Advanced echocardiographic imaging in valvular and systemic diseases

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CHAPTER 5

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 N-terminal pro-brain natriuretic peptide (NT-proBNP) and strain imaging.

Methods and results: Sixty-five patients with symptomatic moderate and severe mitral regurgitation (MR) (age 75±9 years, 57% male, 89% functional MR) treated with MitraClip were evaluated. Patients were divided according to the 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*=0.045) and LV end-systolic volumes (120± 70 ml to 111± 69 ml, *P*=0.040 respectively) 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: While MitraClip induces hemodynamic unloading in patients with predominantly functional MR, myocardial wall stress is not consistently improved. In patients with reduction in NT-proBNP, improvements in LA volume, LV and LA strains were observed. Patients who showed an increase in NT-proBNP exhibited impairment in LV and LA strains suggesting an increase of myocardial wall stress.

INTRODUCTION

Transcatheter mitral valve repair using the MitraClip device (Abbott Vascular, Menlo Park, CA) is a minimally invasive, alternative method 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-brain natriuretic peptide (NT-proBNP). NT-proBNP is a parameter frequently used in clinical practice to monitor the treatment of heart failure patients. Additionally, improvements in LV and LA mechanics (strain) measured with 2-dimensional speckle tracking can be observed after reductions of myocardial wall stretch. NT-proBNP and LV and LA strain measured with speckle tracking echocardiography have been associated with prognosis of heart failure patients and patients with mitral regurgitation(7-11). However, little is known about the effects of MitraClip on NT-proBNP levels and LV and LA strain. The present study hypothesizes that MitraClip may induce hemodynamic unloading as reflected by decreases in LV and LA volumes, leading to reductions in myocardial wall stress as assessed with NT-proBNP and LV and LA strains.

METHODS

Patient population

All consecutive patients with symptomatic, moderate-to-severe or severe mitral regurgitation who underwent transcatheter mitral valve repair with the MitraClip device and completed 6-month clinical and echocardiographic follow-up were included (Figure 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 analysed. 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 the 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 analysed and compared for each tertile 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.

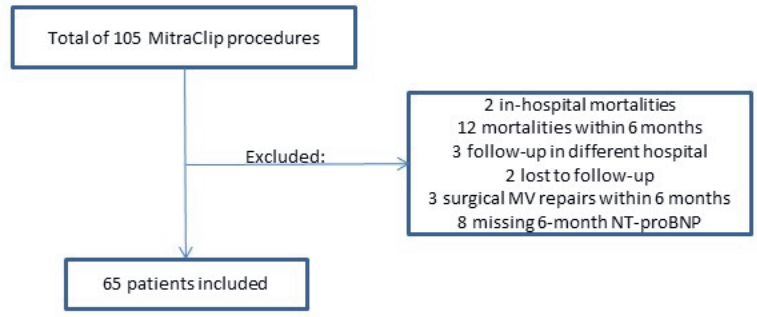

Figure 1: *Patient population: CONSORT diagram. MV, mitral valve; NT-proBNP, N-terminal pro–B-type natriuretic peptide*

2D echocardiography data acquisition and analysis

Echocardiography was performed with the patient in the left lateral decubitus position, using a commercially available system (E9; General Electric-Vingmed, Horten, Norway). Images were obtained using a 5MS transducer in the standard parasternal and apical views. M-mode and two-dimensional (2D), colour, pulsed and continuous wave Doppler data were stored in cine-loop format. Offline analysis was performed using commercially available post-processing data software (EchoPAC BT13; GE Medical Systems, Horten, Norway).

The mean transmitral gradient was measured using the continuous wave Doppler method. Mitral regurgitation (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 using 2D colour Doppler recordings of the mitral valve. Residual MR grade at 6 months follow-up was quantified as previously described and graded

as none or mild (grade 0-1), moderate (grade 2), moderate to severe (grade 3) and severe (grade 4) (14).

Conventional echocardiographic parameters included LV ejection fraction (LVEF), LV end-diastolic (LEDV) and end-systolic (LVESV) volumes measured in the apical 4- and 2-chamber views according to the biplane Simpson's method (15). The LA volumes were measured on the apical 4- and 2-chamber views according to the biplane Simpson's method. 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 x 100. In patients with sinus rhythm, the LA conduit function reflecting passive emptying of the LA was calculated as (LAmax-LApreP)/LAmax x 100 while the LA booster pump function, representing the active LA emptying, was calculated as (LApreP – LAmin)/LApreP x 100 (16).

