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Clinical Investigation

Effects of Transcatheter Mitral Valve Repair With MitraClip on Left Ventricular and Atrial Hemodynamic Load and Myocardial Wall Stress

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ABSTRACT

Aims: To evaluate the effects of MitraClip on left ventricular (LV) and left atrial (LA) myocardial wall stress as assessed with the use of N-terminal pro–B-type natriuretic peptide (NT-proBNP) and strain imaging.
Methods and results: Sixty-five patients with symptomatic moderate and severe mitral regurgitation (MR; age 75 ± 9 y, 57% male, 89% functional MR) treated with the use of MitraClip were evaluated. Patients were divided according to 6-month NT-proBNP tertiles. Changes in echocardiographic parameters over 6 months were assessed. Reductions in LV end-diastolic volumes (178 ± 77 mL to 170 ± 79 mL; $P = .045$) and LV end-systolic volumes (120 ± 70 mL to 111 ± 69 mL; $P = .040$) were observed in the overall population. Interestingly, low–NT-proBNP–tertile patients showed slight improvements in LV and LA longitudinal strain, whereas high–NT-proBNP–tertile patients showed impairment.
Conclusions: Although MitraClip induces hemodynamic unloading in patients with predominantly functional MR, myocardial wall stress is not consistently improved. In patients with reduced NT-proBNP, improvements in LA volume index and LV and LA strains were observed. Patients who showed an increase in NT-proBNP exhibited impairment in LV and LA strain, suggesting an increase of myocardial wall stress. (*J Cardiac Fail 2018;24:137–145*)
Key Words: Mitral regurgitation, transcatheter mitral valve repair, left ventricular function, left atrial function, left ventricular wall stress, hemodynamic response.

Transcatheter mitral valve repair with the use of the MitraClip device (Abbott Vascular, Menlo Park, California) is a minimally invasive alternative to surgery to treat severe mitral regurgitation (MR) in symptomatic patients with high operative risk or contraindications for surgery.[1] In addition to MR reduction and improvement of clinical and functional outcomes, the transcatheter MitraClip implantation procedure induces hemodynamic unloading with significant reductions of both left ventricular (LV) and left atrial (LA) volumes.[1–6] Hemodynamic unloading reduces myocardial wall stretch and theoretically may induce reductions in N-terminal pro–B-type natriuretic peptide (NT-proBNP). NT-proBNP is a parameter frequently used in clinical practice to monitor the treatment of heart failure patients. In addition, improvements in LV and LA mechanics (strain), measured with the use of 2-dimensional speckle tracking, can be observed after reductions of myocardial wall stretch. NT-proBNP and LV and LA strain measured with the use of speckle tracking echocardiography have been associated with the prognosis of heart failure patients and patients with MR.[7–11] However, little is known about the effects of MitraClip on NT-proBNP levels and LV and LA strain. The present study hypothesized that MitraClip may induce hemodynamic unloading as reflected by decreases in LV and LA volumes, leading to reductions in

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myocardial wall stress as assessed by NT-proBNP and LV and LA strains.

Methods

Patient Population

All consecutive patients with symptomatic moderate-to-severe or severe MR who underwent transcatheter mitral valve repair with the use of the MitraClip device and completed 6-month clinical and echocardiographic follow-up were included (Fig. 1). Demographic, clinical, echocardiographic, and procedural data were prospectively collected in the departmental information system (EPD-Vision; Leiden University Medical Center, Leiden, The Netherlands) and retrospectively analyzed. Patients with incomplete data were excluded. Changes in plasma levels of NT-proBNP were assessed at 6 months of follow-up, and the patient population was divided according to tertiles of NT-proBNP at 6 months. Changes in clinical symptoms (New York Heart Association [NYHA] functional class, 6-minute walk distance, and quality of life [QoL] according to the Minnesota Living With Heart Failure questionnaire)[12] and echocardiographic parameters of LV and LA dimensions and functions at 6 months after MitraClip device implantation were analyzed and compared for each tertile of NT-proBNP. For retrospective analysis of clinically collected data, the Institutional Ethical Committee approved this evaluation and waived the need for patient written informed consent.

Two-Dimensional Echocardiography Data Acquisition and Analysis

Echocardiography was performed with the patient in the left lateral decubitus position, with the use of a commercially available system (E9; General Electric–Vingmed, Horten, Norway). Images were obtained with the use of a 5MS transducer in the standard parasternal and apical views. M-mode and 2-dimensional (2D) color pulsed- and continuous-wave Doppler data were stored in cine-loop format. Offline analysis was performed with the use of commercially available postprocessing data software (Echopac BT13; GE Medical Systems, Horten, Norway). The mean transmitral gradient was measured with the use of the continuous-wave Doppler method. MR grade at baseline was determined according to current recommendations,[13] which include the proximal isovelocity surface area method and assessment of the vena contracta by means of 2D color Doppler recordings of the mitral valve. Residual MR grade at 6 months of follow-up was quantified as previously described and graded as none or mild (grade 0–1), moderate (grade 2), moderate to severe (grade 3), or severe (grade 4).[14]

