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ORIGINAL PAPER

Structural and functional abnormalities of left-sided cardiac chambers in Barlow's disease without significant mitral regurgitation

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Aims This study aims to explore the presence of left ventricular (LV) and left atrial (LA) morphological and functional abnormalities in patients with Barlow's disease (BD) without significant mitral regurgitation (MR) and to investigate whether these abnormalities may predict MR progression.

Methods and results Consecutive patients with BD were retrospectively identified from two tertiary centres; those with MR graded from trivial to mild-to-moderate were selected and matched with healthy controls in a 1:1 ratio. Conventional and speckle-tracking echocardiographic data were collected. The development of moderate-to-severe or greater MR was evaluated on follow-up echocardiograms. Patients with BD ($n = 231$) showed increased LV dimensions and indexed LV mass (LVMi) in comparison with controls ($P < 0.001$); LV remodelling worsened with higher MR severity and was accompanied by an increased prevalence of eccentric LV hypertrophy (eLVH). Moreover, BD patients had larger LA volumes and more impaired LA reservoir strain vs. controls ($P < 0.001$), while LV strain was similar between the two groups. Multivariable linear regression analyses in the overall population identified BD and MR grade as independent predictors of remodelling markers (LV dimensions, LVMi, and LA volume) and BD as independent correlate of LA strain. MR progression was observed in 51 BD subjects (out of 170 patients with available follow-up). On Cox regression analysis, age, eLVH, mild-to-moderate MR, and mitral annular disjunction (MAD) emerged as independent predictors of MR progression.

Conclusion BD patients without significant MR show early LV and LA remodelling, together with reduced LA strain. MR progression was associated with eccentric LV remodelling, MAD, and MR severity.

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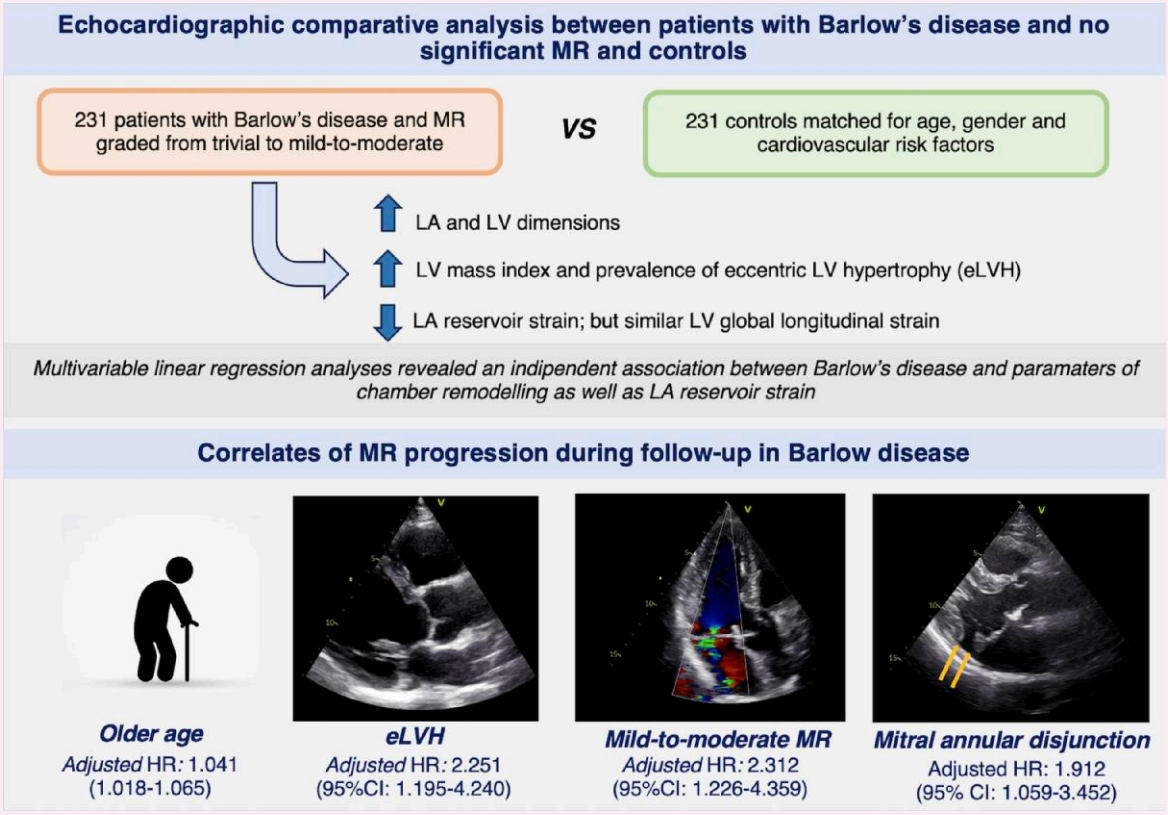
Graphical Abstract



Keywords Barlow's disease • mitral regurgitation • ventricular remodelling • left atrium • speckle-tracking echocardiography

Introduction

Mitral valve prolapse (MVP) is the most common cause of primary mitral regurgitation (MR) and may be categorized in two distinct phenotypes, i.e. fibroelastic deficiency (FED) and Barlow's disease (BD).[1] FED is typically characterized by a single-segment prolapse/flail with thin leaflets. In turn, BD is defined by a bileaflet or multi-scallop MVP, with diffuse thickening and redundancy of leaflets, elongated chordae, and annular abnormalities, and typically affects younger patients than FED.[1]

The clinical course of patients with BD is often complicated by the development of severe MR, which may result in progressive structural and functional remodelling of the left-sided chambers. Importantly, the presence of left ventricular (LV) dysfunction or severe left atrial (LA) enlargement is a criterion for mitral valve (MV) intervention in asymptomatic patients with severe MR, based on current guidelines (with Class I and IIa indications, respectively).[2] Recently, impaired LV or LA mechanics, as assessed by speckle-tracking echocardiography, have also been suggested as early markers of cardiac damage in patients with primary severe MR and of potential additive value in the decision-making regarding the timing of surgical intervention.[3,4]

On the other hand, recent studies in BD patients[5–7] have observed significant remodelling of the left-sided chambers even in patients with mild or moderate MR, suggesting the presence of a myocardial damage independent or disproportionate from MR severity. However, advanced echocardiographic measures were not applied and the interpretation of these findings was challenged by other authors, remaining a matter of debate.[1,8] Furthermore, whether these chamber abnormalities have clinical implications for disease progression is still unclear.