Using 2D speckle tracking echocardiography, LV and LA functions were assessed (EchoPAC BT13; GE Medical Systems, Horten, Norway)(17). LV global longitudinal strain (GLS) was measured on the three standard apical views and automatically calculated as the average value of the peak systolic strain of the apical 4-, 2- and long-axis views. Conventionally, LV GLS is presented as negative values since 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 using 2D speckle tracking echocardiography. The LA reservoir function was measured as the LA peak longitudinal strain at the 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 (Figure 2) (18;19).

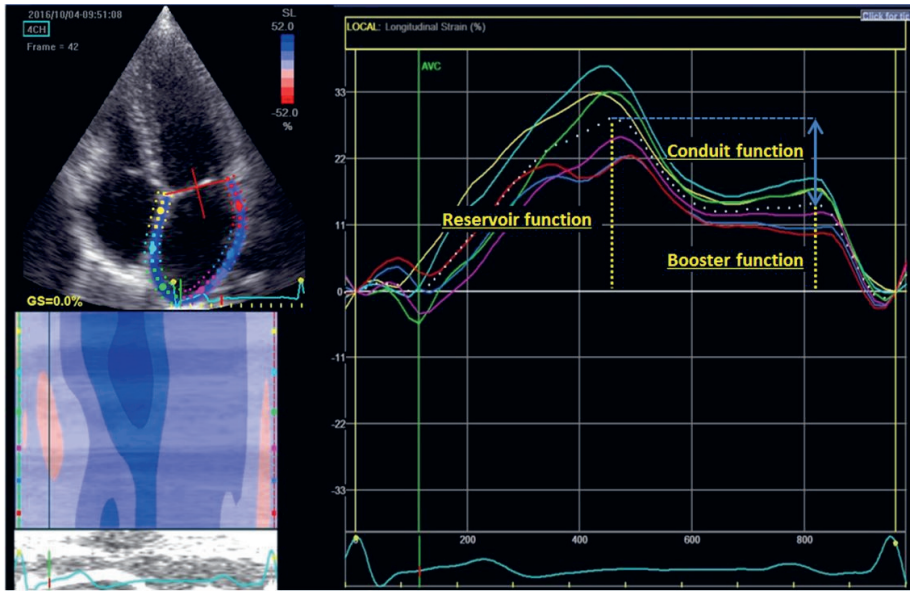

Figure 2. 2D speckle tracking strain analysis of the left atrial function. *The LA reservoir function is measured as the peak longitudinal strain of the LA myocardium whereas the booster pump function is measured as the value of longitudinal strain after the P-wave on the surface electrocardiogram. The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

Transcatheter mitral valve repair procedure

Transcatheter MitraClip implantation was performed with the patient under general anaesthesia with the guidance of fluoroscopy and transoesophageal 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 using the SPSS® software version 23.0 (IBM, Armonk, NY, USA). Continuous variables are presented as mean ± standard deviation if normally distributed or as median and interquartile range (IQR) if not normally distributed.

Normal distribution was tested with a Shapiro-Wilk test. Categorical variables are reported as frequencies and percentages. Patients were divided according to tertiles of NT-proBNP at 6 months follow-up. Continuous variables were compared using the one-way analysis of variance (ANOVA), applying the Bonferroni's post-hoc analysis, or the Kruskal-Wallis one-way analysis of variance. Categorical variables were compared with the Fisher-Freeman-Halton exact test. Changes over time were compared with paired *t*-test or Wilcoxon signed-rank test for continuous variables. To compare the changes over time between groups, the one-way ANOVA assessing the absolute differences applying the Bonferroni's post-hoc analysis was performed. The univariable and multivariable correlates of NT-proBNP levels at 6 months follow-up were analysed with linear regressions analysis. A *P* value of <0.05 was considered 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 (95%) patients 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 due to worsening of heart failure and 19 patients died.

In the overall population, no significant changes in NT-proBNP were observed at 6 months follow-up (from 2,959 ng/L [IQR: 1,271 – 5,978] to 2,805 ng/L [IQR: 1,137 – 5,449], *P*=0.603). Table 2 provides the univariable and multivariable correlates of NT-proBNP levels at 6 months of follow-up. Impaired renal function (worse glomerular filtration 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.

