Aus der Klinik für Kardiologie

der Medizinischen Fakultät Charité – Universitätsmedizin Berlin

DISSERTATION

The role of echocardiography for evaluation of left ventricular and left atrial function in patients undergoing percutaneous mitral valve repair with the MitraClip© system

zur Erlangung des akademischen Grades

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To my Family

Table of Contents

Abstract

Background: Long-standing mitral regurgitation (MR) causes chronic volume overload leading eventually to left ventricular (LV) and left atrial (LA) enlargement and remodeling. The objective of the present study was therefore to investigate LV and LA function following percutaneous mitral valve repair (PMVR) using the MitraClip© system. In particular, we aimed to assess the value of longitudinal strain in predicting postprocedural patient clinical recovery.

Methods: 66 patients with moderate to severe MR (2+) undergoing percutaneous mitral valve repair underwent two-dimensional speckle-tracking echocardiography (2D STE) at baseline(BL) and at six-months follow-up (FU).

Results: Despite no notable improvement in LV ejection fraction (LVEF), the study patients showed an increase in effective forward stroke volume (SV) determined by means of PW Doppler in left ventricular outflow tract (63 ± 27ml vs. 76 ± 35ml, $p<0.001$), implying an improvement of global cardiac performance. Based on left ventricular geometry, we differentiated 35 patients with LV remodeling (LVR) and 31 patients without (LVN). Patients without remodeling showed preserved LV function with higher baseline LVEF than LVR patients (51 vs. 35%). LV global longitudinal strain (GLS) was considerably higher in LVN than in LVR patients (-13.8 ± 3.5 vs. -9.9.0 ± 4.5%, $p<0.001$), indicating better myocardial contractility. Most importantly, LVN patients exhibited ameliorated GLS following PMVR (-13.8 ± 3.5 vs. -16.3 ± 3.8%, $p<0.001$), whereas no improvement was observed in LVR group (-9.9 ± 4.5 vs. -9.9 ± 5.1%, $p=0.936$).

Conclusion: In patients with moderate to severe MR PMVR using MitraClip© system results in increased effective forward stroke volume. 2D STE detects significant intrinsic remodeling in patients undergoing mitral valve repair, demonstrating that patients without LV remodeling show better response in terms of LV contractile function than patients who exhibit LV remodeling. Therefore, one might conclude that LVN patients experience a more pronounced benefit from the procedure, underlining the role of prompt interventional treatment of MR.

Zusammenfassung

Hintergrund: Die chronische Mitralklappeninsuffizienz (MI) verursacht eine stetige Volumenbelastung, die schließlich zur linksventrikulären (LV) und linksatrialen (LA) Vergrößerung und Umbau führt. Das Ziel dieser Studie war es daher, die LV- und LA-Funktion nach perkutaner Mitralklappenrekonstruktion (PMVR) mittels Mitraclip© System zu untersuchen. Insbesondere wollten wir die Stellung der neuen Deformationsparameter zur Vorhersage der postprozeduralen Patientengenesung beurteilen.

Methodik: 66 Patienten mit mittelschwerer-bis-schwerer MI (2+) sind einer perkutanen Mitralklappenrekonstruktion unterzogen worden. Die Patienten sind sowohl vor als auch sechs Monate nach PMVR echokardiographisch mittels Speckle-Tracking Echokardiographie (STE) untersucht worden.

Ergebnisse: Die Studienpatienten haben eine erhebliche Zunahme des effektiven Vorwärtsschlagvolumen (SV) (bestimmt mittels PW-Doppler im linksventrikulären Ausflusstrakt (63 ± 27ml vs. 76 ± 35ml)) gezeigt trotz fehlender signifikanter Unterschiede in Ejektionsfraktion (LVEF), was auf eine Verbesserung der globalen Herzleistung hinweist. Anhand der linksventrikulären Geometrie sind 35 Patienten mit LV Remodeling (LVR) und 31 Patienten ohne Remodeling (LVN) unterschieden worden. Patienten ohne Remodeling zeigten eine global erhaltene linksventrikuläre Funktion mit höheren LVEF-Ausgangswerten im Vergleich zu LVR Patienten (51 vs. 35%). Die Deformationsparameter (global longitudinal systolic strain – GLS) waren in LVN deutlich höher als in der LVR-Gruppe (-13.8 ± 3.5 vs. -9.9.0 ± 4.5%, $p<0.001$), was auf eine bessere myokardiale Kontraktilität hinweist. Die wichtigste Beobachtung der Studie war, dass die LVN Patienten eine Besserung des GLS nach der PMVR aufgezeigt haben (-13.8 ± 3.5 vs. -16.3 ± 3.8%, $p<0001$), wobei kein signifikanter Unterschied in der LVR-Gruppe beobachtet wurde (-9.9 ± 4.5 vs. -9.9 ± 5.1%, $p=0.936$).

Schlussfolgerung: Die interventionelle Therapie der chronischen Mitralklappeninsuffizienz führt zu einer erheblichen Zunahme des effektiven Vorwärtsschlagvolumen. STE ermittelt wesentliche Eigenschaften des Myokards und ermöglicht des Weiteren die Erkennung von Patienten die vorwiegend von einer Mitralklappenrekonstruktion profitieren. Daher könnte man schlussfolgern, dass die Patienten, die kein linksventrikuläres Remodeling aufweisen (LVN), einen ausgeprägten Nutzen aus dem Verfahren ziehen.

1. Introduction

1.1 Mitral regurgitation

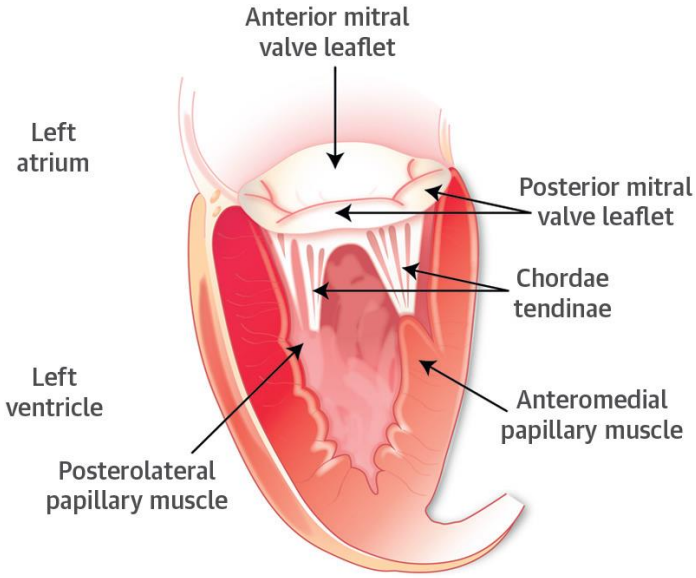
Epidemiology and prognosis

Mitral regurgitation (MR) is a common valvular heart disease with high morbidity and mortality rates, representing nearly one-third of acquired valve pathology in developed countries.[1] In the European Union, the prevalence of mitral regurgitation in the overall population reaches 2%, making it the second most frequent disease requiring surgery.[2] Continuing improvement of healthcare, population ageing and growth make mitral regurgitation a considerable public health problem in western countries. Men and women are equally burdened with MR, but women are less often diagnosed in the community, which might have serious prognostic consequences. The incidence of rheumatic heart disease, which used to be the primary cause of MR in the past, has prominently fallen in western countries, leading to the predominance of degenerative etiology of MR. On the other hand, rheumatic fever and its consequences are still considerably prevalent in young adults in developing countries.[3] Despite essential advances to improve its diagnosis, quantification and medical therapy, MR management remains a challenging issue, especially in elderly patients and those with ischemic MR etiology. Moderate-to-severe regurgitation is becoming more frequent and rising with age, affecting up to 10% in the population over 75 years of age.[4, 5] Recent studies have demonstrated that without medical treatment moderate-to-severe regurgitation carries a poor prognosis with a 5-year mortality rate of up to 60%.[6] Prompt valve repair reduces mortality in patients with severe MR by about 70%, which is a promising outcome underlining the importance of timely diagnosis, assessment and careful consideration for minimally invasive interventional treatment, markedly contributing to the restoration of quality of life in patients with severe chronic mitral regurgitation.[7, 8]

Pathophysiology of mitral regurgitation

The mitral valve (MV) apparatus comprises two mitral leaflets (anterior and posterior), embedded within the mitral annulus and two papillary muscles (anterolateral and posteromedial) arising from the left ventricular myocardium and attached to the leaflets by chordae tendinae (Fig. 1). Given its central position and network of valvular and subvalvular connections within the left ventricle, the mitral valve complex plays an important role in maintaining the shape and function of the left ventricle.

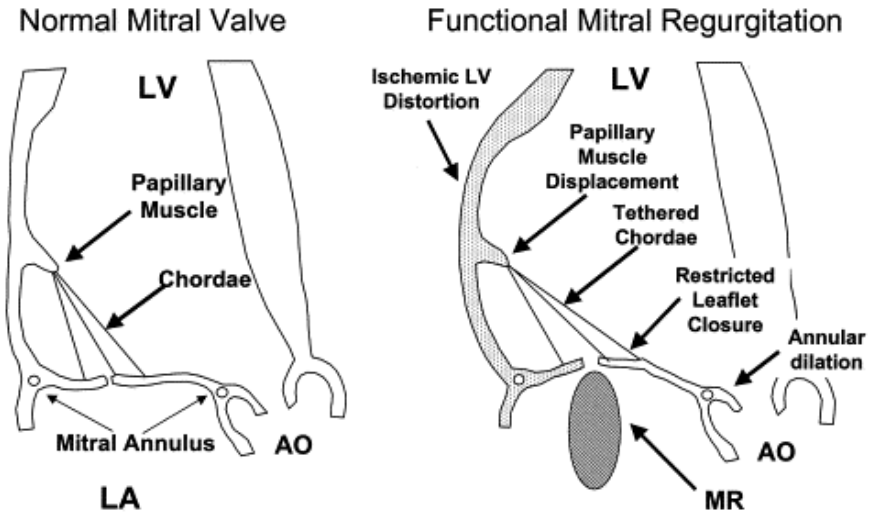
Figure 1. Anatomy of the mitral valve (by Asgar et al. *Secondary Mitral Regurgitation in Heart Failure: Pathophysiology, Prognosis, and Therapeutic Considerations*).[9]



By definition, mitral regurgitation is a pathologic retrograde flow under systolic pressure, from the left ventricle to the left atrium. Accordingly, pathology of any element of the MV apparatus that impairs the coaptation between the leaflets leads to some degree of regurgitation. Primary (or organic) MR occurs due to an intrinsic valve abnormality, whether of the leaflets, papillary muscles or the mitral annulus. The most common causes of primary MR are mitral valve prolapse, infective endocarditis and rheumatic heart disease. In elderly patients, secondary or functional MR prevails, which results primarily from left ventricular dysfunction and is therefore associated with a worse prognosis. Functional MR is caused by geometric ventricular remodeling without primary valve leaflet pathology. The most frequent underlying cause of secondary MR is persistent myocardial ischemia. Papillary muscles are supplied by the terminal

portion of the coronary vascular bed, thus being particularly sensitive to ischemia. As a consequence, approximately 50% of patients have some degree of mitral regurgitation following a myocardial infarction. Moreover, prolonged disturbance in coronary perfusion may result in permanent papillary muscle dysfunction and scarring leading to chronic MR.[10] Left ventricular remodeling in ischemic cardiomyopathy leads to LV distortion, papillary muscle displacement and annular dilatation resulting in impaired leaflet coaptation of a structurally normal MV, leading to a backflow of blood into the left atrium (Fig. 2).

Figure 2. Mechanism of functional mitral regurgitation (by Levine at al. *Ischemic mitral regurgitation, the dynamic lesion: clues to the cure*).[11]

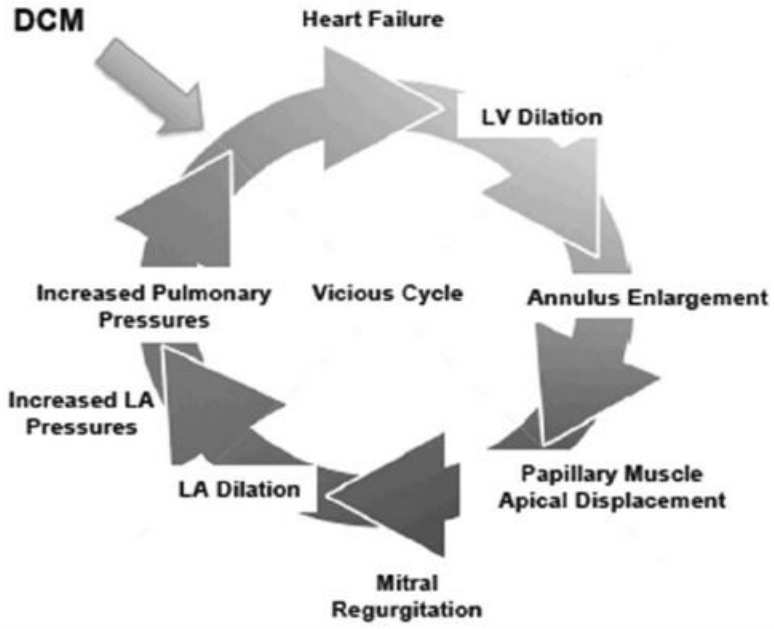


In the course of the disease, patients become progressively breathless, fatigued and disabled. Medication is of limited benefit, however some drugs such as diuretics improve the symptoms by decreasing the amount of fluid in the body.[12] In the elderly population presenting with clinically relevant MR, the disease has a multifactorial origin, whose pathophysiology lies not within the valve alone but arises predominantly from the dysfunction of the left ventricle. The success of mitral regurgitation therapy is achieved by targeting the mechanism of dysfunction in the individual patient, therefore, understanding the mechanism of MR is the clue to adequate treatment. Although minor regurgitant volume is observed in healthy individuals and might exist for years before symptoms occur, chronic volume load exerted on the left heart chambers leads to a series of circulatory and myocardial alterations.[13]

Left ventricular function in MR

In the course of chronic mitral regurgitation, regurgitant backflow causes a decrease in left ventricular volume at the end of isovolumetric contraction.[14] The left ventricle (LV) initially compensates for this in accordance with Frank-Starling principle by increasing preload defined by end-diastolic pressure of the ventricle.[15] However, sustained elevated preload generates higher LV volume and increased systolic wall stress, which eventually leads to LV enlargement. Progressive chamber expansion gradually translates into mitral annular dilation, followed by papillary muscle displacement further impairing leaflet closure which gives rise to a vicious circle continuously aggravating the degree of mitral regurgitation (Fig 3.).

Figure 3. Vicious circle of mitral regurgitation (by Schmitto et al. *Functional Mitral Regurgitation*).[16]



Prolonged volume overload and excessive stretching of the left chambers result in a series of left ventricular adaptations called ***left ventricular remodeling***. This compensatory adjustment is possible through breakdown of collagen in the interstitial matrix, allowing free rearrangement of myocardial fibers and synthesis of new sarcomeres.[17] In this phase, developing eccentric hypertrophy affords compensation, increasing the strength of individual cardiomyocytes and, thus, contributing to increased LV stroke volume. At this point in the course of the disease, the

patient might be completely asymptomatic and is able to have a normal lifestyle.[18] However, adequate myocardial oxygen supply cannot be sufficiently guaranteed without parallel angiogenesis. Simultaneously, the myocardial oxygen demand increases as a consequence of elevated LV muscle mass, augmented intracardiac pressure and prolonged ejection period. The net result of these pathophysiological processes is progressive development of myocardial ischemia.[19] Inevitably, underperfused cardiomyocytes become irreversibly damaged and are gradually replaced by interstitial fibrosis.[20] Expanded end-systolic volume and increased wall stress cause LV dilatation and, ultimately, eccentric hypertrophy, leading to irreversible alterations in left ventricular geometry.[21] In patients with long-standing volume overload, decompensation often occurs as a result of disturbed intrinsic LV muscle function. Eventually, LV becomes severely weakened due to diminishing viable myocardium and can no longer contract well, retaining more volume at the end of the systole which is reflected in reduced forward stroke volume. LV dysfunction is observed in about one third of patients and indicates poor prognosis despite medical treatment. Moreover, due to concomitant hypertrophy and ischemia, intraventricular dyssynchrony develops which exacerbates MR by delaying papillary muscle contraction, thus deteriorating mitral leaflet closure timing. Some studies have shown that cardiac resynchronization therapy, which improves myocardial efficiency, reduces the amount of MR, reverses LV remodeling and improves cardiac output.[22] It is crucial to underline that LV remodeling is a continuous and dynamic process which becomes irreversible despite interventional correction of MR, thus emphasizing the role of medical treatment in a timely manner. This mechanism originally helps to restore cardiac output, however, due to progressive myocardial deterioration, patients with chronic MR bear higher risk of sudden cardiac death.[23]

Left atrial function in MR

Left atrium (LA) is imperative for adequate circulatory performance, causing morbidity and mortality in several valvular heart diseases.[24] In healthy individuals, LA plays a threefold role in maintaining optimal cardiac performance: reservoir, conduit and contractile.[25] *Reservoir* function denotes the ability of the LA to fill during ventricular systole and is crucial for LV filling by conserving energy in the form of pulmonary venous blood. This phase is predominantly dependent on atrial compliance and atrial contraction and especially relevant, because 40% of LV systolic volume is stored in the LA during ventricular systole. *Conduit* function refers to passive LV filling during early diastole and diastasis. *Contractile* function refers to active atrial contraction during which blood is expelled into the LV. The atrial