Thus, the aims of the present study were (i) to explore the presence of LV and LA morphological and functional abnormalities, assessed by conventional and speckle-tracking echocardiography, in BD patients without significant MR as compared with controls, and (2) to investigate whether these abnormalities may predict MR progression during follow-up.

Methods

Patient population

We retrospectively identified consecutive patients with BD evaluated in two tertiary centres: Leiden University Medical Center, Leiden, the Netherlands and Centro Cardiologico Monzino, IRCCS, Milan, Italy between January 2010 and December 2021. The diagnosis of BD was based on the echocardiographic findings[9]: MVP involving both leaflets and multiple scallops of one leaflet, due to excessive tissue and chordal elongation, associated with annular abnormalities, such as annular dilatation with or without calcification and/or mitral annular disjunction (MAD). Patients were included only when MR was graded from trivial to mild-to-moderate, as defined by an integrated echocardiographic assessment, including thresholds of effective regurgitant orifice area (EROA) < 30 mm^2 and regurgitant volume (Rvol) < 45 mL.[10]

In order to avoid potential confounding causes of left-sided chambers remodelling, the following exclusion criteria were applied: (i) congenital heart disease, (ii) Marfan's syndrome or other connective tissue diseases, (iii) hypertrophic or dilated cardiomyopathy, (iv) concomitant moderate or severe valvular heart disease, (v) LV ejection fraction (LVEF) < 50%,

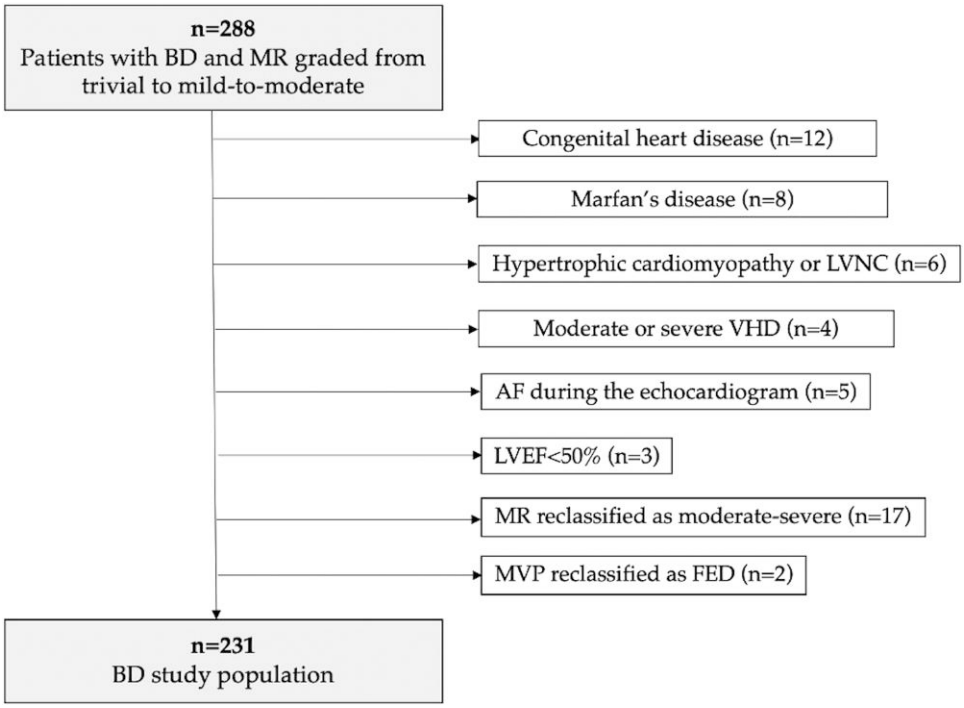


Figure 1 Study flow chart. AF, atrial fibrillation; BD, Barlow's disease; FED, fibroelastic deficiency; LVEF, left ventricular ejection fraction; LVNC, left ventricular non-compaction; MR, mitral regurgitation; MVP, mitral valve prolapse.

and (vi) atrial fibrillation (AF) during echocardiography (*Figure 1*). Patient data were collected at the time of the baseline echocardiogram from the departmental cardiology information systems (EPD-VisionVR at Leiden University Medical Center and W-Hospital at Centro Cardiologico Monzino). Additionally, healthy controls matched for demographic characteristics, cardiovascular risk factors, and history of AF (in a ratio 1:1) were selected from echocardiographic databases in both centres, during the same time period of data acquisition. Indications for echocardiography in controls were (i) cardiovascular screening (presence of cardiovascular risk factors, pre-operative, heart murmur, systemic diseases, and COVID-19, but without evidence of any cardiac abnormalities also with multi-modality imaging), (ii) detection of source of embolism, and (iii) symptoms of chest pain or palpitations or dyspnoea.

The study complies with the Declaration of Helsinki and was approved by the Institutional Review Boards. Due to the retrospective design of this study, the Medical Ethical Committees waived the need for written informed consent.

Conventional echocardiographic examination

Comprehensive echocardiographic examinations were performed with commercially available ultrasound systems (Vivid E7, E9, E95, GE-General Electric Vingmed, Horten, Norway). Images were digitally stored for offline analyses, which were performed by an experienced operator at each institution (M.C.M. and V.M.).