Table 1. Clinical characteristics of the total population and per tertile of NT-proBNP at 6 months follow up.

Clinical variables	All patients N=65	Low NT-proBNP N=21	Medium NT-proBNP N=23	High NT-proBNP N=21	ANOVA P value
Age ,years ± SD	75 ± 9	72 ± 8	78 ± 7	74 ± 10	0.086
Male, n (%)	37 (57)	12 (57)	14 (61)	11 (52)	0.950
BSA index, mean ± SD	1.91 ± 0.26	1.97 ± 0.27	1.89 ± 0.22	1.87 ± 0.29	0.452
Sinus rhythm, n (%)	39 (60)	11 (52)	12 (52)	16 (76)	0.209
CRT, n (%)	17 (26)	4 (19)	8 (35)	5 (24)	0.528
Prior myocardial infarction, n (%)	31 (48)	10 (48)	12 (57)	8 (38)	0.584
CABG, n (%)	20 (31)	9 (42)	8 (38)	3 (14)	0.122
Previous PCI, n (%)	30 (46)	9 (43)	12 (57)	7 (33)	0.674
Hypertension, n (%)	32 (49)	9 (43)	12 (57)	10 (48)	0.743
Hypercholesterolemia, n (%)	27 (42)	11 (52)	9 (43)	7 (33)	0.307
Diabetes, n (%)	20 (31)	9 (45)	3 (14)	7 (35)	0.114
(Ex-)Smoker, n (%)	27 (42)	6 (29)	11 (48)	9 (48)	0.277
COPD, n (%)	11 (17)	3 (14)	2 (10)	6 (28)	0.242
6 minute walk distance, mean ± SD	342 ± 117	341 ± 129	337 ± 112	292 ± 135	0.385
Quality of life, median (IQR)	35 (26–58)	34 (23 – 50)	31 (19-48)	44 (31-57)	0.387
eGFR, ml/min/1.73m2, mean ± SD	55 ± 22	65 ± 24	48 ± 15	51 ± 22	0.018
NT-proBNP ng/L, median (IQR)	2959 (1271 – 5978)	1197 (714 – 3071)	2783 (1917 – 4160)	6280 (3655 – 7311)	<0.001
Log EuroSCORE, mean ± SD	19.8 ± 14.3	17.45 ± 13.76	20.65 ± 14.23	21.11 ± 15.41	0.671
Medications, n (%)					
ACEi/ARB	50 (78)	16 (76)	19 (90)	13 (62)	0.074
Beta-blocker	54 (83)	19 (91)	16 (76)	17 (81)	0.598
Ca^{2+} channel blocker	6 (9)	2 (10)	2 (10)	1 (5)	0.994
Statin	45 (70)	13 (62)	15 (71)	16 (76)	0.710
Diuretics	56 (86)	16 (76)	20 (95)	19 (91)	0.082

