

Daily non-invasive haemodynamic telemonitoring for efficacy evaluation of MitraClip[®] implantation in patients with advanced systolic heart failure

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Abstract

Aim Patients with advanced systolic chronic heart failure frequently suffer from progressive functional mitral regurgitation. We report our initial experience in patients with an implanted pulmonary artery pressure (PAP) sensor, who developed severe mitral regurgitation, which was treated with the MitraClip system. We non-invasively compared changes in PAP values in patients after MitraClip with PAP changes in patients without MitraClip.

Methods and results Among 28 patients with New York Heart Association III heart failure with implanted PAP sensor for haemodynamic telemonitoring from a single centre, four patients (age 66 ± 6 years, left ventricular ejection fraction $21 \pm 3\%$, and cardiac index 1.8 ± 0.3) received a MitraClip procedure and were compared with 24 patients (age 72 ± 8 years, left ventricular ejection fraction $26 \pm 9.9\%$, and cardiac index 2.0 ± 1.0) without MitraClip procedure in a descriptive manner. Ambulatory PAP values were followed for 90 days in both groups. In comparison with the PAP values 4 weeks before MitraClip procedure, PAP was profoundly reduced in all four patients after 30 days (Δ PAPmean -11 ± 5 , Δ PAPdiast -7 ± 3 mmHg, $P < 0.02$) as well as after 90 days (Δ PAPmean -6.3 ± 6 , Δ PAPdiast -1 ± 3 mmHg). Reductions in PAP were accompanied by a profound reduction in N terminal pro brain natriuretic peptide as well as clinical and echocardiographic improvement. When analysing the dynamics with a regression model, reductions in all PAP values were significantly greater after MitraClip compared with conservative haemodynamic monitoring ($P < 0.001$).

Conclusions The efficacy of the interventional MitraClip procedure on clinical symptoms can be confirmed by haemodynamic telemonitoring. Thus, daily non-invasive haemodynamic telemonitoring allows, for the first time, for a continuous assessment of the haemodynamic efficacy of novel therapies in patients with chronic heart failure.

Keywords Chronic heart failure; Remote monitoring; Pulmonary artery pressure; MitraClip

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Introduction

Heart failure affects approximately 1–2% of the adult population in developed countries and demonstrates increasing incidence and prevalence due to the growing life expectancy.^{1,2} Acute heart failure hospitalization is a major contributor to the economic burden of heart failure,³ and more than 75% of acute heart failure hospitalizations occur in people with pre-existing chronic heart failure.⁴ In addition, every cardiac decompensation is associated with further myocardial injury,

which contributes to the progression of the disease.⁵ Although initial decongestion is clinically successful in the vast majority of admitted patients, almost 30% of acute heart failure patients are readmitted to hospital for recurrence of acute heart failure within 30 days after discharge.⁶ Therefore, improved strategies for early detection of heart failure deterioration are required. Multiple approaches to remote monitoring of heart failure patients have been evaluated; however, classical telemonitoring of weight or changes in intrathoracic impedance have not been effective in reducing

hospitalization rates.^{7,8} Data from trials of implantable haemodynamic pulmonary artery pressure (PAP) monitoring show that pulmonary filling pressures start to rise several days prior to the development of symptoms, thus providing a time slot for intervention to prevent heart failure hospitalization with an early detection of congestion.⁹ Thus, heart failure management guided by continuous access to PAP values, as provided by the CardioMEMS® system, was associated with a significant and profound reduction in heart failure hospitalization rate in New York Heart Association (NYHA) functional class III patients.^{10,11}

Severe functional mitral regurgitation is a frequent comorbidity in patients with chronic systolic heart failure, with an adverse impact on prognosis of patients regardless whether they suffer from ischaemic or non-ischaemic cardiomyopathy.¹² In a considerable number of these patients, surgery is associated with unacceptable risk; thus, a less invasive, interventional approach using the MitraClip® system may be recommended by the interdisciplinary heart team.^{13,14}

In the present manuscript, we report on our cohort of NYHA class III heart failure patients who received an implantable haemodynamic sensor for daily PAP-guided heart failure measurement for prevention of heart failure hospitalization and a subgroup who developed severe functional mitral regurgitation requiring interventional repair. Using the CardioMEMS system, we were able to non-invasively document long-term haemodynamic improvement of PAPs in patients with MitraClip implantation.

