

# Pulmonary capillary wedge pressure and natriuretic peptide levels in patients with sinus rhythm and severe left atrial enlargement following mitral valve surgery: early and late changes

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## ABSTRACT

**Introduction:** Chronic mitral regurgitation is often accompanied by left atrial and ventricular remodeling and elevated natriuretic peptide levels. Our aim was to examine the relation between severe preoperative left atrial enlargement and changes in hemodynamics and natriuretic peptide levels after mitral valve surgery.

**Methods:** A prospective study was conducted including 40 consecutive patients in sinus rhythm, with severe degenerative mitral regurgitation. N-terminal protype-B natriuretic peptide levels and hemodynamics were measured at predefined time points. An echocardiographic evaluation was performed the day before valve surgery and six months postoperatively.

**Results:** Patients with left atrial volume index  $\geq 60$  mL/m<sup>2</sup>, n = 26, had higher baseline mean pulmonary capillary wedge pressure ( $17 \pm 9$  mmHg vs  $9 \pm 4$  mmHg,  $p = 0.010$ ) and N-terminal protype-B natriuretic peptide ( $1326 \pm 2573$  ng/L vs  $233 \pm 221$  ng/L,  $p = 0.002$ ) than patients with left atrial volume index  $< 60$  mL/m<sup>2</sup>. The mean pulmonary capillary wedge pressure decreased to normal in patients with severe left atrial enlargement early after surgery, while it remained normal in patients without severe left atrial enlargement. The natriuretic peptide levels increased during the early postoperative period and decreased in both groups at 6-month follow-up.

**Conclusions:** A severe left atrial enlargement in patients with chronic degenerative mitral regurgitation and sinus rhythm indicates higher pulmonary capillary wedge pressure and natriuretic peptide levels than in those without. These findings may support early referral to surgery and may facilitate perioperative management. The potential reversibility of left atrial enlargement after surgery may be associated with postoperative reductions in pulmonary capillary wedge pressure and natriuretic peptide levels.

**Keywords:** mitral regurgitation, cardiac surgery, pulmonary capillary wedge pressure, natriuretic peptide.

## INTRODUCTION

Severe chronic mitral regurgitation (MR) is often accompanied by left atrial (LA) and ventricular remodeling, which may reflect

the severity of the regurgitation volume and thus the severity of disease (1). LA remodeling is characterized by chamber enlargement and contractile dysfunction due to volume and pressure overload. In addition, the increase in atrial and ventricular wall tension induces hormonal activation, leading to elevated levels of natriuretic peptides (2, 3). The current evidence suggests that preoperative LA enlargement or elevated levels of natriuretic peptides, in combina-

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tion with severe degenerative MR, may be indicators for referral to surgery (4).

Mitral valve surgery (MVS), especially repair, relieves the volume and pressure overload on the left sided chambers inducing left ventricular and left atrial reverse remodeling (LARR) (5, 6), leading to an early reduction in natriuretic peptide levels (7, 8). In previous studies on conservatively treated MR, severe LA enlargement has been suggested as a predictor of impaired cardiovascular outcome (9). However, the outcome in conservatively managed MR may not be the same in surgically managed patients (9). In a previous study by our group, we were not able to verify any negative effects of persistent postoperative LA enlargement (10).

The early changes in postoperative hemodynamics and the release of natriuretic peptides in relation to preoperative LA enlargement in chronic degenerative MR following surgery have not been fully elucidated. The aim of the present study was, therefore, to examine the relation between severe preoperative LA enlargement and early and late changes in hemodynamics and natriuretic peptide levels following MVS.

## METHODS

*Patient population.* This single-center study was a prospective study, in which 40 consecutive adult patients in sinus rhythm scheduled for elective MVS at Skane University Hospital, Lund, Sweden, were recruited between April 2010 and March 2013. The primary aim was to study changes in hemodynamic variables and N-terminal protype-B natriuretic peptide (NT-proBNP) levels in patients with severe preoperative LA enlargement ( $\geq 60$  mL/m<sup>2</sup>) in sinus rhythm and compare them to those without ( $< 60$  mL/m<sup>2</sup>). Patients with an echocardiographic diagnosis of chronic se-

vere degenerative MR with leaflet prolapse in which the intention of surgery was repair were included.

