Author: Debonnaire, Philippe Jean Marc Rita
Title: Advanced echocardiography and clinical surrogates to risk stratify and manage patients with structural heart disease
Issue Date: 2016-04-28

Chapter 9

Left atrial function by two-dimensional speckle tracking echocardiography in patients with severe organic mitral regurgitation: association with guidelines-based surgical indication and postoperative (long-term) survival

Philippe Debonnaire, Darryl P Leong, Tomasz G Witkowski, Ibtihal Al Amri, Emer Joyce, Spyridon Katsanos, Martin J Schalij, Jeroen J Bax, Victoria Delgado, Nina Ajmone Marsan

J Am Soc Echocardiogr, 2013 Sep 26(9): 1053-1062.

ABSTRACT

Objectives

Left atrial (LA) mechanics in patients with severe mitral regurgitation (MR) remain largely unexplored. The present evaluation assessed the effect of severe mitral regurgitation (MR) on left atrial (LA) function, its potential relation with conventional surgery indications and long-term postoperative survival.

Methods and Results

2D-speckle tracking strain and volumetric indices of LA reservoir, conduit and contractile function were assessed in 121 severe MR patients and 70 controls. Patients were divided according to presence (n=46) or absence (n=75) of ≥1 guidelines-based criteria for mitral surgery (symptoms, left ventricular (LV) ejection fraction ≤60%, LV end-systolic diameter ≥40mm, atrial fibrillation or systolic pulmonary arterial pressure >50mmHg).

In patients with severe MR, as compared to controls, significant LA reservoir and contractile dysfunction was observed, which was more pronounced in patients with mitral surgery indication (all $p<0.05$ for strain and volumetric indices). Of all LA function indices, LA reservoir strain was an independent predictor (OR=0.88, 95%CI 0.82-0.94, $p<0.001$) and had the highest accuracy to identify patients with indication for mitral surgery (area under ROC curve=0.8, 95%CI 0.72-0.87). A total of 117 patients underwent mitral valve surgery. Patients with LA reservoir strain ≤24% showed worse survival at a median of 6.4 years (4.7-8.7 years) after mitral surgery ($p=0.02$), regardless the symptomatic status prior to surgery. LA reservoir strain, on top of mitral surgery indications, provided incremental predictive value for postoperative survival.

Conclusion

Impaired LA reservoir strain in patients with severe organic MR relates to long-term survival after mitral valve surgery, independently of and incremental to current guidelines-based indications for mitral surgery.

INTRODUCTION

Severe chronic mitral regurgitation (MR) causes a significant left atrial (LA) volume overload, leading to LA dilatation as compensatory mechanism to maintain LA pressure homeostasis and prevent pulmonary congestion.[1] Measures of LA remodeling, such as LA diameter and LA volume index, have been shown to predict outcome in patients with severe organic MR, and are helpful for risk stratification and clinical decision-making in these patients.[2-4] However, chronic MR may induce significant LA ultra-structural changes, potentially affecting LA myocardial contractility and relaxation before LA dilatation occurs.[3,5-8] Therefore, assessment of LA function, rather than dimension, might be of significant value to guide therapy in patients with severe MR. However, data on the effect of severe MR on LA function are scarce and the potential incremental value of LA function assessment to predict timing for surgery is unexplored.[9-12]

Different LA functions can be evaluated, including reservoir (storage of pulmonary venous inflow during ventricular systole), conduit (passive emptying during early diastole) and contractile (active emptying at late diastole) functions. These sequential LA functions play a crucial role in cardiac performance by optimizing left ventricular (LV) filling,[13,14] and can be measured with conventional 2-dimensional (2D) echocardiography by detecting the phasic changes of LA volume during the cardiac cycle. More recently, 2D speckle tracking longitudinal deformation (strain and strain rate) imaging also showed accurate characterization of all phases of LA function.[14-18]

Therefore, the aim of this study was 1) to characterize LA reservoir, conduit and contractile function using 2D-speckle tracking deformation imaging in patients with chronic severe organic MR, 2) to determine its clinical relation to the presence of guidelines-based conventional indications for mitral surgery and 3) to explore its association with long-term survival after mitral valve surgery.[2,19]

METHODS

Patient population

The patient population consisted of patients presenting with chronic severe organic MR, who were referred to our centre within the last decade. Clinical and echocardiographic data were prospectively collected in the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Center, Leiden, and the Netherlands) and retrospectively analyzed.

Clinical assessment included demographics, medications, identification of co-morbidities and symptoms according to the New York Heart Association (NYHA) functional class. Echocardiographic evaluation included conventional measurements and speckle tracking analysis for LA deformation analysis. Patients with prior cardiac surgery or myocardial infarction, congenital heart disease, concomitant mitral stenosis exceeding mild severity (mean gradient ≥5 mmHg) or significant aortic valve disease were excluded. In addition, in order to avoid confounders for increased pulmonary pressure, patients with significant pulmonary disease were excluded.

Patients were further dichotomized based on the presence of ≥1 conventional criterion for mitral surgery indication, according to current guidelines: NYHA class 3 to 4 symptoms, LV ejection fraction (EF) ≤60 %, LV end-systolic diameter ≥40 mm, atrial fibrillation or systolic pulmonary arterial pressure at rest >50 mmHg.[2] Accordingly, phasic LA functions were evaluated in both patient groups.

In addition, 70 individuals with similar age, body surface area and gender distribution served as a control group. These subjects underwent clinically indicated echocardiography for evaluation of potential cardiac symptoms, murmur or increased cardiovascular risk profile, but all showed absence of significant structural or functional abnormalities.

A total of 117 (97%) patients underwent mitral valve surgery at a mean of 85 ± 19 days after the baseline echocardiographic exam. This practice is in line with current guidelines, advocating that early mitral valve surgery may be performed in experienced valve centers with high repair rate for patients presenting with severe organic mitral regurgitation, despite absence of symptoms or LV dysfunction.[2] All-cause mortality was assessed in all operated patients by reviewing patients' medical files and by evaluation of the official Dutch National Survival Registry for patients that were followed by the referring center postoperatively.

