Left atrial function is associated with earlier need for cardiac surgery in moderate to severe mitral regurgitation: usefulness in targeting for early surgery

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Abstract:

Background: We sought to determine whether assessment of LA function helps to identify patients at risk of early deterioration during follow-up with mitral valve prolapse (MVP) and mitral regurgitation (MR).

Methods: We retrospectively identified patients with moderate-to-severe MR, but no guideline-based indication for surgery, from a dedicated clinical database. Maximal and minimal LA volumes (LAVmax; LAVmin) were used to derive the total left atrial emptying fraction (TLAEF: LAVmax-LAVmin)/LAVmax x100%). Average peak contractile, conduit, and reservoir strain were obtained using 2D speckle-tracking imaging. Study outcome was time to mitral surgery.

Results: 117 patients were included; median follow-up was 18 months. 68 patients underwent surgery. ROC curves were used to derive optimal cut-offs for TLAEF (>50.7%) and strain (reservoir >28.5%; contractile >12.5%). Using Cox analysis, TLAEF, contractile, reservoir and conduit strain were univariate predictors of time-to-event. After multivariate analysis, TLAEF (HR 2.59, p=0.001), reservoir (HR 3.06, p<0.001), and contractile strain (HR 2.01, p=0.022) remained independently associated with events, but conduit strain did not. Using Kaplan-Meier curves, event-free survival was considerably improved in patients with values above the derived thresholds. TLAEF: 1-year survival 78±5% vs. 28±8%; 3-year survival: 68±6% vs. 13±5%; both p<0.001. Reservoir strain: 1-year survival 79±5% vs. 29±7%; 3-year survival 67±6% vs. 15±6% (both p<0.001). Contractile strain: 1-year survival 80±5% vs. 41±7%; 3-year survival 69±6% vs. 24±6% (both p<0.001).

Conclusion: LA function is independently associated with surgery-free survival in MVP with moderate-to-severe MR. Quantitative assessment of LA function may have clinical utility in guiding early surgical intervention in these patients.

Keywords: mitral valve prolapse; mitral regurgitation; atrial function; prognosis; mitral valve surgery

Abbreviations:

AF	Atrial fibrillation
BSA	Body surface area
EF	Ejection fraction
EROA	Effective regurgitant orifice area
LA	Left atrium
LAVmax	Maximal LA volume
LAVmin	Minimal LA volume
LV	Left ventricle
LVEDV	Left ventricular end diastolic volume
LVESV	Left ventricular end systolic volume
LVIDd	Left ventricular internal diameter in diastole
LVIDs	Left ventricular internal diameter in systole
MR	Mitral regurgitation
MVP	Mitral valve prolapse
PA	Pulmonary artery
TLAEF	Total Left Atrial Emptying Fraction

Introduction:

Mitral valve prolapse (MVP) has a prevalence of 2% in the West[1], and is the second most common valve lesion requiring cardiothoracic surgery[2]. Despite this, controversy remains as to the optimal timing of surgery[3-5]. Severe mitral regurgitation with associated cardiovascular symptoms provides a clear mandate for intervention[6,7]. Furthermore, it is well established that there are a number of clinical and echocardiographic features that, if present, should prompt surgical referral even in the absence of cardiovascular symptoms. Left ventricular (LV) volume overload, LV systolic impairment, the development of elevated pulmonary artery (PA) pressures, and the development of atrial fibrillation (AF) are embedded in both American and European practice guidelines as indications for surgery in MVP[8,9]. Unfortunately, it is the case that by the time one or more of these additional features has developed, outcomes including patient survival are poorer whether or not surgery is performed[2,10-16]. As a result, there is a trend toward early surgical referral, particularly when the valve lesion in question is deemed to have a high likelihood of repair[3-5,17]. There is the current unmet clinical need to find parameters that could help distinguish those patients in whom clinical deterioration is likely to occur, thereby allowing targeting of early surgery, reducing the chances of irreversible complications and improving survival.