Exclusion criteria were: MR of etiologies other than degenerative mitral valve disease; permanent atrial fibrillation, concomitant aortic, tricuspid or pulmonary valve stenosis or more than mild regurgitation; concomitant Cox-Maze procedure; previous cardiac surgery; infective valve endocarditis and emergency surgery. Written consent was obtained from all the participants, and the study was approved by The Ethics Committee for Clinical Research at Lund University, Sweden.

*Perioperative data and invasive measurements.* Mitral valve surgery was performed under general anesthesia and followed the study protocol using midazolam, fentanyl, propofol, celocurine and rocuronium, and isoflurane or sevoflurane in oxygen/air. MVS was performed using a standard cardiopulmonary bypass technique with aorto-bicaval cannulation.

Transesophageal echocardiography was used to assess valve repair or prosthesis function perioperatively. All patients were admitted postoperatively to the intensive care unit (ICU) intubated, ventilated and sedated with propofol.

The following hemodynamic variables were studied: arterial blood pressure, pulmonary artery pressure, pulmonary capillary wedge pressure (PCWP), central venous pressure, and cardiac output. Data were collected at predefined time points using a 7.5F single-lumen, balloon-tipped, flow-directed thermodilution fiberoptic pulmonary artery catheter (ICU Medical, Inc., San Clemente, CA USA). The wedge position of the catheter was confirmed by demonstrating a definite difference between the waveforms in the pulmonary artery and PCWP tracings. Cardiac output was determined using the bolus thermodilution method taking the average of the three middle measurements in

a sequence of five, and indexing the result to the body surface area.

Systemic and pulmonary vascular resistances were calculated as the ratio between the pressure drop along the vascular bed and the cardiac output, and were indexed to the body surface area ( $\text{dynes} \cdot \text{sec} \cdot \text{m}^2/\text{cm}^5$ ). All pressure monitors were zeroed at the mid-axillary line before each measurement. Invasive hemodynamic measurements were performed by a single investigator after the induction of anesthesia (T0), after extracorporeal circulation weaning (T1), after admission to the ICU (T2), and on postoperative day 1 (T3). Complete hemodynamic data were obtained for all 40 patients.

*Blood sampling.* In order to indirectly evaluate the left-sided filling pressures we measured NT-proBNP levels for each patient by collecting blood samples at the following time points: preoperatively (Dpre), after admission to the ICU (D0), on postoperative day 1 (D1), on postoperative day 4 (D4), and six months after surgery.

The timing and number of blood samples were similar to previous studies presenting data on mitral valve and cardiac surgery (7, 8, 11, 12). Plasma levels of NT-proBNP were determined using the Elecsys proBNP® electrochemiluminescence immunoassay (Roche Diagnostics, Mannheim, Germany).

*Echocardiography.* An echocardiographic evaluation was performed the day before MVS and six months postoperatively. An additional echocardiographic study was performed within 4-7 days postoperatively as routine practice outside the study protocol. All echocardiographic measurements within the study protocol were performed by two investigators who were blinded to the clinical data.

The severity of MR, and the chamber size and function were quantified using color Doppler and 2D echocardiography, and evaluated according to previously validated

criteria (13, 14). The atrial volumes were determined using the bi-plane modified Simpson method, and indexed to the body surface area. The ejection fraction was measured using the bi-plane Simpson disk method. LARR was defined as a postoperative reduction in left atrial volume index (LAVi)  $\geq 15\%$  (5, 6). Patients were categorized as having severe preoperative LA enlargement when LAVi exceeded  $60 \text{ mL}/\text{m}^2$  (9).

*Statistical analysis.* Categorical variables were expressed as proportions and percentages and continuous variables as the mean  $\pm 1$  standard deviation. The paired-samples T-test was used for continuous variables, and categorical data were compared using the chi-squared test, or Fisher's exact test when the expected frequency was less than five. For skewed distributed variables, the Mann-Whitney U test was used. Statistical significance was defined as  $p < 0.05$ . Statistical analysis was performed using the SPSS software package (SPSS 20.0 Chicago, IL, USA)

*Follow-up.* Follow-up was 100% complete for survival at  $6.3 \pm 1.5$  months (median 6.1 months, interquartile range 6.0-7.2), and totaled 18.7 patient-years. One 84-year-old patient succumbed from pneumonia 3.5 months after surgery.