Echocardiography

Transthoracic 2D-echocardiography was performed in left lateral decubitus position using commercially available ultrasound systems (System-5, Vivid-7 and E9, GE-Vingmed, Milwaukee, WI) equipped with a 3.5 MHz transducer. ECG-triggered standard 2D gray-scale and color-Doppler images were acquired in cine-loop format and transferred to a workstation for off-line analysis (EchoPAC 110.0.0, GE Medical Systems, Horten, Norway). Chamber quantification was performed conform to current recommendations.[20] Left atrial anteroposterior linear diameter was measured on 2D left parasternal long axis view. LV and LA volumes were assessed using Simpson biplane method and were indexed to body surface area.[20] LVEF was calculated from LV volumes as recommended. In accordance with recent guidelines, a multi-parametric integrative approach was used to assess MR severity (additional transesophageal images were used when available).[21] In particular, an effective regurgitant orifice area ≥40 mm² or regurgitant volume ≥60 ml, using the proximal isovelocity surface area method (PISA), as well as the presence of flail mitral leaflet or ruptured papillary muscle defined severe mitral regurgitation. If none of these factors were present or PISA was not feasible (due to excentricity of regurgitant jet), presence of vena contracta width ≥7 mm in combination with ≥1 qualitative (large central jet, severe coanda effect, large flow convergence radius, dense mitral envelope at continuous wave Doppler) and/or semi-quantitative (pulmonary Doppler systolic venous flow reversal, E wave dominance ≥1.5 m/s) variable(s) defined severe mitral regurgitation.[21] MR etiology was categorized as flail (free mitral leaflet edge reversing into the LA), prolapse (mitral leaflet coaptation line behind annular plane without edge reversing into LA) or degenerative (degenerative mitral valve abnormalities without flail or prolapse).[20] All Doppler measurements represented the average of 3 beats and 5 beats if atrial fibrillation was present. Mitral inflow was analyzed to assess early flow (E wave), deceleration time and mitral valve pressure gradient.[22] Early diastolic peak velocity (E`) was derived from the lateral wall on the apical four-chamber view color tissue Doppler acquisition. Systolic pulmonary arterial pressure at rest was calculated using the maximal tricuspid regurgitant jet velocity and right atrial pressure estimation, based on diameter and respiratory variation of the inferior caval vein.[20]

Left atrial function: volumetric indices

LA volumes were assessed just before mitral valve opening (maximal LA volume, Vol_{max}), at mitral valve closure (minimal LA volume, Vol_{min}) and at P-wave onset on ECG just before atrial contraction, if sinus rhythm (pre-A LA volume, Vol_P). As previously reported, LA reservoir function was calculated as LA expansion index (Vol_{max} - Vol_{min} / Vol_{min} x 100), LA conduit function as LA passive emptying fraction (Vol_{max} - Vol_P / Vol_{max} x 100) and LA contractile function as LA active emptying fraction (Vol_P - Vol_{min} / Vol_P x 100).[14,17] In patients with atrial fibrillation, LA contractile function could not be calculated.

Left atrial function: deformation indices

LA longitudinal strain and strain rate was assessed with 2D-speckle tracking analysis with QRS onset as the reference point, applying a commercially available LV strain software package on the LA (EchoPAC 110.0.0).[23] In summary, the region of interest was adjusted to include the LA myocardium in both the four-chamber and two-chamber apical views that included both the LA and LV. Manual correction was performed to optimize tracking results if needed. The values of LA strain and strain rate were calculated as the average value of the four-chamber and two-chamber view, as described in Figure 1. As previously reported, LA reservoir function was calculated as peak systolic LA strain (LA reservoir strain), while LA contractile function was measured as the LA strain value at P-wave onset on ECG, if sinus rhythm (LA contractile strain). Finally, LA conduit function was assessed as the difference between LA reservoir and contractile strain (LA conduit strain).[15] In addition, LA reservoir strain rate was measured as peak systolic positive value, LA conduit strain rate as the early diastolic negative peak and LA contractile strain rate as the late diastolic negative peak (if in sinus rhythm) (Figure 1). In patients with atrial fibrillation, LA contractile strain (rate) could not be calculated.

Fifteen subjects were randomly selected to perform a blinded inter- and intra-observer (one week after the first observation) agreement test for LA strain measurements.

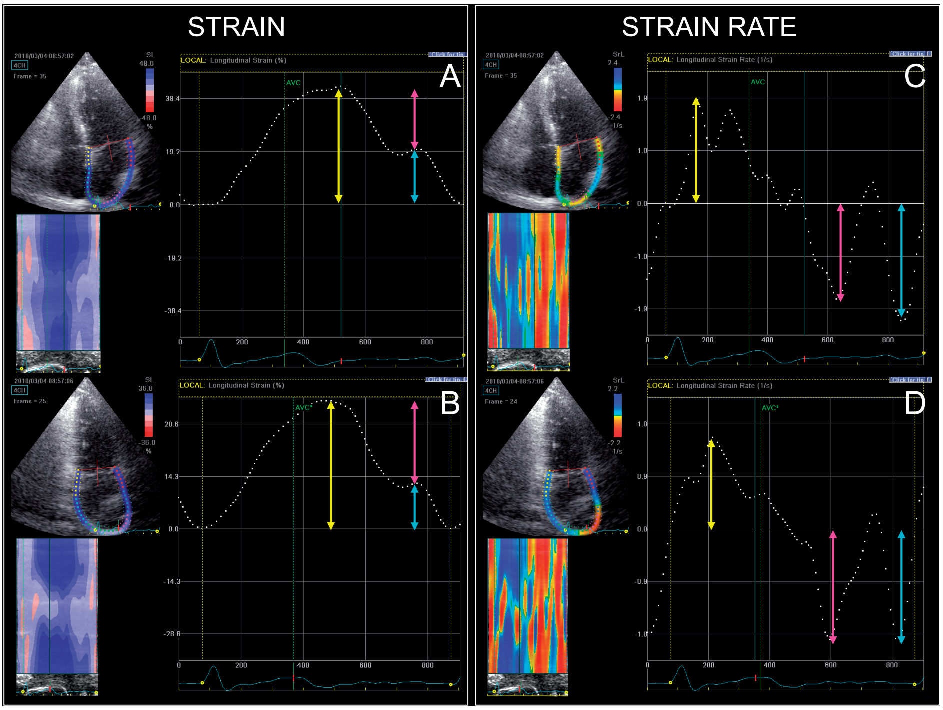

Figure 9.1
Assessment of left atrial phasic function by 2D-speckle tracking echocardiography in a control subject. Panel A: four-chamber longitudinal strain, panel B: two-chamber longitudinal strain, panel C: four-chamber longitudinal strain rate, panel D: two-chamber longitudinal strain rate. The white dotted line represents the mean value of the tracked left atrial segments. Reservoir, conduit and contractile phase are represented by color-coded arrows (yellow, pink and blue respectively). Measurements are averaged over the four-chamber and two-chamber views. In this subject, reservoir, conduit, and contractile strain and strain rate were 38.6%, -22.1%, -16.5% and 1.75 s^{-1}, -1.8 s^{-1}, -2.0 s^{-1} respectively.