The left atrium is central to the heart's adaptive mechanism in chronic MR, and has an important functional role. In mitral valve prolapse, loss of atrial contractile function in atrial fibrillation clearly impacts upon prognosis[15,16]. We have previously examined patients with MR with or without conventional indications for surgical intervention and demonstrated that impaired LA functional indices correspond to accepted adverse prognostic findings in MVP[18]. The current study expands upon our previous work: we wished to determine whether the analysis of LA function could help identify individuals without conventional guideline-based indications for surgical intervention in whom clinical or echocardiographic deterioration occurs sooner during follow-up, thereby potentially allowing identification of the optimal window for intervention in MVP.

Methods:

Study Population:

Suitable patients were retrospectively identified from a dedicated clinical database, which included all individuals assessed in our specialist imaging service between August 2009 and February 2013 (Figure 1). Patient-specific data including clinical status and echocardiographic findings were entered into the database contemporaneously. Patients were deemed suitable for inclusion in the current study if, at the point of initial review, they demonstrated: 1) the presence of at least moderate to severe MR due to MVP or mitral leaflet flail, where MVP was defined as the displacement of the tip of one or more segments of the mitral valve by ≥2mm relative to the hingepoints of the leaflets, and leaflet flail as the systolic eversion of the leaflet tip into the LA; and 2) the absence of a surgical indication according to American guidelines[8]. All patients were therefore asymptomatic, in sinus rhythm, pulmonary artery (PA) pressures were <50mmHg at rest and <60mmHg after exertion, had left ventricular (LV) ejection fractions (EF) >60% and LV internal diameter in systole (LVIDs) <40mm. We excluded patients with prior mitral valve surgery, more than mild co-existent aortic valve disease, evidence of infective endocarditis or a known history of ischaemic heart disease. Using the same database, we have previously published a descriptive analysis of atrial function in patients with MR ranging from mild to severe, including a large group with symptoms and other guideline-based criteria for surgical intervention[18]. Accordingly, the cohorts of the two studies substantially overlap, although for the current analysis we extended the timeframe for inclusion, focused on a specific subset of patients as outlined above, and reported on long-term outcomes. The institutional review board of Papworth Hospital NHS Foundation Trust approved the study and waived the need for signed consent for the retrospective analysis.

Image acquisition:

Transthoracic echocardiography was performed in the lateral decubitus position, using an S5-1 transducer and an iE33 imaging platform (Philips; Andover, MA, USA). Data was analyzed offline using commercially available software (Xcelera, Philips). Care was taken to optimize sector width, depth, gain settings and frame rates. LV dimensions were recorded from the parasternal long-axis window, and LV volumes and EF derived from the apical windows using Simpson's biplane method. Doppler tissue imaging of the mitral annulus was obtained at the inferoseptal and anterolateral positions from the apical 4-chamber view. S' represents average peak systolic velocity and E' average peak diastolic velocity. In addition, diastolic function was described as the ratio of E/E', where E was measured using pulsed Doppler of the mitral inflow from the apical 4-chamber view. MR severity was determined using a multiparametric approach: the effective regurgitant orifice area (EROA), estimated using the Proximal Isovelocity Surface Area method, was used for the purposes of statistical analysis. Great care was taken in order to obtain acceptable spectral Doppler waveforms of the MR jet from multiple acoustic windows to ensure that in all patients an assessment of EROA was possible. In the case of wall-hugging jets however, it is possible that on some occasions the EROA was over- or under-estimated, but in all patients the overall severity of MR was confirmed by assessment of additional features including the vena contracta, and the presence of pulmonary venous flow reversal[19]. PA pressure was estimated through assessment of the tricuspid regurgitant jet and right atrial pressure according to American guidelines[20].

Atrial function:

LA parameters were obtained from the apical windows, ensuring the images were optimized in order to avoid foreshortening of the atrium. Maximal and minimal left atrial volumes (LAVmax; LAVmin) were determined using Simpson's biplane method combining the 4- and 2-chamber views. From these, the total left atrial emptying fraction (TLAEF: LAVmax-LAVmin)/LAVmax x100%) was derived[21]. Similar to a previous definition[22], we recorded three phases of atrial strain: contractile (active atrial emptying, corresponding with the P-wave on the surface ECG), conduit (passive emptying: after MV opening in early diastole but prior to active emptying), and reservoir (representing atrial filling during cardiac systole, and equivalent to the sum of contractile and conduit: Figure 2). To acquire this data, standard grey-scale images from apical 4- and 2-chamber views were analyzed using semi-automated, commercially available software (Cardiac Motion Quantification; Qlab v8.0 and 9.0; Philips). The onset of the QRS was used as the zero-reference point, which by convention results in all phases of atrial strain being reported as positive values (Figure 2)[23]. Frame rates were in the range of 39-76 fps (median 47; interquartile range 40-52). The LA endocardial-blood border was manually identified by a point and click method, allowing the software to generate a region of interest, which was manually optimized to include the LA wall. Visual inspection of the cine image ensured that the software was tracking the myocardium appropriately. The atrium was divided into 6 segments in each apical view, and the mean of all 12 segments was recorded (Figure 2). Analysis of atrial strain and volumes were feasible in the entire cohort and no patients were excluded owing to poor image quality.