One patient declined to participate in the study 5 months postoperatively, and two patients had incomplete echocardiographic data. Data obtained six months after surgery included NT-proBNP levels and an echocardiographic assessment including severity of residual MR, determination of LAVi with assessment of LARR.

## RESULTS

*Patient characteristics.* The clinical characteristics of the study population are given in *Table 1*. The etiology of MR was degenerative in all cases, including prolapse of the

10

posterior leaflet (77.5 %,  $n = 31$ ), anterior leaflet (5 %,  $n = 2$ ), or both leaflets (17.5 %,  $n = 7$ ). Five patients with no history of angina or myocardial infarction underwent concomitant coronary artery by-pass grafting in addition to mitral valve repair. All patients were scheduled for repair, although three patients underwent valve replacement: two due to repair failure (replacement with a bioprosthesis and a mechanical prosthesis) and one due to extensive valvulo-annular calcification (replacement with a bioprosthesis). Perioperative trans-

esophageal echocardiography did not reveal any systolic anterior motion, stenosis, paravalvular leakage, or more than residual mitral valve regurgitation in any of the patients after weaning from extracorporeal circulation. The early postoperative clinical outcome is presented in *Table 2*. The 30-day mortality was 0%. At six months follow-up 100% of the patients ( $n = 36$ ) were in NYHA functional class I to II.

*Hemodynamic changes.* The mean PCWP was significantly higher at T0 in patients with severe preoperative LA enlargement

**Table 1** - Pre- and perioperative characteristics.

	Preoperative LAVi < 60 mL/m <sup>2</sup> (n = 14)	Preoperative LAVi ≥ 60 mL/m <sup>2</sup> (n = 26)	p-value
<i>Preoperative data</i>			
Age (y)	68 ± 9	66 ± 10	0.551
Male	11 (79)	17 (65)	0.484
BMI (kg/m <sup>2</sup> )	26 ± 4	26 ± 4	0.819
e-GFR (mL/min/1.73 m <sup>2</sup> )	92 ± 19	80 ± 20	0.063
COPD (patients)	0	1 (4)	1.000
NYHA class III-IV	6 (43)	16 (62)	0.257
Sinus rhythm	14 (100)	26(100)	
Hypertension	7 (50)	17 (65)	0.343
Beta-blockers or/and ACEinhibitors	8 (57)	18 (69)	0.501
Diuretics	7 (50)	16 (62)	0.481
Diabetes mellitus	0	2 (8)	0.533
Logistic EuroSCORE I	4.0 ± 3.2	4.2 ± 2.4	0.830
<i>Biochemical data</i>			
NT-proBNP (ng/L)	233 ± 221	1326 ± 2573	0.002
<i>Perioperative data</i>			
Repair failure	0	3 (12)	0.539
ECC time (min)	118 ± 40	121 ± 45	0.819
Cross clamp time (min)	92 ± 38	91 ± 39	0.969
Concomitant surgery CABG (patients)	2 (14)	3 (12)	1.000

The values given are the mean ± standard deviation or numerical values (%).

LAVi = left atrial volume index; BMI = body mass index; e-GFR = estimated glomerular filtration rate; COPD = chronic obstructive pulmonary disease; NYHA = New York Heart Association; ACE = angiotensin converting enzyme; EuroSCORE = European System for Cardiac Operative Risk Evaluation; NT-proBNP = N-terminal protype-B natriuretic peptide; ECC = extracorporeal circulation; CABG = coronary artery by-pass grafting.