For simplicity reasons, the absolute deformation values were reported as positive numbers.

Statistical analysis

Continuous variables were presented as mean ± standard deviation and compared with independent Student-t test and Mann-Whitney or Kruskal-Wallis tests if not normally distributed. Percentages were used for categorical values and compared by χ^2-test. Multiple group comparisons were performed with one-way ANOVA test with post hoc Bonferroni test. Receiver-operating characteristic (ROC) analysis was performed to assess the accuracy of various deformation and volumetric indices of LA function to predict presence of conventional indications for mitral surgery. The optimal cut-off value was obtained by maximizing the sum of sensitivity and specificity. Subsequently, multiple logistic regression analysis identified independent predictors of the presence of mitral surgery indications. Covariates with a significance $p<0.05$ at univariate level were included in the multivariate logistic regression analysis, which was performed using a backward elimination approach. In addition, Cox regression analysis including conventional guidelines-based criteria for mitral surgery and LA reservoir strain was performed to identify the independent determinants of long-term mortality after mitral surgery. To maximize the possibility to detect any relationship of this clinical model with post-operative mortality, covariates with univariate significance of $p<0.10$ were introduced in the multivariate analysis. Kaplan-Meier curves were constructed to explore differences in long-term survival after mitral valve surgery in different patient subgroups that were stratified according to LA reservoir strain, using the previously mentioned ROC curve-based cut-off value and compared by log-rank test. The incremental value of successive conventional guidelines-based criteria for mitral surgery and LA reservoir strain to predict postoperative mortality was assessed with the likelihood ratio test: the model containing the covariate of interest was tested against the nested model not containing the covariate. Finally, linear regression analysis was performed to explore the correlation between LA reservoir strain, LA diameter and LA volume indexed to body surface area (LAVI) respectively. Statistical analysis was performed using SPSS version 17.0. (SPSS Inc., Chicago, Illinois) and STATA version 12.1 (STATA Corp., College Station, Texas) software. All tests were two-sided and a p-value of <0.05 was considered statistically significant.

RESULTS

Patient population

A total of 160 patients with chronic severe organic MR who underwent complete clinical and echocardiographic examination were included. Thirty-nine patients (24%) with poor acoustic window were excluded. Mean frame rate for echocardiographic exams performed within the first half of the last decade did not significantly differ from those performed during the most recent half (56.4 frames/s versus 59.4 frames/s, respectively, p=0.31). Clinical and echocardiographic characteristics of the remaining 121 patients (mean age 63 ± 13 years, 77% men) are summarized in Table 1. Overall, a preserved LV systolic function was observed, with mild LV dilatation and severe LA dilatation. Severe mitral regurgitation was documented with a mean mitral vena contracta width of 8 ± 0.9 mm, E wave 1.3 ± 0.2 m/s and PISA radius of 11 ± 2 mm. Forty-six patients did not have any conventional criterion for mitral surgery indication whereas 75 patients had ≥1 criterion. In particular, symptoms were present in 34 (28%) patients, LVEF ≤60 % in 19 (16%) patients, LV end-systolic diameter ≥40 mm in 27 (22%) patients, atrial fibrillation in 26 (21%) patients and systolic pulmonary arterial pressure at rest >50 mmHg in 29 (24%) patients. Of note, no patients presented with LVEF ≤30 %. By definition, presence of atrial fibrillation, NYHA class III and IV, LV end-systolic diameter, LVEF and pulmonary arterial pressure significantly differed between patients with conventional criteria for mitral surgery versus patients without (Table 1). In addition, age, use of β-blockers, use of diuretics, LAVI, MR vena contracta width, E wave and deceleration time were significantly different between both groups (all p<0.05).

Left atrial function in severe mitral regurgitation

Patients with severe organic MR showed significantly impaired LA reservoir function as compared to control subjects, assessed both by volumetric expansion index or strain and strain rate (all p<0.001), as indicated in Table 2. In addition, LA conduit function assessed with volumetric passive emptying fraction (p=0.20) or LA strain rate (p=0.57) did not differ significantly between patients with severe organic MR and controls, whereas LA strain was significantly impaired only in patients with severe organic MR (p=0.01). In 95 (79%) patients who were in sinus rhythm during echocardiography, LA contractile function was reduced when measured by volumetric active emptying function, LA strain and strain rate (all p<0.001).

Table 9.1
Baseline characteristics of controls and the overall study population with dichotomization according to presence or absence of mitral surgery indication.

Variable	Controls (n=70)	All Patients (n=121)	No surgical indication (n=46)	Surgical indication (n=75)	p *
Clinical characteristics					
Age, years	63 ± 12	63 ± 13	59 ± 14	66 ± 11	0.008
Men, n (%)	47 (67)	77 (64)	32 (70)	45 (60)	0.30
BSA, kg/m²	1.9 ± 0.21	1.9 ± 0.20	1.9 ± 0.21	1.9 ± 0.20	0.80
AF, n (%)	0 (0)	26 (21)	0 (0)	26 (35)	< 0.001
NYHA class, n (%)					< 0.001
I	70 (100)	38 (32)	20 (43)	18 (24)	
II	0 (0)	49 (40)	26 (57)	23 (31)	
III	0 (0)	30 (25)	0 (0)	30 (40)	
IV	0 (0)	4 (3)	0 (0)	4 (5)	
Hypertension, n (%)	31 (45)	11 (10)	4 (10)	7 (11)	1.00
Hypercholesterolemia, n (%)	20 (29)	11 (10)	4 (10)	7 (11)	1.00
Diabetes, n (%)	9 (13)	4 (3)	0 (0)	4 (5)	0.30
Smoking history, n (%)	25 (43)	21 (21)	7 (18)	14 (23)	0.20
Medication use, n (%)					
β-Blocker	8 (12)	41 (34)	8 (17)	33 (44)	0.003
Diuretic	9 (13)	36 (30)	7 (15)	29 (39)	0.006
ACE-I/ARB	22 (32)	54 (45)	17 (37)	37 (49)	0.20
Statin	21 (31)	20 (17)	5 (11)	15 (20)	0.20
MR etiology					0.13
Degenerative	-	7 (6)	1 (2)	6 (8)	
Flail	-	40 (33)	12 (26)	28 (37)	
Prolapse	-	74 (61)	33 (72)	41 (55)	
Echocardiographic data					
LVESD, mm	25.2 ± 4.1	34.8 ± 6.4	31.9 ± 4.5	36.6 ± 6.7	< 0.001
LVEDVI, mL/m²	55 ± 11	85 ± 21	84 ± 18	87 ± 23	0.70
LVESVI, mL/m²	20 ± 6	28 ± 11	25 ± 7	30 ± 13	0.20
LVEF, %	64 ± 6	68 ± 8	70 ± 5	66 ± 9	0.047
LA diameter, mm	35 ± 4	49 ± 8	46 ± 6	50 ± 8	0.001
LAVI, mL/m²	31 ± 8	76 ± 33	64 ± 23	83 ± 36	0.002
Vena contracta, mm	1.7 ± 1.25	8.0 ± 0.92	7.6 ± 0.81	8.2 ± 0.91	<0.001
E wave, m/s	0.6 ± 0.2	1.3 ± 0.2	1.2 ± 0.2	1.4 ± 0.2	<0.001
E’	7.3 ± 2.0	8.5 ± 2.1	8.5 ± 1.6	8.6 ± 2.4	0.9
DT, ms	218 ± 49	180 ± 43	189 ± 34	174 ± 47	0.01
PAPsys at rest, mmHg	26 ± 5	43 ± 16	32 ± 8	49 ± 17	<0.001