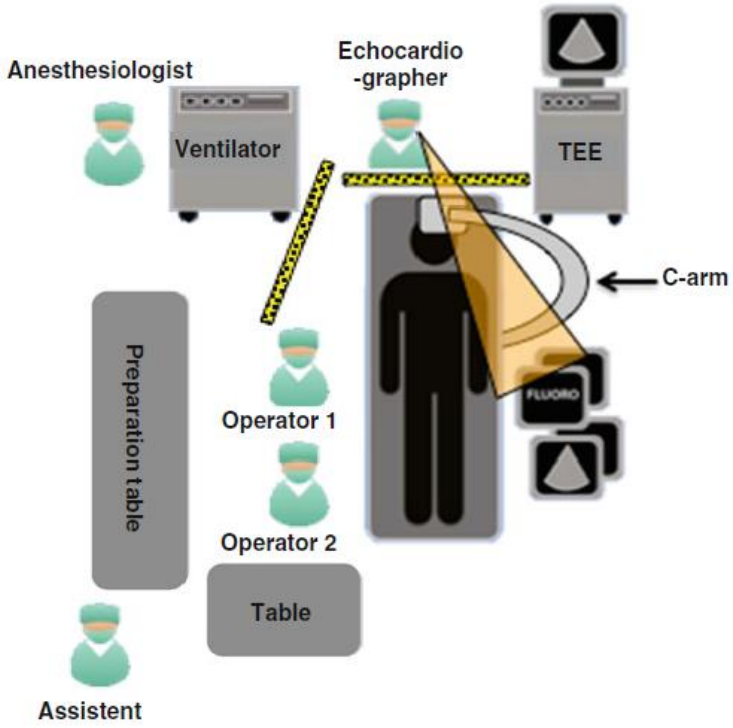
contribution to LV filling is distributed as follows: reservoir accounts for 40%, passive conduit is approximately 35%, while only 25% is attributed to atrial contraction.[26] In general, atrial consequences of mitral regurgitation are similar to left ventricular burden, resulting from disproportionate volume and pressure overload. In severe cases of MR, up to 50% of end-diastolic LV volume is ejected into the left atrium. During compensated stage of chronic MR, the LA steadily enlarges in size allowing compensatory accommodation of the regurgitant volume, which greatly reinforces the LA reservoir function.[27, 28] Previous studies have shown that increased atrioventricular gradient in conjunction with decreased LV stiffness result in increased passive LV filling responsible for enhanced conduit function in chronic MR.[29] The Frank-Starling behaviour of the LA is manifested in increased contraction force, making it initially more compliant with a more effective booster action.[30] Yet LA ejection fraction rises with increasing LA volume up to a certain point, upon which Frank-Starling relationship is overthrown, where atrial myocardium tends to operate on the descending limb of active contractile function.[31] This impaired response might be due to LA structural remodeling defined by chronic inflammatory changes, LA myocyte hypertrophy and interstitial fibrosis. Moreover, these patients are at high risk of major adverse cardiovascular events because LA size is a recognized marker of atrial fibrillation, thromboembolic events and death in patients with heart disease.[32, 33] Besides, cardiac cell atrophy leads to the development of atrial fibrillation in almost 50% of patients with medically treated MR, thus further contributing to LA contractile function deterioration.[34] Ultimately, careful study of all three components of LA function provides additional information on cardiac performance in patients with chronic mitral regurgitation.

1.2 Percutaneous mitral valve repair with the MitraClip© system

According to both European and American guidelines, mitral valve surgery remains the gold standard in the management of symptomatic patients with severe chronic mitral regurgitation.[35] The superiority of mitral valve repair over replacement with a valve prosthesis has been demonstrated in previous studies, and mitral valve repair is the standard of care especially in the setting of combined coronary bypass procedures, reoperations, double-valve procedures and in elderly patients.[36] Nevertheless, in the prevailing group of patients over 75 years of age with severe left ventricular dysfunction (LVEF<30%) and/or relevant co-morbidities such as atrial fibrillation or pulmonary hypertension, neither surgical mitral valve replacement nor repair is an acceptable treatment option bearing a mortality risk of 14%.[37] The need for a less-invasive, low-risk procedure characterized by low procedural mortality and minimal procedural

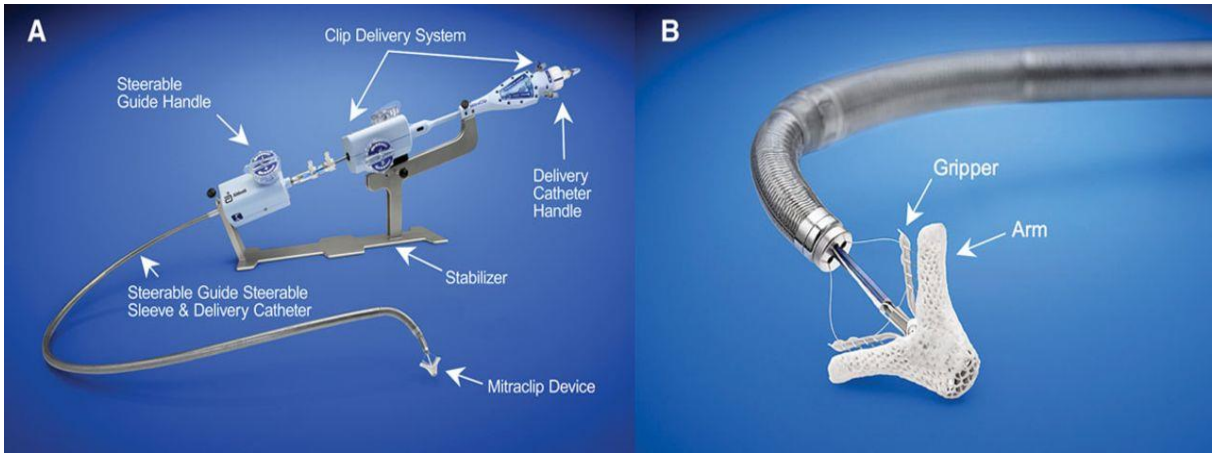
complications led to the development of transcatheter devices such as the MitraClip© system, Noechord DS 1000 and Carillon Mitral Contour. The applicability of the latter two devices is currently very limited, whereas the use of MitraClip© system has been growing experience across Europe and the USA.[38] Since its debut in 2009, MitraClip© has gained many supporters among interventional cardiologists with over 20,000 procedures performed to date.[39] This device concept is based on the surgical edge-to-edge repair originally developed by Ottavio Alfieri in the 1990s to successfully treat patients with both organic and functional MR. This surgical technique involves the suture of the free edges of both leaflets at the site of regurgitation, thus creating a double orifice valve (hence the other name for the procedure – the double orifice technique).[40] In contrast to conventional surgical techniques, the Alfieri method corrects mitral regurgitation by eliminating the regurgitant orifice instead of amending the anatomy of the valve. The technical simplicity and versatility of this innovative method has been the foundation for the development of the MitraClip© system. Implantation of MitraClip© for the correction of MR is a catheter-based procedure controlled by transesophageal echocardiographic guidance and assisted by fluoroscopy. The procedure is performed under general anaesthesia in the presence of an interventional cardiologist (with experience in treatment of valvular heart disease), skillful echocardiographer (with expertise in transesopageal echocardiography (TEE), including the application of 3D technique) and an anaesthesiologist (particularly experienced in cardiac anaethetics). The possible arrangement of the catheterization laboratory is presented in Fig. 4. below.

Figure 4. The arrangement of the catheterization laboratory recommended for MitraClip© procedure (by Boekstegers et al. *Percutaneous interventional mitral regurgitation treatment using the MitraClip system*).[41]



The fundamental step of the procedure is the transseptal puncture. The localization of the puncture is performed solely under TEE-control, underlining the essential role of interventional echocardiography for successful clip delivery. The steerable guide catheter is inserted through femoral vein into superior vena cava. The puncture should be performed in the *Fossa ovalis* whose location may vary in patients with structural heart disease. The Clip Delivery System (CDS) has the MitraClip© attached to its distal end. The MitraClip© itself is a 4 mm-wide implant with two arms which can be opened and closed by a mechanism on the Delivery System handle (Fig. 5).[42]

Figure 5. ***The MitraClip System***. Picture **A** shows the MitraClip system with Clip Delivery System. **B** displays the implantable MitraClip© including two arms and two grippers (reprinted with permission from Abbott Vascular (2013, Menlo Park, CA)).



The CDS is placed in the guide catheter and the clip is carefully moved forward into the left atrium. Under echocardiographic guidance, the clip is then aligned over the root of the regurgitant jet. After extending the two arms, the clip is advanced into the left ventricle just below the mitral valve leaflets. Beneficial reduction in mitral regurgitation can only be achieved by precise gripping of both leaflets and prompt closure of the MitraClip©, which explains why this step of the procedure requires considerable effort for the sake of accuracy and safety. If MR reduction assessed by Doppler echocardiography is not satisfactory, the clip can be reopened and repositioned for more effective leaflet coaptation. Recently, real-time three-dimensional echocardiography has become a convenient tool for optimal positioning of the clip simultaneously in anterior-posterior and lateral-medial directions and precise assessment of valvular regurgitation jet, thus improving procedural result.[43] When acceptable MR reduction has been accomplished, MitraClip© is deployed and CDS and guide catheter are removed. In order to avoid thromboembolic adverse effects, patients should be anticoagulated during the whole peri-procedural period and endocarditis prophylaxis is recommended for at least six months after the procedure.[44]

The choice of the patient suitable for the clip placement is the cornerstone for ensuring procedural success. Echocardiography plays a decisive role in preprocedural patient assessment and selection for interventional treatment allowing three-dimensional depiction of valve anatomy thus providing detailed information of underlying valve pathology. An ideal lesion for MitraClip© lies within the central portion of the coaptation line (the point where the two leaflets meet), has a flail width of <15mm and a flail gap <10mm. Key eligibility criteria, including recommended anatomical criteria, are summarized in Table 1.[45]

Table 1. Anatomical and clinical patient selection criteria for MitraClip© system.

Key inclusion criteria	**Recommended anatomical criteria**
1) Candidate for mitral valve repair or replacement surgery 2) Moderate-to-severe (2+) or severe (3) chronic mitral valve regurgitation and severely symptomatic (NYHA class III to IV) with LVEF>25% and LVEDs<55 mm or asymptomatic with 1 or more of the following: • LVEF >25% • LVEDs 40-55 mm • New onset of atrial fibrillation • Pulmonary hypertension defined as pulmonary artery systolic pressure >50 mmHg at rest or >60 mmHg at exercise	1) MR originating from the A2-P2 area 2) Coaptation length >2mm 3) Coaptation depth <11mm 4) Flail gap <10mm 5) Flail width <15mm 6) Mitral valve orifice area >4 cm^2

1.3 The role of echocardiography in mitral regurgitation

Determination of MR severity

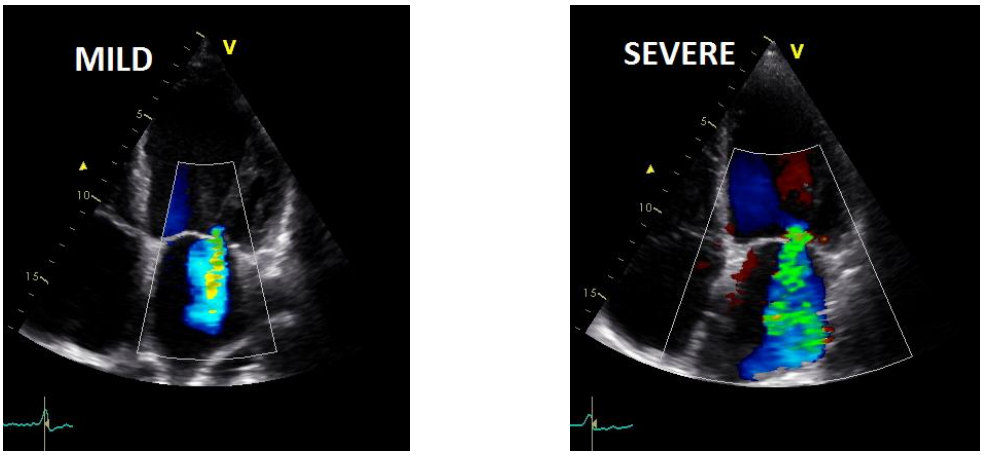
Conventionally, the diagnosis of mitral regurgitation might be propounded on the basis of the presence of typical clinical signs such as chronic weakness, fatigue, shortness of breath, orthopnea and pulmonary congestion. Physical examination reveals laterally displaced apical impulse, loud systolic murmur, low-pitched S3. Further diagnostic evaluation modalities might unveil atrial fibrillation on electrocardiography or left atrial enlargement on chest radiography.[46, 47] However, in patients evaluated for interventional treatment, these signs are not specific enough to be solely relied on. Therefore, echocardiography is currently the method of choice for determination of MR severity and assessment of valve morphology and suitability for MitraClip© procedure. Both transthoracic and transesophageal echocardiography provide clinically meaningful information that is crucial for the assessment of mitral valve repairability. Principally, transthoracic echocardiography (TTE) is a quickly and easily accessible technique which can be implemented on an outpatient basis, providing the necessary information on the cause and mechanism of MR, presence of calcification and location of lesions. Most importantly, TTE conveys crucial information on hemodynamic consequences of MR on global cardiac function. Left ventricular end-systolic (LVESD) and end-diastolic dimensions (LVEDD) indicate volume overload, left ventricular ejection fraction (LVEF) reflects ventricular function, whereas interventricular septal wall (SWT) and posterior wall thickness (PWT) exhibit the degree of LV remodeling. Patients with an LVEF of less than 60% or LVESD of at least 45mm are considered as having chronic decompensated MR with overt LV dysfunction. Left atrial diameter (LAD) and left atrial volume (LAV) have established their usefulness for predicting outcomes in patients with severe MR and are suitable measures for risk stratification and clinical decision making.[26, 48] However, if TTE is of poor quality (obesity, previous cardiac surgery, chronic lung disease) or if complex, calcified or endocarditic lesions are suspected, TEE becomes valuable for obtaining essential information on valve morphology. In any case, colour Doppler echocardiography supplies crucial information about mitral regurgitation severity.[49] Current guidelines from the European Association of Cardiovascular Imaging recommend grading MR severity into mild, moderate (with a subclassification into *mild-to-moderate* and *moderate-to-severe*) and severe. Yet, distinguishing between mild and moderate and between moderate and severe might be challenging even for experienced

echocardiographers. There are several acknowledged qualitative and quantitative measures which can be used for quantification of MR severity.[50]

Colour flow Doppler

Colour flow imaging is the most common, yet very intuitive method of assessing MR severity.[51] This visual method is useful for detecting the jet origin and its direction, providing excellent sensitivity and specificity. As a general rule, larger colour jets extending deep into the LA represent more severe MR. However, this can be misleading in the case of eccentrically directed jets. Entrainment of the eccentric jet to LA wall (Coanda effect) results in smaller jet area even when MR is severe.[52] Moreover, since colour flow display is influenced by many technical (transducer frequency, pulse repetition frequency, colour gain) and hemodynamic factors, this method is a source of many errors and, thus is not currently recommended to assess MR severity, but should only be used as screening method for detecting MR.[53]

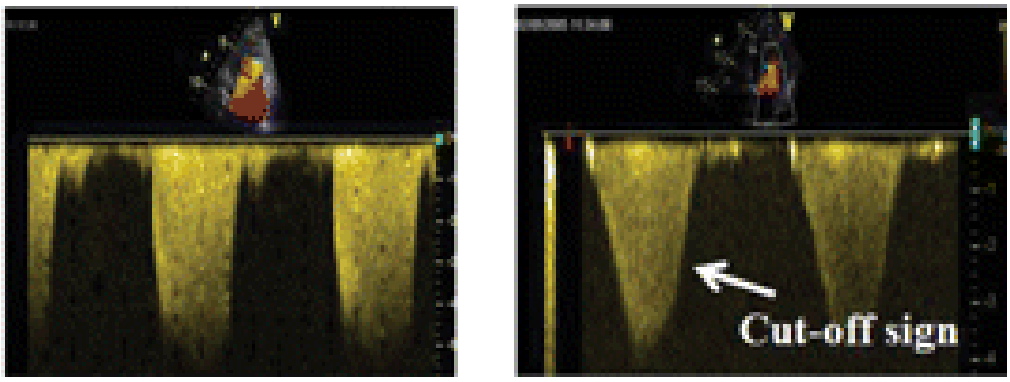
Figure 6. Visual assessment of MR jet using colour flow imaging.



Continuous wave Doppler signal intensity

The intensity of the jet signal obtained from continuous wave (CW) Doppler placed over the MV can be another convenient qualitative guide to MR severity. Dense, triangular signal with a full envelope indicates more severe regurgitation than a faint, parabolic signal (presented in Fig 7.). However, in eccentric MR and in patients with ventricular systoles, it is difficult to record the full CW envelope of the jet due to its eccentricity and variability.[54]

Figure 7. Parabolic vs. triangular CW Doppler signal intensity.



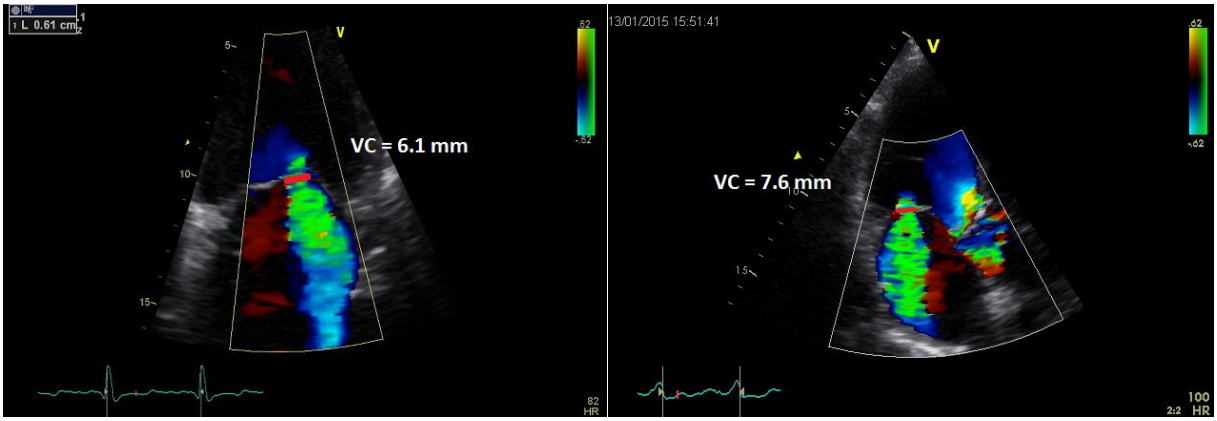
Systolic flow reversal in pulmonary veins

The Doppler evaluation of pulmonary venous flow is a valuable accessory parameter for the assessment of haemodynamic consequences of MR. In severe MR, the systolic component of the pulmonary flow becomes reversed. Elevated LA pressure and concomitant AF may disturb forward systolic pulmonary vein flow. Despite its high specificity, the finding of pulmonary vein flow reversal lacks sensitivity for routine identification of severe MR.