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. 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 variables	B	95% CI	*P* value	B	95% CI	*P* value
Age	0.442	-0.013 – 0.031	0.442			
Male	-0.063	-0.471 – 0.346	0.760			
Sinus rhythm	0.321	-0.085 – 0.726	0.119			
CRT	0.080	-0.380 – 0.540	0.730			
Prior myocardial infarction	-0.185	-0.588 – 0.217	0.362			
Prior CABG	-0.433	-0.858 – -0.009	0.046	-0.180	-0.543 – 0.183	0.325
Previous PCI	-0.124	-0.529 – 0.281	0.543			
Hypertension	-0.062	-0.466 – 0.343	0.762			
Hypercholesterolemia	-0.317	-0.720 – 0.086	0.121			
Diabetes	-0.212	-0.584 – 0.160	0.259			
(Ex-)Smoker	0.078	-0.149 – 0.304	0.496			
COPD	0.328	-0.205 – 0.862	0.223			
6 minute walk distance (m)	-0.001	-0.003 – 0.001	0.211			
Quality of life	0.004	-0.006 – -0.014	0.388			
eGFR (ml/min/1.73m2)	-0.010	-0.019 – -0.001	0.037	-0.008	-0.016 – 0.000	0.042
NT-proBNP per 10 units (ng/L)	0.001	0.000 – 0.001	0.004	0.001	0.000 – 0.001	0.008
Log EuroSCORE (%)	0.006	-0.008 – 0.020	0.413			
Number of implanted clips	0.156	-0.104 – 0.415	0.236			
LV ejection fraction (%)	-0.010	-0.024 – 0.004	0.150			
LVEDV (mL)	0.004	0.001 – 0.006	0.003	0.003	0.001 – 0.005	0.004
LVESV (mL)	0.004	0.001 – 0.007	0.005			
LV longitudinal strain (%)	0.024	-0.016 – 0.064	0.244			
LA volume (mL)	0.004	-0.003 – 0.012	0.254			
LA Reservoir function volumetric (%)	-0.008	-0.026 – 0.011	0.394			
LA Conduit function volumetric (%)	-0.028	-0.058 – 0.001	0.060			
LA Booster function volumetric (%)	-0.013	-0.041 – 0.015	0.339			
LA Reservoir strain volumetric (%)	-0.011	-0.060 – 0.038	0.654			
LA Conduit strain volumetric (%)	0.028	-0.108 – 0.164	0.679			
LA Booster strain volumetric (%)	-0.034	-0.097 – 0.028	0.277			
Trans-mitral gradient (mmHg)	0.191	0.044 – 0.339	0.012	0.138	0.015 – 0.261	0.029
Peak tricuspid regurgitant gradient (mmHg)	0.026	0.008 – 0.044	0.006	0.010	-0.006 – 0.025	0.226

CABG; coronary artery bypass graft. COPD; chronic obstructive pulmonary disease. CRT; cardiac resynchronization therapy. eGFR; estimated glomerular filtration rate. LV, left ventricular. LVEDV, left ventricular end-diastolic volume. LVESV, left ventricular end-systolic volume. NT-ProBNP, N-terminal pro-Brain Natriuretic Peptide. PCI; percutaneous coronary intervention

When dividing the patients into groups according to the tertiles of NT-proBNP at 6 months follow-up, patients within the low NT-proBNP tertile showed a significant decrease of NT-proBNP at follow-up (*P*=0.046) and remained stable in those within the medium NT-proBNP tertile (*P*=0.670), whereas patients within the high NT-proBNP tertile showed a significant increment compared to baseline (*P*=0.014) (Figure 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 follow-up, successful MR reduction was more often accomplished in patients within the low and medium NT-proBNP tertiles, with 14% and 13% of patients having grade ≥3 MR, respectively, whereas among patients within the high NT-proBNP tertile, 43% remained with grade ≥3 MR (*P*=0.046). High NT-proBNP tertile patients more often received 3 or 4 MitraClips (5 [23%]) compared to the low and medium tertiles (1 [5%] and 2 [8%] respectively, *P*=0.233).

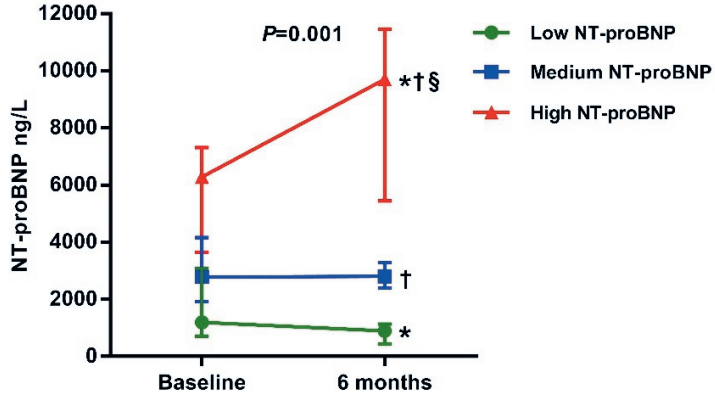

Figure 3. Changes in NT-proBNP according to tertiles of NT-proBNP at 6 months follow-up. *Legends: * P<0.05 baseline versus 6 months. † P<0.05 versus Low NT-proBNP. § P<0.05 versus Middle NT-proBNP. NT-proBNP, N-terminal pro-brain natriuretic peptide.*

Changes in clinical symptoms at 6 months follow-up

In the overall population, there were significant improvements in NYHA functional class (the number of patients with NYHA functional class ≥III reduced from 42 [65%] to 11 [17%] patients, *P*=0.011) and in the QoL score (from 35 [IQR: 26-58] to 27 [IQR: 9-43],

P=0.005). In contrast, there were no changes in the 6-minute walking distance (321±137 m to 357±122 m, *P*=0.144), however, this was not available in 13 patients.