Conventional echocardiographic parameters included LV ejection fraction (LVEF) and LV end-diastolic (LVEDV) and end-systolic (LVESV) volumes measured in the apical 4- and 2-chamber views according to the biplane Simpson method.[15] The LA volumes were measured on the apical 4- and 2-chamber views according to the biplane Simpson method and indexed for body surface area. The maximum LA volume (LAmax) was measured before the mitral valve opening, the minimum LA volume (LAmin) at the mitral valve closure and the LA volume before the atrial contraction (LApreP) at the onset of the P-wave on the surface electrocardiogram, when sinus rhythm was present. From these LA volumes, the LA reservoir, conduit, and booster pump functions were measured. The LA reservoir function was calculated as (LAmax − LAmin)/LAmax × 100. In patients with sinus rhythm, the LA conduit function, reflecting passive emptying of the LA, was calculated as (LAmax – LApreP)/LAmax × 100, and the LA booster pump function, representing active LA emptying, was calculated as (LApreP – LAmin)/LApreP × 100.[16] With the use of 2D speckle tracking echocardiography, LV and LA functions were assessed (Echopac BT13).[17] LV global longitudinal strain (GLS) was measured on the apical 4-, 2- and long-axis views and automatically calculated as the average value of the peak systolic strain of each view. Conventionally, LV GLS is presented as negative values because myocardial deformation in the longitudinal direction represents shortening of the myofibers. The reservoir, conduit, and booster pump function of the LA were assessed on the apical 4-chamber view with the use of 2D speckle tracking echocardiography. The LA reservoir function was measured as the LA peak longitudinal strain at ventricular systole. In patients in sinus rhythm, the LA booster pump function was measured as the LA longitudinal strain value after P-wave onset. The LA conduit function was calculated as the difference between peak systolic LA longitudinal strain and the LA longitudinal strain value after the P-wave onset (Fig. 2).[18,19]

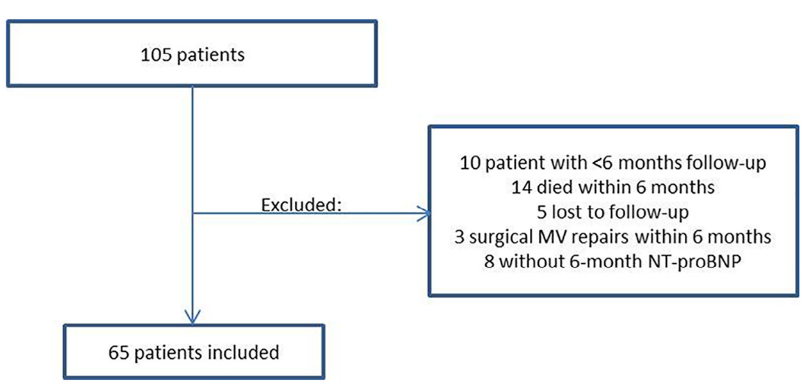

Fig. 1. Patient population: CONSORT diagram. MV, mitral valve; NT-proBNP, N-terminal pro–B-type natriuretic peptide.