Methods

Patients with chronic heart failure in NYHA functional class III and a cardiac decompensation within the last 12 months were offered implantation of the PAP sensor CardioMEMS and participation in a single centre telemonitoring registry. A total of 29 patients received implantation of a CardioMEMS sensor and were repeatedly trained in heart failure care by a European Society of Cardiology-certified heart failure nurse. However, only 28 patients were compliant after implantation and regularly transmitted their data at least five times per week at a certain time point.

Haemodynamic telemonitoring and follow-up

Regular telephone contact was performed by European Society of Cardiology-certified heart failure nurses in all patients, using a standardized questionnaire [adopted from the INH (Interdisciplinary Network for Heart Failure) trial¹⁵]. The nurses were supported by a heart failure specialist, according to the internal standard operating procedure (weekly telephone contact in the first 4 weeks after implantation,

followed by twice-weekly telephone contact Weeks 5 to 8 after implantation, and finally, four times per week telephone/email contact from Week 9 onwards during telemonitoring, if no individual alerts occurred due to crossing of the individually adapted optimal PAP target area). We applied the haemodynamic-guided heart failure management previously used in the CHAMPION trial.¹⁰ In brief, medication was adjusted with the aim to have diastolic PAP in the range of 8–20 mmHg (optivolemic state). If the patients had signs of low perfusion, reduction of diuretics, fluid repletion, and/or administration of inotropic agents were considered. Pressure measurements were reviewed weekly in case of optivolemia and two to three times per week if diastolic PAP was outside the individually defined optimal range. Regular outpatient visits were scheduled every 3 months in the heart failure outpatient department.

For comparison of the diuretic dose, furosemide was converted into torasemide equivalent assuming a ratio of 4:1.

All patients who received the CardioMEMS sensor provided written informed consent for participation in the single centre registry (NCT03020043). The study complies with the Declaration of Helsinki and was approved by the local ethics committee. Written informed consent has been obtained from all patients.

MitraClip® procedure

Patients who had an implanted CardioMEMS sensor and who developed symptomatic functional mitral regurgitation, which could not successfully be managed conservatively, were, after heart team discussion, scheduled to the MitraClip implantation procedure. Implantation of the MitraClip(s) was performed under general anaesthesia and three-dimensional transesophageal echocardiography guidance, according to the manufacturer instructions.

Statistics

This study is a descriptive comparison of two patient cohorts. Baseline characteristics were compared with the parametric *t*-test or the non-parametric Mann–Whitney *U*-test for continuous variables and with the χ^2 or Fisher exact test, as appropriate, for categorical variables. Comparison between paired baseline and follow-up values was performed using the *t*-test or Wilcoxon signed-rank test as appropriate. Statistical comparison of the time course of the PAP values pre-implantation and up to 90 days after MitraClip implantation in the MitraClip group and analogously 50 days after PAP-sensor implantation in the control group was performed with a linear mixed-effect regression model that accounts for the time series correlation structure within the single patients and differentiate between the treatment groups. The

parametric regression model is composed by a linear trend, which may change at implantation time and a potential non-linear exponential decay after MitraClip implantation such that the effect of the implantation can be quantified and tested by the respective regression coefficients. This parametric fit was supplemented with non-parametric summary curves obtained after applying slight non-parametric kernel smoothing.

Statistical significance was assumed if $P < 0.05$, and all reported P values are two-sided. Statistical analysis was performed with SPSS (Version 23.0, SPSS Inc.) and R (Version 3.3.1, R Foundation for Statistical Computing, Vienna, Austria).

Results

The present haemodynamic telemonitoring patient cohort comprises a total of 28 patients with advanced chronic heart failure. All patients received haemodynamic telemonitoring with the CardioMEMS system for severe NYHA class III heart failure and had a recent hospitalization between 2015 and 2017. During telemonitoring, four of these advanced heart failure patients received a MitraClip procedure for progressive severe functional mitral regurgitation. As shown in *Table 1A*, the baseline characteristics of patients from the MitraClip cohort were comparable with the baseline characteristics of the control cohort, except for significantly more severe mitral regurgitation (*Table 1A*) and, therefore, higher PAP values (*Table 2B*). Likewise, baseline medication was comparable with non-significant higher doses of loop diuretics in patients with severe mitral regurgitation (*Table 1B*).

