaccarino G, et al. *Exercise training and beta-blocker treatment ameliorate age-dependent impairment of beta-adrenergic receptor signaling and enhance cardiac responsiveness to adrenergic stimulation*. Am J Physiol Heart Circ Physiol 2007;293:H1596-603.

54 Rengo G, Perrone-Filardi P, Femminella GD, et al. *Targeting the β-adrenergic receptor system through G-protein-coupled receptor kinase 2: a new paradigm for therapy and prognostic evaluation in heart failure: from bench to bedside.* Circ Heart Fail 2012;5:385-91.

55 Rengo G, Pagano G, Filardi PP, et al. *Prognostic value of lymphocyte G protein-coupled receptor kinase-2 protein levels in patients with heart failure*. Circ Res 2016;118:1116-24.

56 Rengo G, Cannavo A, Liccardo D, et al. *Vascular endothelial growth factor blockade prevents the beneficial effects of β-blocker therapy on cardiac function, angiogenesis, and remodeling in heart failure.* Circ Heart Fail 2013;6:1259-67.

57 Corbi G, Conti V, Davinelli S, et al. *Dietary phytochemicals in neuroimmunoaging: a new therapeutic possibility for humans?* Front Pharmacol 2016;7:364.

58 Corbi G, Acanfora D, Iannuzzi GL, et al. *Hypermagnesemia predicts mortality in elderly with congestive heart disease: relationship with laxative and antacid use.* Rejuvenation Res 2008;11:129-38.

59 Sharma UC, Pokharel S, van Brakel TJ, et al. *Galectin-3 marks activated macrophages in failure-prone hypertrophied hearts and contributes to cardiac dysfunction*. Circulation 2004;110:3121-8.

60 de Boer RA, Yu L, van Veldhuisen DJ. *Galectin-3 in cardiac remodeling and heart failure.* Curr Heart Fail Rep 2010;7:1-8.

61 Liu YH, D'Ambrosio M, Liao TD, et al. *N-acetyl-seryl-aspartyl-lysyl-proline prevents cardiac remodeling and dysfunction induced by galectin-3, a mammalian adhesion/growth-regulatory lectin.* Am J Physiol Heart Circ Physiol 2009;296:H404-12.

62 Lancellotti P, Magne J, Donal E, et al. *Clinical outcome in asymptomatic severe aortic stenosis.* J Am Coll Cardiol 2012:235-43.

63 Jander N, Minners J, Holme I, et al. *Outcome of patients with low-gradient "severe" aortic stenosis and preserved ejection fraction*. Circulation 2011;123:887-95.

64 Czarny MJ, Resar JR. *Diagnosis and management of valvular aortic stenosis*. Clin Med Insights Cardiol 2014;8(Suppl 1):15-24.

65 Corbi G, Gambassi G, Pagano G, et al. *Impact of an innovative educational strategy on medication appropriate use and length of stay in elderly patients*. Medicine (Baltimore) 2015;94:e918.

66 Corbi G, Grattagliano I, Catanesi R, et al. *Elderly residents at risk for being victims or offenders.* J Am Med Dir Assoc 2012;13:657-9.

67 Baldacci S, Maio S, Simoni M, et al. *The ARGA study with general practitioners: impact of medical education on asthma/rhinitis management*. Respir Med 2012;106:777-85.

68 Otto CM, Burwash IG, Legget ME, et al. *Prospective study of asymptomatic valvular aortic stenosis. Clinical, echocardiographic, and exercise predictors of outcome*. Circulation 1997;95:2262-70.

69 Marechaux S, Hachicha Z, Bellouin A, et al. *Usefulness of exercise-stress echocardiography for risk stratification of true asymptomatic patients with aortic valve stenosis.* Eur Heart J 2010;31:1390.

70 Beach JM, Mihaljevic T, Rajeswaran J, et al. *Ventricular hypertrophy and left atrial dilatation persist and are associated with reduced survival after valve replacement for aortic stenosis.* J Thorac Cardiovasc Surg 2014;147:362-9.e8.

71 Hess OM, Ritter M, Schneider J, et al. *Diastolic stiffness and myocardial structure in aortic valve disease before and after valve replacement.* Circulation 1984;69:855-65.

72 Krayenbuehl HP, Hess OM, Monrad ES, et al. *Left ventricular myocardial structure in aortic valve disease before, intermediate, and late after aortic valve replacement*. Circulation 1989;79:744-55.

73 Monrad ES, Hess OM, Murakami T, et al. *Time course of regression of left ventricular* hypertrophy after aortic valve replacement. Circulation 1988;77:1345-55.

74 Kannegieter LM, Tap L, Oudshoorn C, et al. *Mobility and handgrip strength but not aortic stiffness are associated with frailty in the elderly.* Journal of Gerontolory and Geriatrics 2016;64:2-8.

75 Gjertsson P, Caidahl K, Bech-Hanssen O. *Left ventricular diastolic dysfunction late after aortic valve replacement in patients with aortic stenosis*. Am J Cardiol 2005;96:722-7.

76 Villari B, Vassalli G, Betocchi S, et al. *Normalization of left ventricular nonuniformity late after valve replacement for aortic stenosis*. Am J Cardiol 1996;78:66-71.

77 Ikonomidis I, Tsoukas A, Parthenakis F, et al. *Four year follow-up of aortic valve replacement for isolated aortic stenosis: a link between reduction in pressure overload, regression of left ventricular hypertrophy, and diastolic function*. Heart 2001;86:309-16.

78 Milano AD, Faggian G, Dodonov M, et al. *Prognostic value of myocardial fibrosis in patients with severe aortic valve stenosis.* J Thorac Cardiovasc Surg 2012;144:830-7.

79 Cayli M, Kanadaşi M, Akpinar O, et al. *Diastolic function predicts outcome after aortic valve replacement in patients with chronic severe aortic regurgitation*. Clin Cardiol 2009;32:E19-23.

80 Clavel MA, Webb JG, Rodes-Cabau J, et al. *Comparison between transcatheter and surgical prosthetic valve implantation in patients with severe aortic stenosis and reduced left ventricular ejection fraction*. Circulation 2010;122:1928-36.

81 Elmariah S, Palacios IF, McAndrew T, et al. *Outcomes of transcatheter and surgical aortic valve replacement in high-risk patients with aortic stenosis and left ventricular dysfunction: results from the placement of aortic transcatheter valves (PARTNER) trial (cohort A).* Circ Cardiovasc Interv 2013;6:604-14.

82 Rost C, Korder S, Wasmeier G, et al. *Sequential changes in myocardial function after valve replacement for aortic stenosis by speckle tracking echocardiography*. Eur J Echocardiogr 2010;11:584-9.

83 Brown J, Shah P, Stanton T, et al. *Interaction and prognostic effects of left ventricular diastolic dysfunction and patient-prosthesis mismatch as determinants of outcome after isolated aortic valve replacement*. Am J Cardiol 2009;104:707-12.

84 Lund O, Emmertsen K, Dorup I, et al. *Regression of left ventricular hypertrophy during 10 years after valve replacement for aortic stenosis is related to the preoperative risk profile.* Eur Heart J 2003;24:1437-46.

85 Tasca G, Brunelli F, Cirillo M, et al. *Impact of valve prosthesis-patient mismatch on left ventricular mass regression following aortic valve replacement*. Ann Thorac Surg 2005;79:505-10.