Clinical assessment and outcomes:

The evaluation of each patient, and decisions regarding frequency and timing of patient follow-up, was independently determined and supervised by the lead cardiologist of our specialist valve service, therefore ensuring consistency in the clinical approach to the patient cohort. At each visit, patients underwent comprehensive clinical and echocardiographic assessment. Particular attention was paid to establish the symptomatic status of all patients, including the use of exercise testing in order to help demonstrate the presence or absence of cardiovascular symptoms when appropriate. The clinical and echocardiographic parameters were recorded in a dedicated clinical database at the time of initial review. The primary endpoint of the study was cardiac surgery or all-cause mortality, which was recorded for all patients up to January 2017. Outcomes were identified through review of the dedicated clinical database and individual patient clinical records. Deaths were also identified using the UK Health and Social Care Information Service to ensure none were missed. Patients who were offered surgery but declined were considered an event for the purposes of the analysis, and any patient whose care was transferred to another institution after our initial assessment but before mitral valve surgery was required, had final follow-up recorded as the point of their last review in our service. The ultimate decision to proceed to surgery was the responsibility of the lead cardiologist, often after discussion in a multi-disciplinary team environment, which included two surgeons with a specialist interest in mitral valve surgery and a second cardiologist with an expertise in percutaneous valve intervention. All decisions were based upon clinical and echocardiographic findings in accordance with American guidelines[8]. Atrial functional indices, including TLAEF and strain, were analyzed by an individual who was not involved in clinical decision-making. The supervising cardiologist was blinded to the results of atrial functional analysis.

Statistical analysis:

Data was analyzed using SPSS v19.0 (SPSS Inc., Chicago, IL, USA). Continuous variables are summarized as mean ± standard deviation (SD) or median (inter-quartile range (IQR)) where appropriate. To determine whether atrial function was associated with the need for mitral valve surgery during, Cox proportional hazard models were employed. Clinical, echocardiographic and LA functional indices that were significant or borderline ($p<0.1$) on univariate analysis were entered into a multivariate model of time-to-event with cardiac surgery as the dependent variable. To avoid colinearity between volumetric and strain markers of LA function, separate models were constructed for each parameter in turn. Atrial functional indices were entered into the multivariate models as dichotomous variables. The optimal cut-off values for atrial parameters for use in the multivariate models were determined from receiver-operator characteristic curves as the value with optimal sensitivity and specificity as defined by the Youden index. Sequential Cox models were employed to determine the incremental prognostic usefulness of atrial function indices over standard clinical and echocardiographic data. Kaplan-Meier estimator curves were constructed for atrial indices to estimate surgery-free survival, and were compared using the log-rank test. Measurement reproducibility was determined by selecting 10 patients at random, and the measurements repeated by the original and a second operator whilst blinded to the original results. The within-subject coefficient of variation and 95% limits of agreement were calculated using the Bland-Altman method. Statistical significance was defined as $p<0.05$.

Results:

A total of 117 patients were identified (85 male, median age 61 (50-71) years). Baseline characteristics are in Table 1. We were able to follow all patients for the duration of the study. The longest follow-up was 81 months (median 18 (7-43) months). During follow-up, 68 patients required mitral valve surgery. Three patients died: one had undergone successful mitral valve repair 2 years prior to death, and the remaining two deaths occurred in patients who had been offered mitral valve surgery but declined. Therefore all events included in the outcome analysis were mitral valve surgery. In all patients, surgery was recommended on the basis of their mitral valve disease alone, and not as part of any other surgery. Indications for surgical referral were: isolated cardiovascular symptoms (n=40); LV dysfunction (n=11, of whom 8 were asymptomatic); raised PA pressures (n=13, of whom 9 were asymptomatic); and new onset atrial fibrillation (n=4). Of the 117 patients, 89 were included in our earlier descriptive study as mentioned previously.