When analysing the data according to the 6-month NT-proBNP tertiles, significant reductions in NYHA functional class symptoms (Figure 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 [IQR: 6-41], *P*=0.020 and 31 [IQR: 19-48] to 15 [IQR: 8-26], *P*=0.009 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.

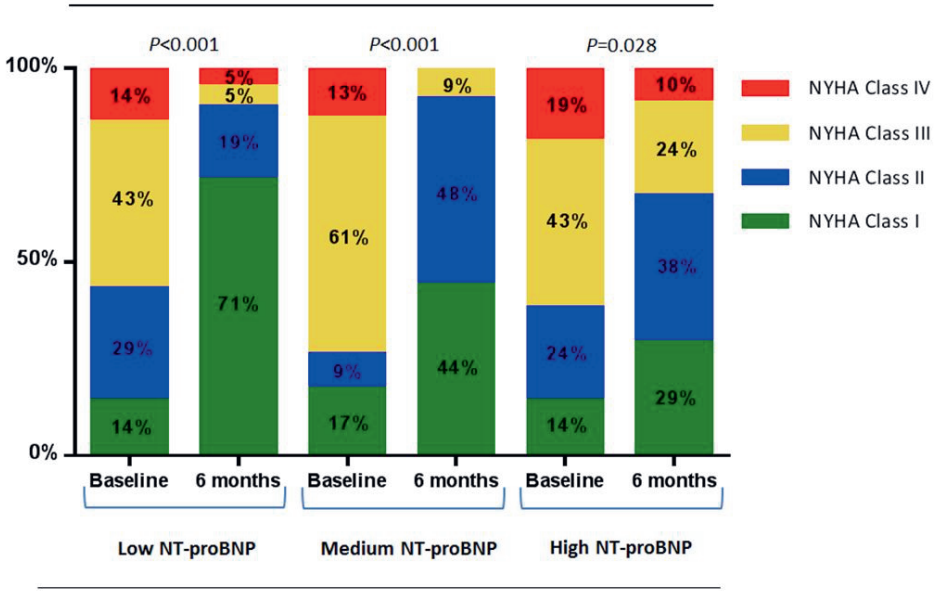

Figure 4. Changes in NYHA functional class according to the NT-proBNP tertiles at 6 months
follow-up. *Legends: NYHA, New York Heart Association. NT-proBNP, N-terminal pro-brain natriuretic peptide.*

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 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 as compared with the other groups.

Table 3. Conventional echocardiographic parameters at baseline per 6 months NT pro-BNP group

Echocardiographic variables	Low NT-proBNP N=21	Medium NT-proBNP N=23	High NT-proBNP N=21	*P* value
Left ventricular parameters				
LV ejection fraction (%)	39 ± 15	39 ± 14	33 ± 14	0.247
LVEDV (ml)	149 ± 48	170 ± 70	219 ± 93*†	0.008
LVESV (ml)	95 ± 43	108 ± 61	155 ± 88*†	0.012
Left atrial parameters				
Left atrial volume (ml)	65 ± 15	64 ± 24	74 ± 34	0.414
Reservoir function volumetric (%)	29.6 ± 12.3	30.3 ± 10.4	26.7 ± 10.1	0.520
Conduit function volumetric (%)	21.5 ± 11.4	17.0 ± 5.4	14.9 ± 8.3	0.162
Booster function volumetric (%)	20.6 (13.2 – 27.9)	15.6 (8.2 – 27.3)	15.4 (8.9 – 21.3)	0.645
Trans-mitral gradient (mmHg)	1.16 (0.92 – 2.26)	1.68 (1.05 – 2.67)	1.87 (1.44 – 3.36) †*	0.013
Peak tricuspid regurgitant gradient (mmHg)	29 ± 7	35 ± 10	38 ± 12*	0.021

**P*<0.05 versus low NT-proBNP, † *P*<0.05 versus medium NT-proBNP. LV, left ventricular. LVEDV, left ventricular end-diastolic volume. LVESV, left ventricular end-systolic volume. NT-ProBNP, N-terminal pro-Brain Natriuretic Peptide.