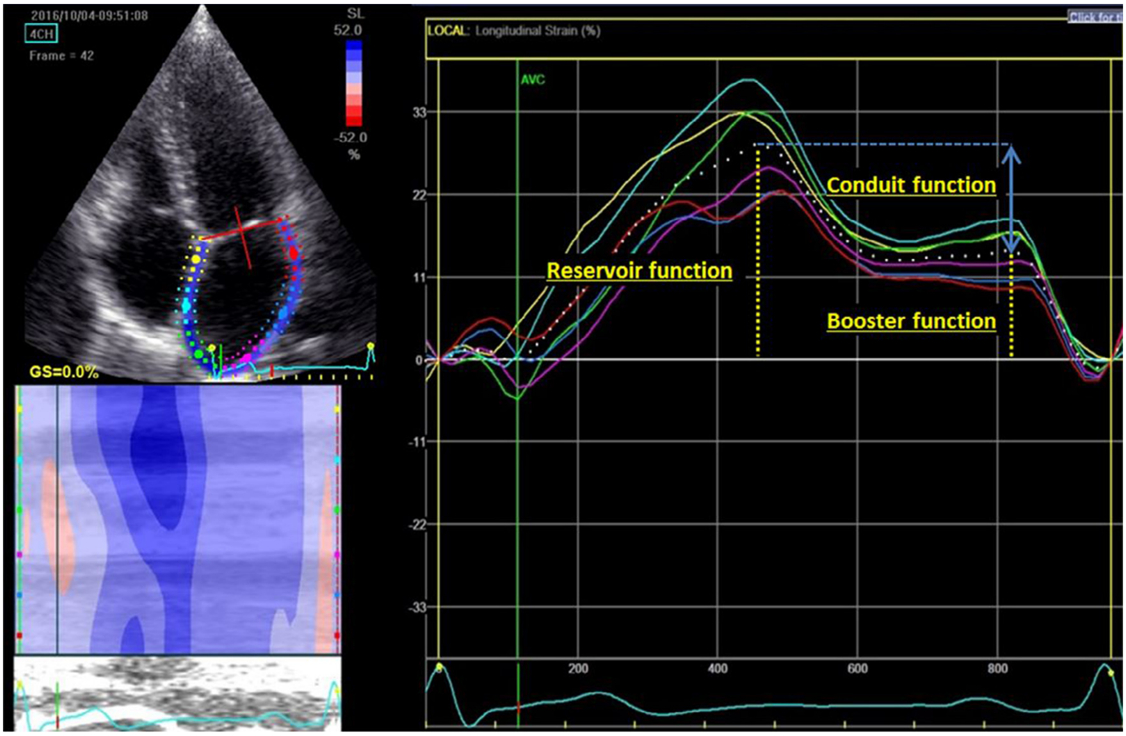

Fig. 2. Two-dimensional speckle tracking strain analysis of left atrial (LA) function. The LA reservoir function is measured as the peak longitudinal strain of the LA myocardium, and the LA booster pump function is measured as the value of longitudinal strain after the P-wave on the surface electrocardiogram. The difference between peak longitudinal strain and the value of longitudinal strain after the P-wave results in the LA conduit function (*blue double-headed arrow*).

Transcatheter Mitral Valve Repair Procedure

Transcatheter MitraClip implantation was performed with the patient under general anesthesia with the guidance of fluoroscopy and transesophageal echocardiography as previously described.[20,21] After trans-septal puncture, the MitraClip was placed in the LV and the arms of the device were perpendicularly aligned with the coaptation line of the mitral leaflets at the point with the largest regurgitant jet. If needed, more than one device was implanted, to ensure MR reduction without creating valve stenosis. Transcatheter MitraClip implantation success was defined as a reduction of MR to grade ≤2 after deploying one or more MitraClip devices.

Statistical Analyses

All data analyses were performed with the use of SPSS software version 23.0 (IBM, Armonk, New York). Continuous variables are presented as mean ± SD if normally distributed or as median (interquartile range [IQR]) if not normally distributed. Normal distribution was tested with the use of a Shapiro-Wilk test. Categoric variables are reported as n (%). Patients were divided according to tertiles of NT-proBNP at 6 months of follow-up. Continuous variables were compared by means of 1-way analysis of variance (ANOVA), applying the Bonferroni post hoc analysis, or Kruskal-Wallis 1-way analysis of variance. Categoric variables were compared by means of the Fisher-Freeman-Halton exact test. Changes over time were compared by means of paired *t*-test or Wilcoxon signed-rank test for continuous variables. To compare the changes over time between groups, the absolute differences of echocardiographic parameters were calculated and compared with the use of 1-way ANOVA and applying the Bonferroni post hoc analysis. The univariable and multivariable correlates of NT-proBNP levels at 6 months of follow-up were analyzed with the use of linear regressions analysis. A P value of <.05 was considered to be statistically significant.

Results

Changes in NT-proBNP After MitraClip Implantation

Clinical characteristics of the overall population (mean age 75 ± 9 years, 57% male) are summarized in Table 1. The majority of the patients had secondary MR (89%). The transcatheter MitraClip implantation procedure was successful in 62 patients (95%), and only 3 patients remained with grade 3 MR immediately after the procedure. The majority of patients received 1 (49%) or 2 (39%) MitraClip devices. During follow-up after the 6-month clinical and echocardiographic evaluation, 14 patients were hospitalized owing to worsening of heart failure and 19 patients died.

In the overall population, no significant changes in NT-proBNP were observed at 6 months of follow-up (from 2,959 ng/L [IQR 1,271–5,978] to 2,805 ng/L [IQR 1,137–5,449]; P = .603). Table 2 provides the univariable and multivariable correlates of NT-proBNP levels at 6 months of follow-up. Impaired renal function (worse glomerular filtration

Table 1. Clinical Characteristics of the Total Population and per Tertile of NT-ProBNP at 6 Months of Follow-Up, n (%)