The MitraClip procedure was successful in all four cases with indication for interventional repair, leading to a substantial reduction in the NYHA heart failure class,

Table 1A Patient baseline characteristics

	MitraClip® cohort	Control cohort	P value
Age (years)	68 ± 6	72 ± 8	0.26
Aetiology of CHF	ICM 75% DCM 25%	ICM 79.2% DCM 12.5% Other 8.3%	0.67
NYHA class	3 ± 0.5	3 ± 0.2	0.27
Systolic BP (mmHg)	108 ± 7	116 ± 19	0.73
Creatinine (mg/dL)	1.62 ± 0.66	1.54 ± 0.53	1.0
MR severity (grade)	3 ± 0	1 ± 0.65	<0.001
LVEF (% echo)	21 ± 5.4	26 ± 9.9	0.29
Cardiac index	1.8 ± 0.26	2.0 ± 0.95	0.87
Transpulmonic gradient (mmHg)	13 ± 6	10 ± 9	0.22

CHF, chronic heart failure; DCM, non-ischmeic dilated cardiomyopathy; ICM, ischemic cardiomyopathy with heart failure; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; NYHA, New York Heart Association.

Table 1B Medication

	MitraClip cohort (n = 4)		Control group (n = 24)		Between-group comparison		
	Baseline N (%)	90 day FU N (%)	Baseline N (%)	90 day FU N (%)	P value	Baseline	90 day FU
Antiplatelet therapy	1 (25)	1 (25)	12 (50)	11 (46)	0.32	0.35	0.44
OAC	3 (75)	3 (75)	14 (58)	14 (58)	1.0	0.53	0.53
ACE-I/ATRB	3 (75)	2 (50)	19 (79)	18 (75)	0.32	0.85	0.31
ARNI	1 (25)	2 (50)	5 (21)	6 (25)	0.32	0.85	0.31
Beta-blocker	4 (100)	4 (100)	23 (96)	23 (96)	1.0	0.68	0.68
MRA	4 (100)	3 (75)	16 (67)	15 (63)	0.32	0.17	0.63
Loop diuretic	4 (100)	4 (100)	22 (92)	23 (96)	0.32	0.55	0.68
Torsemide (dose equivalent in mg; mean ± SD)	43 ± 39	25 ± 13	23 ± 14	39 ± 43	0.41	0.16	0.98
Thiazide diuretic	0 (0)	0 (0)	7 (29)	8 (33)	0.32	0.21	0.17
Digitalis	0 (0)	0 (0)	5 (21)	6 (24)	1.0	0.26	0.26

ACE-I, angiotensin-converting enzyme inhibitor; ARNI, angiotensin receptor blocker neprilysin inhibitor; ATRB, angiotensin receptor blocker; FU, follow-up; MRA, mineralocorticoid antagonist; OAC, oral anticoagulation; SD, standard deviation.

echocardiographic vena contracta, and N terminal pro brain natriuretic peptide (NT-proBNP) serum levels at follow-up. In addition, there was an almost 50% reduction in mean loop diuretic dose in patients with MitraClip but no change in the control group (Tables 1B, 2A and Figure 2).

The perioperative PAP changes after MitraClip are shown in Table 2A, demonstrating significant reductions in systolic, mean, and diastolic pulmonary pressure. In addition, intermediate follow-up at 30 and 90 days after MitraClip shows a further decline in PAP (30 days ΔPAPsys -16 ± 4, ΔPAPmean -11 ± 5, ΔPAPdiast -7 ± 3 mmHg, P < 0.02; 90 days ΔPAPsys -13 ± 10, ΔPAPmean -6.3 ± 6, ΔPAPdiast -1 ± 3 mmHg). The individual PAP time courses after MitraClip implantation are shown in Figure 1A.

For comparison of PAP values between the MitraClip and the control group, we defined a time interval of 30 days prior to MitraClip, whereas in the control group, we started using the PAP values from 50 days after implantation.

As shown in Figure 1B, following MitraClip implantation, the PAP values decreased exponentially at the beginning, followed by linear decrease during further follow-up (P < 0.05 for all PAP values). In comparison, there was a slight but significant steady linear decrease in the 24 patients of the control group (P < 0.001).

Comparing the long-term course of PAP values, it is evident that correction of severe mitral regurgitation was associated with a persistent haemodynamic improvement. Whereas prior to the MitraClip procedure, PAP values were significantly higher in the MitraClip cohort compared with the control group, PAP values of the MitraClip cohort approached values of the control group at the end of follow-up and did not longer differ significantly at 90 day follow-up (Figure 1C).

During the 90 day follow-up, no patient died, and there was no hospitalization for cardiac decompensation.