On univariate analysis, TLAEF, reservoir, contractile and conduit strain were all strongly associated with the dependent variable (Table 2). In addition, LVIDd, LA volume, PA pressure, EROA and E/E' were all significantly associated with the need for cardiac surgery during follow-up on univariate analysis (Table 2). After multivariate analysis, TLAEF, contractile and reservoir strain remained independent predictors of surgery-free survival but conduit strain did not (Table 3): TLAEF (Hazard ratio (HR) 2.59, 95% CI 1.44-4.65; p=0.001), reservoir (HR 3.06, 95% CI 1.66-5.61; p<0.001), and contractile strain (HR 2.01, 95% CI 1.11-3.65; p=0.022).

To estimate surgery-free survival, Kaplan-Meier estimator curves were constructed using LA function indices. Optimal cut-offs for the atrial function indices were: TLAEF 50.7% (area under the ROC curve (AUC) 0.728; sensitivity 54%; specificity 88%); reservoir strain 28.5% (AUC 0.733; sensitivity 56%; specificity 88%); and contractile strain 12.5% (AUC 0.763; sensitivity 66%; specificity 80%). Patients with TLAEF above the threshold value were afforded superior 1- and 3-year event-free survival (1-year survival: 78±5% vs. 28±8%; 3-year survival: 68±6% vs. 13±5%; p<0.001; Figure 3). Similarly, patients in whom reservoir or contractile strain were above the derived cut-off values were noted to have superior outcomes. For reservoir strain, the difference in observed 1- and 3-year survival was as follows: 1-year survival 79±5% vs. 29±7%; 3-year survival 67±6% vs. 15±6% (both p<0.001; Figure 4). For contractile strain, the difference in 1-year survival was 80±5% vs. 41±7%; and for 3-year survival was 69±6% vs. 24±6% (both p<0.001; Figure 5).

Finally, we repeated the analysis, specifically focusing only on those patients with an EROA of ≥0.4cm^2. This was in order to establish the value of atrial functional indices in patients with clearly severe MR. TLAEF, reservoir and contractile strain all remained independently associated with the combined outcome. Similarly, those patients in whom atrial functional indices were above the derived cut-offs demonstrated superior 1- and 3-year event-free survival: TLAEF HR 2.85 (95% CI

1.42-5.75), p=0.003; 1-year event-free survival 59±9% vs. 30±8%; 3-year event-free survival 41±9% vs. 7±5%. Contractile strain: HR 2.07 (95% CI 1.06-4.07), p=0.034; 1 year survival 58±11% vs. 37±8%; 3-year event-free survival 38±11% vs. 16±6%. Reservoir strain: HR 3.28 (95% CI 1.62-6.66), p=0.001; 1 year survival 61±9% vs. 29±8%; 3-year event-free survival 39±9% vs. 10±5%.

Sequential Cox models were used to determine the additional value obtained from TLAEF and strain indices when combined with standard echocardiographic indications for surgery (LVIDs, EF, PA pressure, LA volume and EROA). The baseline model (χ^2= 41.4) was improved with the addition of either TLAEF (χ^2 56.9; p<0.001), or combined reservoir and contractile strain (χ^2 59.2; p=0.001).

Measurement variability (coefficient of variation and 95% limits of agreement) for intra-observer differences were: TLAEF 4.6% and ±3.7%; reservoir 4.9% and ±2.2%; contractile 5.7% and ±1.0%; conduit 8.5% and ±2.3%. Inter-observer differences were: TLAEF 7.8% and ±6.4%; reservoir 7.7% and ±3.3%; contractile 8.0% and ±1.6%; conduit 8.9 and ±2.1%.

Discussion:

This retrospective study demonstrates that left atrial function parameters are associated with poorer outcomes in patients with moderate to severe mitral regurgitation but no conventional indication for surgical intervention. We propose that the routine analysis of atrial function may be of clinical utility in identifying patients in whom early surgery for MVP with mitral regurgitation may be warranted.