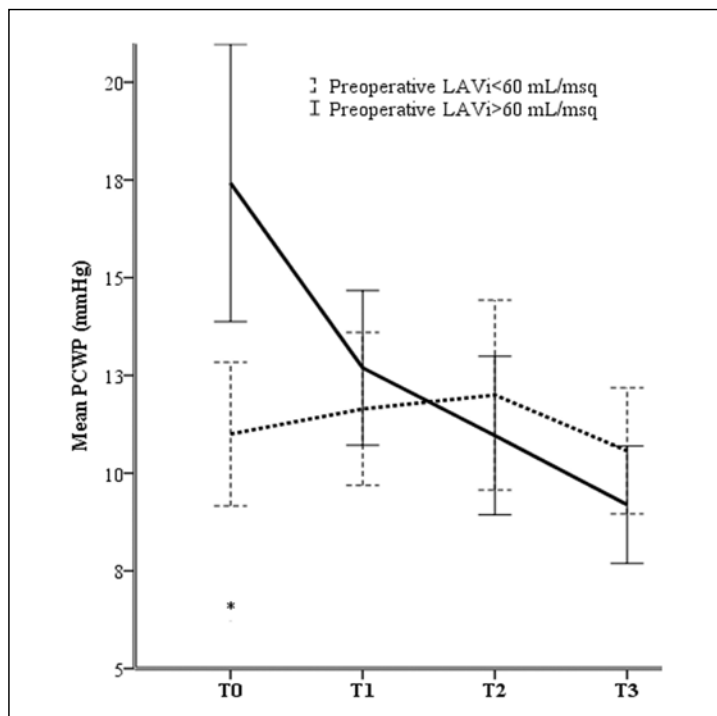
(LAVi $\geq$ 60 mL/m<sup>2</sup>) than in those without ( $p=0.010$ ). The mean PCWP decreased from 17 $\pm$ 9 mmHg (T0) to 9 $\pm$ 4 mmHg (T3) over the first 24 hours, in patients with severe preoperative LA enlargement, which is equivalent to a 32% reduction from

baseline ( $p<0.001$ ), *Figure 1*. In patients without severe preoperative LA enlargement, the mean PCWP was 11 $\pm$ 3 mmHg (T0) and 11 $\pm$ 3 mmHg (T3),  $p=0.644$ . No significant differences were seen in mean pulmonary artery pressure, central venous

**Table 2** - Postoperative clinical outcome.

	Preoperative LAVi < 60 mL/m <sup>2</sup> (n = 14)	Preoperative LAVi $\geq$ 60 mL/m <sup>2</sup> (n = 26)	p-value
30 days mortality	0	0	
CVI	0	0	
Atrial fibrillation	6 (43)	16 (62)	0.257
Reoperation for bleeding	0	1 (4)	1.000
Time on ventilator (hours)	5.0 $\pm$ 2.8	6.7 $\pm$ 4.4	0.204
Inotropic-vasoactive drugs requirement > 12 hours			
- norepinephrine	1 (7)	3 (12)	1.000
- dobutamine or levosimendan	1 (7)	5 (19)	0.399
- nitroglycerine or sodium nitroprusside	2 (14)	1 (4)	0.276
ICU LOS (hours)	21.6 $\pm$ 2.9	31.2 $\pm$ 16.5	0.067

The values given are the mean  $\pm$  standard deviation or numerical values (%). LAVi = left atrial volume index; CVI = cerebrovascular insult; ICU = intensive care unit; LOS = length of stay.



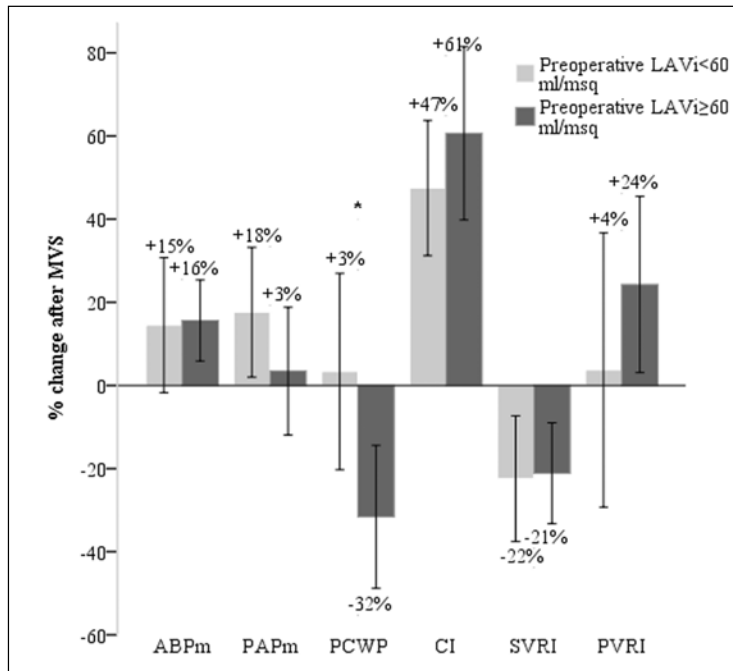
**Figure 1** - Per- and early postoperative changes in pulmonary capillary wedge pressure (PCWP). LAVi = left atrial volume index. Error bars indicate the 95% confidence interval. \* $p < 0.05$ .