Table 2A Perioperative efficacy (immediate pre-procedure and post-procedure haemodynamic parameters)

	MitraClip cohort (n = 4)		
	Pre-procedure	Post-procedure	P value
Transmitral peak gradient (mmHg, echocardiography)	3.3 ± 0.5	7.8 ± 2.6	0.11
Transmitral mean gradient (mmHg, echocardiography)	1.3 ± 0.5	2.8 ± 0.5	0.08
MR severity (Vena Contracta; mm)	8 ± 1	4 ± 1	0.004
PAP systolic (mmHg)	67 ± 5.0	52.0 ± 7.6	0.008
PAP mean (mmHg)	45.5 ± 2.5	35.3 ± 4.1	0.006
PAP diastolic (mmHg)	32.8 ± 2.5	24.3 ± 3.2	0.006
Proportional pulmonary artery pulse pressure	0.51 ± 0.05	0.53 ± 0.05	0.017

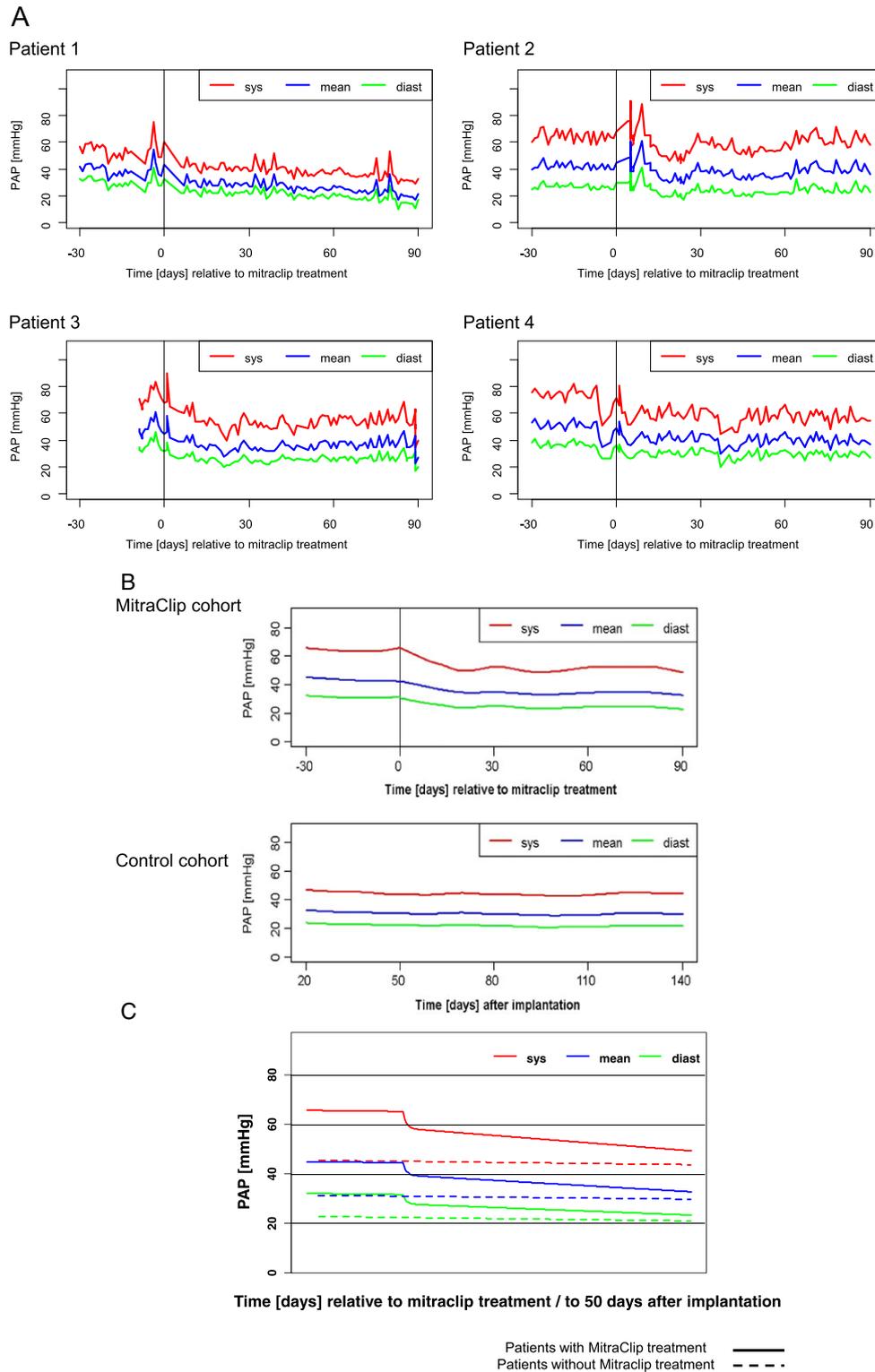
MR; mitral regurgitation; PAP, pulmonary artery pressure.