The LA is an essential aspect of the heart's adaptive mechanism to mitral regurgitation. When MR develops acutely, the inability of the LA to absorb the sudden increase in blood volume results in pulmonary edema[24,25]. In MVP, MR usually worsens gradually, allowing the LA to undergo morphological adaptations. Eventually, these adaptations become disadvantageous, and excessive LA enlargement is associated with increased mortality in patients with MVP and severe MR[26,27].

The left atrium additionally has an important functional role. In healthy individuals the contribution of LA function to cardiac output is relatively modest, but in cardiovascular disease and even normal ageing, the importance of LA function is more pronounced[28-31]. By convention, the LA has three phases during which it demonstrates specific functional capabilities: reservoir, representing LA expansion during ventricular systole; conduit, occurring after opening of the mitral valve during which there is passive atrial emptying; and contractile, which corresponds with the p-wave on the surface ECG, representing active atrial emptying just prior to mitral valve closure[32]. Prior work using volumetric methods has demonstrated that the contractile phase of LA function is impaired following mitral valve repair, suggesting that pre-operative atrial dysfunction is masked by the presence of MR[33,34]. More recently, speckle-tracking techniques have been used to examine atrial function, and has subsequently proved useful in a number of clinical scenarios, including predicting the development of atrial fibrillation during cardiac surgery or in the presence of mitral valve disease[22,35,36]. Alterations in LA strain may reflect histopathological changes occurring within the atrium: in a group of patients who underwent LA biopsy at the time of surgery for MVP, the extent of fibrosis corresponded to reductions in atrial function derived using speckle-tracking imaging[37]. We have previously examined atrial function in a cross-section of patients with MVP and MR. Marked reductions in reservoir and contractile strain particularly were observed in patients with established cardiovascular symptoms, elevations of PA pressures, or adverse alterations in LV size or function[18].

Yang et al have examined the prognostic value of LA deformation in patients with asymptomatic severe mitral regurgitation[38]. They noted that impaired atrial strain predicted the development of heart failure symptoms or cardiovascular death, although a significant proportion of the study cohort had an established indication for surgery at enrolment, including the presence of AF, elevated PA pressures or LV enlargement, and as such this work does not reflect the management of these patients in American guidelines. Debonnaire and colleagues have demonstrated that LA reservoir strain <24% is associated with poorer survival in patients after mitral valve surgery, although again this was a heterogenous group of patients, many of whom had existing surgical indications at baseline[39]. There appear to be consistencies with the current study: whereas reservoir strain of <24% is associated with adverse survival, our proposed cut-off of 28.5% is linked to the need for earlier cardiac surgery, but with excellent long-term outcomes. Additionally, both studies confirm the value of reservoir strain, re-iterating that both active and passive aspects of LA function are important in the hearts adaptation to chronic MR. This may be because reservoir strain reflects the ability of the LA to absorb the regurgitant jet, the overall burden of LA scar, or atrial adaptation to increased filling pressures[18,37].

Conventional guidelines for intervention in MVP with MR include the development of cardiovascular symptoms, the presence of elevated pulmonary pressures, or the development of left ventricular dysfunction[8]. Unfortunately, it is usually the case that when these criteria have been met, patient outcomes are poorer irrespective of whether surgery is performed[6,12,13,40]. Consequently, there is a current trend toward early surgical referral, particularly if the valve in question has a high likelihood of repair[3,17]. We believe the current study may provide value in this regard. We have shown that contractile and reservoir strain display subtle early alterations that precede the development of clinical or echocardiographic features that mandate intervention and are independently associated with time to cardiac surgery. Combining derived cut-offs for reservoir and contractile strain of 28.5% and 12.5% respectively was able to identify patients in whom indications for surgery occurred much sooner during follow-up. We therefore propose that assessment of atrial strain may be useful to help target individuals for early surgical intervention, or at the very least closer clinical and echocardiographic surveillance, but at the same time avoiding unnecessary intervention in those in whom a watchful waiting approach may be suitable.