12

pressure, cardiac index, systemic and pulmonary vascular resistances between patients with and without severe preoperative LA enlargement at any of the time points. Changes in hemodynamic variables at the

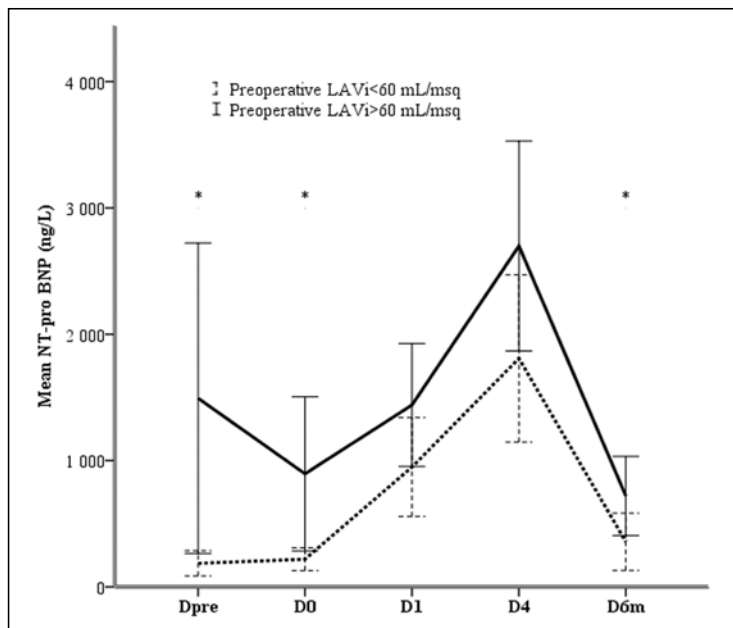
different time points are presented in *Figure 2* and *Table 3*.

*Natriuretic peptide levels.* The mean NT-proBNP level in patients with severe preoperative LA enlargement was higher preop-



**Figure 2** - Mean percentage change in hemodynamic variables after induction of anesthesia (T0) and on postoperative day 1 (T3). Error bars indicate the 95% confidence interval.

MVS=mitral valve surgery; LAVi=left atrial volume index; ABPm=mean arterial blood pressure; PAPm=mean pulmonary artery pressure; PCWP=pulmonary capillary wedge pressure; CI=cardiac index; SVRI=systemic vascular resistance index; PVRI=pulmonary vascular resistance index. \* $p < 0.05$ .



**Figure 3** - Changes in NT-proBNP measured preoperatively (Dpre), on postoperative day 1 (D1), on postoperative day 4 (D4), and 6 months after surgery (D6m).

LAVi=left atrial volume index. Error bars indicate the 95% confidence interval. \* $p < 0.05$ .