Vena contracta width

Vena contracta (VC) is a more reliable parameter of MR severity grade with powerful advantages over previously mentioned measures, being a semi-quantitative method for MR assessment. VC is defined as the narrowest cross-sectional area of the regurgitant flow jet as it traverses the regurgitant orifice.[55, 56] Nevertheless, a single VC width measurement is a 2D snapshot across the regurgitant orifice area. Conventional 2D colour Doppler imaging does not provide an accurate cross-sectional view of the VC.[57] Therefore, for more accurate measurement, scanning through multiple planes and selecting the largest and best visualized VC is recommended.[58] In case of multiple MR jets, the individual widths of multiple VC are not additive. A VC < 3mm signifies mild MR, whereas a width ≥ 7mm indicates severe MR, while intermediate values are not sufficiently reliable for distinguishing between moderate and severe MR, therefore, they require further investigation with more meticulous quantification methods for confirmation.

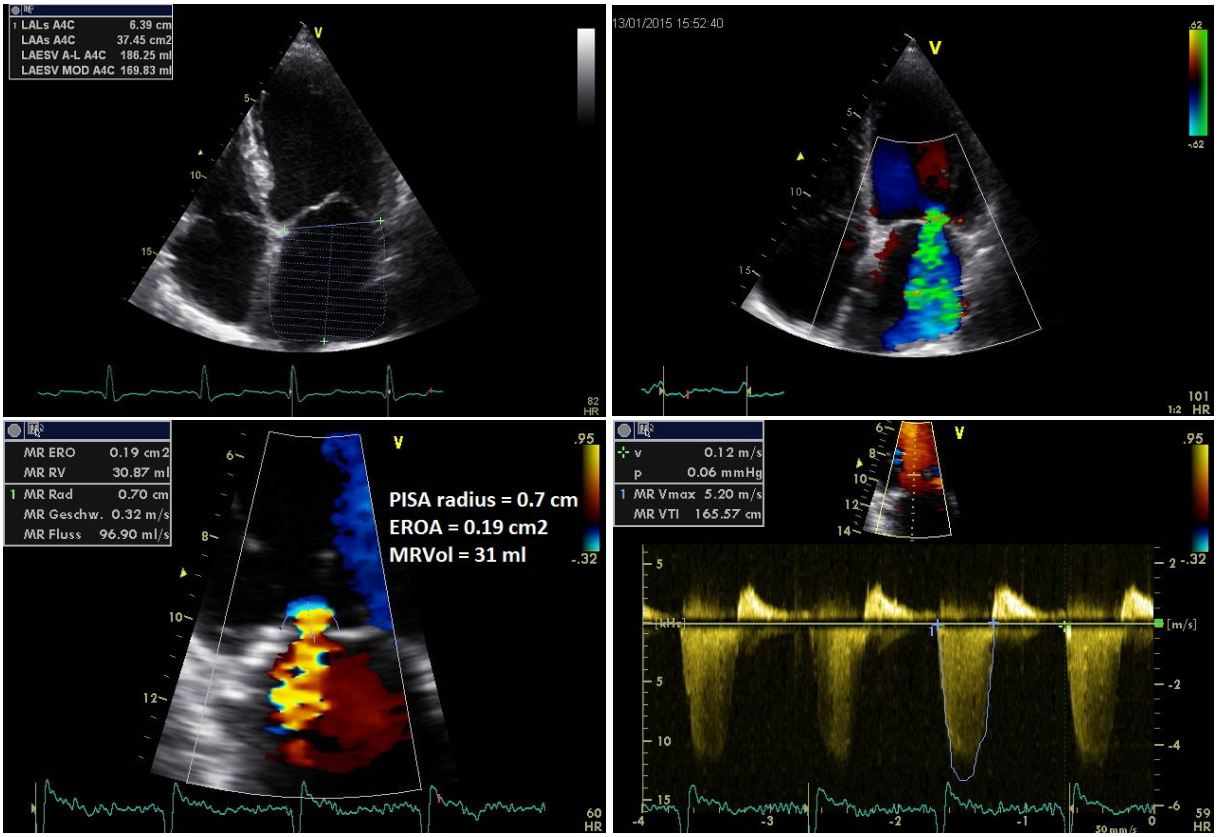
Figure 8. Semi-quantitative assessment of MR severity using the vena contracta (VC) width.



Proximal isovelocity surface area

The proximal isovelocity surface area (PISA) method allows the most precise quantification of MR severity whenever feasible.[59] As blood in the LV stream converges towards the regurgitant orifice at the proximal convergence zone, the magnitude and velocity of the innermost shell (in the form on a hemisphere) can be determined. Conforming to the continuity principle, the flow volume passing through the regurgitant orifice is the same as the amount flowing in the regurgitant jet.[60] Therefore, the flow at the proximal isovelocity surface area will equal the total flow in the distal MR jet.[61] Optimal visualization of the PISA is obtained in an apical four-chamber view. The aliasing velocity should be shifted in the direction of MR jet to between 20 and 40 cm/s and the colour Doppler variance should be turned off.[62] The measurement of PISA radius is performed where the first isovelocity shell is best visualized. In conjunction with CW Doppler measurement (essential calculation of VTI of the MR curve), the PISA method enables accurate calculation of the effective regurgitant orifice area (EROA) and mitral regurgitant volume (MRVol). Similarly to VC, the PISA method can be scrupulously used for central and eccentric jets. However, this technique is based on the assumption that the velocity distribution proximal to the regurgitant orifice is hemispheric in character, thus it is not applicable for multiple regurgitant jets.

Figure 9. The proximal isovelocity surface area (PISA) method for quantitative assessment of MR severity.



Other methods of MR quantification are beyond the scope of this work, but most commonly used methods are summarized in Table 2. below.

Table 2. Grading the severity of organic MR (by Galiuto L et al. *The EAE Textbook of Echocardiography*).[54]

Parameter	***Mild***	***Moderate***	***Severe***
<u>Qualitative:</u>			
MV morphology	Normal/Abnormal	Normal/abnormal	Flail leaflet/ ruptured PMs
Colour flow MR jet	Small, central	Intermediate	Very large central jet or eccentric jet adhering, swirling and reaching the posterior wall of the LA
Flow convergence zone	None or small	Intermediate	Large
CW signal of MR jet	Faint/parabolic	Dense/parabolic	Dense/triangular
<u>Semi-quantitative:</u>			
VC width (mm)	<3	Intermediate	≥7
Pulmonary vein flow	Systolic dominance	Systolic blunting	Systolic flow reversal
<u>Quantitative:</u>			
EROA (mm^2)	<20*	20-29[a]/ 30-39[b]	≥ 40*
RVol (ml)	<30*	30-44[a] / 45-59[b]	≥ 60*

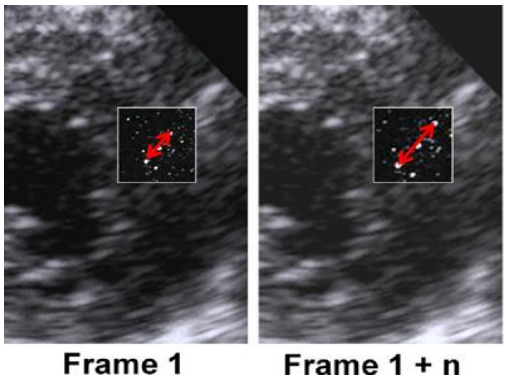
[a] *mild-to-moderate,* [b] *moderate-to-severe*

for functional MR, EROA >20mm^2 and RVol ≥30 is* ***severe*

1.4 Strain and Speckle-tracking echocardiography

The term *strain* applied to echocardiography is used to describe lengthening, shortening or thickening of myocardial fibers, also known as regional deformation.[63] Speckle-tracking echocardiography (STE) is a new angle-independent technique based on frame-to-frame tracking of natural acoustic markers (or speckles) providing sensitive and reproducible indexes of myocardial dysfunction beyond the limitations of Doppler-derived strain measurements (Fig. 10.).[64] Principally, gray-scale digital images of the myocardium contain speckle patterns. These speckles result from continuous constructive and destructive interference of ultrasound, back-scattered from structures smaller than ultrasound wavelength.[65]

Figure 10. Frame-to-frame tracking of acoustic markers (speckles) used in speckle-tracking echocardiography.



Consecutive frames are automatically analyzed in search of the new location of speckles within multiple user-defined regions of interest (ROI). The location shift of these acoustic markers allows the calculation of strain according to the formula:

$$\text{Strain} = \frac{\Delta\text{Length}}{\text{Original Length}}\ \%$$

Conventional Doppler-based measurements are done within a predefined myocardial area with reference to an external point i.e. the transducer, therefore, strain is estimated as the time integral of spatial velocity i.e. strain rate. In contrast to TDI, the speckle-tracking technique enables direct measurement of myocardial deformation in three directions: longitudinal, radial and circumferential, making STE a more robust method for quantifying myocardial deformation.

Strain is signified by a dimensionless parameter, defined as the percentage change from the original dimension, while strain rate is the rate of myocardial deformation measuring the velocity at which myocardial deformation occurs. Originally, STE was implemented for the detection of myocardial ischemia, but this method provides crucial information about the degree of myocardial damage in any disease affecting the heart muscle, therefore it has been extensively used for early identification of incipient myocardial dysfunction in various cardiac diseases, establishing its use for evaluation of LV systolic and diastolic function, myocardial ischemia and viability, right ventricular function, cardiomyopathies and valvular heart disease.[66, 67] Strain echocardiography is a promising method for assessing LV function in terms of myocardial contractility displaying higher sensitivity than conventional echocardiographic parameters such as LVEF.[68] What is more, STE is a valuable tool for detecting LV reverse remodeling, therefore adding further insights into the assessment of LV function in patients undergoing interventional valve repair procedures.[69] The use of strain for evaluation of patients undergoing percutaneous mitral valve repair has not yet been established in clinical practice, but some studies have proven its value for predicting left ventricular dysfunction after surgical mitral valve repair.[70] In patients with severe MR, strain imaging might be of significant value to assess LA contractility and relaxation reflecting LA function before LA dilation occurs.[71] In healthy subjects, left atrium plays a threefold role in maintaining optimal cardiac performance: reservoir (storage of pulmonary venous blood during ventricular systole), conduit (passive emptying during early diastole and diastasis) and contractile (active emptying during late diastole).[72] LA longitudinal systolic strain (LA-LSS) was found to be inversely correlated with histologically assessed atrial fibrosis.[73] LA-LSS reflects passive stretching of the LA during systole and is recorded as a positive value on the LA strain curve, being a reliable measurement of LA reservoir function. Prolonged volume overload in chronic MR leads to atrial remodeling expressed by decreased atrial wall elasticity due to progressive interstitial fibrosis. LA-LSS decreases with increasing MR severity and many studies confirm the prognostic value of LA deformation indices for long-term outcome.[74] Moreover, on multivariate analysis, LA strain rate was associated with a sensitivity of 88% and a specificity of 81% for early detection of atrial dysfunction in terms of LA conduit and contractile function, demonstrating that strain rate is a more sensitive index of atrial dysfunction than conventional volumetric parameters.[24] Interestingly, studies have demonstrated the potential of left atrial strain parameters as independent predictors of indication for surgery, concluding that careful assessment of LA function by means of STE is a valuable tool to guide optimal timing for surgical treatment in patients with severe MR.[75]

2. Hypothesis

Long-standing volume overload due to chronic mitral regurgitation leads to left ventricular and left atrial remodeling which might be reversed by prompt transcatheter mitral valve repair using the MitraClip© device. Postprocedural recovery of LV and LA function might be also related to prognosis and mortality.[76] In routine clinical practice, left ventricular ejection fraction is the most requested parameter for the assessment of LV systolic function. However, LVEF illustrates the mere change in LV volume from end-diastole to end-systole without taking into consideration the direction of the blood flow and the intrinsic properties of the myocardium. Therefore, in patients with MR, conventional ejection fraction might not reliably reflect LV systolic function.[77] Two-dimensional speckle-tracking echocardiography is an established tool for evaluation of myocardial wall movements and deformation, especially because it is more sensitive compared with LVEF in detecting early changes in left ventricular performance. Moreover, it has also proven its value for the assessment of left atrial function in patients with chronic MR.[78] Previous haemodynamic studies have confirmed favourable effects resulting from treatment with MitraClip© demonstrating that a reduction in intracardiac volumes is accompanied by an increase in forward cardiac output.[79] Nevertheless, a significant number of patients experience no symptomatic improvement despite successful MR correction, which is presumably the result of irreversible LV remodeling.[80] Accordingly, it is crucial to find a suitable, easy-attainable parameter which will allow reliable prediction of functional recovery in patients undergoing the MitraClip© procedure. **Therefore, the primary aim of this investigation was to study the effect of percutaneous mitral valve repair on left ventricular and left atrial function assessed by means of two-dimensional echocardiography, including volume and speckle-tracking analysis.** The secondary objective was to determine the extent of preprocedural LV remodeling and to investigate its impact on LV function six months after the procedure. Additionally, we aimed to evaluate the use of novel deformation imaging parameters and whether they provide an incremental value for assessing patient clinical recovery.

3. Methods

3.1 Study population

From January 2013 to April 2015, 87 consecutive patients underwent percutaneous mitral valve repair using the MitraClip© device at the Department of Cardiology, Campus Benjamin Franklin, Charité – Universitätsmedizin Berlin, Germany; clinical and echocardiographic data from these patients was analyzed. The patients included in the present study were symptomatic in terms of heart failure (New York Heart Association functional class >II) and suffered from moderate to severe mitral regurgitation (grade 2+), despite optimal pharmacotherapy and cardiac resynchronization therapy (7 patients). The surgical risk of all patients was calculated according to the European System for Cardiac Operative Risk Evaluation Score (EuroSCORE II). Prior to the procedure, all patients underwent a physical examination, 12-lead-electrocardiography (ECG), and echocardiographic examination. Coronary angiography was performed in order to identify relevant coronary artery disease. The decision for MitraClip© implantation was evaluated by a Heart Team. The main exclusion criteria for the procedure were severe clinical co-morbidities, including end-stage cancer, or other severe diseases with an unfavourable prognosis. The Ethics Committee of the Charité – Universitätsmedizin Centre approved the study. Clinical evaluation of NYHA class, ECG and transthoracic echocardiography were performed six months after the procedure. During the follow-up period, one patient required an urgent cardiothoracic surgery and died in the operating room, whereas one patient died as a result of acute decompensated heart failure. Nineteen patients had to be excluded from the study due to inadequate image quality. Complete baseline and follow-up transthoracic echocardiographic studies were achieved in 66 patients with optimal views (at least three acquisition windows with low image noise: apical four-chamber, two-chamber and three-chamber views)

3.2 Echocardiographic examination

All patients included in our study underwent two-dimensional transthoracic echocardiography to quantify MR and to assess valve morphology for MitraClip© implantation. Echocardiograms were obtained by experienced investigators using commercially available ultrasound diagnostic systems (Vivid 7 and Vivid E9, General Electric Medical Systems, Horten, Norway). Three cardiac cycles were stored in cine loop format for offline analysis.

Due to the predominance of either eccentric MR or presence of two regurgitation jets in the study population, the method of the proximal isovelocity surface area for grading MR was not applicable for all study patients. Therefore, MR was quantified by vena contracta width (VCW) defined as the narrowest cross-sectional area of the regurgitant jet determined by color flow Doppler echocardiography. MR severity was graded from 1 to 3 (1=mild, 2=moderate, 3=severe). Moderate and severe mitral regurgitation was defined as VCW >3mm and >7mm, respectively, according to current European Association of Cardiovascular Imaging recommendations. VCW was not determined after clip deployment, because of the resulting double-orifice valve.

Left ventricular geometry and function

Standard LV dimensions were obtained and LV mass was calculated in accordance with the Devereux formula:[81]

$$\mathbf{LVM = 0.8 \times (1.04 \times [(LVEDd + PWTd + SWTd)^3 - (LVEDd)^3]) + 0.6}$$

where:
LVM – left ventricular mass (in grams)
LVEDd – left ventricular end-diastolic diameter (mm)
PWTd – end-diastolic posterior wall thickness (mm)
SWTd – end-diastolic septal wall thickness (mm)

The evaluation of LV geometry and function was performed based on the following parameters: LV end-diastolic and end-systolic volumes (LVEDV and LVESV), calculated by Simpson´s method from apical four- and two-chamber views, LV ejection fraction (LVEF) obtained using the biplane Simpson´s method and LV mass indexed to body surface (LVMi).