LV linear dimensions were measured from parasternal long-axis views and LV mass was calculated using the Devereux formula and indexed for body surface area (BSA).[11] Eccentric LV hypertrophy (eLVH) was defined by the presence of LV mass index (LVMi) > 115 g/m^2 for men and >95 g/m^2 for women, in association with regional wall thickness < 0.42.[11] From the apical two- and four-chamber views, LV end-diastolic and end-systolic volumes were measured and indexed for BSA (LVEDVi and LVESVi, respectively) and LVEF was calculated using the biplane Simpson's method.[11] Maximal and minimal LA volumes were measured from the apical two- and four-chamber views, at end-systole and end-diastole, respectively, using the biplane Simpson's method and subsequently indexed for BSA (LAVi max and LAVi min, respectively).[12] The LA sphericity index, defined as the ratio between the medio-lateral and superior–inferior LA diameters in the end-systolic phase, was also calculated. Parameters of diastolic function were assessed according to the most recent guidelines.[13]

Morpho-functional measurements of the MV were performed on the parasternal long-axis view, according to current evidence.[14] MVP was identified as a systolic displacement (>2 mm) of either one or both mitral leaflets into the LA and the anteroposterior diameter of the MV annulus was measured in the end-diastolic phase. MAD was assessed as the separation between the insertion of the posterior leaflet to the LA wall and the base of the LV posterior wall and considered significant when ≥5 mm.

MR grading was performed using a multi-parametric approach, including qualitative, semi-quantitative, and quantitative measures,[10] and confirmed after a blinded review by a second echocardiographer.[10] MR was classified as trivial, mild, or mild-to-moderate, and, in order to extrapolate the impact of MR severity on cardiac remodelling, patients with BD were divided into patients with trivial or mild MR vs. patients with mild-to-moderate MR.

Speckle-tracking strain imaging

LV global longitudinal strain (LVGLS) and LA reservoir strain were assessed with two-dimensional speckle-tracking echocardiography, and the strain values were calculated offline using EchoPAC version 204 software (General Electric Vingmed Ultrasound). For the measurement of LVGLS, apical four- and two-chamber views and long-axis views zoomed on the LV (acquired with a frame rate ≥ 50 frames/s) were used. LVGLS was calculated using endocardial border tracing method and derived by the software averaging all segmental peak strain values and subsequently by averaging values of all apical views.[11]

LA reservoir strain was calculated from an apical four-chamber view, selecting the QRS complex as a reference point (R–R gating). After the

endocardial border tracing, LA reservoir strain was obtained as the average of the peak values during the cardiac cycle of all six segments.[15]

According to current evidence,[16,17] an impairment of LV or LA mechanics was defined by values of LVGLS < 17.5% and LA reservoir strain < 24%, respectively.

MR progression

Follow-up echocardiograms, when available, were reviewed by two experienced observers to evaluate the progression of MR grade in patients with BD. For patients having more than one subsequent examination, the most recent (before MV surgery, if applicable) was considered. MR progression was defined by the presence of a MR grade at least moderate-to-severe.

Statistical analysis

Continuous variables are expressed as mean (SD) or median [interquartile range (IQR)] and compared between two groups using the Student's *t*-test or Mann–Whitney *U* test, as appropriate. Categorical data are presented as frequencies and percentages and compared using χ^2 test or the Fisher's exact test. One-way analysis of variance with Bonferroni *post hoc* tests and Kruskal–Wallis test were used for the comparison of continuous variables between three groups, as appropriate.

Univariable and multivariable linear regression analyses were performed to identify clinical and echocardiographic variables associated with LA or LV parameters that were significantly abnormal in BD patients (LVEDVi, LVMi, LAVi max, and LA reservoir strain).

The predictors of MR progression were investigated using univariable and multivariable Cox proportional hazard regression models, censoring patients at the time of the last available echocardiogram. Variables with a significant correlation at univariable analysis ($P < 0.05$) were selected for multivariable analysis. Significant collinearity was excluded for each multivariable model estimating the variance inflation factor (<0.5).

All tests were two-sided, and *P*-values of <0.05 were considered statistically significant. Data analysis was performed using SPSS version 25.0 (SPSS, Chicago, IL, USA) and R version 4.0.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 231 patients with BD fulfilled the inclusion criteria for the present study (*Figure 1*) and were matched in a 1:1 ratio ($n = 231$) with controls with similar demographic characteristics and prevalence of cardiovascular risk factors and paroxysmal AF.

The comparative analysis between the two groups is shown in *Table 1*. BD patients and controls showed similar clinical features, while echocardiography revealed remarkable differences. BD patients had increased LV dimensions and LVMi as compared with the control group, resulting in a higher prevalence of eLVH (all $P < 0.001$). In addition, BD patients showed larger LA volumes ($P < 0.001$), accompanied by a higher LA sphericity index, reflecting a more spherical remodelling of the LA cavity. However, parameters of LV systolic performance, including LVEF and LVGLS, were similar between the two groups. Particularly, 30 patients with BD had LVGLS < 17.5%, with a prevalence not different from controls (12.9% vs. 11.1%, $P = 0.594$). LA reservoir strain values were significantly lower in BD patients ($P < 0.001$) and an impairment of LA mechanics (defined by values of LA strain < 24%) was more common among BD patients than controls (20.4% vs. 5.7%, $P < 0.001$). Conversely, there were no relevant differences between the two groups in other diastolic parameters including *E*/*e*′ ratio and peak velocity of the tricuspid regurgitant jet.

Among patients with BD, the vast majority ($n = 189$; 79%) had bileaflet MVP.

MR was graded as trivial in 36 (16%) patients, mild in 93 (40%) patients, and mild-to-moderate in the remaining 102 (44%) subjects. Among BD patients in which the quantitative assessment was feasible ($n = 169$, with mild or mild-to-moderate MR; not feasible in trivial MR), the median values of EROA and RVol were 15 (10–21) mm^2 and 18 (11–25) mL, respectively. Finally, BD patients were characterized by larger tricuspid annular diameter, higher values of TAPSE, and higher prevalence of mild-to-moderate tricuspid regurgitation, as compared with controls.