**Table 3 - Hemodynamic variables.**

Variables	After induction of anesthesia (T0)	After ECC-weaning (T1)	On admission to ICU (T2)	Post-operative day 1 (T3)
<i>Patients with preoperative LAVi &lt; 60 mL/m<sup>2</sup> (n = 14)</i>				
HF (bpm)	64 ± 16	82 ± 6	82 ± 5	79 ± 10
ABPm (mmHg)	71 ± 17	70 ± 12	84 ± 12	77 ± 6
PAPs (mmHg)	34 ± 14	32 ± 13	35 ± 12	41 ± 12
PAPd (mmHg)	15 ± 7	14 ± 5	17 ± 4	17 ± 5
PAPm (mmHg)	23 ± 10	21 ± 6	24 ± 6	25 ± 7
PCWP (mmHg)	11 ± 3	12 ± 3	12 ± 4	11 ± 3
CVP (mmHg)	7 ± 3	8 ± 2	9 ± 2	10 ± 4
CI (L/min/m <sup>2</sup> )	2.1 ± 0.4	2.7 ± 0.6	2.2 ± 0.4	3.1 ± 0.5
SVRI (dynes · sec · m <sup>2</sup> /cm <sup>5</sup> )	2463 ± 717	1957 ± 564	2844 ± 668	1771 ± 290
PVRI (dynes · sec · m <sup>2</sup> /cm <sup>5</sup> )	433 ± 232	283 ± 161	422 ± 168	395 ± 180
<i>Patients with preoperative LAVi ≥ 60 mL/m<sup>2</sup> (n = 26)</i>				
HF (bpm)	64 ± 14	85 ± 10	85 ± 6	84 ± 7
ABPm (mmHg)	70 ± 14	70 ± 12	83 ± 15	78 ± 11
PAPs (mmHg)	37 ± 15	35 ± 12	39 ± 12	40 ± 11
PAPd (mmHg)	19 ± 8	17 ± 7	18 ± 5	17 ± 6
PAPm (mmHg)	27 ± 10	24 ± 8	26 ± 7	25 ± 7
PCWP (mmHg)	17 ± 9	13 ± 5	11 ± 5	9 ± 4
CVP (mmHg)	9 ± 4	10 ± 4	9 ± 3	11 ± 4
CI (L/min/m <sup>2</sup> )	2.0 ± 0.5	2.6 ± 0.5	2.4 ± 0.4	3.1 ± 0.7
SVRI (dynes · sec · m <sup>2</sup> /cm <sup>5</sup> )	2501 ± 748	1779 ± 736	2568 ± 778	1820 ± 433
PVRI (dynes · sec · m <sup>2</sup> /cm <sup>5</sup> )	374 ± 164	345 ± 226	500 ± 186	418 ± 168

The values given are the mean ± standard deviation or numerical values (%).

ECC = extracorporeal circulation; ICU = intensive care unit; LAVi = left atrial volume index; HF = heart frequency; bpm = beat per minute; ABPm = mean arterial blood pressure; PAPs = pulmonary artery pressure systolic; PAPd = pulmonary artery pressure diastolic; PAPm = mean pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; CVP = central venous pressure; CI = cardiac index; SVRI = systemic vascular resistance index; PVRI = pulmonary vascular resistance index.

eratively (1326 ± 2573 ng/L) than in those without severe preoperative LA enlargement (233 ± 221 ng/L), *p* = 0.002. Following MVS, the mean NT-proBNP in patients with severe preoperative LA enlargement was highest on D4 (3515 ± 4316 ng/L) and decreased to 708 ± 680 ng/L six months postoperatively (Figure 3). In patients without severe preoperative LA enlargement, an increase in mean NT-proBNP to 1936 ± 1099 ng/L was seen on D4, which fell to 355 ± 341 ng/L six month postop-

eratively. The mean NT-proBNP levels differed significantly between the two groups at the 6-month follow-up, *p* = 0.028.

*Late outcome.* The pre- and postoperative echocardiographic data are presented in Table 4. Patients with severe preoperative LA enlargement demonstrated a 32 ± 18% reduction in LAVi, compared to 20 ± 15% in those without severe preoperative LA enlargement (*p* = 0.059) six months postoperatively. LARR was observed in 75% (27/36) of the study population six months