Left ventricular diastolic function was assessed using pulsed-wave (PW) Doppler and pulsed-wave TDI recordings in apical four-chamber view. Transmitral flow was acquired to obtain the peak at early filling (*E*-wave) and the peak at late diastolic filling corresponding to atrial contraction (*A*-wave), allowing the calculation of *E/A* ratio. Average peak systolic (*S´*), early diastolic (*E´*) and late diastolic (*A´*) annular velocities were obtained from the septal and lateral sides of the mitral annulus. The *E/E´* ratio was calculated to estimate LV filling pressures.[82]

Left ventricular myocardial function was studied using two-dimensional speckle-tracking echocardiography with a frame rate of >60 frames per second obtained from the apical four-, two- and three-chamber views. Care was taken to obtain true apical images in order to avoid foreshortening of the LV. Offline speckle-tracking strain analysis was performed by an experienced reader using a commercially available workstation (EchoPac PC, Version 112.1.1, GE Medical Systems, Horton, Norway). A semi-automatic algorithm was applied for tracking the LV myocardial wall, which was divided into 17 segments to obtain global peak systolic longitudinal strain (GLS). In case of unsatisfactory myocardial tracking, manual adjustments were made or the software parameters such as region of interest (ROI) width or smoothing function were changed. GLS was defined as the peak negative value on the strain curve during the entire cardiac cycle; an average GLS value was obtained from three apical different views.

In order to assess left ventricular haemodynamic function, effective forward stroke volume (SV) was obtained using PW Doppler-derived velocity time integral (VTI) in the LV outflow tract (LVOT) and LVOT diameter.

Left atrial volume and function

Left atrial volumes were measured just before mitral valve opening when LA was filled at its maximum (diastolic LA volume), at mitral valve closure (systolic LA volume) and at P-wave onset on ECG before atrial contraction (when sinus rhythm was present; LA volume at P-wave). All volume measurements were performed in the apical four-chamber and two-chamber views and the mean values were calculated.[83]

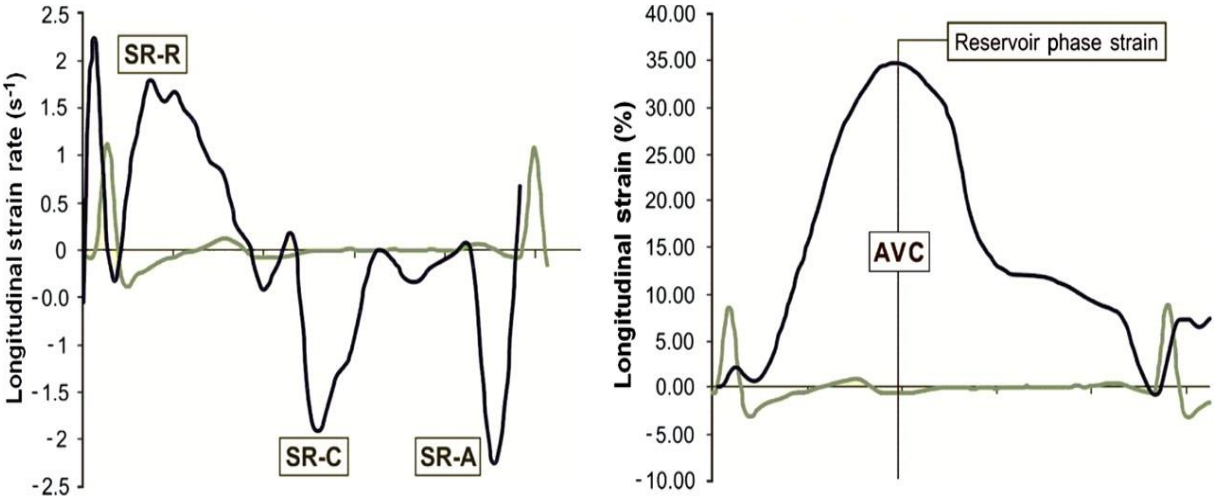
Left atrial myocardial function was determined by means of two-dimensional speckle-tracking echocardiography as described above. ROI was delineated manually in both four- and two-chamber views and tracked by the software. Assessment of left atrial reservoir, conduit and contractile function was performed as follows (schematic representation shown in Fig 11.):

1) LA longitudinal systolic strain (LA-LSS), denoting *LA reservoir function*, which is a parameter of the longitudinal lengthening of the left atrium, was derived as the average value of the peak positive systolic strain of all LA segments obtained from four- and two-chamber views during LV systole (at aortic valve closure),
2) LA longitudinal early-diastolic strain rate (LA-EDSR), describing *LA conduit function*, expressed by atrial shortening, was recorded as the average value of the early negative

diastolic strain rate of all LA segments obtained from four- and two-chamber views during early LV diastole,

3) LA longitudinal late-diastolic strain rate (LA-LDSR) corresponding to the longitudinal contraction of the left atrium, thus describing *LA contractile function*, was calculated as the average value of the peak late diastolic strain rate of all LA segments obtained in four- and two-chamber views during atrial contraction or, in the presence of atrial fibrillation, during LV late-diastole.[84]

Figure 11. Assessment of LA function by 2D speckle-tracking echocardiography. Strain rate and strain traces for the reservoir (SR-R), conduit (SR-C) and atrial contractile (SR-A) phases of atrial function (by Borg AN et al. *Left atrial function and deformation in chronic primary mitral regurgitation*.).



AVC – aortic valve closure

3.3 Follow-up

Patients included in the study were followed up for six months after PMVR. Clinical evaluation of NYHA class, 12-lead electrocardiography and two-dimensional echocardiography, including speckle-tracking analysis were performed at the follow-up visit. Follow-up data were retrieved from our outpatient clinic and completed with telephone calls. The final population consisted of 66 patients who were followed-up for six months.

3.4 Statistical Analysis

Statistical analysis was performed using IBM SPSS for Windows (version 22.0, SPSS Inc. Chicago, IL, USA). The distribution of variables was evaluated using the 1-sample Kolmogorov-Smirnov test. Normally distributed variables are expressed as means ± 1 standard deviation, while non-normally distributed parameters are expressed as median (interquartile range). Comparisons between groups were carried out using Student's *t*-test. Spearman´s Rank Correlation analysis was used to establish the relationship between continuous variables. For all tests, a value of $p < 0.05$ was accepted as statistically significant.

4. Results

4.1 Clinical patient characteristics

Clinical baseline and demographic characteristics of the study cohort are summarized in Table 3. below. Mean age of the study population was 76 ± 6 years, with a prevalence of female patients (53%). The study population patients showed moderate (21%) – to – severe (79%) mitral regurgitation, whereas MR etiology was predominantly functional (47 patients), and one third of patients presented degenerative MV disease. Acute procedural success was obtained in all patients. However, out of 68 patients undergoing percutaneous mitral valve repair, 2 patients died during the follow-up period. All patients were symptomatic with NYHA functional class >II, with the majority of patients (93%) in NYHA classes III or IV. In terms of heart failure laboratory parameters, N-terminal fragment of brain natriuretic peptide (NT-pro-BNP) was significantly reduced after mitral valve repair (3525 ± 1107 pg/ml vs. 1502 ± 629 pg/ml, p<0.001). Most of the patients had comorbidities such as arterial hypertension (89%), coronary artery disease (62%), dyslipidemia (58%) and atrial fibrillation (50%). Patient mean European System for Cardiac Operative Risk Evaluation (EuroSCORE II) was 22.1 ± 12.5% with 27 patients (41%) having a baseline EuroSCORE II >20%. Patient clinical recovery, defined as NYHA functional class improvement > 1 class, was achieved in 38 patients (63%). At six months, 39 patients were in NYHA functional class I or II (Fig. 12.).

Figure 12. New York Heart Association (NYHA) functional class improvement after MitraClip© implantation.

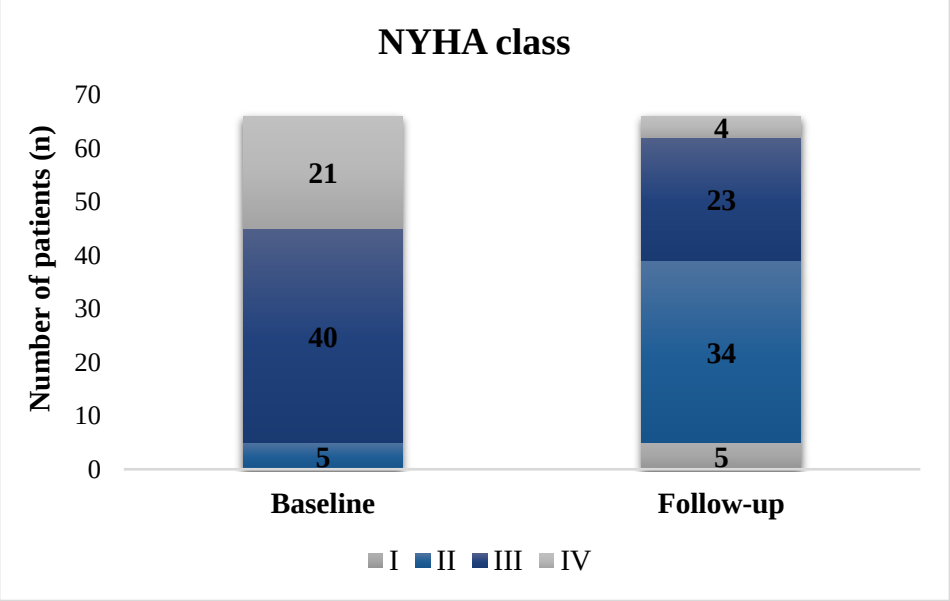
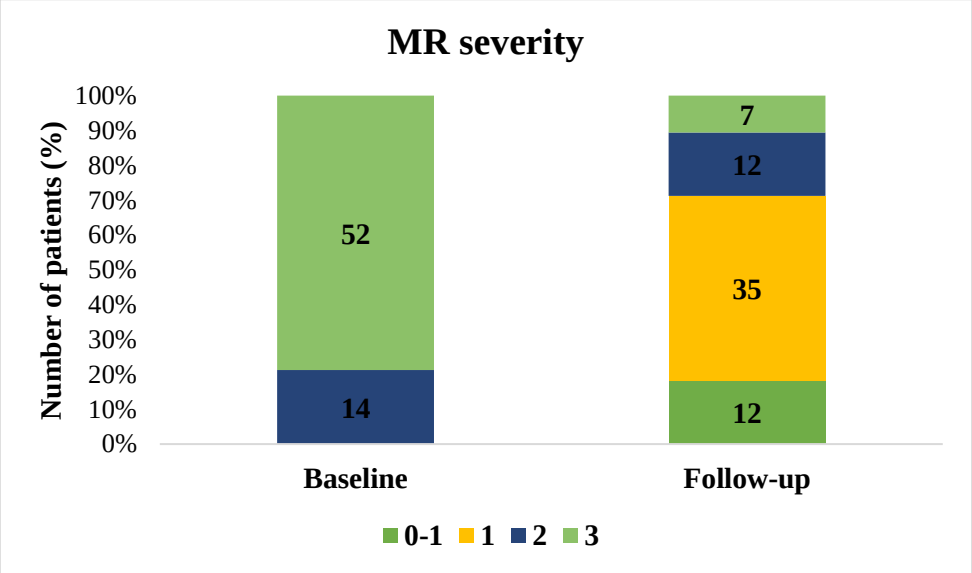


Table 3. Baseline clinical and demographic patient characteristics.

Variable	**Value, n (%)**
Age (years)	76 ± 6
Women	35 (53)
Body Mass Index (kg/m²)	25.8 ± 3.5
Body Surface Area (m²)	1.86 ± 0.19
MR severity	
2+	14 (24)
3	52 (79)
MR etiology	
Functional	47 (71)
Degenerative	17 (26)
Mixed	2 (3)
NYHA functional class	
II	5 (7)
III	40 (61)
IV	21 (32)
Comorbidities:	
Arterial Hypertension	59 (89)
Diabetes Mellitus	21 (32)
Atrial Fibrillation	30 (45)
Coronary Artery Disease	41 (62)
Dyslipidemia	38 (58)
Chronic Obstructive Lung Disease	21 (32)
Chronic Kidney Disease	37 (56)
Previous Cardiac Surgery	16 (24)
Ex-Smoker	41 (62)
Current medication	
ACE-inhibitor or angiotensin receptor blocker	61 (92)
β-blocker	59 (89)
Diuretic	62 (94)
Mineralocortocoid or aldosterone receptor antagonist	13 (20)
Antiplatelet agent/oral anticoagulation	63 (96)
Statin	57 (86)
Cardiac Resynchronization Therapy	7 (11)
EuroSCORE II (%)	22.1 ± 12.5

Most importantly, the grade of mitral regurgitation was successfully reduced in 58 patients. Follow-up echocardiography revealed minimal (none, grade 0-1) residual MR in 12 patients, 35 patients showed MR grade 1 postprocedurally, and only 19 patients still presented MR grade of >2+, indicating a long-term procedural success rate of 71%. On the whole, 42 patients experienced at least a 1-grade MR improvement from baseline to 6 months, whereas 16 patients improved by 2 or more grades. The effect of MitraClip© implantation on MR severity is presented in Fig. 13. below.

Figure 13. Mitral regurgitation severity at baseline and six months after MitraClip© implantation.



4.2 Conventional echocardiographic parameters

Comparison of baseline and follow-up echocardiographic characteristics are presented in Tables 4. and 5. below. Patients in the study population presented mean *vena contracta* width of 7.17 ± 0.20 mm. Although PMVR generated a minor increase in LVEF in the overall population (from baseline 43.3 ± 14.6% to 44.5 ± 14.9% postprocedurally), we observed a considerable increase in estimated LVOT stroke volume (63.4 ± 27.1 vs. 76.2 ± 35.1 ml; $p<0.001$), suggesting that LVOT stroke volume might be a more valuable parameter for the evaluation of postprocedural haemodynamic success. The results confirm a temporal response to mitral valve repair in terms of left chamber volumetric burden. In the study patients, both LV and LA volumes declined substantially after PMVR, implying an alleviating effect of the MitraClip© device on left ventricular stress and left atrial volume overload. Moreover, LV mass and LV mass index showed a regressive tendency during the follow-up period, yet remained

statistically insignificant. Regarding LV diastolic function, surprisingly, the correction of mitral regurgitation led to a pronounced increase in LV filling pressure represented by elevated *E/E´* ratio (16.1 ± 9.3 vs 21.3 ± 10.9). On the other hand, *E´*, which represents early diastolic LV filling, was essentially reduced. Both *E* - and *A* -waves increased without any significant change in the *E/A* ratio. Furthermore, right ventricular (RV) function remained unaffected at follow-up, however, echocardiography revealed a considerable decline in systolic pulmonary arterial pressure (53.6 ± 11.4 mmHg vs. 40.8 ± 11.6 mmHg, p<0.001).

Table 4. Comparison of baseline and follow-up standard echocardiographic parameters.

Variable	***Baseline***	***Follow-up***	***p value***
LVEF (%)	43.3 ± 14.6	44.5 ± 14.9	.163
Interventricular septum thickness (mm)	10.2 ± 1.3	10.3 ± 1.5	.599
LV end-diastolic diameter (mm)	53.8 ± 9.5	52.4 ± 8.6	**.040**
LV end-systolic diameter (mm)	39.2 ± 10.3	36.8 ± 9.4	**.001**
Posterior wall thickness (mm)	8.8 ± 1.4	9.2 ± 2.0	.092
LV end-diastolic volume (ml)	152.7 ± 67.9	139.4 ± 58.4	**<.001**
LV end-systolic volume (ml)	92.5 ± 59.4	83.0 ± 54.8	**<.001**
LV mass (g)	206.5 ± 85.1	200.0 ± 77.6	.241
LV mass index (g/m²)	109.9 ± 42.1	106.6 ± 38.3	.287
Relative wall thickness	0.32 ± 0.07	0.35 ± 0.06	.050
LVOT stroke volume (ml)	63.4 ± 27.1	76.2 ± 35.1	**<.001**
LVOT cardiac output (l/min)	3.88 ± 2.24	4.57 ± 2.33	**<.001**
sPAP (mmHg)	53.6 ± 11.4	40.8 ± 11.6	**<.001**
TAPSE (mm)	20.9 ± 5.0	21.1 ± 4.7	.494

Table 5. Diastolic and left atrial conventional parameters.

Variable	***Baseline***	***Follow-up***	***p value***
E wave (m/s)	1.07 ± 0.27	1.31 ± 0.40	**.002**
A wave (m/s)	0.57 ± 0.39	0.79 ± 0.30	**.022**
E/A ratio	1.61 ± 0.61	1.73 ± 1.11	.722
Deceleration Time (ms)	238 ± 96	292 ± 101	**.015**
Tissue Doppler parameters			
E´ mean (cm/s)	7.9 ± 2.7	6.4 ± 2.1	**.003**
A´ mean (cm/s)	6.4 ± 5.7	5.7 ± 2.5	.280
S´ (cm/s)	5.8 ± 3.5	6.5 ± 2.6	.321
E/E´ mean	16.1 ± 9.3	21.3 ± 10.9	**.023**
LA volumes			
Systolic LA volume (ml)	68 ± 29	62 ± 30	**.009**
Systolic LA volume index (ml/m^2)	40.3 ± 14.9	37.0 ± 15.6	**.007**
Diastolic LA volume (ml)	97 ± 31	89 ± 35	**.001**
Diastolic volume index (ml/m^2)	56.6 ± 18.4	51.2 ± 17.4	**.001**
LA volume at P wave (ml)	75 ± 26	68 ± 21	.531
Mean LA volume (ml)	91 ± 36	83 ± 36	**.001**
LAVi (ml/m^2)	48.4 ± 16.5	44.1 ± 16.4	**.001**

4.3 Speckle-tracking echocardiographic parameters

More detailed information on LV and LA myocardial function was obtained by means of speckle-tracking echocardiography. Baseline left ventricular strain parameters were substantially impaired and despite showing some improvement after PMVR, remained poor at follow-up. On the other hand, left atrial strain parameters showed significant improvement, thus reflecting notable amelioration of LA function. The results imply marked recovery of LA reservoir (defined by LA-LSS) and contractile (expressed by LA-LDSR) function without any prominent effect on LA conduit function. Speckle-tracking-derived strain parameters are presented in Table 6. below.