Limitations:

This study represents retrospective analysis of patients in a single-center with the inherent possibility of referral bias, and therefore requires confirmation in multiple centers through a prospective trial. Atrial strain indices may vary according to imaging platform and software systems, and therefore current results may not be applicable to all manufacturers. Although in our specialist service great care was taken to elicit the presence of cardiac symptoms, including the use of exercise testing, as with any retrospective analysis, it is possible (although we feel it unlikely) that some patients were erroneously labeled as being asymptomatic. During the course of this study, the American guidelines for surgical intervention in mitral valve disease have been updated. One substantial change has been the removal of exercise-induced elevation of PA pressures as a Class IIa indication, but as no patients in our study were operated on for this reason alone our results are unaffected. In the 2017 update, progressive change in LV size or function has been included as a Class IIa indication, although no clear guidance as to the rapidity or magnitude of change that should prompt intervention is provided. Therefore we believe that this addition does not detract from the potential clinical utility the analysis of atrial function may provide in this scenario.

Conclusion:

The left atrium is central to the heart's adaptation to chronic mitral regurgitation. In a cohort of patients with MVP and at least moderate MR, derived cut-offs for atrial functional indices was associated with shorter surgery-free survival, and provided incremental prognostic information to standard clinical and echocardiographic parameters. Quantitative analysis of atrial function may be of clinical utility in the assessment of patients with MVP, for early identification of the optimal surgical window.

Conflicts of interest:

DPD has received unrestricted research support from Sorin and MSD, and grants from the NIHR, MRC and BHF. BSR is a proctor for Boston Scientific. VSV was partly supported by Rosetrees Charity Trust. LR, YAO, NK, WW and AK have no conflicts of interest.

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Figure Legends:

Figure 1: A consort of the patients included in the study.

Figure 2: An example of atrial strain analysis. Top left and right panels depict an example of atrial strain obtained from the apical 4-chamber and 2-chamber windows respectfully. The lower panel gives an example strain-time curve (in this case obtained from the apical 2-chamber view). The atrium is divided into 6 segments (colored lines), with the average strain represented by the dotted white line. The onset of the QRS is marked and is used as the zero reference for our strain analysis. The three phases of atrial strain are annotated, and the onset of contractile strain can be seen to correspond to the p-wave on the ECG (labeled).

Figure 3: Survival according to LA function. Kaplan-Meier curve of surgery-free survival according to stratification by TLAEF.

Figure 4: Survival according to LA strain. Kaplan-Meier curve of surgery-free survival according to stratification by reservoir strain.

Figure 5: Survival according to LA strain. Kaplan-Meier curve of surgery-free survival according to stratification by contractile strain.

Table 1: Baseline characteristics

Variables	All (n=117)	Event (n=68)	No event (n=49)
Clinical			
Male gender, n (%)	85 (73)	48 (71)	37 (76)
Age, years	61 (50-71)	62 (50-71)	56 (49-73)
Range	16-86	16-86	19-82
Body Surface Area, kg/m^2	1.9 (1.8-2.1)	1.9 (1.8-2.1)	1.9 (1.7-2.1)
Echocardiography			
LVIDd, mm	54±6	56±6	53±6
LVIDs, mm	33 (29-36)	33 (28-37)	32 (29-35)
LVEDV, ml	130±36	133±40	125±28
Indexed, ml/m^2	67±17	69±19	66±14
LVESV, ml	43±14	44±14	42±12
Indexed, ml/m^2	22±6	23±7	22±6
EF, %	66 (62-71)	66 (62-71)	65 (62-71)
Avg S' (cm/s)	9.5 (8.5-10.5)	9.5 (8.4-11.0)	9.5 (8.4-10.0)
Avg E' (cm/s)	10.1±2.8	10.2±2.8	9.9±2.8
Avg E/E'	9.6 (7.8-13.1)	8.0 (7.0-10.0)	11.0 (9.1-14.1)
LA volume, ml	104 (74-122)	117 (90-146)	80 (60-105)
Indexed, ml/m^2	52 (38-66)	60 (49-70)	40 (32-53)
PA pressure (mmHg)	25 (20-37)	32 (20-42)	20 (20-30)
Mitral valve detail			
EROA, cm^2	0.4 (0.2-0.5)	0.4 (0.4-0.6)	0.3 (0.2-0.4)
Severe MR (EROA≥0.40cm^2), n (%)	62 (53)	52 (76)	10 (20)
Flail segment, n (%)	22 (19)	18 (26)	4 (8)
LA functional indices			
TLAEF, %	52±10	50±10	56±8
Reservoir strain, %	31 (24-38)	28 (21-35)	35 (30-42)
Contractile strain, %	13 (9-17)	10 (7-15)	15 (13-18)
Conduit strain, %	17 (14-22)	17 (13-21)	18 (15-23)