**Table 4 - Echocardiographic data.**

	Preoperative data	Postoperative data (6 months)	p-value
<i>Patients with preoperative LAVi &lt; 60 mL/m<sup>2</sup> (n = 12)</i>			
LAVi (mL/m <sup>2</sup> )	47 ± 4	37 ± 7	0.001
LAd (mm)	50 ± 8	46 ± 6	0.103
LVEF (%)	66 ± 10	57 ± 9	0.004
LVEF < 50 %	1 (8)	1 (8)	
LVEF < 30 %	0	0	
IVSD (mm)	12 ± 2	12 ± 2	0.851
LVEDD (mm)	62 ± 6	52 ± 4	< 0.001
LVPWD (mm)	10 ± 2	10 ± 2	0.586
LVESD (mm)	37 ± 7	31 ± 9	0.101
RAVi (mL/ m <sup>2</sup> )	27 ± 5	27 ± 8	0.935
RVIT (mm)	39 ± 5	38 ± 5	0.833
RVMCD (mm)	30 ± 5	31 ± 5	0.652
TAPSE (mm)	25 ± 4	15 ± 2	< 0.001
PASP (mmHg)*	45 ± 12	31 ± 11	0.001
<i>Patients with preoperative LAVi ≥ 60 mL/m<sup>2</sup> (n = 24)</i>			
LAVi (mL/m <sup>2</sup> )	79 ± 17	53 ± 18	< 0.001
LAd (mm)	54 ± 7	49 ± 8	0.015
LVEF (%)	65 ± 10	56 ± 10	< 0.001
LVEF < 50 %	2 (8)	6 (25)	
LVEF < 30 %	0	0	
IVSD (mm)	11 ± 2	11 ± 2	0.502
LVEDD (mm)	63 ± 9	54 ± 8	< 0.001
LVPWD (mm)□	9 ± 1	10 ± 2	0.088
LVESD (mm)	38 ± 8	37 ± 9	0.398
RAVi (mL/ m <sup>2</sup> )	36 ± 13	34 ± 11	0.537
RVIT (mm)	41 ± 6	40 ± 7	0.697
RVMCD (mm)□	32 ± 7	33 ± 7	0.825
TAPSE (mm)	23 ± 6	15 ± 3	< 0.001
PASP (mmHg)	50 ± 15	34 ± 9	< 0.001

The values given are the mean ± standard deviation or numerical values (%).

\*Data arrived from 10 patients

□Data arrived from 23 patients

LAVi = left atrial volume index; LAd = left atrial dimension; LVEF = left ventricular ejection fraction; IVSD = interventricular septal dimension; LVEDD = left ventricular end-diastolic dimension; LVPWD = left ventricular posterior wall dimension; LVESD = left ventricular end-systolic dimension; RAVi = right atrial volume index; RVIT = right ventricular inflow tract; RVMCD = right ventricular mid cavity dimension; TAPSE = tricuspid annular plane systolic excursion; PASP = pulmonary artery systolic pressure.



postoperatively, of which 83 % ( $n = 20$ ) were patients with severe preoperative LA enlargement and 58 % ( $n = 7$ ) without severe preoperative LA enlargement ( $p = 0.126$ ). Another 17 % (6/36) of the patients demonstrated a reduction in LAVi not reaching the cut-off of  $< 15$  % and 8 % (3/36) showed an increase in LAVi. The estimated preoperative mean left ventricular ejection fraction (LVEF) was  $65 \pm 10$  % (median 67, interquartile range 60-72 %) and did not differ significantly between patients with and without severe preoperative LA enlargement ( $p = 0.882$ ). LVEF decreased to  $56 \pm 10$  % in those with severe preoperative LA enlargement ( $p < 0.001$ ) and to  $57 \pm 9$  % in those without ( $p = 0.004$ ). No significant difference was seen between the two groups six months after surgery ( $p = 0.790$ ). The left ventricular end-diastolic dimension decreased to  $52 \pm 4$  mm ( $p < 0.001$ ) in those with severe preoperative LA enlargement and to  $54 \pm 8$  mm ( $p < 0.001$ ) in those without severe preoperative LA enlargement. No significant difference was seen between the two groups six months after surgery ( $p = 0.254$ ). The preoperative left ventricular end-systolic dimension was  $38 \pm 8$  mm in those with severe preoperative LA enlargement and  $37 \pm 7$  mm in those without,  $p = 0.444$ . The left ventricular end-systolic dimension was significantly higher in those with severe preoperative LA enlargement than in those without 6 months postoperatively ( $37 \pm 9$  mm and  $31 \pm 9$  mm, respectively,  $p = 0.045$ ). Three patients with severe preoperative LA enlargement and one patient without had moderate MR at the 6-month echocardiographic follow-up.

## DISCUSSION

In the current study, patients with severe preoperative LA enlargement had significantly higher baseline mean PCWP and NT-proBNP levels than those without se-

vere preoperative LA enlargement. The mean PCWP was reduced to normal levels in patients with severe preoperative LA enlargement early after MVS, while the mean PCWP remained normal in patients without severe preoperative LA enlargement. The overall incidence of postoperative LARR was 75 % six months after surgery, with no significant difference between the groups. The left ventricular end-diastolic dimension and LVEF decreased postoperatively, and no significant difference was seen between patients with and without severe preoperative LA enlargement. The NT-proBNP levels increased initially during the early postoperative period, but had decreased significantly six months after surgery in both groups.