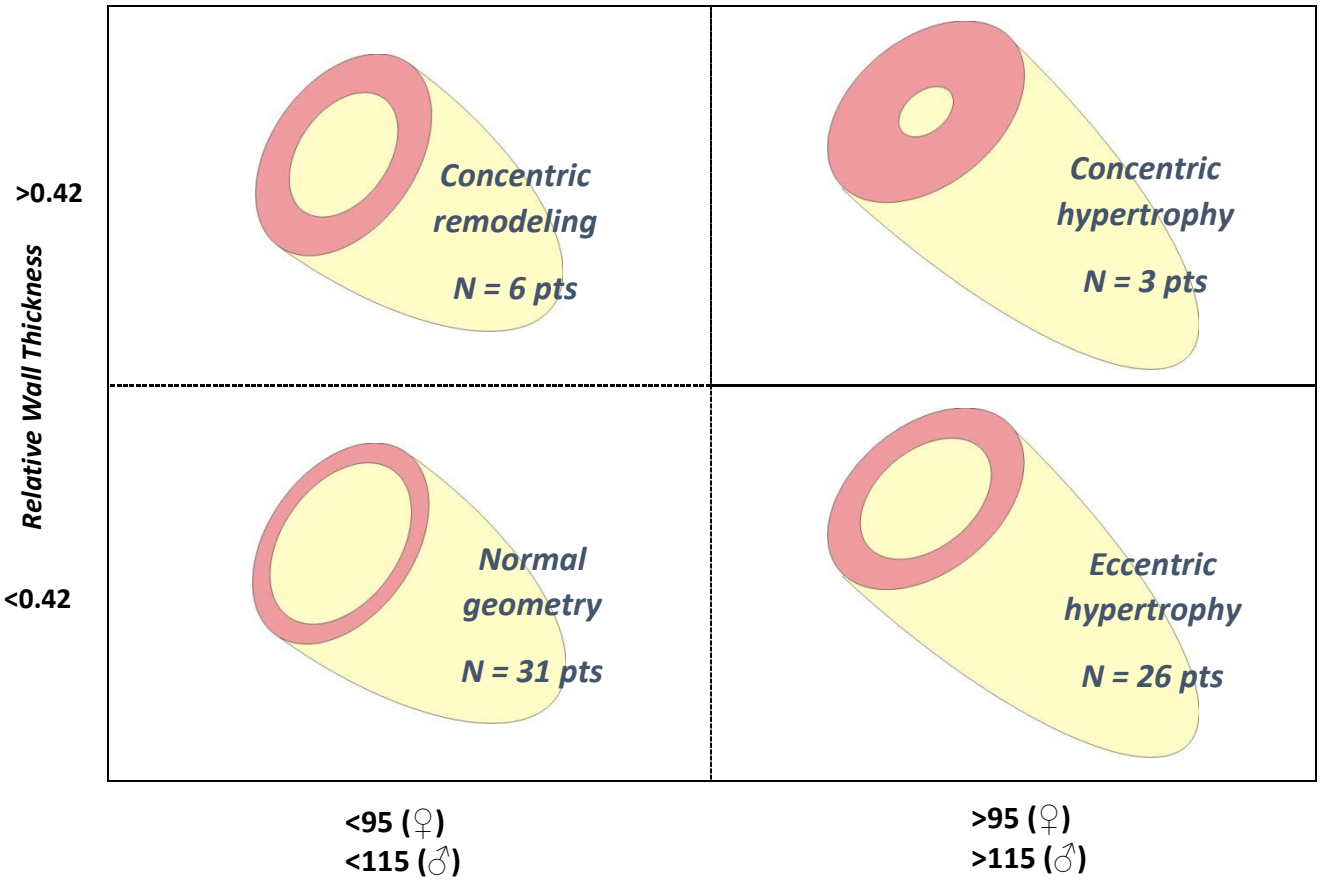
Table 6. Speckle-tracking-derived strain parameters. *For simplicity, all deformation indices are given as positive numbers.*

Myocardial deformation indices	***Baseline***	***Follow-up***	***p value***
LV strain (%)			
Longitudinal PSS – A4C	12.0 ± 4.7	13.5 ± 5.9	**.001**
Longitudinal PSS – A2C	12.2 ± 4.6	13.2 ± 5.4	**.010**
Longitudinal PSS – APLAX	11.8 ± 4.5	13.1 ± 5.4	**<.001**
Global longitudinal PSS	12.0 ± 4.5	13.2 ± 5.5	**.002**
LA strain (%)			
LA-LSS	21.4 ± 4.9	23.2 ± 6.7	**.044**
LA strain rate (1/s)			
LA-EDSR	0.63 ± 0.25	0.67 ± 0.38	.266
LA-LDSR	0.49 ± 0.39	0.61 ± 0.43	**.004**

4.4 Left ventricular performance in regard to LV remodeling

In order to investigate the role of left ventricular remodeling on postprocedural outcome, we identified patients with three different patterns of LV remodeling, based on left ventricular mass index and relative wall thickness (RWT).[85] The study population was divided into four mutually exclusive groups on the basis of LV geometry i.e. concentric hypertrophy (LV hypertrophy and increased RWT; 3 patients), eccentric hypertrophy (LV hypertrophy and normal RWT; 26 patients), concentric remodeling (normal LVMi and increased RWT; 6 patients) and normal geometry (normal LVMi and RWT; 31 patients) (Fig. 14.).

Figure 14. Left ventricular remodeling (by Verma et al. *Prognostic Implications of Left Ventricular Mass and Geometry Following Myocardial Infarction : The VALIANT (VALsartan In Acute myocardial iNfarcTion) Echocardiographic Study.*).



In order to investigate the relevance of LV remodeling to LV function, patients with remodeling (LVR; concentric remodeling + eccentric hypertrophy + concentric hypertrophy = 35 patients) were compared to those showing normal LV geometry (LVN; 31 patients). Clinical patient characteristics of these two groups are presented in Table 7. below.

Table 7. Baseline patient characteristics relating to left ventricular remodeling. *For simplicity, all deformation indices are given as positive numbers.*

Variable	***LVN group***	***LVR group***	***p value***
Age	76.7 ± 6.3	75.9 ± 6.4	.583
Women	20 (65%)	13 (37%)	-
Comorbidities			
Arterial Hypertension	26 (84%)	33 (94%)	
Diabetes Mellitus	8 (26%)	13 (37%)	
Atrial Fibrillation	13 (42%)	20 (54%)	
Coronary Artery Disease	16 (52%)	25 (71%)	
Dyslipidemia	18 (58%)	20 (57%)	
Chronic Obstructive Lung Disease	9 (29%)	12 (34%)	
Chronic Kidney Disease	12 (39%)	25 (71%)	
Previous Cardiac Surgery	5 (16%)	11 (31%)	
Ex-Smoker	19 (61%)	22 (63%)	
NYHA functional class	3.01 ± 0.48	3.03 ± 0.58	.154
MR severity grade	2.50 ± 0.42	2.65 ± 0.42	.164
MR etiology			
Degenerative	23 (74%)	9 (26%)	
Functional	8 (26%)	21 (60%)	
Mixed	0	5 (14%)	
NTproBNP (pg/ml)	2674 ± 1616	4147 ± 2393	.174
EuroSCORE II	19.8 ± 13.9	24.3 ± 10.8	.158
Conventional echocardiographic parameters			
LVEF (%)	50.9 ± 12.2	35.2 ± 12.7	**<.001**
Vena contracta width (mm)	6.35 ± 1.61	8.00 ± 1.81	**<.001**
LV end-diastolic volume (LVEDV, ml)	114.0 ± 33.8	193.5 ± 71.9	**<.001**
LV end-systolic volume (LVESV, ml)	57.1 ± 25.9	129.7 ± 62.7	**<.001**
Interventricular septum thickness (IVSd, mm)	9.7 ± 1.3	10.7 ± 1.2	**<.001**

LV end-diastolic diameter (LVEDd, mm)	48.0 ± 6.9	60.4 ± 7.7	**<.001**
LV end-systolic diameter (LVEDs, mm)	32.8 ± 7.2	46.2 ± 8.6	**<.011**
Posterior wall thickness (PWT, mm)	8.2 ± 1.1	9.6 ± 1.3	**<.001**
LV mass (g)	161.2 ± 43.2	256.4 ± 83.7	**<.001**
LV mass index (g/m^2)	79.9 ± 16.2	136.4 ± 40.1	**<.001**
Relative wall thickness (RWT)	0.29 ± 0.04	0.37 ± 0.07	**<.001**
sPAP (mmHg)	52.2 ± 12.2	55.1 ± 10.7	.489
TAPSE (mm)	23.3 ± 4.0	18.5 ± 5.0	.001
LVOT diameter (mm)	19.8 ± 3.7	21.6 ± 6.8	.279
LVOT stroke volume (ml)	64.9 ± 30.7	52.1 ± 32.1	**<.001**
Myocardial deformation indices (%) Longitudinal PSS – A4C Longitudinal PSS – A2C Longitudinal PSS – APLAX Global longitudinal PSS	 13.9 ± 3.8 13.9 ± 3.8 13.5 ± 3.5 13.8 ± 3.5	 9.9 ± 4.8 10.1 ± 4.5 13.5 ± 4.7 9.9 ± 4.5	 **<.001** **.002** **<.001** **<.001**

Primarily, LVR group showed preponderance of significant comorbidities. NYHA functional status or MR grade were similar in both study groups. However, LVN patients presented rather degenerative MR etiology (74%), whereas in LVR group functional etiology was more prevalent (60%). MR severity grade was markedly reduced in both groups following PMVR. Regarding LV function, patients without LV remodeling showed essentially higher baseline LVEF values than patients with LV remodeling (50.9 ± 12.2% vs. 35.2 ± 12.7%, $p<0.001$). Nonetheless, no significant improvement in systolic function assessed by means of conventional Simpson´s biplane method was observed in either group postprocedurally.

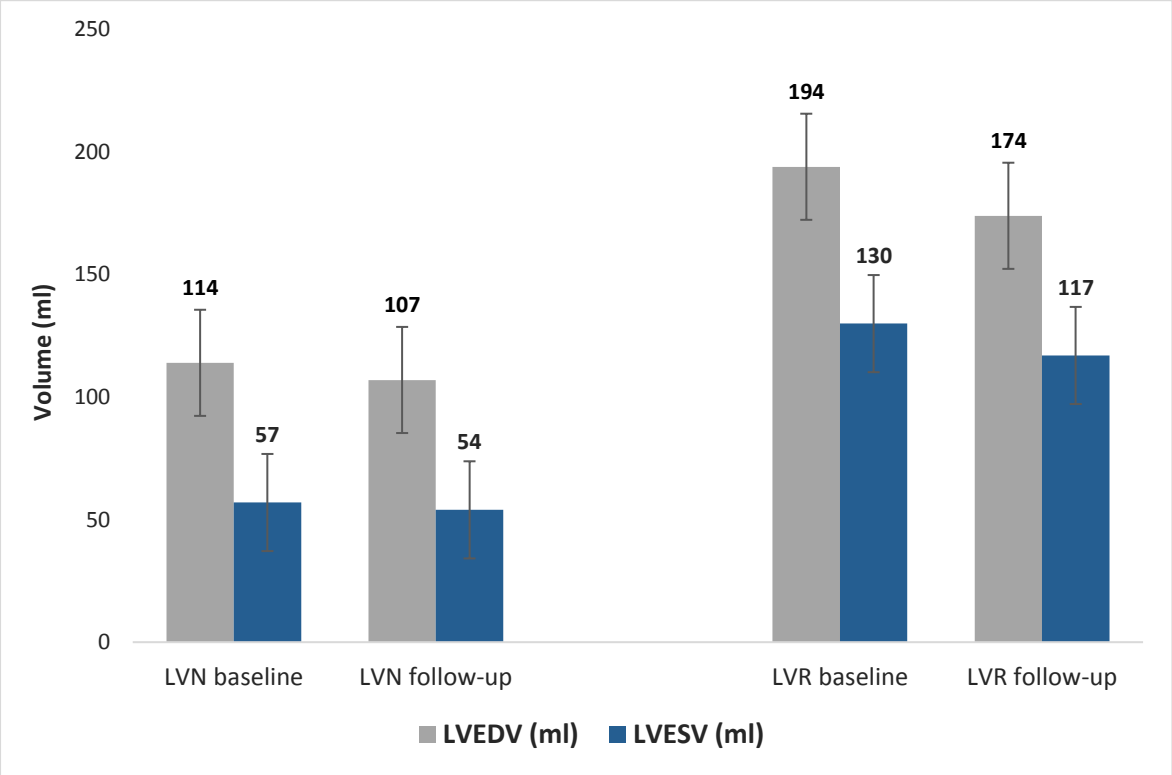
In terms of LV volume overload, patients without remodeling presented considerably lower baseline left ventricular end-diastolic and end-systolic volumes (LVEDV and LVESV) and according LV dimensions were essentially higher in LVR patients. Percutaneous mitral valve repair resulted in a notable diminution in LV volumes, especially in the LVR group, thus implying potential mitigating effect of clip implantation on LV wall stress. Nevertheless, this tendency was not unequivocally expressed in LVN patients. Similarly, we observed a considerable reduction in LVM and LVMi only in LVR group, implying significant postprocedural LV reverse remodeling. The echocardiographic findings at baseline and at follow-up in both study groups are presented in Table 8. below.

Table 8. Echocardiographic findings at baseline and at follow-up relating to left ventricular remodeling.

Variable	**LVN group**			**LVR group**		
	Baseline	***Follow-up***	*p*	***Baseline***	***Follow-up***	*p*
LVEF (%)	50.9 ± 12.2	52.6 ± 10.3	.181	35.2 ± 12.7	35.8 ± 14.3	.578
MR grade	2.50 ± 0.42	1.45 ± 0.69	**<.001**	2.65 ± 0.42	1.50 ± 0.79	**<.001**
LVEDV (ml)	114.0 ± 33.8	106.6 ± 30.5	**.005**	193.5 ± 71.9	174.4 ± 61.2	**<.001**
LVESV (ml)	57.1 ± 25.9	54.2 ± 20.7	.116	129.7 ± 62.7	116.8 ± 59.7	**<.001**
IVSd (mm)	9.7 ± 1.3	9.8 ± 1.6	.530	10.7 ± 1.2	10.8 ± 1.3	.853
LVEDd (mm)	48.0 ± 6.9	48.6 ± 7.0	.457	60.4 ± 7.7	56.8 ± 7.8	**.001**
LVEDs (mm)	32.8 ± 7.2	31.4 ± 7.7	.166	46.2 ± 8.6	42.9 ± 7.4	**.001**
PWTd (mm)	8.2 ± 1.1	8.7 ± 1.4	**.029**	9.6 ± 1.3	9.8 ± 1.4	.545
LVM (g)	161.2 ± 43.2	150.0 ± 38.9	.058	256.4 ± 83.7	234.0 ± 85.5	**.017**
LVMi (g/m^2)	86.6 ± 22.4	79.9 ± 16.2	**.042**	136.4 ± 40.1	124.2 ± 41.0	**.013**
TAPSE (mm)	23.3 ± 4.0	23.1± 3.6	.704	18.5 ± 5.0	18.6 ± 4.7	.728
sPAP (mmHg)	52.2 ± 12.2	39.5 ± 11.1	**<.001**	55.1 ± 10.7	42.2 ± 12.3	**<.001**
LVOT SV (ml)	64.9 ± 30.7	80.9 ± 30.8	**<.001**	52.1 ± 32.1	62.3 ± 28.2	**<.001**

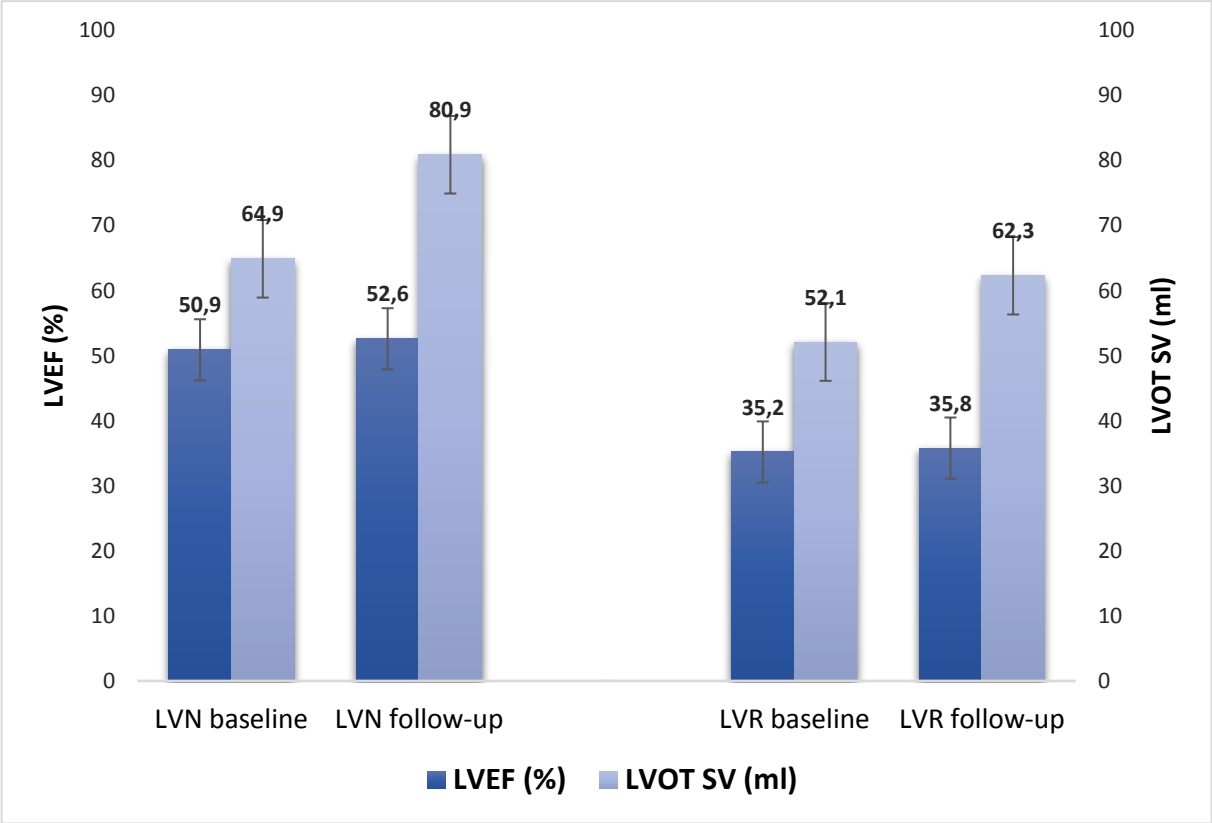
The present echocardiographic study demonstrated significant reductions in intracardiac volumes after mitral regurgitation was corrected (Fig. 15.). This tendency was especially pronounced in LVR group, implying that the abatement of volume overload might partially reverse already existing LV remodeling.