Clinical Variable	All Patients (n = 65)	Low NT-Pro-BNP (n = 21)	Medium NT-ProBNP (n = 230)	High NT-ProBNP (n = 21)	*P* Value
Age, y, mean ± SD	75 ± 9	72 ± 8	78 ± 7	74 ± 10	.086
Male	37 (57%)	12 (57%)	14 (61%)	11 (52%)	.950
BSA index, mean ± SD	1.91 ± 0.26	1.97 ± 0.27	1.89 ± 0.22	1.87 ± 0.29	.452
Sinus rhythm	39 (60%)	11 (52%)	12 (52%)	16 (76%)	.209
CRT	17 (26%)	4 (19%)	8 (35%)	5 (24%)	.528
Prior myocardial infarction	31 (48%)	10 (48%)	12 (57%)	8 (38%)	.584
CABG	20 (31%)	9 (42%)	8 (38%)	3 (14%)	.122
Previous PCI	30 (46%)	9 (43%)	12 (57%)	7 (33%)	.674
Hypertension	32 (49%)	9 (43%)	12 (57%)	10 (48%)	.743
Hypercholesterolemia	27 (42%)	11 (52%)	9 (43%)	7 (33%)	.307
Diabetes	20 (31%)	9 (45%)	3 (14%)	7 (35%)	.114
(Ex-)Smoker	27 (42%)	6 (29%)	11 (48%)	9 (48%)	.277
COPD	11 (17%)	3 (14%)	2 (10%)	6 (28%)	.242
6-minute walk distance, mean ± SD	342 ± 117	341 ± 129	337 ± 112	292 ± 135	.385
Quality of life, median (IQR)	35 (26–58)	34 (23–50)	31 (19–48)	44 (31–57)	.387
eGFR, mL • min^{-1} • 1.73 m^{-2}, mean ± SD	55 ± 22	65 ± 24	48 ± 15	51 ± 22	.018
NT-proBNP ng/L, median (IQR)	2959 (1271–5978)	1197 (714–3071)	2783 (1917–4160)	6280 (3655–7311)	<.001
Log EuroSCORE, mean ± SD	19.8 ± 14.3	17.45 ± 13.76	20.65 ± 14.23	21.11 ± 15.41	.671
Medications					
ACEi/ARB	50 (78%)	16 (76%)	19 (90%)	13 (62%)	.074
Beta-blocker	54 (83%)	19 (91%)	16 (76%)	17 (81%)	.598
Ca^{2+} channel blocker	6 (9%)	2 (10%)	2 (10%)	1 (5%)	.994
Statin	45 (70%)	13 (62%)	15 (71%)	16 (76%)	.710
Diuretics	56 (86%)	16 (76%)	20 (95%)	19 (91%)	.082

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blockers; BSA, body surface area; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; IQR: interquartile range; NT-proBNP, N-terminal pro–B-type natriuretic peptide; PCI, percutaneous coronary intervention.

Table 2. Univariable and Multivariable Correlates of NT-proBNP Levels at 6 Months of Follow-up (n = 65)

	Univariable Analysis			Multivariable Analysis		
Baseline Variable	B	95% CI	*P* Value	B	95% CI	*P* Value
Age	0.442	−0.013 to 0.031	.442			
Male	−0.063	−0.471 to 0.346	.760			
Sinus rhythm	0.321	−0.085 to 0.726	.119			
CRT	0.080	−0.380 to 0.540	.730			
Previous myocardial infarction	−0.185	−0.588 to 0.217	.362			
Previous CABG	−0.433	−0.858 to −0.009	.046	−0.180	−0.543 to 0.183	.325
Previous PCI	−0.124	−0.529 to 0.281	.543			
Hypertension	−0.062	−0.466 to 0.343	.762			
Hypercholesterolemia	−0.317	−0.720 to 0.086	.121			
Diabetes	−0.212	−0.584 to 0.160	.259			
(Ex-)Smoker	0.078	−0.149 to 0.304	.496			
COPD	0.328	−0.205 to 0.862	.223			
6-minute walk distance	−0.001	−0.003 to 0.001	.211			
Quality of life	0.004	−0.006 to −0.014	.388			
eGFR	−0.010	−0.019 to −0.001	.037	−0.008	−0.016 to 0.000	.042
NT-proBNP per 10 ng/L	0.001	0.000 to 0.001	.004	0.001	0.000 to 0.001	.008
Log EuroSCORE	0.006	−0.008 to 0.020	.413			
No. of implanted MitraClip	0.156	−0.104 to 0.415	.236			
LVEF	−0.010	−0.024 to 0.004	.150			
LVEDV	0.004	0.001 to 0.006	.003	0.003	0.001 to 0.005	.004
LVESV	0.004	0.001 to 0.007	.005			
LV longitudinal strain	0.024	−0.016 to 0.064	.244			
LA volume index	0.004	−0.003 to 0.012	.254			
LA reservoir function volumetric	−0.008	−0.026 to 0.011	.394			
LA conduit function volumetric	−0.028	−0.058 to 0.001	.060			
LA booster pump function volumetric	−0.013	−0.041 to 0.015	.339			
LA reservoir strain volumetric	−0.011	−0.060 to 0.038	.654			
LA conduit strain volumetric	0.028	−0.108 to 0.164	.679			
LA booster pump strain volumetric	−0.034	−0.097 to 0.028	.277			
Transmitral gradient	0.191	0.044 to 0.339	.012	0.138	0.015 to 0.261	.029
Peak tricuspid regurgitant gradient	0.026	0.008 to 0.044	.006	0.010	−0.006 to 0.025	.226

LA, left atrial; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; other abbreviations as in Table 1.