ACE-I/ARB: angiotensin-converting enzyme / angiotensin receptor blocker, AF: atrial fibrillation, BSA: body surface area, DT: deceleration time, EDVI: end-diastolic volume indexed to BSA, EF: ejection fraction, ESD: end-systolic diameter, ESVI: end-systolic volume indexed to BSA, LAVI: left atrial volume indexed to BSA, LV: left ventricle, MR: mitral regurgitation, NYHA: New York Heart Association, PAPsys: systolic pulmonary artery pressure, *: for comparison between patient group with versus without mitral surgery indication

Table 9.2
Phasic left atrial function indices of controls and the overall study population with dichotomization according to presence or absence of mitral surgery indication.

Left atrial function variable	Controls (n=70)	All patients (n=121)	No surgical indication (n=46)	Surgical indication (n=75)	p *
Reservoir function					
Strain (%)†	31 ± 6.1†	22 ± 8.4 †	27 ± 6.6 †	19 ± 7.7 †	<0.001†
Strain rate (s^{-1}) †	1.25 ± 0.28†	0.95 ± 0.32 †	1.12 ± 0.27	0.85 ± 0.31 †	<0.001†
Expansion index (%)†	191 ± 61†	111 ± 64 †	150 ± 70 †	87 ± 46 †	<0.001†
Conduit function					
Strain (%)†	17 ± 5.1†	15 ± 5.0 †	17 ± 4.7†	13 ± 4.7 †	<0.001†
Strain rate (s^{-1}) †	1.08 ± 0.38†	1.0 ± 0.32†	1.14 ± 0.34†	0.98 ± 0.32 †	0.04†
Passive emptying fraction (%)†	35 ± 9.9†	34 ± 9.6†	37 ± 9.9†	33 ± 9.1 †	<0.001†
Contractile function ‡					
Strain (%)†	14 ± 3.0†	9.2 ± 3.5 †	10 ± 3.5 †	8 ± 3.4 †	0.03†
Strain rate (s^{-1}) †	1.65 ± 0.55†	1.04 ± 0.39 †	1.15 ± 0.4 †	0.94 ± 0.35 †	0.06†
Active emptying fraction (%)†	44 ± 9.4†	28 ± 11 †	32 ± 12 †	24 ± 10 †	0.001†

All deformation indices are presented as positive absolute numbers. *: p-value for comparison between patient group without versus with mitral surgery indication, †: p<0.05 for comparison with controls, ‡: patients in sinus rhythm only

Left atrial function to predict surgical indication

As summarized in Table 2, LA dysfunction was more pronounced in patients with mitral surgery indications versus patients without and all phases of LA function (reservoir, conduit and contractile) were affected, either assessed by volumetric or deformation parameters. Patients without mitral surgery indications showed impairment of LA reservoir and contractile function but preserved conduit function.

Subsequently, ROC analysis was performed to determine the value of all different deformation and volumetric indices of phasic LA function to predict the presence of guidelines-based mitral surgery indications (Table 3). This analysis showed that LA reservoir strain had the highest predictive value among all LA function indices, evidenced by an area under the curve of 0.80 (CI 95% 0.72-0.87, Figure 2A). In particular, a value of LA reservoir strain ≤24 % predicted the presence of mitral surgery indications with a sensitivity and specificity of 76% and 72%, respectively (Figure 2B).

LA reservoir strain was therefore implemented into further analysis to explore the independent predictive value of LA function for the presence of mitral surgery indications in patients with severe organic MR. Univariate logistic regression analysis showed that age (OR 1.04, 95% CI 1.01-1.07, p=0.01), use of β-blockers (OR 3.7, 95% CI 1.5-9.1, p=0.004), use of diuretics (OR 3.5, 95% CI 1.4-8.9, p=0.008),

Table 9.3
Receiver operating characteristic analysis to assess predictive value for presence of conventional guidelines-based mitral surgical indication(s).

Parameter	ROC AUC	95% CI
Reservoir function		
Strain (%)	0.80	0.72-0.87
Strain rate (s^{-1})	0.75	0.66-0.84
Expansion index (%)	0.79	0.71-0.87
Conduit function		
Strain (%)	0.73	0.64-0.82
Strain rate (s^{-1})	0.66	0.56-0.76
Passive emptying fraction (%)	0.60	0.49-0.71
Contractile function*		
Strain (%)	0.65	0.54-0.76
Strain rate (s^{-1})	0.66	0.55-0.77
Active emptying fraction (%)	0.70	0.59-0.81

Positive absolute numbers for all deformation indices were used. AUC: area under curve, CI: confidence interval, ROC: receiver operating characteristic, *: measured only in 95 out of 121 patients in sinus rhythm.

LAVI (OR 1.02, 95% CI 1.01-1.04, p=0.003), MR vena contracta width (OR 2.29, 95% CI 1.43-3.66, p=0.001) and LA reservoir strain (OR 0.86 95% CI 0.81-0.92, p<0.001) were significantly related to the presence of mitral surgery indications in patients with severe MR. Multivariate logistic regression analysis subsequently identified LA reservoir strain as an independent predictor of the presence of mitral surgery indication (OR 0.88, 95% CI 0.82-0.94, p<0.001), together with MR vena contracta width (OR 2.04, 95% CI 1.21-3.47, p=0.008) and use of β-blocker (OR 3.2, 95% CI 1.2-8.7, p=0.03). Each 1% decrease in LA reservoir strain increased the risk of having an indication for mitral surgery by 12%.