Figure 15. Left ventricular volumes in LVN and LVR patients at baseline and at follow-up.



Previous haemodynamic studies suggested favourable effects resulting from treatment with MitraClip© demonstrating that a reduction in intracardiac volumes is accompanied by an increase in forward cardiac output. The present study provides valid results that could substantiate this hypothesis. Particularly, the most compelling finding was a considerable increase in effective forward stroke volume measured in LVOT (SV LVOT). Both study groups showed meaningful improvement of LVOT SV following PMVR (LVN group: 64.9 ± 30.7 ml at baseline vs. 80.9 ± 30.8 ml at follow-up and LVR group: 52.1 ± 32.1 ml vs. 62.3 ± 28.2 ml; $p<0.001$) despite minor amelioration in LVEF in both study groups. These results underline the positive hemodynamic effect of MitraClip© implantation on LV function assessed beyond conventional echocardiographic parameters (Fig. 16.).

Figure 16. Left ventricular ejection fraction (LVEF) vs. effective forward stroke volume (LVOT SV) in LVN and LVR patients at baseline and at follow-up.

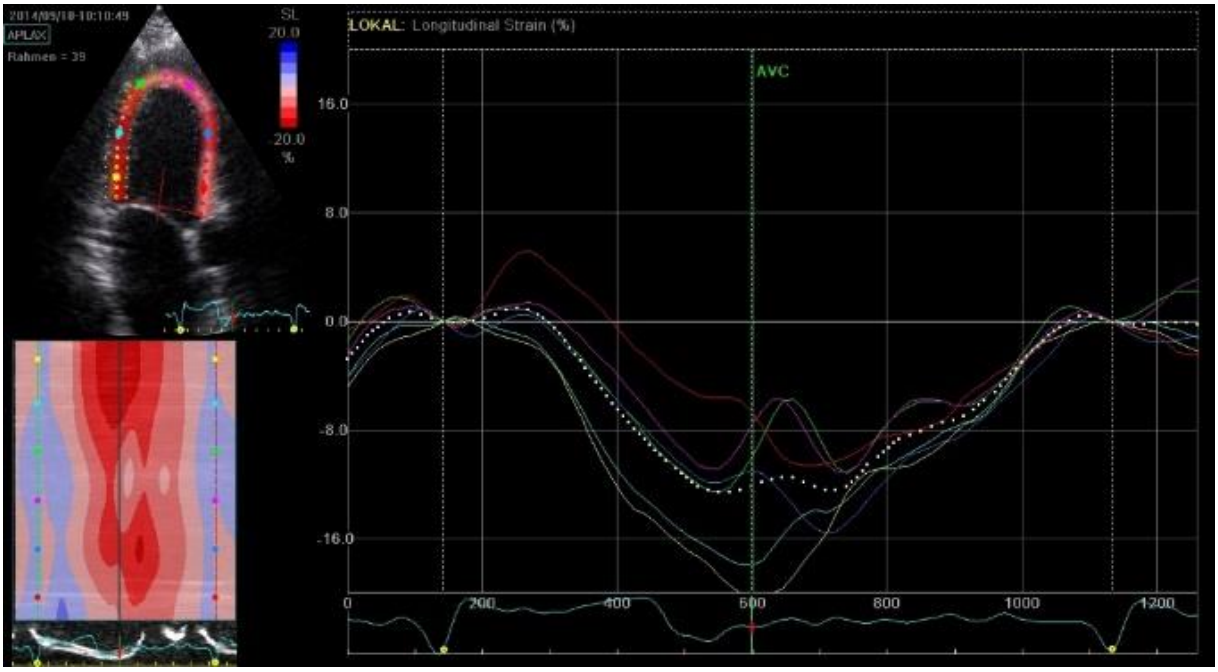


4.5 Two-dimensional speckle-tracking echocardiography

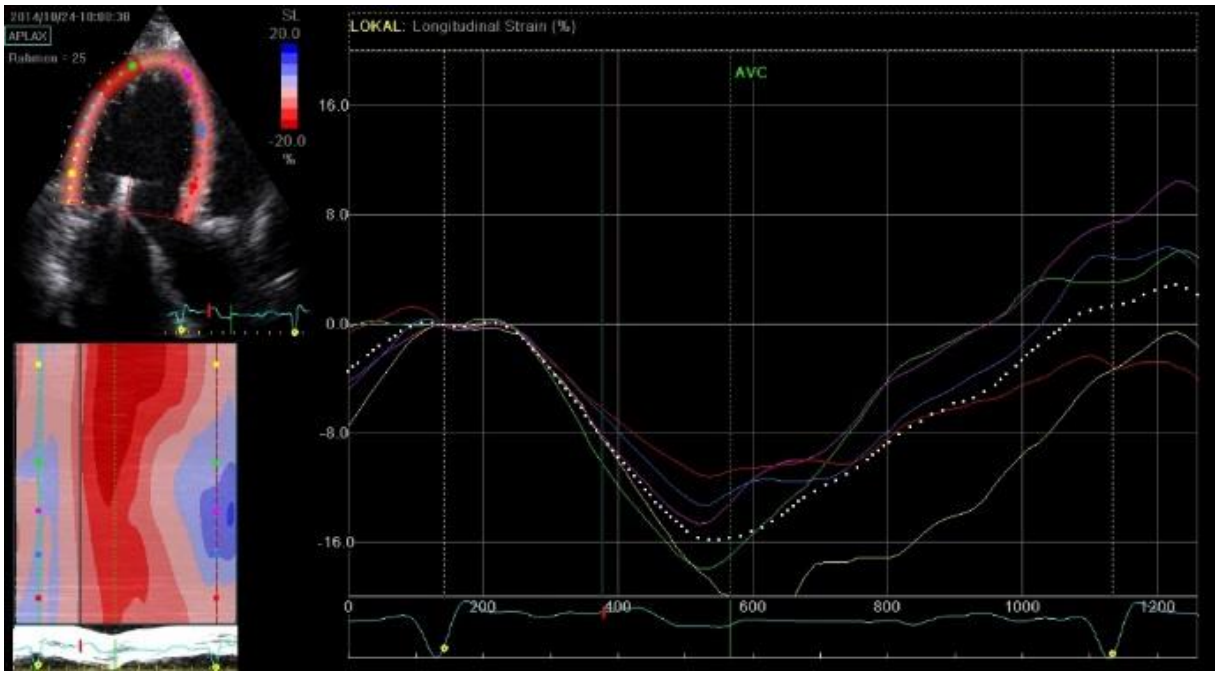
Speckle-tracking analysis delivered interesting results on LV myocardial deformation in patients with distinct LV geometry (presented in Fig. 17. and 18.). Despite normal to mildly reduced LVEF, speckle-tracking analysis revealed substantially impaired global longitudinal strain (GLS) in LVN patients in comparison to healthy individuals.[87] Important LV deformation parameters in regard to LV remodeling are summarized in Table 9. below.

Figure 17. Speckle-tracking analysis study. Patient without LV remodeling presenting baseline longitudinal peak systolic strain of -12.7% (A). At six-months follow-up, longitudinal strain improved to -16.5% (B). Bull´s eye representation of global longitudinal strain of the same patient at baseline (C) and follow-up (D).

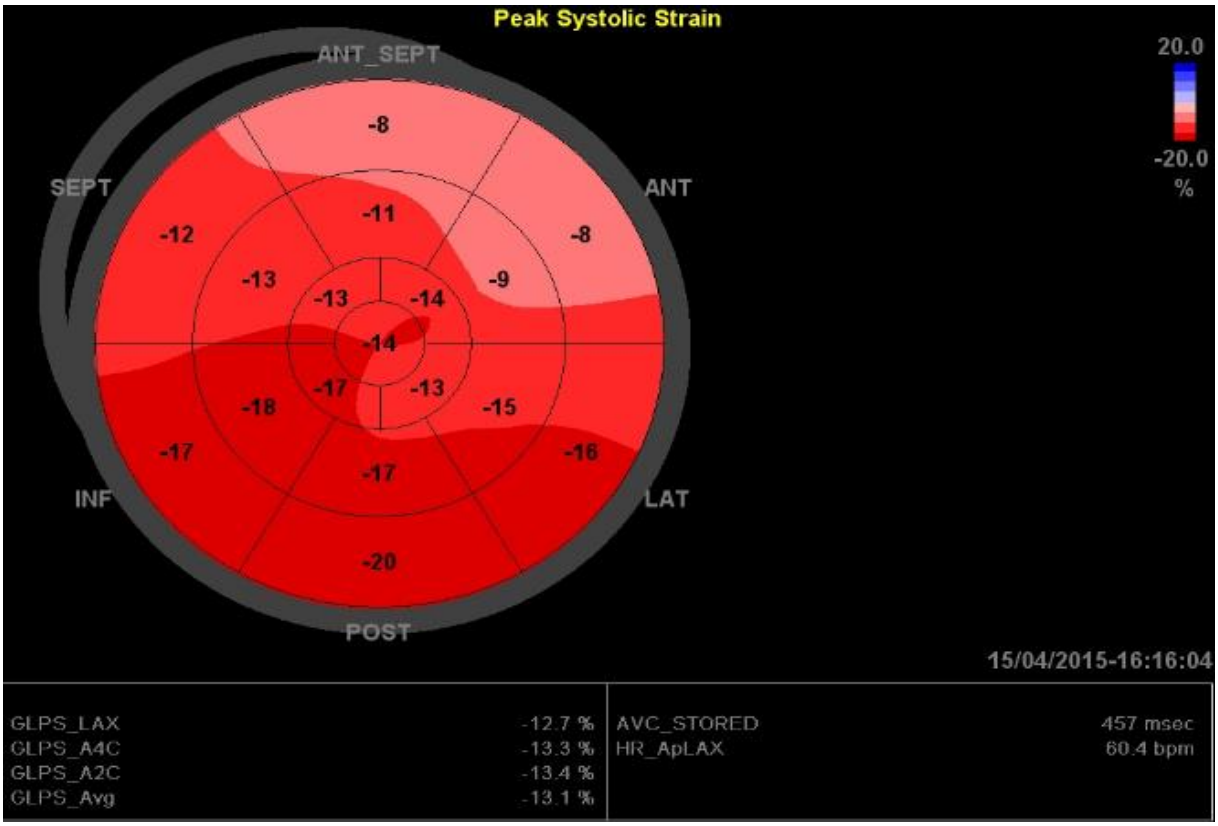
(A)



(B)



(C)


Peak Systolic Strain
ANT_SEPT
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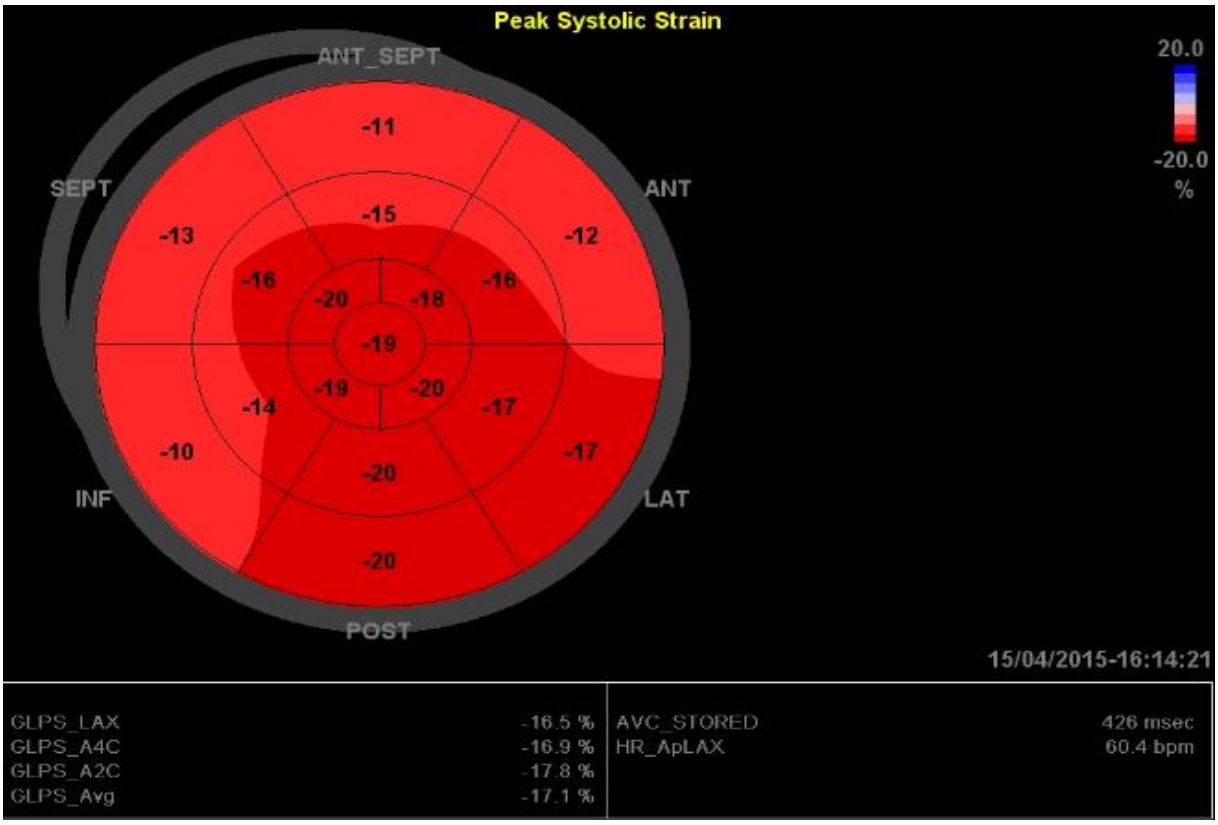
-9
-13
-14
-14
-17
-13
-18
-15
-17
-16
-17
-20
20.0
-20.0
%
15/04/2015-16:16:04
GLPS_LAX -12.7 %
GLPS_A4C -13.3 %
GLPS_A2C -13.4 %
GLPS_Avg -13.1 %
AVC_STORED 457 msec
HR_ApLAX 60.4 bpm

(D)