Patients with BD stratified according to MR grade

When stratifying the BD population on the basis of MR grade, both patients with trivial or mild MR ($n = 129$) and patients with mild-to-moderate MR ($n = 102$) had significantly larger LA and LV dimensions and increased LVMi, together with a higher prevalence of eLVH in comparison with controls (*Figure 2* and Supplementary data online, *Table S1*). However, these signs of chamber remodelling progressively worsened with more severe MR and eLVH were more commonly present in patients with mild-to-moderate MR as compared with patients with trivial or mild MR (39% vs. 20%, $P = 0.001$). Both BD subgroups showed lower values of LA reservoir strain than controls but without relevant differences in MR severity. Parameters of LV performance, including LVGLS, were also similar between BD patients with trivial or mild and those with mild-to-moderate MR.

In addition, BD patients with mild-to-moderate MR presented larger MV annular dilatation and a higher prevalence of MAD (42% vs. 29%, $P = 0.033$), as compared with patients with trivial or mild MR. *Figure 3* shows an illustrative case of a patient with BD and mild MR, showing LA and LV dilatation, as well as eLVH and impaired LA strain.

Finally, we performed a comparative analysis, selecting the subgroup of patients with trivial MR (36 BD vs. 210 controls), as displayed in Supplementary data online, *Table S2*. Notably, this analysis confirmed the presence of larger volumes of left-sided chambers and MV annulus, together with lower LA reservoir strain in BD patients, as compared with controls.

Determinants of LA and LV remodelling in the overall population (BD and controls)

Linear regression models in the total population ($n = 462$) were built to investigate the determinants of LA or LV parameters that differ between the two study groups: LVMi, LVEDVi, LAVi max, and LA reservoir strain. Multivariable regression analyses are shown in *Table 2*, while results of the univariable analyses are illustrated in Supplementary data online, *Table S3*. Age, male sex, BD, and MR grade were independent associates of increased LVMi. Similarly, larger LVEDVi was independently associated with age, male sex, BD, and MR grade and also with the presence of MAD. LAVi max was independently related with age, paroxysmal AF, BD, and MR grade. Finally, LA reservoir strain was independently associated with age, male gender, BD, LVGLS, LA sphericity index, and *E*/*e*′, but not with MR grade.

MR progression in BD patients

A total of 170 patients with BD had at least one follow-up echocardiogram performed after a median interval of 37 months (IQR: 24–68) from the baseline echocardiogram. Progression to moderate-to-severe or greater MR was observed in 51 (30%) subjects, and 20 patients were consequently referred for MV intervention. On univariable Cox regression analysis (shown in *Table 3*), age, MR grade, the presence of MAD, LVMi (expressed as continuous or categorical variable: eLVH), LAVi max, and *E*/*E*′ ratio were significantly associated with MR progression. In order to avoid over-fitting of the models, multivariable analyses were performed including alternatively LAVi max and *E*/*E*′ ratio. On multivariable analysis age, MR grade, presence of MAD, and LVMi emerged as independent predictors of MR progression. When

Table 1 Clinical and echocardiographic features of the study population

	BD ($n = 231$)	Controls ($n = 231$)	*P*-value
Clinical variables			
Age (years)	48 ± 15	47 ± 12	0.602
Female gender (*n*, %)	130 (55)	119 (52)	0.305
Hypertension (*n*, %)	27 (12)	28 (12)	0.645
Hypercholesterolemia (*n*, %)	19 (8)	22 (10)	0.822
Diabetes (*n*, %)	1 (0.5)	6 (3)	0.124
Obesity (*n*, %)	1 (0.5)	4 (2)	0.372
PAF (*n*, %)	16 (7)	10 (4)	0.313
CAD (*n*, %)	3 (1)	3 (1)	0.922
COPD (*n*, %)	2 (1)	4 (2)	0.469
Creatinine (mg/dL)	0.87 ± 0.19	0.88 ± 0.20	0.816
NYHA functional class			0.999
I/II/III-IV (*n*)	210/20/0	210/20/0	
Syncope (*n*, %)	9 (4)	3 (1)	0.141
Echocardiographic variables			
LVEDDi (mm/m^2)	28.1 ± 3.6	25.4 ± 2.9	<0.001
LVESDi (mm/m^2)	16.7 ± 3.3	15.6 ± 2.6	<0.001
IVS thickness (mm)	9 (8–10)	10 (8–11)	0.053
PW thickness (mm)	9 (8–11)	9 (8–10)	0.329
LVMi (g/m^2)	93 (80–109)	81 (72–93)	<0.001
eLVH (*n*,%)	66 (29)	17 (7)	<0.001
LVEDVi (mL/m^2)	61 ± 12	51 ± 9	<0.001
LVESVi (mL/m^2)	24 ± 6	20 ± 5	<0.001
LVEF (%)	61 ± 6	61 ± 5	0.314
LVGLS (%)	20.5 ± 2.7	20.2 ± 2.4	0.165
LAVi max (mL/m^2)	35 ± 12	25 ± 8	<0.001
LAVi min (mL/m^2)	17 ± 9	11 ± 5	<0.001
LA sphericity index	0.84 ± 0.11	0.78 ± 0.09	<0.001
LA reservoir strain (%)	31.2 ± 8.0	34.4 ± 7.0	<0.001
E/*A* ratio	1.2 (0.9–1.5)	1.3 (0.9–1.6)	0.365
E/*e*′ ratio	7.0 (6.0–8.4)	6.8 (5.7–8.0)	0.082
MV annulus (mm)	34 ± 5	28 ± 3	<0.001
MAD (*n*, %)	91 (39)	-	-
Mild-to-moderate MR	102 (44)	0 (0)	<0.001
TAPSE (mm)	25 ± 4	24 ± 3	0.002
TV annulus (mm)	32 (30–36)	31 (27–35)	0.001
TR grade (*n*, %)			0.015
Trivial or mild	224 (97)	231 (100)	
Mild-to-moderate	7 (3)	0 (0)	
TR jet velocity (m/s)	2.2 (2.0–2.4)	2.3 (2.1–2.4)	0.111
PASP (mmHg)	25 (22–29)	26 (22–29)	0.101