Left atrial strain and long-term survival after mitral valve surgery

After a median follow-up of 6.4 years (interquartile range 4.7-8.7 years) after mitral valve surgery, all-cause mortality occurred in 20 out of the 117 operated patients (17%). Cox regression analysis, restricted to LA function (reservoir strain) and remodeling parameters (LA diameter and LAVI), together with conventional criteria for mitral surgery, indicated that LA reservoir strain, using the ≤24 % cut off value (HR 3.8, p=0.04, CI 1.10-12.93), and symptoms (HR 2.3, p=0.07, CI 0.94-5.71) were related to long-term mortality after mitral valve surgery. In addition, LA diameter ≥55 m or LAVI ≥60 mL/m^2 did not show significant relation with postoperative mortality.[3,4] At multivariate level, only LA reservoir strain (HR 3.5, p=0.045, CI 1.03-12.20) showed to be independently related to mortality (Table

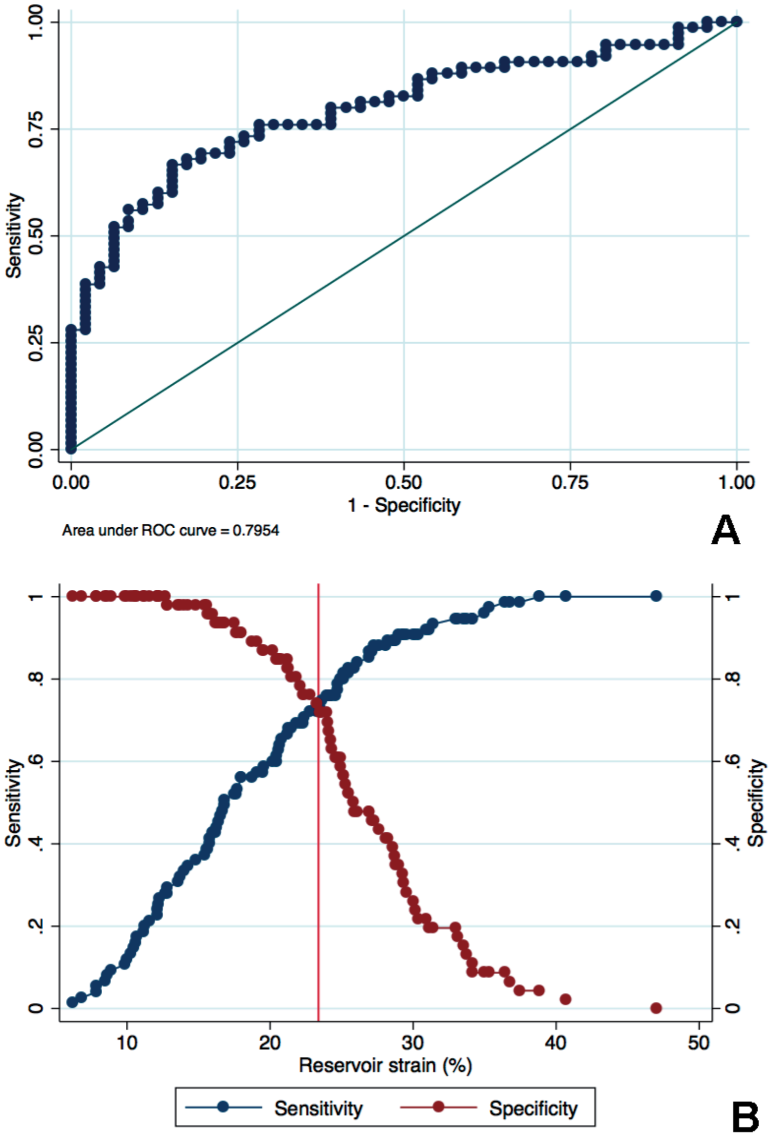

Figure 9.2
Left atrial reservoir strain to predict the presence of mitral surgery indication in patients with severe mitral regurgitation. Panel A: receiver operating characteristic curve. Panel B: sensitivity-specificity curve with vertical line indicating a reservoir strain cut-off value of ≤24 % to predict presence of surgical indication with sensitivity of 76 % and specificity of 72 %.

4). In addition, likelihood ratio test indicated that assessment of LA reservoir strain, using the cut-off value, on top of assessment of conventional guidelines-based indications for mitral surgery provides significant incremental value to predict long-term postoperative mortality (p=0.03). (Figure 3)

Table 9.4
Cox regression analysis for postoperative all-cause mortality. The relation of currently recommended clinical and echocardiographic variables for decision-making in severe organic mitral regurgitation with long-term postoperative mortality is explored.

	Univariate			Multivariate		
Variables	HR	(95% CI)	p	HR	(95% CI)	p
Symptoms (NYHA 3 or 4)	2.3	0.94-5.71	0.07	2.1	0.86-5.26	0.10
LVEF ≤60 %	1.1	0.31-3.63	0.93			
LVESD ≥40 mm	2.0	0.77-4.96	0.16			
Atrial fibrillation	1.8	0.70-4.87	0.21			
PAPsys at rest >50 mmhg	1.2	0.46-3.20	0.67			
LA diameter ≥55 mm	2.5	0.57-10.8	0.23			
LA volume index ≥60 mL/m2	1.8	0.58-5.35	0.32			
LA reservoir strain ≤24 %	3.8	1.10-12.93	0.04	3.5	1.03-12.20	0.045

CI: confidence interval, HR: hazard ratio, LA: left atrial, LVEF: left ventricular ejection fraction, LVESD: left ventricular end-systolic diameter, NYHA: New York Heart Association, PAPsys: systolic arterial pulmonary artery pressure.

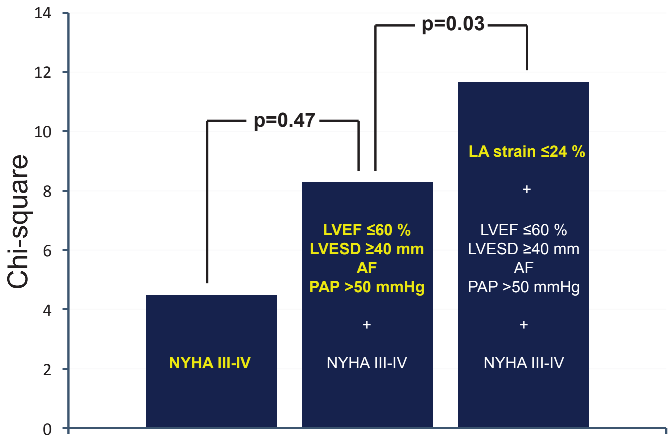

Figure 9.3
Likelihood ratio test for prediction of long-term mortality after mitral valve surgery. Left atrial reservoir strain shows incremental value to predict long-term postoperative mortality in severe organic mitral regurgitation when assessed on top of conventional guidelines-based indications for surgery. AF: atrial fibrillation, LVEF: left ventricular ejection fraction, LVESD: left ventricular end-systolic diameter, NYHA: New York Heart Association, PAP: systolic pulmonary artery pressure at rest.