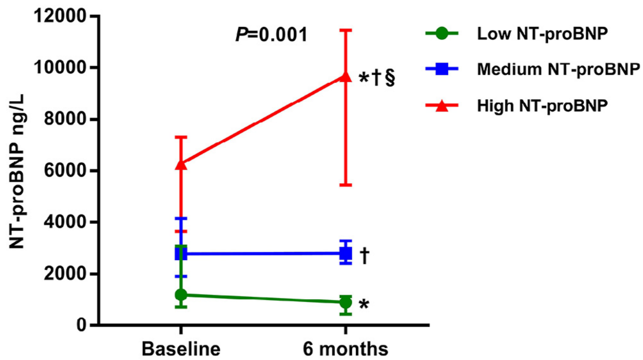

Fig. 3. Changes in NT-proBNP according to tertiles of NT-proBNP at 6 months of follow-up. Legends: *$P < .05$ baseline vs 6 months. †$P < .05$ vs low NT-proBNP. §$P < .05$ vs middle NT-proBNP. NT-proBNP, N-terminal pro–B-type natriuretic peptide.

rate), higher levels of NT-proBNP, larger LVEDV, and higher transmitral gradient at baseline were associated with higher levels of NT-proBNP at 6 months of follow-up.

When dividing the patients into groups according to the tertiles of NT-proBNP at 6 months' follow-up, NT-proBNP at follow-up showed a significant decrease ($P = .046$) in patients within the low NT-proBNP tertile, remained stable ($P = .670$) in patients within the medium NT-proBNP tertile, and showed a significant increment ($P = .014$) in patients within the high NT-proBNP tertile compared with baseline (Fig. 3). When dividing the population according to 6-month NT-proBNP tertiles, there were no differences in demographic and clinical characteristics at baseline (Table 1). At 6 months of follow-up, successful MR reduction was more often accomplished in patients within the low and medium NT-proBNP tertiles, with only 14% and 13% of patients, respectively having grade ≥3 MR, whereas among patients within the high NT-proBNP tertile, 43% remained with grade ≥3 MR ($P = .046$). High–NT-proBNP–tertile patients more often received 3 or 4 MitraClip devices (5 [23%]) compared with those in the low and medium tertiles (1 [5%] and 2 [8%], respectively; $P = .233$).

Changes in Clinical Symptoms at 6 Months of Follow-Up

In the overall population, there were significant improvements in NYHA functional class (the number of patients with NYHA functional class ≥III decreased from 42 [65%] to 11 [17%]; $P = .011$) and QoL score (from 35 [IQR 26–58] to 27 [9–43]; $P = .005$). Information on 6-minute walking distance was complete for all patients but 13. There were no changes in the 6-minute walking distance (321 ± 137 m to 357 ± 122 m; $P = .144$). When analyzing the data according to 6-month NT-proBNP tertiles, significant reductions in NYHA functional class symptoms (Fig. 4) and QoL score were observed among the patients within the low and medium NT-proBNP tertile groups (QoL score from 34 [IQR 23–50] to 24 [6–41; $P = .020$] and 31 [19–48] to 15 [8–26; $P = .009$], respectively). In contrast, QoL did not show significant changes in the patients within the high NT-proBNP tertile. No significant changes were observed in the 6-minute walking distance in any group.

Changes in LV and LA Dimensions and Function on Conventional Echocardiography

The baseline echocardiographic characteristics for the overall population and for the 6-month tertiles of NT-proBNP are summarized in Table 3. Patients within the high NT-proBNP tertile showed significantly larger LVEDV and LVESV compared

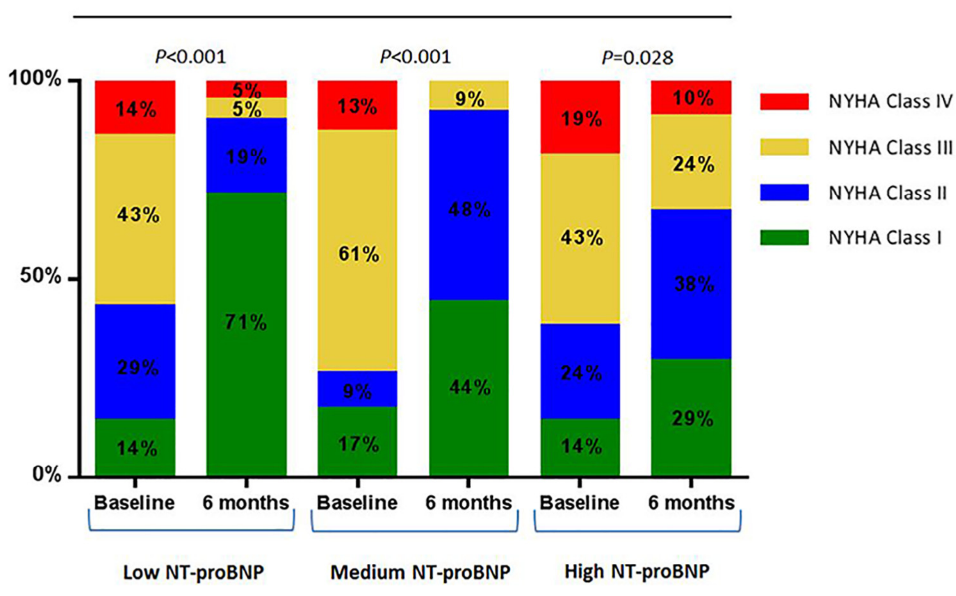

Fig. 4. Changes in New York Heart Association (NYHA) functional class according to the NT-proBNP tertiles at 6 months of follow-up. NT-proBNP, N-terminal pro–B-type natriuretic peptide.