BD, Barlow's disease; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; IVS, interventricular septum; LA, left atrial; LAVi, indexed LA volume; LV, left ventricular; eLVH, eccentric LV hypertrophy; LVEDDi, indexed LV end-diastolic diameter; LVESDi, indexed LV end-systolic diameter; LVEDVi, indexed LV end-diastolic volume; LVESVi, indexed LV end-systolic volume; LVEF, LV ejection fraction; LVGLS, LV global longitudinal strain; LVMi, indexed LV mass; MAD, mitral annular disjunction; MV, mitral valve; NYHA, New York Heart Association; PAF, paroxysmal atrial fibrillation; PASP, pulmonary arterial systolic pressure; TR, tricuspid regurgitation; TV, tricuspid valve.

expressed as a dichotomous variable, eLVH was also independently associated with MR progression, after adjustment for age, MR grade, presence of MAD, and LAVi max (hazard ratio 2.251; 95% confidence interval 1.195–4.240, $P = 0.012$). Event-free survival rates in BD population stratified according to MR grade or the presence of MAD or eLVH are shown in *Figure 4A–C*, respectively.

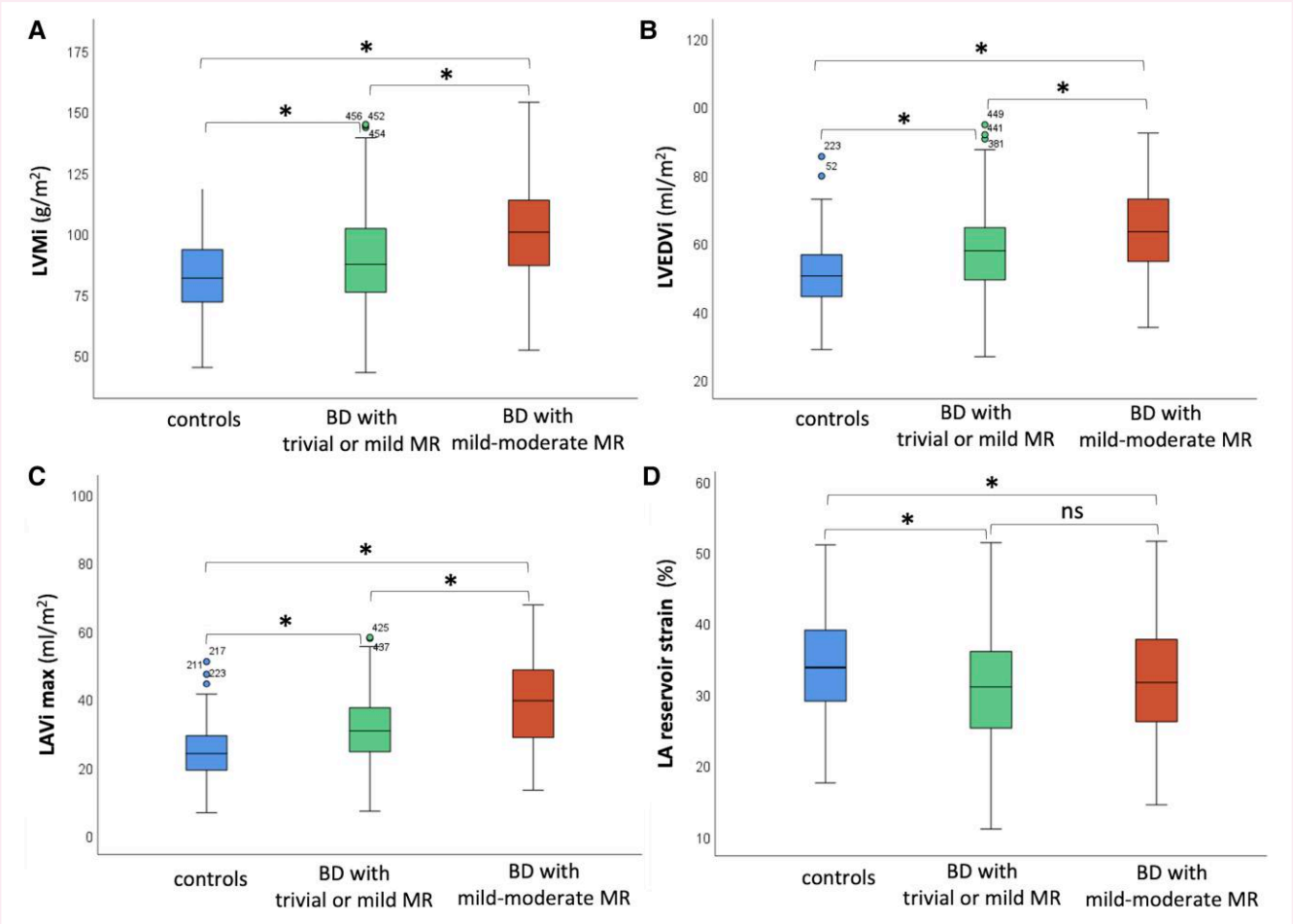


Figure 2 Parameters of left-sided chamber remodelling stratified according to MR severity in BD patients: LVMi, LVEDVi, LAVi max and LA reservoir strain (*A–D*). Asterisks indicate statistically significance ($P < 0.05$). BD, Barlow's disease; LA, left atrial; LAVi max, indexed maximal LA volume; LV, left ventricular; LVEDVi, indexed LV end-diastolic volume; LVMi, indexed LV mass; ns, non-significant.

Discussion

The main findings of the present study can be summarized as follows: (i) Patients with BD and MR grade from trivial to mild-to-moderate show early LV and LA remodelling, together with a mild impairment of LA reservoir strain, but not of LV systolic function as compared with matched controls; (ii) these abnormalities of BD are at least partially independent from MR severity (within a range of non-significant MR grade); (iii) MR progression during follow-up was associated with baseline MR grade and also with the presence of eccentric LV remodelling and MAD.