LVIDd=left ventricular internal diameter diastole; LVIDs=left ventricular internal diameter systole; LVEDV=left ventricular end-diastolic volume; LVESV=left ventricular end-systolic volume; EF=ejection fraction; Avg S=average systolic velocity mitral annular tissue Doppler imaging; LA=left atrial; PA=pulmonary artery; EROA=effective regurgitant orifice area; TLAEF=total left atrial emptying fraction

Table 2: Univariate associations of time to event during follow-up

	Hazard ratio	95% Confidence interval	P-value
Clinical			
Male gender	0.952	0.565-1.606	0.855
Age	1.010	0.995-1.026	0.184
Echocardiography			
LVIDd	1.748	1.176-2.598	0.006
LVIDs	1.233	0.773-1.965	0.380
LVEDV	1.002	0.996-1.009	0.495
LVESV	1.001	0.984-1.019	0.903
EF	1.012	0.968-1.057	0.602
Avg S’	1.059	0.940-1.192	0.346
Avg E’	1.020	0.930-1.118	0.678
Avg E/E’	1.080	1.032-1.130	0.001
LA volume	1.014	1.008-1.020	<0.001
PA pressure	1.059	1.034-1.085	<0.001
EROA	2.290	1.540-3.404	<0.001
Atrial functional indices			
TLAEF			<0.001
Continuous	1.070	1.044-1.096	
Optimal cut-off (50.7%)	3.867	2.373-6.302	
Reservoir			<0.001
Continuous	1.064	1.036-1.092	
Optimal cut-off (28.5%)	4.078	2.500-6.652	
Contractile			<0.001
Continuous	1.149	1.089-1.212	
Optimal cut-off (12.5%)	3.114	1.851-5.238	
Conduit			0.018
Continuous	1.046	1.008-1.087	
Optimal cut-off (15.5%)	1.43	0.89-2.32	

Abbreviations as previously

Table 3: Multivariate Cox proportional hazard models for prediction of need for cardiac surgery

Model 1 with TLAEF

Variables	**Hazard ratio (95% CI)**	**P-value**
LVIDd	1.22 (0.74-2.02)	0.439
E/E’	1.03 (0.97-1.09)	0.416
LA volume	1.00 (0.99-1.01)	0.777
PAP	1.03 (1.01-1.06)	0.017
EROA	2.06 (1.23-3.46)	0.006
TLAEF	**2.59 (1.44-4.65)**	**0.001**

Model 2 with reservoir strain

Variables	**Hazard ratio (95% CI)**	**P-value**
LVIDd	1.42 (0.86-2.35)	0.169
E/E’	1.03 (0.97-1.10)	0.283
LA volume	1.00 (0.99-1.01)	0.759
PAP	1.03 (1.00-1.06)	0.036
EROA	2.11 (1.27-3.51)	0.004
Reservoir strain	**3.06 (1.66-5.61)**	**<0.001**

Model 3 with contractile strain

Variables	**Hazard ratio (95% CI)**	**P-value**
LVIDd	1.22 (0.73-2.04)	0.454
E/E’	1.03 (0.97-1.10)	0.287
LA volume	1.00 (0.99-1.01)	0.476
PAP	1.03 (1.00-1.06)	0.038
EROA	1.97 (1.16-3.35)	0.012
Contractile strain	**2.01 (1.11-3.65)**	**0.022**

Model 4 with conduit strain

Variables	Hazard ratio (95% CI)	P-value
LVIDd	1.26 (0.76-2.10)	0.365
E/E’	1.04 (0.99-1.11)	0.139
LA volume	1.00 (1.00-1.01)	0.293
PAP	1.04 (1.01-1.07)	0.007
EROA	2.06 (1.23-3.46)	0.006
Conduit strain	1.24 (0.72-2.15)	0.444

Abbreviations as previously