Peak Systolic Strain
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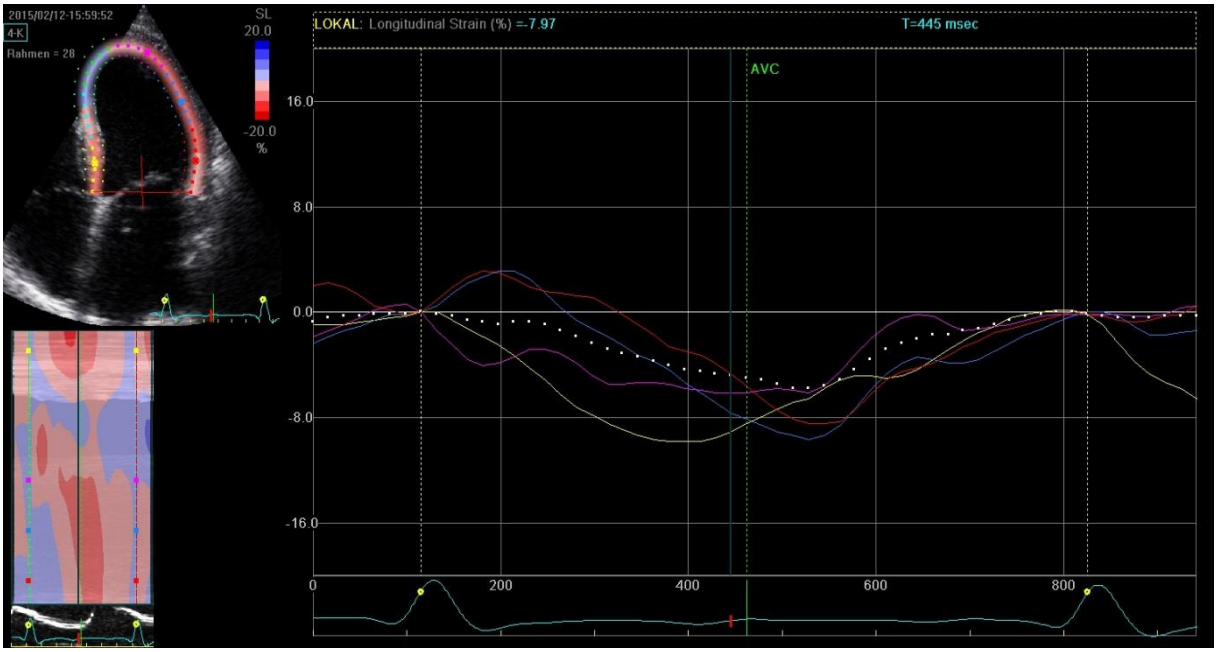
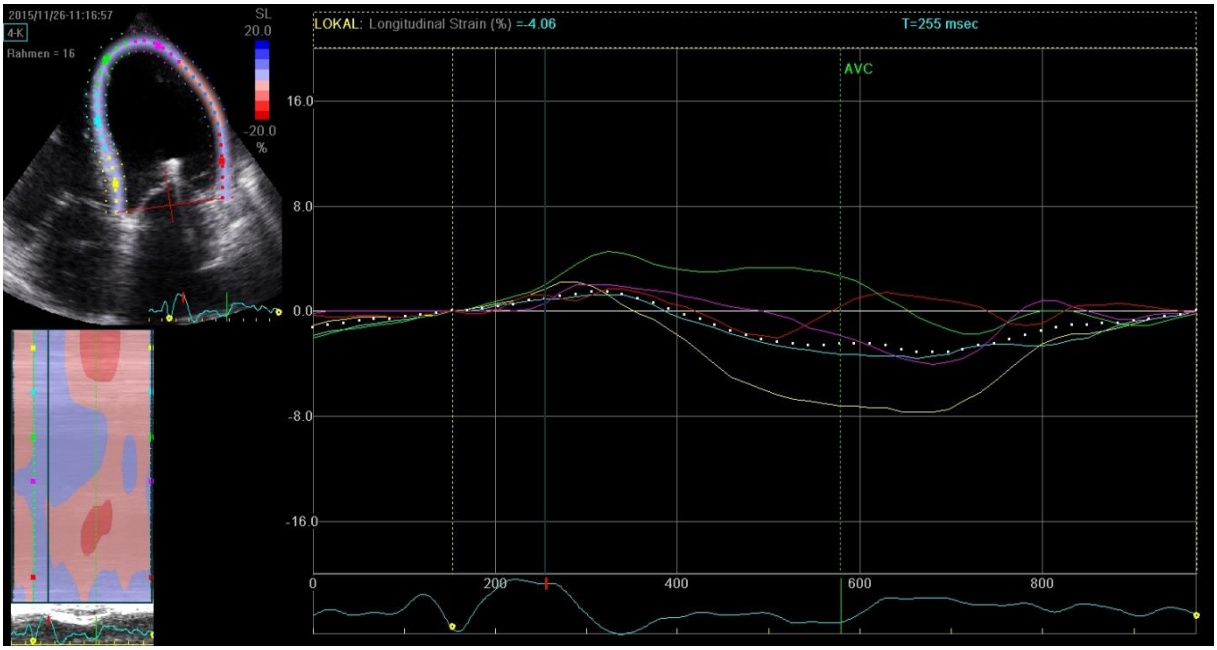
-20
20.0
-20.0
%
15/04/2015-16:14:21
GLPS_LAX -16.5 %
GLPS_A4C -16.9 %
GLPS_A2C -17.8 %
GLPS_Avg -17.1 %
AVC_STORED 426 msec
HR_ApLAX 60.4 bpm

Figure 18. Patient presenting LV remodeling with baseline longitudinal peak systolic strain of -3.9% (A). At six-months follow-up, longitudinal strain was estimated to be -5.1% (B). Bull´s eye representation of global longitudinal strain of the same patient at baseline (C) and follow-up (D).

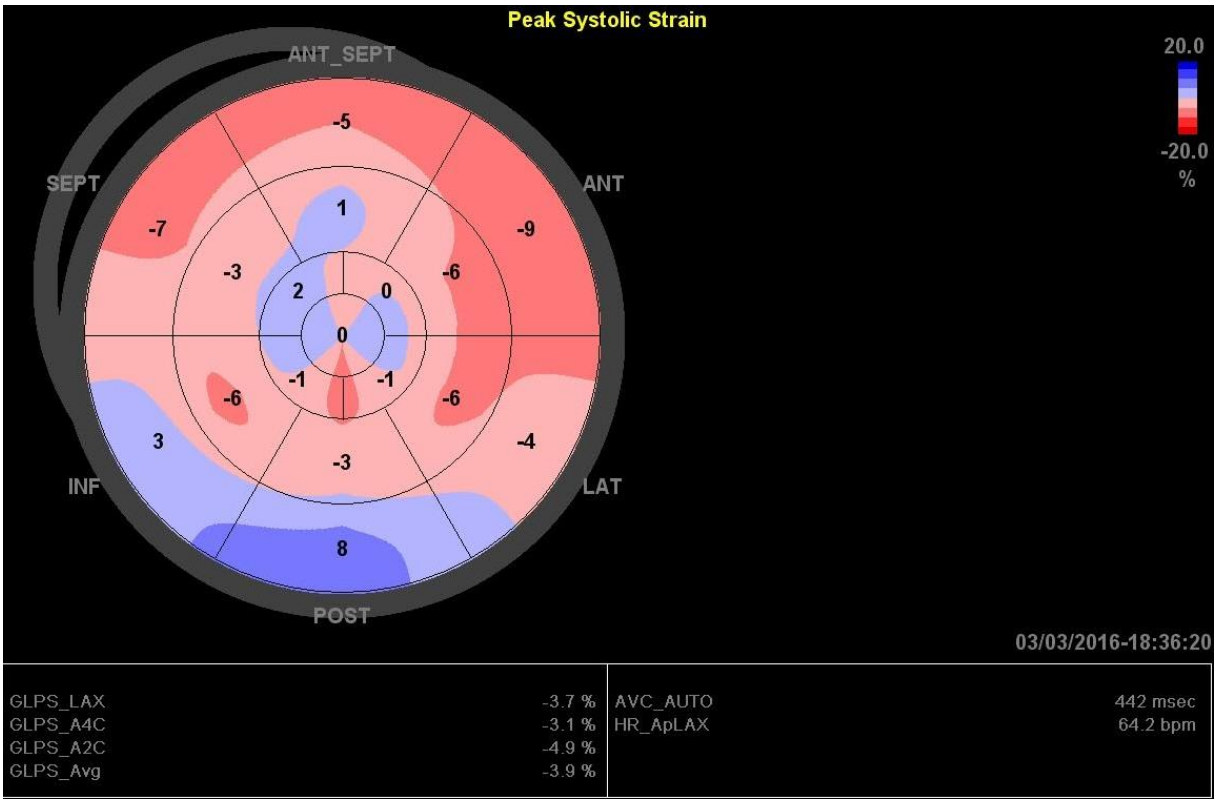
(A)



(B)



(C)


Peak Systolic Strain
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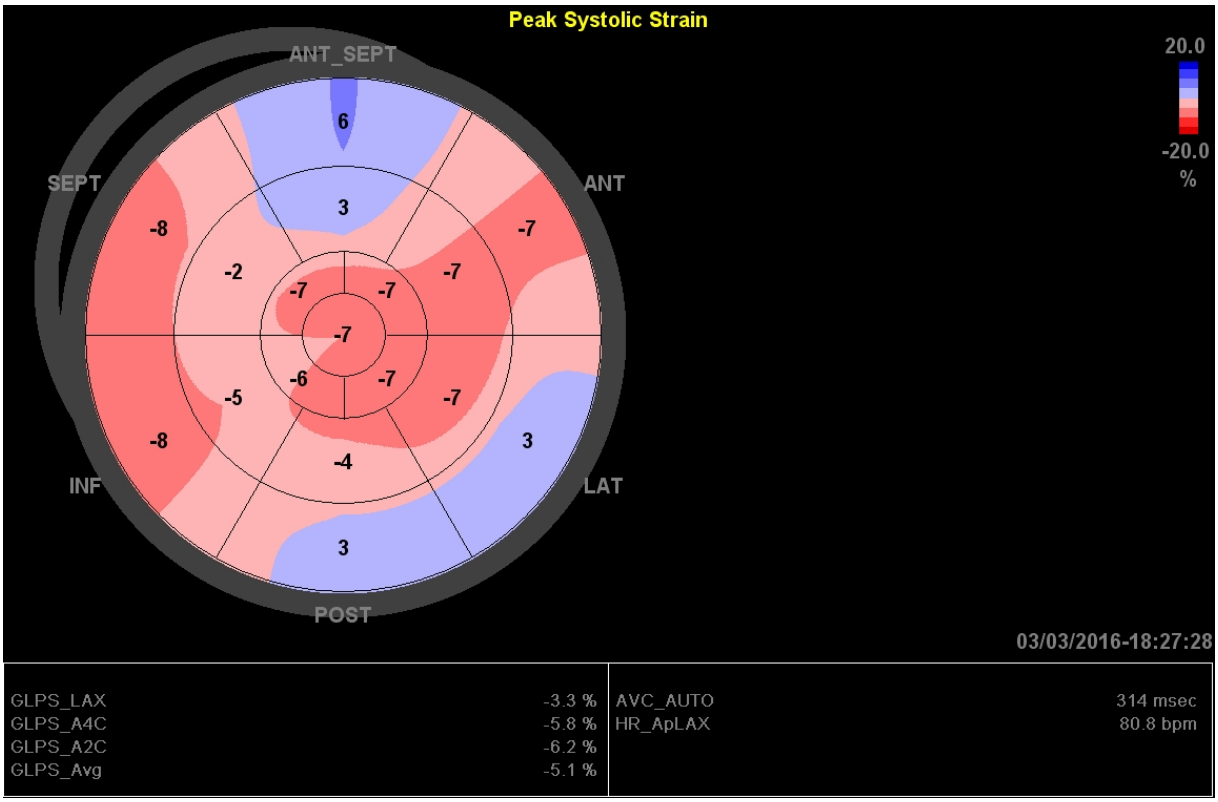
3
-4
-3
8
20.0
-20.0
%
03/03/2016-18:36:20
GLPS_LAX -3.7 %
GLPS_A4C -3.1 %
GLPS_A2C -4.9 %
GLPS_Avg -3.9 %
AVC_AUTO 442 msec
HR_ApLAX 64.2 bpm

(D)


Peak Systolic Strain
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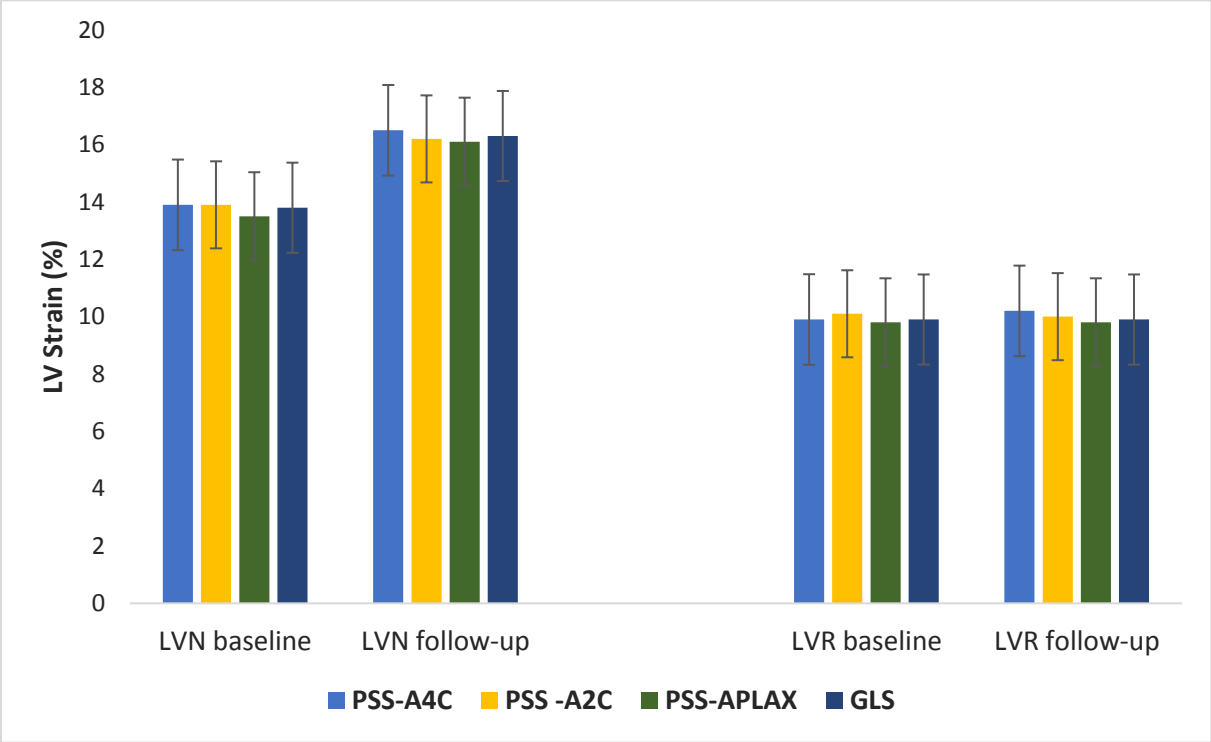
20.0
-20.0
%
03/03/2016-18:27:28
GLPS_LAX -3.3 %
GLPS_A4C -5.8 %
GLPS_A2C -6.2 %
GLPS_Avg -5.1 %
AVC_AUTO 314 msec
HR_ApLAX 80.8 bpm

Table 9. Left ventricular strain parameters in regard to left ventricular remodeling. *For simplicity, all deformation indices are given as positive numbers.*

		Left ventricular strain parameters (%)			
		PSS-A4C	***PSS-A2C***	***PSS-APLAX***	***GLS***
LVN	Baseline	13.9 ± 3.8	13.9 ± 3.8	13.5 ± 3.5	13.8 ± 3.5
	Follow-up	16.5 ± 4.1	16.2 ± 3.7	16.1 ± 3.9	16.3 ± 3.8
	p value	<.001	<.001	<.001	<.001
LVR	Baseline	9.9 ± 4.8	10.1 ± 4.5	9.8 ± 4.7	9.9 ± 4.5
	Follow-up	10.2 ± 5.8	10.0 ± 4.9	9.8 ± 4.7	9.9 ± 5.1
	p value	.587	.681	.957	.936

As already mentioned above, speckle-tracking analysis revealed substantially impaired global longitudinal strain (GLS) in LVN patients in comparison to healthy individuals.[87] Nevertheless, baseline GLS was considerably higher in LVN than LVR patients (13.8 ± 3.5% vs. 9.9 ± 4.5%, p<0.001), suggesting better preprocedural myocardial contractility. Most importantly, GLS showed a tendency to a notable recovery at follow-up in LVN group (13.8% ± 3.5% improved to 16.3% ± 3.8%, p<0.001), whereas no improvement in GLS was observed in LVR group (9.9 ± 4.5% vs. 9.9 ± 5.1%, p=0.936). Graphical representation of GLS in both groups is presented in Figure 19. below.

Figure 19. Left ventricular strain values in patients with and without LV remodeling at baseline and follow-up. It is of note that no significant improvement of strain was observed in LVR patients.



4.6 Left atrial function

Atrial function is determined by preload, afterload and LA myocardial contractility. Correspondingly to the ventricular myocardium, atrial muscle fibers obey Frank-Starling principle by increasing contractility in response to augmented preload in the presence of mitral regurgitation.[88] However, in decompensated state of MR, LA contractility decreases as a result of progressive myocardial ischemia.[89] This impaired atrial systolic function is believed to be associated with increased intraatrial pressure, which might lead to electrical remodeling chiefly predisposing for the development of atrial fibrillation (AF). Prior studies showed that 48% of patients with medically treated MR present AF during 10 years of follow-up period, which is related to higher morbidity and mortality.[90] Therefore, in the present study, the effects of LV remodeling and preprocedural AF on LA function have been carefully studied. Left atrial deformation parameters in regard to LV remodeling are presented in Table 10. below.

Table 10. Left atrial volumetric and strain parameters in regard to left ventricular remodeling. For simplicity, all deformation indices are given as positive numbers.

Variable	LVN group			LVR group		
	Baseline	**Follow-up**	**p**	**Baseline**	**Follow-up**	**p**
LA Vol sys (ml)	69 ± 23	62 ± 22	**.021**	83 ± 38	78 ± 43	.067
LA Vol dias (ml)	98 ± 27	87 ± 26	**.003**	114 ± 50	106 ± 46	**.032**
LA Vol mean (ml)	84 ± 25	76 ± 24	**.018**	99 ± 44	92 ± 44	**.048**
LAVi (ml/m2)	37.0 ± 13.0	33.2 ± 12.0	**.022**	43.7 ± 16.3	41.1 ± 18.0	.644
LA-LSS (%)	21.9 ± 4.4	24.5 ± 5.9	**.002**	21.1 ± 6.0	20.8 ± 9.3	.524
LA-EDSR (1/s)	0.67 ± 0.22	0.68 ± 0.35	.571	0.57 ± 0.27	0.66 ± 0.41	.112
LA-LDSR (1/s)	0.49 ± 0.40	0.59 ± 0.38	.341	0.49 ± 0.40	0.64 ± 0.49	**.015**

Patients with normal LV geometry showed improved LA reservoir function, whereas conduit and contractile function remained unaltered. On the contrary, LVR patients expressed notable amelioration in LA contractile function following the procedure without showing a marked impact on reservoir or conduit function. In agreement with previous studies, LA volumes were significantly reduced after MR correction in both groups, but patients without LV remodeling showed more pronounced volume regression.[91] The recovering LA function in terms of volume reduction and myocardial contractility is called *LA reverse remodeling*. The reversal of LA function may give additional information regarding the prognosis. There is little data on left atrial reverse remodeling in patients undergoing PMVR, but based on previous studies, it is highly possible that LA reverse remodeling might carry predictive value for patient clinical recovery.[92]

In the study population, 30 patients (45%) presented with preprocedural AF. Left atrial longitudinal systolic strain (LA-LSS) is an established parameter for atrial fibrillation. Therefore, left atrial function was assessed in regard to preexisting AF. The results of speckle-tracking analysis for the assessment of left atrial function regarding atrial fibrillation are presented in Table 11. below.