Early abnormalities of left-sided chambers in BD patients without significant MR

In asymptomatic patients with severe primary MR, current indications for MV intervention rely on the assessment of the haemodynamic impact of MR and thus primarily on parameters of LV dimensions and function (i.e. with LV end-systolic diameter > 40 mm or LVEF < 60% providing a class I recommendation for surgery). On the other hand, initial studies have suggested that in patients with MVP, especially with BD phenotype, LV enlargement and systolic impairment may be disproportionate in relation to MR severity,[5–7] challenging the assumption that LV remodelling is a direct effect of the MR-related volume overload. However, the concept of disproportionate LV remodelling in MVP patients has been criticized by other authors[8,18] and to date remains controversial. Particularly, the theory of a 'prolapse volume', which would determine LV volume overload on top of the transvalvular MR volume, has been postulated by El-Tallawi *et al.*,[8] while an alternative hypothesis to explain these findings relies on the methodological variability of LV volumes quantification.[18] Moreover, whether the presence of early remodelling of left-sided chambers in BD may have clinical and prognostic implications is currently unknown.

In the echocardiographic study performed by Yang *et al.*,[7] 253 MVP patients with less than moderate MR exhibited larger LV and LA dimensions and higher LVMi than matched controls; however, an advanced analysis of myocardial mechanics to better address the myocardial damage was not provided. Our results confirm and further expand the findings reported by Yang *et al.*, in a multi-centric, selected cohort of BD patients. In the present study, patients with BD and MR graded from trivial to mild-to-moderate showed early LV and LA enlargement, together with an increased prevalence of eLVH and impaired LA mechanics in comparison with matched subjects, while conventional and speckle-tracking parameters of LV systolic performance were similar between the two groups. Notably, despite LV and LA remodelling worsen in parallel to MR severity, current findings were confirmed when only the subset of BD patients with trivial or mild MR was included in the comparative analysis. In addition, multivariable linear regression

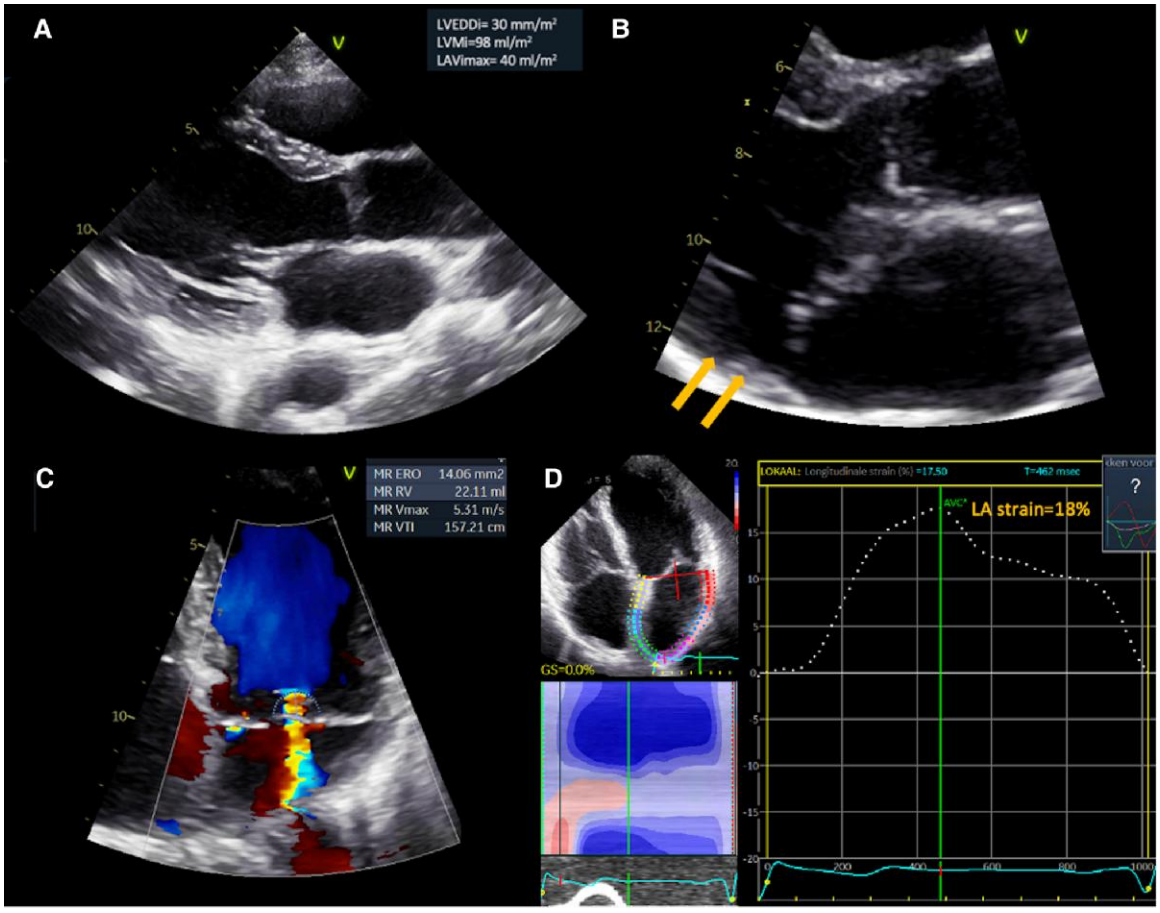


Figure 3 Example of echocardiographic measurements in a BD patient. (*A*, *B*) Images from a 37-year-old woman with BD and bileaflet MVP are shown. She presented a mild LV and LA dilatation, with eLVH. A MAD is also evident (indicated by arrows). (*C*) MR was graded as mild MR (EROA 14 mm^2), with an end-systolic, central jet. (*D*) Speckle-tracking analysis revealed an impairment of LA reservoir strain. BD, Barlow's disease; EROA, effective regurgitant orifice area; LA, left atrial; LV, left ventricular; eLVH, eccentric LV hypertrophy; MAD, mitral annular disjunction; MR, mitral regurgitation; MVP, mitral valve prolapse.

analyses revealed an independent association between BD and the dimensions of left-sided chambers, after adjustment for important covariates including MR severity. Of importance, the detection of an early remodelling of left-sided chambers in BD patients (at least partially independent from MR) may have important implications regarding decision-making on patients' management and specifically the indication for MV intervention.