Kaplan Meier survival analysis showed that patients with baseline LA reservoir strain values ≤24 % had worse long-term survival compared with patients with LA reservoir strain >24 % (log rank p=0.02) (Figure 3). This association was observed also among asymptomatic patients before mitral surgery (n= 83/117, log rank p=0.04) (Figure 3). Interestingly, a significant trend towards worse survival was observed in 44 out of 117 patients with baseline LA reservoir strain ≤24 % who underwent early mitral valve surgery despite absence of any conventional surgical indication compared to patients with LA reservoir strain >24 % (log rank p=0.06) (Figure 4).

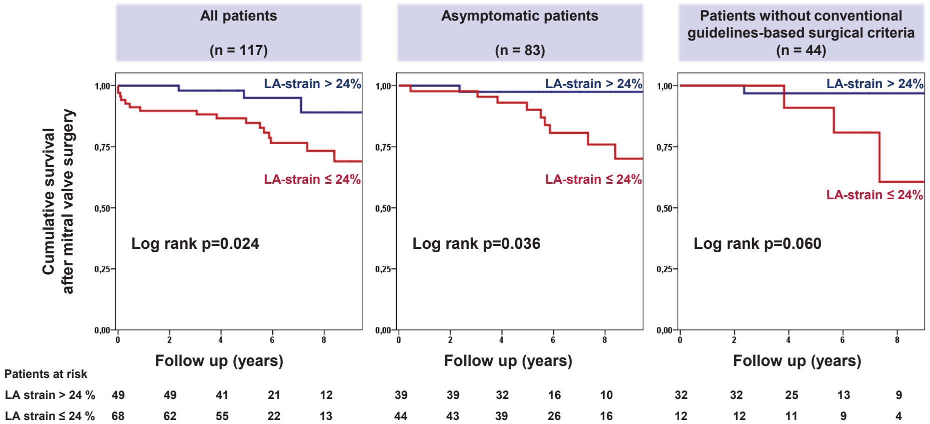

Figure 9.4

Kaplan-Meier survival after mitral valve surgery according to left atrial reservoir strain. Conventional surgical criteria: symptoms, left ventricular (LV) ejection fraction ≤60 %, LV end-systolic diameter ≤40 mm, atrial fibrillation and/or systolic arterial pulmonary pressure at rest >50 mmHg. LA: left atrial.

Left atrial reservoir strain versus diameter and volume

LA reservoir strain showed significant linear correlation with LA diameter (R -0.57, R^2 0.33, p<0.001, 95% CI -0.79 to -0.46) and LAVI (R -0.57, R^2 0.32, p<0.001, 95% CI -0.18 to -0.11) (Figure 5). However, 47 out of 98 patients (48%) with LA diameter <55 mm and 15 out of 44 patients (34%) with LAVI <60 mL/m^2 had LA reservoir strain ≤24 % (Figure 5).

Observer variability

Bland-Altman analysis showed an intra-observer bias of 1.1% (95% CI -4.2 to 6.4%), -0.02% (95% CI -5,1 to 5.0%) and -1.1% (95% CI -4.5 to 2.3%) for LA reservoir, conduit and contractile strain assessment, respectively. Similarly, respective inter-observer biases of -1.3% (95% CI -6.6 to 3.9%), 1.2% (95% CI -2.8 to 5.1%) and 0.1% (95% CI -4.1 to 4.3%) were noted.

DISCUSSION

The main findings of current study can be summarized as follows: 1) patients with chronic severe organic MR are characterized by overall impaired LA reser-

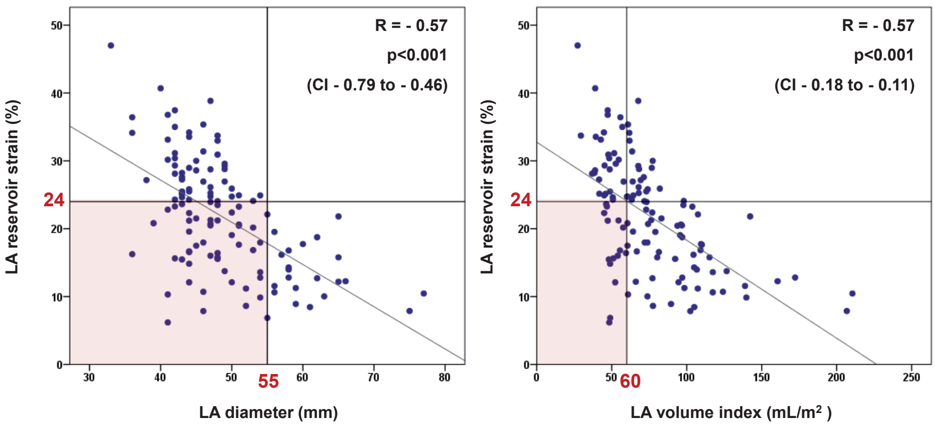

Figure 9.5
Correlation between left atrial reservoir strain, diameter and indexed volume. LA reservoir strain ≤24 % (associated with worse survival after mitral valve surgery) is present in 48% and 34% of patients despite LA diameter <55 mm and LAVI <60 mL/m^2, respectively (purple squares).

voir, conduit and contractile function, 2) LA reservoir strain is an accurate and independent predictor of the presence of conventional guidelines-based mitral surgery indications and 3) LA reservoir strain relates to long-term survival after mitral valve surgery, independently of and incremental to current conventional guidelines-based mitral surgery indications.

Phasic LA function in severe MR

LA reservoir function

During LV systole, pulmonary venous inflow distends the LA, which acts as a reservoir by storing energy under the form of pressure.[14] LA reservoir function is mainly determined by LA compliance (stiffness) and LV systolic function (systolic apical motion of the LV base, facilitating LA filling), and to a lesser extent by right ventricular systole (pulmonary venous inflow). [13,14,24] While increased LA reservoir function has been reported in mild MR, due to an initial increase in LA compliance,[1,9,10] decreased LA reservoir function has been described in patients with severe MR, as assessed with several imaging techniques. [9,10,12] Similarly, the current study showed that severe MR is associated with a significant reduction in LA reservoir function.