In the overall population, a significant reduction in LVEDV (from 178±77 ml to 170± 79 ml, *P*=0.045) and LVESV (from 120± 70 ml to 111± 69 ml, *P*=0.040 respectively) was noted at 6 months follow-up without significant changes in LVEF (from 37 ± 14% to 39± 14%, *P*=0.138). Furthermore, there were no significant changes in LA volume (from 68 ±26ml to 70±31ml, *P*=0.321) or volumetric LA functions (LA reservoir: 29±10% to 29±11%, *P*=0.650; LA conduit: 17±9% to 14±9%, *P*=0.051; LA booster, 17% [IQR: 10–24] to 16 [IQR: 10–28], *P*=0.404).

Similarly, there were no significant changes in LV volumes and LVEF in any of the 6-month NT-proBNP tertiles (Figure 5). However, LA volume reduced in patients within the low 6-month NT-proBNP tertile whereas significantly increased in the high 6-month NT-proBNP tertile (from 74±34ml to 83±38ml, *P*=0.041). Finally, no changes were observed in any of the volumetric measurements of LA function across the three 6-month NT-proBNP tertiles. All groups showed a significant increase in mean transmitral gradient at 6 months follow-up with a similar distribution; high NT-proBNP tertiles exhibited higher gradients compared to low and medium tertiles (4.49 [IQR: 2.37 – 6.69], 3.69 [IQR:1.95 – 4.35] and 3.99 [IQR: 2.88 – 5.03] respectively, *P*=0.204), however, without achieving statistical significance.

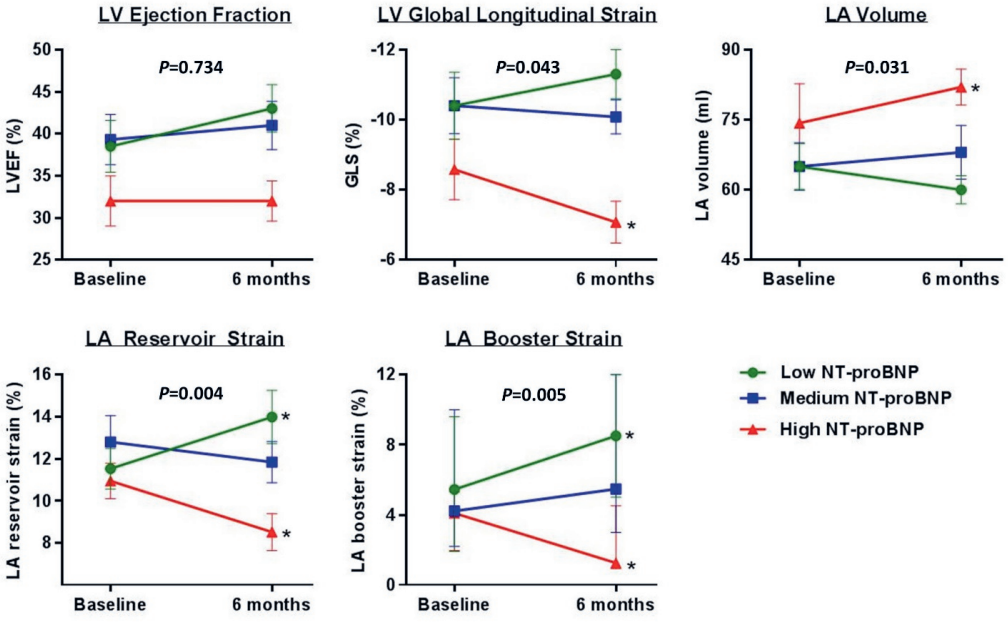

Figure 5. Graphic display of the development (baseline versus 6-month follow-up) of left ventricular and left atrial volumes and function by both volumetric and 2D speckle tracking strain analyses. *Legends: * P<0.05 baseline versus 6 months. LV, left ventricular. LA, left atrial. LVESV, left ventricular end-systolic volume. NT-proBNP, N-terminal pro-brain natriuretic peptide. LV GLS longitudinal strain corrected for LVESV and LA booster strain are expressed as median and interquartile range. The other variables are expressed as mean and standard error.*

LV and LA function by 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*=0.398). However, LV GLS slightly improved in patients within the low NT-proBNP tertile (from -10.4±5.2% to-11.3±4.3%, *P*=0.245), remained unchanged in patients in the medium NT-proBNP tertile (from -10.4±5.0% to -10.0±3.7%, *P*=0.205) and significantly impaired in patients within the high NT-proBNP tertile (from -8.6±8.0% to -7.0±3.9%, *P*=0.036).