In line with a growing body of evidence, current data support the hypothesis of an early myocardial involvement in patients with BD.[19] As previously suggested, a disproportionate LV remodelling in BD might be the phenotypical expression of a genetically mediated process or reflect the genetic substrate to develop maladaptive myocardial responses to a 'second hit' such as a mild volume overload or frequent ventricular ectopic beats.[1] In this regard, there is increasing evidence that BD has a strong inheritable component[1,19,20] and recent investigations have shown the association between BD and pathogenetic variants in several cardiomyopathy-related genes (such as titin and filamin C), suggesting a potential shared genetic background in the development of MV and myocardial disease.[20,21] Additionally, cardiac magnetic resonance (CMR) imaging studies revealed the presence of LV replacement myocardial fibrosis, mostly located in the basal inferolateral wall, in approximately one-third of patients with BD, irrespective from MR severity.[19,22]

Intriguingly, in our study population, LA remodelling was accompanied by a mild impairment of LA reservoir function that was not related to MR severity, and, similar to previous observations in the setting of cardiomyopathies,[23] might be an expression of an intrinsic atrial myopathy. On the other hand, it is also conceivable that mitral annular abnormalities play a role in this setting. Indeed, mitral annular alterations, and MAD especially, have been demonstrated as early features of the BD phenotype[14] and are associated with paradoxical annular dynamics, which may in turn affect atrial deformation.[24]

In the present study, LVGLS values were not significantly reduced in BD and within the normal range in most patients. Accordingly, our data suggest that LV mechanics are usually preserved in the early phases of BD, while later, secondary to MR progression, an impairment of LVGLS may be observed and precede the development of an overt LV dysfunction.[3]

MR progression in BD and its determinants

In a previous longitudinal analysis including 63 MVP patients from the Framingham Offspring, serial changes in LV end-systolic diameter and MVP severity emerged as the strongest correlates of MR worsening, evaluated by the increase in MR jet height.[25] However, the association with specific annular abnormalities was not evaluated and data on

Table 2 Multivariable linear regression analyses for LVMi, LVEDVi, LAVi max, and LA strain in the overall population

	Unstandardized *B* (95% CI)	SE (*B*)	Standardized beta	*P*-value
1) Multivariable regression for LVMi				
Age	0.212 (0.077–0.347)	0.069	0.140	0.002
Male gender	9.765 (6.164–13.366)	1.832	0.233	<0.001
Hypertension	4.274 (−1.300 to 9.848)	2.836	0.068	0.133
BD	8.813 (4.305–13.320)	2.293	0.210	<0.001
Mild-to-moderate MR	11.483 (6.292–16.673)	2.614	0.227	<0.001
MAD	−2.985 (−8.270 to 2.301)	2.689	−0.055	0.268
2) Multivariable regression for LVEDVi				
Age	−0.169 (−2.41 to −0.096)	0.037	−0.193	<0.001
Male gender	6.617 (4.685–8.549)	0.983	0.272	<0.001
BD	6.128 (3.710–8.546)	1.230	0.253	<0.001
Mild-to-moderate MR	6.714 (3.929–9.499)	1.417	0.229	<0.001
MAD	3.710 (0.874–6.545)	1.443	0.118	0.010
3) Multivariable regression for LAVi max				
Age	0.158 (0.089–0.226)	0.035	0.193	<0.001
PAF	4.698 (0.777–8.618)	1.995	0.095	0.019
E/*e*′ ratio	0.376 (−0.097 to 0.848)	0.240	0.069	0.119
BD	7.370 (5.300–9.440)	1.053	0.323	<0.001
Mild-to-moderate MR	5.998 (3.397–8.599)	1.324	0.214	0.010
4) Multivariable regression for LA reservoir strain				
Age	−0.124 (6.557–23.173)	0.028	−0.224	<0.001
Male gender	−2.206 (−0.178 to −0.069)	0.666	−0.146	0.001
PAF	−1.087 (−3.821 to 1.647)	1.391	−0.034	0.435
Hypertension	0.162 (−1.805 to 2.129)	0.999	0.007	0.872
LVGLS	0.860 (0.611–1.110)	0.127	0.294	<0.001
LA sphericity index	13.514 (7.412–19.616)	3.104	0.194	<0.001
E/*e*′ ratio	−0.444 (−0.799 to −0.110)	0.170	−0.124	0.009
BD	−4.353 (−5.900 to −2.805)	0.787	−0.288	<0.001
Mild-to-moderate MR	1.400 (−0.479 to 3.279)	0.956	0.076	0.144

BD, Barlow's disease; CI, confidence interval; LA, left atrial; LAVi, indexed LA volume; LVEDVi, indexed LV end-diastolic volume; LVGLS, LV global longitudinal strain; LVMi, indexed LV mass; MAD, mitral annular disjunction; MR, mitral regurgitation; PAF, paroxysmal atrial fibrillation.

baseline MR grade were not clearly reported. In the study from Yang *et al*.,[8] among 153 patients with MVP and follow-up echocardiographic data, an isolated involvement of the posterior leaflet was associated with a higher risk of developing moderate-to-severe or greater MR, while parameters of LV remodelling or MAD were not. Conversely, in the present cohort, eccentric LV remodelling emerged as independent predictors of MR progression, together with older age, MR severity, and MAD. These discordant findings may be primarily related to the different characteristics of the two cohorts, since the study by Yang *et al*. was conducted in a mixed MVP population, including either patients with BD and FED, as confirmed by a considerably older mean age (61 vs. 48 years), and adopting a lower threshold of MR severity (EROA < 20 mm^2 and Rvol < 30 mL), as inclusion criteria.