Reduced LV systolic function may lead to impaired LA reservoir function as previously demonstrated.[24] However, in the present study LV ejection fraction was preserved in the majority of the patients and therefore this factor may not explain per se the impairment of LA reservoir function.

Furthermore, significant ultra-structural changes of the LA myocardium, including presence of interstitial fibrosis, myocyte hypertrophy, chronic inflammatory changes and decreased capillary density have been reported in patients with severe MR and might cause the reduction in LA reservoir function.[5-7,25] In particular, a recent study on 46 severe MR patients that underwent mitral valve surgery showed a strong negative correlation between histological LA fibrosis and LA reservoir strain.[26] Ultra-structural changes are due to the chronic volume overload and increased LV filling pressures and significantly affect LA myocardial wall properties, such as relaxation and compliance (stiffness), ultimately leading to the observed reduction in LA reservoir function.[3]

LA conduit function

Following the reservoir phase, the LA functions as a conduit during early diastole, allowing for a passive transfer of blood from the pulmonary veins towards the LV. LA conduit function is mainly determined by LA elasticity (recoil) and afterload (LV relaxation and early LV filling pressure).[13,14] In the current study, reduced LA conduit function was observed in patients with severe MR and mitral surgery indication. Increased early diastolic LV filling pressures have been reported in subjects with MR, due to increased atrio-ventricular pressure gradient, increased LV stiffness and decreased LA recoil, and might therefore be an explanation of impaired LA conduit function in these patients.[9,25,27] In addition, ultra-structural changes of the LA wall may cause impaired LA elasticity, reducing LA recoil and affecting LA conduit function.[3,12]

LA contractile function

In patients in sinus rhythm, active LA contraction finalizes LV filling during late diastole and depends on LA afterload (LV compliance and end-diastolic filling pressure) and LA intrinsic contractility, following Starling's law.[13,14,28] Improved LA contractile function has been reported in patients with mild MR and may be explained by the fact that LA myocardial wall operates higher on the Frank-Starling curve (larger LA volumes leads to higher contractility).[9,10,28] In the current study, including severe organic MR patients, impaired LA contractile function assessed with speckle tracking echocardiography was observed. This finding may be related to the presence of a decreased LA contractility, due to exhaustion of the Frank-Starling mechanism by severe volume overload and to ultra-structural alterations of the atrial myocardium. Moreover, increased LA afterload may have also contributed to the impairment of LA contractile function, since increased LV end-diastolic filling pressures have been observed in the presence of severe MR.[28]

LA reservoir strain and mitral surgical indication

Optimal timing of surgical treatment of severe organic MR is crucial, particularly in asymptomatic patients.[2] Current guidelines recommend mitral valve surgery based on the presence of symptoms, LV systolic dysfunction, atrial fibrillation or pulmonary hypertension, which reflect MR severity and its impact on cardiac performance and symptomatic status.[2,19] However, severe MR primarily affects the LA causing significant LA dysfunction and remodeling, which implies that LA characteristics may indicate the hemodynamic implications of severe MR at an earlier stage than conventional criteria for surgical indication.[30] The predictive value of LA reservoir strain observed in the present evaluation might be explained by the fact that reduced LA compliance, and therefore impaired LA reservoir function, is directly related to the duration and severity of MR and represents an important substrate for the occurrence of symptoms, atrial fibrillation or the development of pulmonary hypertension. In fact, decreased atrial compliance due to increased LA stiffness may cause inadequate LA pressure homeostasis. Therefore small increases in LA volume may lead to significant increases of LA and pulmonary artery pressures, which can be associated with the development of pulmonary hypertension and symptoms during exercise.[13] This has been demonstrated in other clinical conditions, for example in patients with diastolic heart failure.[29] Reduced LA reservoir strain, and not LA volume, was shown to be associated with the presence of symptoms and was directly related to atrial stiffness.[29] In addition, LA reservoir strain was demonstrated to be inversely related to LA wall fibrosis (affecting atrial compliance), and to be associated to a higher burden of atrial fibrillation[14]. Finally, at more advanced stages, severe MR may cause LV systolic dysfunction which can decrease LA reservoir function by reduced systolic apical motion of the LV base.[24]

LA reservoir strain and mortality after mitral valve surgery

The present evaluation showed that LA reservoir strain is related to long-term survival in patients operated for severe organic MR, independently of conventional indications for mitral surgery, including symptoms, LV dysfunction, atrial fibrillation and significant pulmonary hypertension. In particular, LA reservoir strain ≤24 % was associated with increased risk for postoperative mortality. In addition to conventional mitral surgery indications, LA diameter ≥55 mm or LAVI ≥ 60 mL/m² have been recently proposed as additional criteria for indication to mitral surgery as they yield increased mortality under conservative management, but not after mitral valve surgery. We indicated, however, that LA reservoir might be a more sensitive approach than LA diameter or LAVI to detect the impact of MR on cardiac performance, as previously shown in diabetic and hypertensive patients.[8] A significant proportion of patients in fact showed LA reservoir strain <24 %, implying increased mortality risk after mitral valve surgery, despite LA diameter <55 mm or LAVI <60 mL/m².

Limitations

Some limitations to the current study should be acknowledged: 1) no invasive assessment of LA mechanical properties or afterload was performed to prove the determinants of reduced LA function, which must be the focus of further specific studies; 2) Limited impairment of LA function in the control group of current study can not be excluded, due to a fairly high proportion of subjects with cardiovascular risk factors such as diabetes and hypertension. This population, however, represents a real-life population without presence of overt structural or functional disease and more stringent selection of patients without any risk factors most likely would have only amplified significance of differences in LA function found between controls and severe MR patients. 3) To firmly establish the predictive value of LA reservoir strain independent of conventional indications for mitral surgery, our findings need validation in larger patient cohorts.

CONCLUSION

Severe MR is associated with significant LA dysfunction that strongly relates to presence of conventional indications for mitral surgery and, more important, is associated with long-term postoperative survival. LA dysfunction, measured as reservoir strain, may be a valuable clinical marker for follow-up and decision-making in patients with severe organic MR, irrespective of conventional mitral surgery indications and more sensitive than LA diameter and volume.