Table 2B 90 day efficacy

	MitraClip cohort (n = 4)		Control group (n = 24)		Between-group comparison	
	Baseline N (%)	90 day FU N (%)	Baseline N (%)	90 day FU N (%)	P value	90 day FU
NT-proBNP (pg/mL; log NT-proBNP)	3446 ± 2539 (3.4 ± 0.4)	1668 ± 1142 (3.1 ± 0.3)	5597 ± 13996 (3.3 ± 0.5)	4229 ± 8089 (3.2 ± 0.6)	0.07	0.24
PAP systolic (mmHg)	62 ± 9	49 ± 12	44 ± 18	43 ± 14	0.09	0.97
PAP mean (mmHg)	40 ± 5	33 ± 7	28 ± 13	29 ± 10	0.14	0.55
PAP diastolic (mmHg)	25 ± 3	24 ± 3	18 ± 10	20 ± 8	0.59	0.12
NYHA class	3.3 ± 0.3	2.4 ± 0.5	3.0 ± 0.2	2.7 ± 0.6 (n = 23)	0.006	0.01

FU, follow-up; NT-proBNP, N terminal pro brain natriuretic peptide; NYHA, New York Heart Association; PAP, pulmonary artery pressure.

Figure 1 (A) MitraClip® long-term haemodynamic follow-up (90 days). Pulmonary artery pressure (PAP) values (raw data) shown for all four patients over the time; vertical bar, date of MitraClip implantation. (B) PAP evolution after MitraClip in comparison with classic PAP-guided heart failure treatment using non-parametric smoothing regression methods when summarizing over the patients. (C) Prediction regression model comparing patients with (solid line) and without (dotted line) MitraClip treatment; $P < 0.001$ for all PAP. Red line, systolic PAP; blue line, mean PAP; green line, diastolic PAP.



Discussion

The present study is, to our knowledge, the first descriptive report about daily non-invasive haemodynamic monitoring with the CardioMEMS system in patients with advanced heart failure receiving MitraClip therapy for severe functional mitral regurgitation. Our series demonstrates that, after an exponential decrease in PAP immediately after successful MitraClip implantation, there is a further continuous and significant reduction of PAP values for at least 90 days.

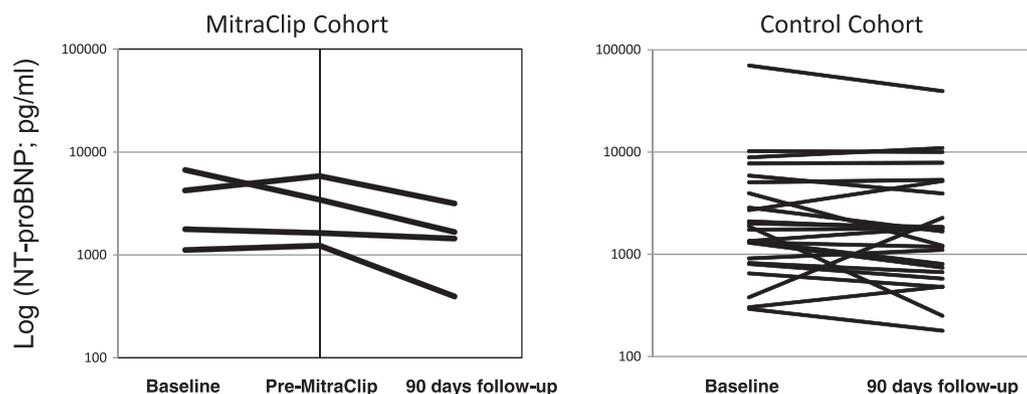
In previous clinical investigations of haemodynamic changes following MitraClip implantation, Swan–Ganz catheter measurements and/or echocardiographic assessments were performed to assess the effects of the MitraClip implantation on mitral valve gradient. The very early study by Herrmann *et al.*¹⁶ focused on changes in transmitral gradients due to double orifice construction. They demonstrated that echocardiographically assessed pressure gradients increased slightly but significantly after MitraClip implantation, whereas direct haemodynamic assessment revealed no significant changes in transmitral gradients. In our descriptive study, we found similar transmitral pressure changes with a slight but non-relevant increase in transmitral mean gradient by echocardiography.