The association between higher LVMi and MR worsening may have important clinical implications, since patients with eccentric LV remodelling may benefit from a tailored follow-up strategy, with closer echocardiographic surveillance and screening of other potential aetiologies, including ventricular arrhythmias. Despite chronologically causality may not be ascertained from our study, it is conceivable that eLVH may reflect a more severe disease phenotype, which is also associated with an increased risk of MR progression. Similarly, the presence of MAD may act a predisposing factor for the evolution of MV abnormalities and MR severity, as a consequence of the abnormal annular mechanics and increased mechanical stress on the MV apparatus.[14]

Whether BD patients with less than severe MR and LV remodelling may benefit from an earlier referral for MV intervention may not be ascertained from our study and deserve future specifically designed investigations.

Limitations

Several limitations of the current study should be mentioned. First, this study concerns a retrospective analysis of patients referred to two high-volume tertiary centres and selection bias cannot be fully excluded. Therefore, future prospective studies are warranted to confirm our findings. Accurate grading of MR severity in patients with BD may be challenging, especially in patients with multiple and eccentric jets, with the risk of underestimating MR severity. In our study, the echocardiographic analysis of MR severity was optimized as performed by experts and confirmed after discussion with a second observer and

Table 3 Univariable and multivariable Cox regressions for MR progression in BD patients

	Univariable		Multivariable (1)		Multivariable (2)	
	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
Age (years)	1.041 (1.019–1.062)	<0.001	1.041 (1.018–1.065)	<0.001	1.041 (1.017–1.066)	<0.001
Male gender	1.464 (0.822–2.606)	0.195	-	-	-	-
Hypertension	1.589 (0.816–3.093)	0.173	-	-	-	-
PAF	1.277 (0.536–2.809)	0.628	-	-	-	-
LVMi (g/m^2)	1.022 (1.010–1.034)	<0.001	1.015 (1.002–1.028)	0.020	1.017 (1.004–1.031)	0.012
LVEDVi (mm/m^2)	1.021 (0.997–1.045)	0.088	-	-	-	-
LVESVi (mm/m^2)	1.007 (0.961–1.055)	0.764	-	-	-	-
LVEF (%)	1.025 (0.979–1.073)	0.294	-	-	-	-
LVGLS (%)	1.014 (0.916–1.123)	0.784	-	-	-	-
LAVi max (mL/m^2)	1.030 (1.009–1.051)	0.004	-	-	0.998 (0.974–1.022)	0.849
LAVi min (mL/m^2)	1.025 (0.997–1.053)	0.077	-	-	-	-
LA strain (%)	0.994 (0.956–1.033)	0.750	-	-	-	-
E/*e*′ ratio	1.125 (1.007–1.258)	0.038	1.021 (0.888–1.173)	0.772	-	-
Bileaflet MVP	0.978 (0.472–2.028)	0.953	-	-	-	-
MAD	1.891 (1.085–3.298)	0.025	1.912 (1.059–3.452)	0.031	1.865 (1.051–3.308)	0.033
Mild-to-moderate MR	2.664 (1–509–4.704)	0.001	2.312 (1.226–4.359)	0.007	2.060 (1.108–3.827)	0.022

Abbreviations: as in *Figures 1* and *2*.

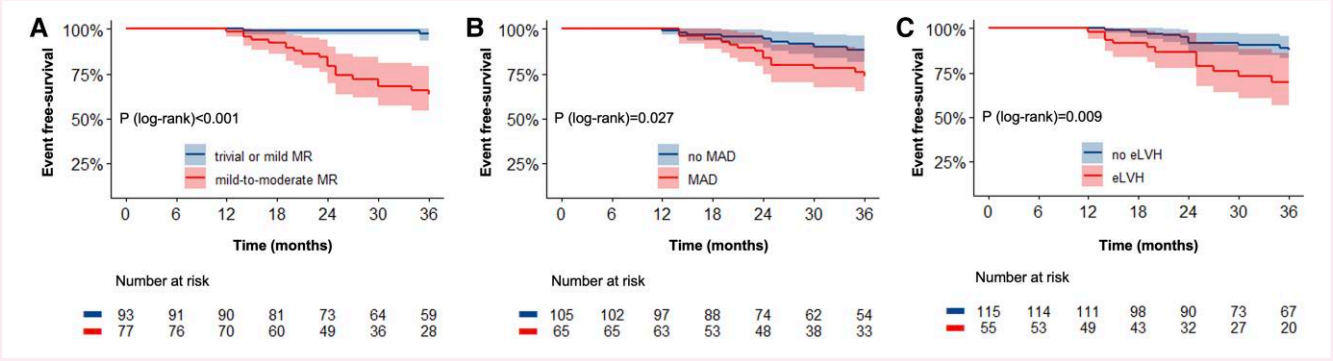


Figure 4 Kaplan–Meyer curves for MR progression according to MR grade, MAD, and eLVH (*A*–*C*). LV, left ventricular; eLVH, eccentric LV hypertrophy; MAD, mitral annular disjunction; MR, mitral regurgitation.

adopting a multi-parametric approach. Nevertheless, quantitative parameters of MR severity obtained by CMR imaging would have provided additive diagnostic value. History of paroxysmal AF was not an exclusion criterion for the present study, but its prevalence in our BD cohort was very low (3%) and the statistical analyses were adjusted for this factor. Finally, cardiopulmonary testing was not performed in most of the patients and, thereby, correlating study findings with exercise capacity was not feasible.

Conclusion

BD patients without significant MR display early LV and LA remodelling, together with mild impairment of LA reservoir strain, but not of LV function. The presence of eccentric LV remodelling, together with MAD and a higher MR grade, portend an increased risk of MR progression and patients with these features may benefit from a closer follow-up strategy.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

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Data availability

The data that support the results of this study are available from the corresponding author upon reasonable request.

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