REFERENCES

1. Kihara Y, Sasayama S, Miyazaki S et al. Role of the left atrium in adaptation of the heart to chronic mitral regurgitation in conscious dogs. *Circ Res*. 1988;62:543-553.
2. Bonow RO, Carabello BA, Chatterjee K et al. 2008 Focused update incorporated into the ACC/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 for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation*. 2008;118:e523-661.
3. Le Tourneau T, Messika-Zeitoun D, Russo A et al. Impact of left atrial volume on clinical outcome in organic mitral regurgitation. *J Am Coll Cardiol*. 2010;56:570-578.
4. Rusinaru D, Tribouilloy C, Grigioni F et al. Left atrial size is a potent predictor of mortality in mitral regurgitation due to flail leaflets: results from a large international multicenter study. *Circ Cardiovasc Imaging*. 2011;4:473-481.
5. Anne W, Willems R, Roskams T et al. Matrix metalloproteinases and atrial remodeling in patients with mitral valve disease and atrial fibrillation. *Cardiovasc Res.* 2005;67:655-666.
6. Corradi D, Callegari S, Maestri R et al. Differential structural remodeling of the left-atrial posterior wall in patients affected by mitral regurgitation with or without persistent atrial fibrillation: a morphological and molecular study. *J Cardiovasc Electrophysiol*. 2012;23:271-279.
7. Verheule S, Wilson E, Everett Tt et al. Alterations in atrial electrophysiology and tissue structure in a canine model of chronic atrial dilatation due to mitral regurgitation. *Circulation.* 2003;107:2615-2622.
8. Mondillo S, Cameli M, Caputo ML et al. Early detection of left atrial strain abnormalities by speckle-tracking in hypertensive and diabetic patients with normal left atrial size. *J Am Soc Echocardiogr*. 2011;24:898-908.
9. Borg AN, Pearce KA, Williams SG et al. Left atrial function and deformation in chronic primary mitral regurgitation. *Eur J Echocardiogr*. 2009;10:833-840.
10. Cameli M, Lisi M, Giacomin E et al. Chronic mitral regurgitation: left atrial deformation analysis by two-dimensional speckle tracking echocardiography. *Echocardiography*. 2011;28:327-334.
11. Cameli M, Lisi M, Righini FM et al. Left atrial speckle tracking analysis in patients with mitral insufficiency and history of paroxysmal atrial fibrillation. *Int J Cardiovasc Imaging*. 2012;28: 1663-1667.
12. Moustafa SE, Alharthi M, Kansal M et al. Global left atrial dysfunction and regional heterogeneity in primary chronic mitral insufficiency. *Eur J Echocardiogr*. 2011;12:384-393.
13. Pagel PS, Kehl F, Gare M et al. Mechanical function of the left atrium: new insights based on analysis of pressure-volume relations and Doppler echocardiography. *Anesthesiology*. 2003;98:975-994.
14. Rosca M, Lancellotti P, Popescu BA et al. Left atrial function: pathophysiology, echocardiographic assessment, and clinical applications. *Heart*. 2011;97:1982-1989.
15. Kim DG, Lee KJ, Lee S et al. Feasibility of two-dimensional global longitudinal strain and strain rate imaging for the assessment of left atrial function: a study in subjects with a

low probability of cardiovascular disease and normal exercise capacity. *Echocardiography*. 2009;26:1179-1187.

16. Saraiva RM, Demirkol S, Buakhamsri A et al. Left atrial strain measured by two-dimensional speckle tracking represents a new tool to evaluate left atrial function. *J Am Soc Echocardiogr.* 2010;23:172-180.
17. Vianna-Pinton R, Moreno CA, Baxter CM et al. Two-dimensional speckle-tracking echocardiography of the left atrium: feasibility and regional contraction and relaxation differences in normal subjects. *J Am Soc Echocardiogr*. 2009;22:299-305.
18. Motoki H, Dahiya A, Bhargava M et al. Assessment of left atrial mechanics in patients with atrial fibrillation: comparison between two-dimensional speckle-based strain and velocity vector imaging. *J Am Soc Echocardiogr*. 2012;25:428-435.
19. Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology, European Association for Cardio-Thoracic Surgeons, Vahanian A, Alfieri O, Andreotti F et al. Guidelines on the management of valvular heart disease (version 2012). *Eur Heart J.* 2012;33:2451-2496.
20. Lang RM, Bierig M, Devereux RB et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr*. 2005;18:1440-1463.
21. Lancellotti P, Moura L, Pierard LA et al. European Association of Echocardiography recommendations for the assessment of valvular regurgitation. Part 2: mitral and tricuspid regurgitation (native valve disease). *Eur J Echocardiogr*. 2010;11:307-332.
22. Nagueh SF, Appleton CP, Gillebert TC et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *J Am Soc Echocardiogr*. 2009;22:107-133.
23. Mor-Avi V, Lang RM, Badano LP et al. Current and evolving echocardiographic techniques for the quantitative evaluation of cardiac mechanics: ASE/EAE consensus statement on methodology and indications endorsed by the Japanese Society of Echocardiography. *J Am Soc Echocardiogr*. 2011;24:277-313.
24. Barbier P, Solomon SB, Schiller NB et al. Left atrial relaxation and left ventricular systolic function determine left atrial reservoir function. *Circulation*. 1999;100:427-436.
25. Zile MR, Tomita M, Nakano K et al. Effects of left ventricular volume overload produced by mitral regurgitation on diastolic function. *Am J Physiol*. 1991;261:H1471-1480.
26. Cameli M, Lisi M, Righini FM et al. Usefulness of atrial deformation analysis to predict left atrial fibrosis and endocardial thickness in patients undergoing mitral valve operations for severe mitral regurgitation secondary to mitral valve prolapse. A*m J Cardiol*. 2013;111:595-601.
27. Katayama K, Tajimi T, Guth BD et al. Early diastolic filling dynamics during experimental mitral regurgitation in the conscious dog. *Circulation*. 1988;78:390-400.
28. Sasayama S, Takahashi M, Osakada G et al. Dynamic geometry of the left atrium and left ventricle in acute mitral regurgitation. *Circulation*. 1979;60:177-186.
29. Kurt M, Wang J, Torre-Amione G et al. Left atrial function in diastolic heart failure. *Circ Cardiovasc Imaging* 2009;2:10-15.
30. Messika-Zeitoun D, Bellamy M, Avierinos JF et al. Left atrial remodelling in mitral regurgitation--methodologic approach, physiological determinants, and outcome implications:

a prospective quantitative Doppler-echocardiographic and electron beam-computed tomographic study. *Eur Heart J*. 2007;28:1773-1781.

Chapter Nine