Table 3. Conventional Echocardiographic Parameters at Baseline per 6-Month NT-Pro-BNP Group

Echocardiographic Variable	Low NT-ProBNP (n = 21)	Medium NT-ProBNP (n = 23)	High NT-ProBNP (n = 21)	*P* Value
LV parameters				
LVEF (%)	39 ± 15	39 ± 14	33 ± 14	.247
LVEDV (mL)	149 ± 48	170 ± 70	219 ± 93*,†	.008
LVESV (mL)	95 ± 43	108 ± 61	155 ± 88*,†	.012
LA parameters				
LA volume index mL/m^2	65 ± 15	64 ± 24	74 ± 34	.414
LA reservoir function volumetric (%)	29.6 ± 12.3	30.3 ± 10.4	26.7 ± 10.1	.520
LA conduit function volumetric (%)	21.5 ± 11.4	17.0 ± 5.4	14.9 ± 8.3	.162
LA booster pump function volumetric (%)	20.6 (13.2–27.9)	15.6 (8.2–27.3)	15.4 (8.9–21.3)	.645
Transmitral gradient (mm Hg)	1.16 (0.92–2.26)	1.68 (1.05–2.67)	1.87 (1.44–3.36)†,*	.013
Peak tricuspid regurgitant gradient (mm Hg)	29 ± 7	35 ± 10	38 ± 12*	.021

Abbreviations as in Tables 1 and 2.
*$P < .05$ vs low NT-proBNP.
†$P < .05$ vs medium NT-proBNP.

with the other groups. In addition, patients in the high NT-proBNP tertile had a significantly higher mean transmitral gradient and tricuspid regurgitant jet velocity compared with the other groups. In the overall population, a significant reduction in LVEDV (from 178 ± 77 mL to 170 ± 79 mL; $P = .045$) and LVESV (from 120 ± 70 mL to 111 ± 69 mL; $P = .040$) was noted at 6 months of follow-up without significant changes in LVEF (from 37 ± 14% to 39 ± 14%; $P = .138$). Furthermore, there were no significant changes in LA volume index (from 68 ± 26 mL/m^2 to 70 ± 31 mL/m^2; $P = .321$) or volumetric LA functions (reservoir: 29 ± 10% to 29 ± 11% [$P = .650$]; conduit: 17 ± 9% to 14 ± 9% [$P = .051$]; booster pump: 17% [IQR 10–24] to 16 [10–28; $P = .404$]).

Similarly, there were no significant changes in LV volumes and LVEF in any of the 6-month NT-proBNP tertiles (Fig. 5). However, LA volume index decreased in patients within the low 6-month NT-proBNP tertile and significantly increased in the high 6-month NT-proBNP tertile (from 74 ± 34 mL to 83 ± 38 mL; $P = .041$). Finally, no changes were observed in any of the volumetric measurements of LA function