In the overall population, only LA conduit function decreased significantly (from 7.0% ± 2.1 to 5.5% ± 2.7, *P*=0.003) whereas LA reservoir and booster functions remained unchanged (from 11.7± 4.1% to 11.3±5.5%, *P*=0.483 and from 4.5% [IQR: 2.0 – 7.5] to 5.3% [IQR: 2.0 – 10.6], *P*=0.120; respectively). When analysing the data according to 6-month NT-proBNP tertiles, patients within the low NT-proBNP tertile showed significant improvement in both LA reservoir and booster pump functions (from 11±4% to 14±6%, *P*=0.025, and from 5% [IQR: 2–9] to 9% [IQR: 5–12], *P*=0.026, respectively), whereas LA conduit function did not change (Figure 5). Patients within the medium NT-proBNP tertile showed no significant changes in the LA reservoir and booster pump function, but did show a decline in LA conduit function (from 8±2% to 6±2%, *P*=0.047), whereas, in patients within the high NT-proBNP tertile, all LA functions assessed with strain analysis showed significant decline (LA reservoir: from 11±3% to 8±3%, *P*=0.013; LA conduit: from 7±2% to 5±2%, *P*=0.041; LA booster: from 4% [IQR: 2–5] to 1% [IQR: 1–4], *P*=0.037, Figure 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 pronounced improvement in symptoms as compared with patients in the low tertile. Echocardiographically, patients within the low NT-proBNP tertile showed significant reductions in LA volumes and improvement in LA reservoir and booster pump functions (as assessed with 2-dimensional 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 volumes 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 mitral regurgitation, 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 mitral regurgitation) treated with MitraClip and a 93% procedural success rate (defined as reduction in mitral regurgitation to grade ≤2), 21% of patients remained with NT-proBNP levels ≥10,000 pg/ml (26). In addition, Yoon et al reported non-significant reductions in NT-proBNP after successful MitraClip implantation in 144 patients with severe mitral regurgitation (from 2,942 (IQR 1,596–5,722) to 2,739 (IQR 1,440–4,296) ng/L, *P*=0.21) (25). These results are consistent with 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, the 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 as compared to patients with lower values (26). However, little is known on 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 results in reduction in LV and LA volumes without changes in LVEF at 12 months follow-up (5). The volumetric reverse remodeling is more pronounced in the absence of residual mitral regurgitation whereas the reduction in LV and LA volumes is minimal when significant mitral regurgitation 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). Similar to the EVEREST II studies (5), the present study also showed

significant reductions in LVEDV and LVESV without changes in LVEF whereas LA volume and functions remained unchanged.

Integrating NT-proBNP and echocardiographic changes after MitraClip

This study integrated the NT-proBNP response after MitraClip with the clinical and echocardiographic response. Despite significant reductions in LV volumes in the overall population, the 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 impact the function of the left atrium which may be severely diseased at baseline. This is particularly notorious among patients with high NT-proBNP tertile at 6 months follow-up in whom the LA functions 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, since 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 mitral regurgitation (32). Therefore, LV GLS may be a valuable surrogate to characterize the changes in LV function in patients treated with 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 eliminating MR, the hemodynamic burden that causes LV dysfunction is resolved (33;34). However, secondary MR is caused by a diseased LV, treatment of MR will not completely correct the underlying cause of MR 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.

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 benefit or MitraClip. The strain measurements were performed with commercially available software and the results may not be comparable to those obtained with other platforms. Quantification of residual MR after MitraClip implantation remains challenging. We performed a qualitative assessment since a volumetric assessment would not be accurate as some patients had concomitant aortic regurgitation.

CONCLUSIONS

Changes in NT-proBNP after MitraClip implantation vary widely. In patients who showed a reduction in NT-proBNP, reductions in LA volumes 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 will improve in terms of hemodynamic unloading and relief of myocardial wall stretch after MitraClip implantation.

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