LA enlargement in patients with conservatively managed MR has previously been described as a predictor of stroke, atrial fibrillation, systo-diastolic ventricular failure, and impaired survival (9, 15). However, those undergoing MVS demonstrate a high potential for left sided reverse remodeling (6) with the same risk of postoperative complications of patients without LARR (10). The predisposing mechanism for this process is not fully understood. Measurement of PCWP has been established as a surrogate for estimation of the left ventricular end-diastolic pressure (16), but also as an accurate method of assessing LA pressure in patients with MR (17). However, the LA pressure in patients with LA enlargement and MR may also be normal (18), indicating preserved compliance of the left atrium during the progression of mitral valve disease (19). Thus, elevated PCWP in patients with a severely enlarged left atrium may reflect impaired compliance as a late stage of MR with long-standing volume overload. We could demonstrate a significant difference in mean baseline PCWP levels in patients with severe preoperative LA enlargement, compared to those without. This is

in contrast to previous studies from the 80s (19, 20), who could not show a relationship between LA size and PCWP. This is probably due to heterogeneous study populations and different methods to estimate LA size in their studies. Normalization of mean PCWP following MVS in patients with severe preoperative LA enlargement occurred rapidly in response to relief of volume overload on the left atrium. These changes may facilitate postoperative left sided reverse remodeling. However, the process of postoperative LARR was not initiated in all patients and the reason for this is not fully understood, but may be related to myocardial fibrosis.

In chronic MR, preload might be increased by the volume overload of the left ventricle, while afterload is decreased in the later part of systole. These adaptive changes tend to normalize the LVEF, even in the presence of left ventricular dysfunction which may be reflected in a high PCWP (21). In the present study, the majority of the patients had normal or hyperdynamic left ventricular function, as assessed by preoperative echocardiography. Simultaneously, invasive hemodynamic measurements demonstrated impaired cardiac output at baseline in the same population. Following MVS, the volume and pressure overload was relieved to the left sided chambers and the PCWP decreased together with an increase in cardiac output (Table 3). At six months follow-up the echocardiographic data demonstrated a postoperative left sided reverse remodeling with a significant reduction in LA volume as previously described (5). Furthermore, the left ventricular end-diastolic dimension decreased and the hyperdynamic LVEF was normalized in analogy with previously published data (22, 23).

The variability in natriuretic peptide release (NT-proBNP or protype-B natriuretic peptide) following cardiac surgery has been extensively investigated previously (24).

Hormonal activation, with the release of natriuretic peptides, has been used to identify asymptomatic patients with MR at high risk of left ventricular dysfunction or death (2) suggesting that hormonal activation in MR is a predictor of poor outcome (3, 4).

However, to date, there have been no reports of changes of NT-proBNP in relation to LA enlargement and reverse remodeling. The present study confirms preoperative NT-proBNP activation, especially in patients with severe preoperative LA enlargement. Levels of NT-proBNP continued to increase during the early postoperative period in both groups, and decreased significantly six months postoperatively. Based on these findings, we conclude that a late postoperative reduction in NT-proBNP may reflect the process of reverse remodeling initiated by the early relief of volume and pressure overload mirrored by the decrease in PCWP as well as the reduction in left-sided chamber dimensions following MVS.

### **Limitations**

Invasive hemodynamic evaluations may be influenced by: different hemodynamic states (*e.g.* hypovolemia, tachycardia), general anesthesia, effects of sternotomy and sternal closure, and pharmacological treatment. However, in this prospective study all patients were evaluated under similar conditions, with the patient being his or her own control. Furthermore, the diastolic heart function, which could influence baseline PCWP and NT-proBNP, was not specifically evaluated preoperatively.

### **CONCLUSION**

A severe LA enlargement in patients with chronic degenerative MR and sinus rhythm indicates higher mean baseline PCWP and NT-proBNP than in those without. In our opinion, these findings may support early referral to surgery and may also facilitate

perioperative management. The potential reversibility of left atrial enlargement after mitral valve repair may be associated with postoperative reductions in PCWP and NT-proBNP.

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