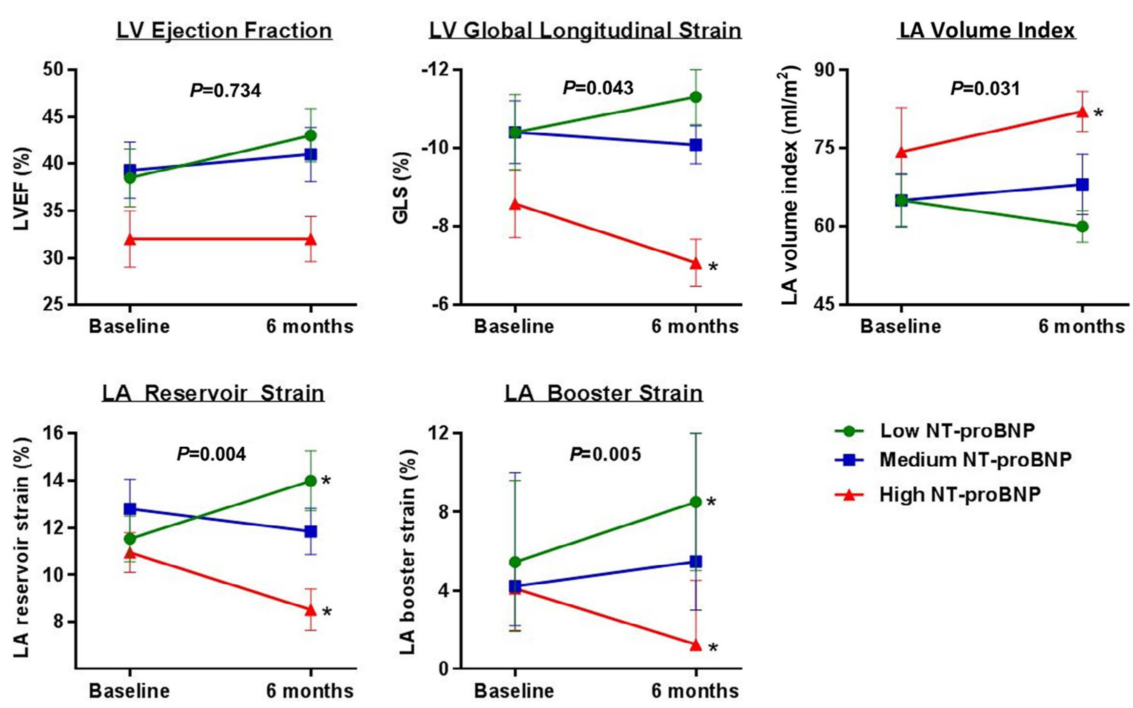

Fig. 5. Graphic display of the development (baseline vs 6-month follow-up) of left ventricular (LV) and left atrial (LA) volumes and function by both volumetric and 2-dimensional speckle tracking strain analyses. *P* values indicate the significance of the comparison of absolute changes over time for each echocardiographic parameter across the groups. LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume. NT-proBNP, N-terminal pro–B-type natriuretic peptide. LV global longitudinal strain (GLS) corrected for LVESV and LA booster strain are shown as median and interquartile range. The other variables are shown as mean and standard error. *$P < .05$ baseline vs 6 months.

across the 6-month NT-proBNP tertiles. All groups showed a significant increase in mean transmitral gradient at 6 months of follow-up with a similar distribution; high–NT-proBNP–tertile patients exhibited higher gradients compared with the low and medium tertiles (4.49 [IQR 2.37–6.69], 3.69 1.95–4.35], and 3.99 [2.88–5.03], respectively; $P = .204$), though without achieving statistical significance.

LV and LA Function in 2D Speckle Tracking Strain Analyses

In the overall population, LV GLS did not change significantly at 6 months of follow-up (from −9.8 ± 5.1% to −9.5 ± 4.3%; $P = .398$). However, LV GLS slightly improved in patients within the low NT-proBNP tertile (from −10.4 ± 5.2% to −11.3 ± 4.3%; $P = .245$), remained unchanged in patients within the medium NT-proBNP tertile (from −10.4 ± 5.0% to −10.0 ± 3.7%; $P = .205$), and significantly worsened in patients within the high NT-proBNP tertile (from −8.6 ± 8.0% to −7.0 ± 3.9%; $P = .036$).

In the overall population, only LA conduit function decreased significantly (from 7.0 ± 2.1% to 5.5 ± 2.7%; $P = .003$) whereas LA reservoir and booster pump functions remained unchanged (from 11.7 ± 4.1% to 11.3 ± 5.5% [$P = .483$] and from 4.5% [IQR2.0–7.5] to 5.3% [2.0–10.6; $P = .120$], respectively). When analyzing the data according to 6-month NT-proBNP tertiles, patients within the low NT-proBNP tertile showed significant improvement in both LA reservoir and LA booster pump functions (from 11 ± 4% to 14 ± 6% [$P = .025$] and from 5% [IQR 2–9] to 9% [5–12; $P = .026$], respectively), whereas LA conduit function did not change (Fig. 5). Patients within the medium NT-proBNP tertile showed no significant changes in LA reservoir and booster pump functions, but did show a decline in LA conduit function (from 8 ± 2% to 6 ± 2%; $P = .047$), whereas in patients within the high NT-proBNP tertile, all LA functions assessed by means of strain analysis showed significant decline (reservoir from 11 ± 3% to 8 ± 3% [$P = .013$], conduit from 7 ± 2% to 5 ± 2% [$P = .041$], and booster from 4% [IQR 2–5] to 1% [1–4; $P = .037$]; Fig. 5).

Discussion

The present study demonstrates a wide range in NT-proBNP response 6 months after MitraClip implantation. Clinically, patients within the high NT-proBNP tertile showed less improvement in symptoms than patients in the low tertile. Echocardiographically, patients within the low NT-proBNP tertile showed significant reductions in LA volume indexes and improvement in LA reservoir and booster pump functions (as assessed with the use of 2D speckle tracking echocardiography), whereas patients within the high NT-proBNP tertile showed impairment in LV systolic function (based on LV GLS measures), an increase in LA volume indexes, and impairment in LA reservoir and booster pump functions.