Immediate changes in PAP were assessed by several studies.^{17–20} Patzelt *et al.* report a series of 101 patients with severe mitral regurgitation with invasive haemodynamic assessment before and after MitraClip. The authors demonstrate an immediate significant decrease in systolic PAP, which was accompanied by a significant increase in cardiac output.¹⁹ An even greater systolic PAP reduction of 13 mmHg was seen in the smaller study by Divchev *et al.*,²⁰ which may be related to the fact that these patients had the highest baseline systolic PAP values. Importantly, in our small patient cohort, systolic PAP measurements obtained with the implanted pulmonary artery sensor

provide identical results with a mean 14 mmHg change of systolic PAP.

Moreover, non-invasive analysis of PAP in 102 patients before and 1 year after MitraClip using transthoracic Doppler echocardiography also documented a significant decrease in systolic PAP, derived from tricuspid regurgitation.²¹ This is in line with our results, where we could not only find a significant reduction in systolic PAP over time but also a substantial and significant, almost 64% decrease in diastolic PAP. However, none of the so far published reports provided daily direct haemodynamic assessment of PAP values during long-term follow-up. Therefore, we took advantage of the fact that four patients already had a haemodynamic sensor implanted, which allowed for direct and daily measurement of PAP changes after successful MitraClip implantation. The CardioMEMS-derived PAP values were previously shown to correlate tightly with Swan–Ganz and echocardiographic measurements in patients with heart failure, during a maximum follow-up of 90 days.²² Interestingly, our small study not only show the expected and well-established immediate effects of percutaneous mitral valve repair but also a continuous, further decrease in PAP after MitraClip, although the diuretic dose was significantly reduced. In our patient cohort, PAP values of the MitraClip cohort do no longer differ significantly from the control cohort at 90 days, who never had a severe functional mitral regurgitation. These data suggest that repair of severe mitral regurgitation might initiate an ongoing beneficial haemodynamic response beyond the acute change in advanced heart failure patients that contributes to the improved haemodynamic cardiac status. This finding is further corroborated by the substantial reduction of NT-proBNP serum levels despite reduced diuretic dose in the MitraClip cohort, whereas the control cohort showed constant NT-proBNP serum levels (*Figure 2*). In addition, during 90 day follow-up, none of our MitraClip patients died or experienced a heart failure hospitalization. Compared with a

Figure 2 Serum N terminal pro brain natriuretic peptide (NT-proBNP) levels in the MitraClip® and the control cohort suggesting reverse remodelling of left ventricular-dysfunction after MitraClip. vertical bar, date of MitraClip implantation.



recent meta-analysis,¹³ this seems to be a favourable outcome. However, in the meta-analysis, a total of 875 patients with severe functional mitral regurgitation in heart failure were treated with MitraClip and were followed for at least 6 months. Within this time, mortality was 9%, and rehospitalisation rate for heart failure was 17%. Taking into account the small number of patients and limited time of follow-up, our results may be seen as an encouraging observation, although we are convinced that the combination of MitraClip and haemodynamic monitoring should have additive positive effects on clinical outcome. However, larger studies are warranted to address this question.

Finally, in the future, non-invasive assessment of PAP with an implanted PAP sensor might be used to directly assess the haemodynamic consequences of novel interventional or pharmacological treatment in heart failure over a longer period of time, without exposing patients at risk for repeated cardiac catheterization.

Limitations

The present study comprises only four patients receiving haemodynamic telemonitoring together with MitraClip for severe functional regurgitation, who were compared with 24 patients with haemodynamic telemonitoring alone. Therefore, our descriptive analysis of the novel possibility to assess the daily PAP profile in an outpatient setting of severe chronic heart failure should be interpreted as hypothesis generating.

In summary, our data demonstrate, for the first time, an ongoing continuous decrease in PAP values after MitraClip

in advanced heart failure patients using daily, non-invasive haemodynamic monitoring.

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Conflict of interest

B.A. reports having received consulting fees and an unrestricted research grant from St. Jude Medical (now Abbott) and lecture fees from Novartis, St. Jude Medical, and Vifor. S.F. reports having received consulting fees from and served as a proctor for Abbott.

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