Effects of MitraClip on NT-proBNP

NT-proBNP is an important prognostic biomarker in heart failure patients.[8,9] In patients with significant MR, MitraClip implantation reduces the regurgitant volume, resulting in hemodynamic unloading and reduction of myocardial wall stretch. These changes would result in parallel reductions in NT-proBNP. However, this theory has not been consistently demonstrated across the studies.[22–27] For example, in the study by Schau et al including 194 patients (73% with functional MR) treated with the use of MitraClip and a 93% procedural success rate (defined as reduction in MR to grade ≤2), 21% of patients remained with NT-proBNP levels ≥10,000 pg/mL.[26] In addition, Yoon et al reported nonsignificant reductions in NT-proBNP after successful MitraClip implantation in 144 patients with severe MR (from 2,942 (IQR 1,596–5,722) to 2,739 (1,440–4,296) ng/L; $P = .21$).[25] These results are consistent with those of the present study. Potential confounders that alter the changes in NT-proBNP after MitraClip could include renal function, body weight, and underlying LV systolic dysfunction.[28] Indeed, multivariable analysis showed that worse renal function, larger LVEDV, and higher transmitral gradient after MitraClip implantation were independently associated with higher levels of NT-proBNP at follow-up. Patients who remain with increased levels of NT-proBNP have shown increased mortality rates at follow-up compared with patients with lower values.[26] However, little is known about the association between changes in NT-proBNP and changes in LV and LA dimensions and function.

Effects of MitraClip on LV and LA Dimensions and Function

From the EVEREST II clinical studies (including the randomized controlled trial, the single-arm EVEREST II High-Risk Study, and the continued access study of the EVEREST II–REALISM), it has been shown that MitraClip implantation results in reduction in LV and LA volumes without changes in LVEF at 12 months of follow-up.[5] The volumetric reverse remodeling is more pronounced in the absence of residual MR, whereas the reduction in LV and LA volumes is minimal when significant MR persists.[5] The results of the GRASP (Getting Reduction of Mitral Insufficiency by Percutaneous Clip Implantation) registry showed significant reductions in LV and LA volumes and improvement in LVEF at follow-up.[29] Similarly to the EVEREST II studies,[5] the present study showed significant reductions in LVEDV and LVESV without changes in LVEF whereas LA volume index and functions remained unchanged.

Integrating NT-ProBNP and Echocardiographic Changes After MitraClip

This study integrated the NT-proBNP response after MitraClip implantation with the clinical and echocardiographic responses. Despite significant reductions in LV volumes in the overall population, NT-proBNP remained unchanged. Furthermore, based on 2D speckle tracking analysis, no changes in LV GLS were observed in the overall population, whereas LA conduit function decreased. The present study investigated which parameters can lead to disparate clinical, biochemical, and echocardiographic responses by dividing the population into tertiles of NT-proBNP at follow-up. Implantation of the MitraClip device leads to a change in mitral function and unloading of the left ventricle. The relative increase in the transmitral gradient may affect the function of the left atrium, which may be severely diseased at baseline. This is particularly likely among patients with high NT-proBNP tertile at 6 months of follow-up, in whom the LA functions were impaired based on conventional and speckle tracking echocardiographic analyses. Most likely, the extent of fibrosis in the LA and LV myocardium is an important determinant for response to MitraClip implantation, because in patients with more myocardial fibrosis, relief of myocardial wall stretch may not occur. Patients within the low NT-proBNP tertile showed better LV GLS compared with patients within the high tertile NT-proBNP subgroup. LV GLS has been shown to reflect LV myocardial fibrosis in heart failure patients[30,31] and more impaired LV systolic function than LVEF in patients with functional MR.[32] Therefore, LV GLS may be a valuable surrogate to characterize the changes in LV function in patients treated with the use of MitraClip.

When assessing LV dysfunction in patients with MR it is important to acknowledge differences between secondary and primary MR. The latter is caused by intrinsic lesions of the mitral valve apparatus, and in eliminating MR, the hemodynamic burden that causes LV dysfunction is resolved.[33,34] However, secondary MR is caused by a diseased LV, and treatment of MR will not completely correct the underlying cause and LV function may not improve.[33] NT-ProBNP may be a valid surrogate to identify the patients with less myocardial fibrosis of the LA and LV and who may better respond in terms of clinical symptoms and echocardiographic parameters. In the present analysis, patients with clinical and echocardiographic improvements had lower baseline NT-proBNP values, and, in contrast, those who showed less improvement or even deterioration had higher baseline values. Whether baseline NT-proBNP values are useful in risk stratification of patients undergoing MitraClip procedure needs further investigation.

Study Limitations

This is a single-center retrospective study with a relatively small number of patients. However, this is so far the largest study with combined assessment of conventional and advanced echocardiography together with assessment of NT-proBNP levels at follow-up, and adds further to our understanding of potential benefits of MitraClip implantation. The strain measurements were performed with the use of commercially available software, and the results may not be comparable to those obtained with the use of other platforms. Quantification of residual MR after MitraClip implantation remains challenging. We performed a qualitative assessment because a volumetric assessment would not be accurate owing to some patients having concomitant aortic regurgitation.

Conclusion

Changes in NT-proBNP after MitraClip implantation vary widely. In patients who showed a reduction in NT-proBNP, reductions in LA volume indexes and improvement in LV GLS and LA strain were observed. In contrast, patients who showed an increase in NT-proBNP exhibited impairment in LV GLS and LA strain, suggesting an increase of myocardial wall stress. Additional studies are needed to better understand which patients would improve in terms of hemodynamic unloading and relief of myocardial wall stretch after MitraClip implantation.

Disclosures

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