Table 11. Left atrial volumetric and strain parameters in regard to preprocedural atrial fibrillation. *For simplicity, all deformation indices are given as positive numbers.*

Variable	No AF group			Pre-AF group		
	Baseline	**Follow-up**	**p**	**Baseline**	**Follow-up**	**p**
LA Vol sys (ml)	64 ± 15	58 ± 17	**.029**	89 ± 41	84 ± 44	.311
LA Vol dias (ml)	91 ± 18	83 ± 22	**.031**	123 ± 52	112 ± 47	**.002**
LAVi (ml/m2)	35.7 ± 8.7	32.1 ± 9.1	**.029**	45.8 ± 18.7	42.9 ± 19.4	.309
LA Vol at P wave (ml)	76 ± 16	70 ± 18	.218	-	-	-
LA-LSS (%)	22.6 ± 5.5	26.3 ± 7.2	**.013**	20.1 ± 3.7	19.5 ± 3.4	.712
LA-EDSR (1/s)	0.65 ± 0.26	0.82 ± 0.43	**.017**	0.61 ± 0.23	0.76 ± 0.24	**.011**
LA-LDSR (1/s)	0.63 ± 0.46	0.85 ± 0.44	**.003**	0.34 ± 0.24	0.36 ± 0.24	.832

In terms of conventional volumetric parameters, our study population patients presented elevated baseline LA volumes and volume indices, regardless of preexistent LV remodeling or AF. It is of note that patients without preprocedural AF showed significantly lower baseline LA volumes. In terms of LA function, these patients showed preserved baseline LA reservoir, conduit and contractile function as determined by means of speckle-tracking echocardiography. In contrast, patients with AF presented higher baseline LA volumes, highlighting the long-term effect of volume overload, resulting in the stretching of LA wall. Consequently, myocardial fibers lose their ability to contract, contributing to the impairment and loss of LA contractile function. Nevertheless, LA reservoir and conduit function remained preserved despite chronic volume overload.

Generally speaking, PMVR yielded notable reductions in LA volumes. Most importantly, patients without AF showed improved global LA function following PMVR. In contrast, in patients with preprocedural AF, only LA conduit function was enhanced after MitraClip© had been deployed. Accordingly, the hypothesis that global and regional LA function is altered in patients with chronic MR could be confirmed by our results.

5. Discussion

5.1 The burden of mitral regurgitation

Mitral regurgitation, being the second most frequent heart valve disease requiring surgery in the EU, is a growing health problem in the ageing Western population.[5] Initial compensatory mechanisms including LA size enhancement for storage of regurgitant volume and increasing LV preload, thus yielding greater pumping force, allow asymptomatic course of the disease for many years. However, the above mentioned series of adaptations leads to progressive left ventricular dysfunction, resulting eventually in acute decompensated heart failure, requiring urgent hospitalization and use of medication to reduce LV filling pressures. It is estimated that nearly half of heart failure patients with impaired systolic function present with some degree of MR, whereas up to 30% of these patients exhibit moderate to severe MR.[93] Without proper medical treatment, chronic severe MR in *asymptomatic* patients bears an extremely high 5-year mortality risk of around 50-75%. What is more, Rossi et al. demonstrated that in the subgroup of heart failure patients, whose LVEF was smaller than 35%, regardless of ischemic or non-ischemic etiology, the presence of functional MR was associated with a two-fold greater risk of all-cause mortality and hospitalization.[6] A recent retrospective study by Borisenko et al. estimated the costs of optimal medical therapy for patients with severe MR, including recurrent hospitalizations and increasing number and dosis of medication, to be around 20,000€ over 10 years, which ows substantially to the multifactorial and complex pathophysiology of the disease.[94] According to current European guidelines, surgery is recommended in symptomatic patients with either degenerative or functional MR who present preserved systolic function (LVEF>35%) and retained left ventricular geometry (LVESD<55mm). When feasible, valve repair is superior to surgical valve replacement, demonstrating lower perioperative mortality, improved survival and lower long-term morbidity.[8] However, surgery is not a viable treatment option in elderly patients with significant comorbidities carrying high surgical risk.

5.2 Percutaneous mitral valve repair for treatment of chronic mitral regurgitation

Percutaneous mitral valve repair using the MitraClip© device has emerged as a promising interventional alternative treatment for high surgical risk patients or patients with reduced LV function. This procedure has been demonstrated to be a safe and viable method for MR reduction, leading to remarkable improvement in patient clinical status and quality of life.[95] However, in the prevalent group of heart failure patients, the long-term prognosis remains poor despite promising procedural outcomes, while the causative role of MR remains uncertain. In patients presenting with functional MR, cardiac resynchronization therapy might reduce MR severity through the enhancement of leaflet coaptation and resynchronization of papillary muscles. Yet, previous studies have shown that only 49% of patients with severe MR showed significant reduction of MR following CRT implantation.[96]

Percutaneous mitral valve repair is associated with a higher procedural success rate in patients with primary MR than those with secondary MR. To date, there is no data from multicenter studies on which patients with functional MR exhibit the most pronounced benefit from this new treatment option. Yet, some assume that prompt timing of interventional treatment i.e., before irreversible left ventricular adaptations occur, is the key for better long-term clinical outcomes. Therefore, further developments in the future and better understanding of the mechanisms of mitral regurgitation are needed for careful patient evaluation and selection for PMVR.

Consistent with large international trials (ACCESS-EU and EVEREST), the present study confirmed that patients who are not suitable for surgery could be successfully treated with the MitraClip© system in order to reduce the degree of mitral regurgitation.[97] The European study showed a clinically meaningful amelioration of MR and patient functional status. The present investigation established vital clinical alleviation of symptoms at six months, expressed by NYHA functional class improvement >1, which is mainly attributed to a notable reduction in MR volumes accompanied by a substantial reduction in systolic pulmonary arterial pressure. In larger studies, improvement of MR obtained six months postprocedurally along with an improved patient clinical status remained stable at one year, suggesting consistency of the results.

It is of note that acute reduction of MR alleviates volume overload exerted especially on the left chambers, leading to improved left ventricular and left atrial haemodynamics. The presented macroscopic findings such as considerable reductions in LVEDV and LVESV suggest a favourable left ventricular response to sudden unloading which, in turn, is evidently reflected on myocardial level in form of contractility enhancement. **The most remarkable finding is that only patients with preserved LV geometry and preserved LV function (smaller baseline LV and LA dimensions, lower LV mass, lesser extent of LV hypertrophy, LVEF>40%) exhibited significant postprocedural reverse remodeling expressed by the improvement of myocardial contractility.** Previous studies, with longer follow-up periods of up to four years, have shown similar results, demonstrating a positive cardiac structural reverse remodeling. Despite initial decline in LVEF, there was a progressive increase in LVEF as LVESV successively diminished to a greater extent than LVEDV.[98] The six-month follow-up period of this investigation gives only a general outline of the tendency of the results that is why longer observation intervals are necessary for reliable evaluation of procedural success.

5.3 Left ventricular function after percutaneous mitral valve repair

The salient finding of the present study was a marked improvement in cardiac performance after percutaneous mitral valve repair which was assessed beyond conventional echocardiographic parameters such as left ventricular ejection fraction. The gain in effective forward LVOT stroke volume and ameliorated longitudinal LV strain was particularly pronounced in patients without LV remodeling, accentuating the role of preexisting LV remodeling in postprocedural myocardial recovery. Furthermore, increase in cardiac performance was accompanied by reduced regurgitation volumes and diminution in systolic pulmonary artery pressure, leading to prominent alleviation of symptoms at six-month follow-up. In addition, echocardiographic data on baseline and follow-up ventricular dimensions were sufficient to prove favorable geometrical remodeling in this high-risk patient population.

Systolic function

Fundamentally, the present study demonstrated significantly impaired LV global longitudinal strain in patients with chronic MR who have undergone percutaneous MV repair. These results corroborate the concept that abnormalities in longitudinal strain are correlated with the geometry of the heart and may predate changes in LV volumes and ejection fraction, thus,

showing a relationship between left ventricular remodeling and myocardial contractility. Although LVEF is the parameter currently recommended to select patients for either surgical or interventional MV repair, it may indeed mask the true LV inotropic status.[77] Previous studies demonstrated that patients with MR have a significantly lower effective forward flow compared with patients without MR despite having comparable LVEF. In patients with MR, a significant percentage of blood is emptied into the left atrium before aortic valve opens. Moreover, wall stress is reduced during systole, accounting for diminished afterload resulting in an increased forward stroke volume.[17] Therefore, LVEF cannot reliably reflect LV performance in patients with severe MR. On the other hand, LV GLS assessed by STE is a well-established tool which detects subclinical LV dysfunction before diminution in conventional echocardiographic measures, such as LVEF, can be recognized.[99, 100] Kim et al. showed that GLS was an earlier echocardiographic marker of LV intrinsic myocardial function than LVEF due to LV remodeling induced by volume overload owing to primary MR.[101] Regardless of normal to mildly reduced LVEF, patients with preserved LV geometry exhibited impaired GLS compared to healthy individuals. Interestingly, LVN patients presented considerably higher baseline longitudinal strain in comparison to LVR patients, suggesting better myocardial contractility. These data support established complexity of LV myocardial mechanics in the guise of coordinated longitudinal contraction, circumferential shortening and radial thickening assessed by previous speckle-tracking echocardiographic studies. LV myocardial systolic function plays a crucial role in the pathophysiology of valvular heart disease, especially MR.[102] Increased volume and pressure load lead to LV hypertrophy, altered geometry and interstitial fibrosis, while impaired subendocardial perfusion affects global LV longitudinal deformation. Marciniak *et al.* demonstrated that in patients with long-standing regurgitation, strain parameters remain unaffected despite surgical MR correction due to chronic wall stress resulting in irreversible myocardial damage and permanently reduced contractility.[103] Moreover, consistent with our data, both concentric remodeling and LV hypertrophy were independently associated with reduced myocardial strain.[104] Therefore, STE detects sheer functional myocardial dysfunction due to irreversible remodeling, adding new insights into the assessment of LV systolic function. Surgical MR correction results indubitably in greater reduction of MR severity than PMVR, but unfavourable and overwhelming consequences of cardiopulmonary bypass cause ischemic injury, adding to further impairment of LV systolic function. MitraClip© implanantion, as opposed to surgery, appears to enhance myocardial performance and should be the preferred recommended therapeutic option for treatment of MR in patients without attendant LV remodeling.

Diastolic function

In patients with severe MR and long-standing LA volume overload, the question arises whether sustained recovery of LV diastolic function can be achieved after MitraClip© implantation. In the study population, baseline *E/E´* ratio, which remains an established parameter for the assessment of LV filling pressure, was elevated, suggesting impaired LV relaxation. This finding could be explained by exacerbated LV chamber stiffness and reduced recoil of the LA. Following PMVR, *E´* markedly decreased, thus indicating improved LV relaxation. In contrast, the *E/E´* ratio, not only did not improve after MR correction, but paradoxically increased (as shown in Table 5.). However, as Cameli *et al.* reported[105], invasively measured LV filling pressures correlated poorly with *E/E´* ratio, but better with LA longitudinal deformation parameters, underlining the role of LA speckle-tracking analysis for the assessment of LV diastolic function. In the study population, the *E/E´* ratio might not be a reliable parameter for the assessment of LV filling, because in advanced systolic heart failure, especially in the presence of large LV volumes (which was the case in 35 patients) and concomitant severe MR (MR >2+), measurement of transmitral *E* wave velocity could be the source of misleading information.[106, 107] Correction of MR generates more dynamic anterograde mitral flow with resultant higher flow velocities leading to falsely elevated *E* wave values. What is more, tissue *E´* might be deceitfully undervalued in Doppler-derived measurements after MV repair as a result of mitral annulus deformation which might be a legitimate explanation to the presented echocardiographic results.[108] Therefore, the beneficial effect of MV repair on diastolic LV function still remains a controversially ambiguous issue.

LV reverse remodeling

Prospective studies examining the extent of LV reverse remodeling after MV repair are scarce.[98] Heretofore, the present study is the first to investigate the role of baseline LV remodeling on postprocedural reverse remodeling in patients undergoing PMVR. The factors influencing reverse remodeling remain unclear, but impaired right ventricular function, baseline reduced ejection fraction (LVEF<45%) and LV end-diastolic dimension are associated with high mortality and worse prognosis.[109] Prior studies associated late mortality, late ventricular dysfunction and lack of reverse remodeling to the presence of preoperative LV dysfunction.[110] Results from the present investigation indicate that the entity of baseline LV remodeling factually implies irreversible LV dysfunction. Theoretically, timely correction of chronic MR

should restore normal LV function or at least improve LV contractility, which was observed in LVN patients, but evidently was not the case in LVR patients. The latter group presents higher rates of adverse cardiac events even after a successful procedure due to irreversible structural and functional adaptations secondary to chronic volume overload. Enriquez-Sarano *et al*. showed that in patients undergoing surgical MV replacement, early post-operative LV dysfunction was linked to a 2.5-fold increase in the risk of cardiac death or heart failure.[111] However, volume overload reversal after MV surgery may generate 10-15% reduction in LVEF, which may be confusing in predicting postprocedural outcome.[76] For this reason, other contractility-related parameters might become valuable tools for clinical patient evaluation. In the present study, LV remodeling showed to have an adverse impact on myocardial contractility, since no enhancement in deformation indices could be observed. Myocardial response, albeit poor, is not synonymous with lacking clinical and functional patient recovery. Even though there is no evident amelioration in LV systolic function, the benefits resulting from the procedure in terms of functional patient status (NYHA class) remain undeniable, even in patients with irrevocably deteriorated LV function. At present, percutaneous mitral valve repair is the procedure of choice for the treatment of secondary MR in high-risk patients. Yet, the purpose of the MitraClip© device is to repair the MV, not to correct LV remodeling. Accordingly, optimal medication commenced in a timely manner plays a pivotal unparalleled role in preventing or actively suppressing progressive LV remodeling. A pronounced effect of angiotensin-converting enzyme (ACE) inhibitors in patients with functional MR is associated with vasodilation, whereas beta-blockers (particularly carvedilol and atenolol) can effectively reduce regurgitation by specifically mitigating LV hypertrophy, lowering filling pressures and improving contractility.[112] Combined analysis of these factors suggests that the best preservation of LV function might be achieved if MV is repaired before LV remodeling becomes irreparable, which can be assessed by novel echocardiographic tools such as speckle-tracking.

5.4 The haemodynamic response following percutaneous mitral valve repair

Prior studies have already documented improvement in haemodynamic profile immediately after edge-to-edge MV repair measured by left and right heart catheterization in a series of more than 100 patients with predominantly functional MR.[79] The present study has not provided direct haemodynamic measurements, but delivered echocardiographic data allowing indirect, but reliable estimation of LV haemodynamics. The most crucial finding is that PMVR resulted in a significant increase in LV forward stroke defined by an increase in LVOT stroke volume (63.4 ± 27.1 ml vs. 76.2 ± 35.1 ml; $p<0.001$) and an illustrous change in cardiac output (3.88 ± 2.24 l/h vs. 4.57 ± 2.33 l/h, $p<0.001$) despite minor changes in LVEF, underscoring the role of LVOT stroke volume for evaluation of procedural success. Very often LVEF is overestimated in MR, even after MR correction, owing to persistent backflow of blood into the left atrium before the aortic valve opens.[113] Our results underline the pivotal role of effective LVOT stroke volume for the assessment of cardiac performance and hemodynamic procedural effects. Tribouilloy *et al.* showed LVEF and LVESD to be useful for the evaluation of patients undergoing surgical MR correction; the sensitivity and specificity of these parameters remains quite low (area under the curve of 0.69 and 0.64, respectively).[114, 115] Our echocardiographic data suggest that conventional LVEF measurement should not be seen as the sole parameter reflecting LV myocardial function in patients with chronic MR. Furthermore, GLS showed parallel tendency to a further improvement at six-month follow-up in patients without LV remodeling. Aforementioned findings indicate a promising effect of MV repair on myocardial contractility in this subgroup of patients, suggesting that the mechanism of reverse remodeling might be peculiar exclusively to LVN patients. Consequently, LV haemodynamic and contractile function could be more accurately investigated by means of Doppler-derived flow measurements and deformation indices obtained from speckle-tracking analysis. In the present study, the evaluation of RV function was principally based on non-invasive determination of TAPSE. RV function is remarkably impaired in LVR patients suggesting the biventricular character of the remodeling process. Interestingly, despite the positive effect on LV systolic function, the correction of MR does not considerably improve RV function. Nevertheless, all study patients demonstrated notable reduction in sPAP six months after PMVR. Consistent with RV haemodynamic studies, both reduced pulmonary artery and pulmonary capillary wedge pressure are reliable predictors of an improved clinical outcome 7-8 months following PMVR.[116]

As previously mentioned, current data provide indirect, yet reliable assessment of LV haemodynamic function. Prior studies investigated LV and RV mechanics using 3D speckle-tracking echocardiography (3D STE) and suggested high feasibility and reproducibility of 3D evaluation of procedural success. In agreement with our data, they showed significant overload reduction and biventricular reverse remodeling. Of note, postprocedural change in 3D strain occurred earlier and was more pronounced compared with changes in LVEF. The implementation of 3D echocardiography could have shown more reliable results for the haemodynamic assessment of the study patients, but despite lower reproducibility (due to higher interobserver variability of volume measurement) our results were consistent with previous 3D echocardiographic studies.[117]

5.5 Left atrial function following percutaneous mitral valve repair

In terms of LA global function, three phases have been distinguished: reservoir, conduit and contractile. *Reservoir* phase refers to storing pulmonary venous blood streaming from the pulmonary veins during ventricular systole, *conduit* phase is characterized by passive LV filling, whereas during *contractile* phase, active atrial emptying occurs. In other words, LA function is influenced by three pivotal factors: preload, afterload and myocardial contractility. Conventional echocardiographic assessment of the three components of atrial function is very often complex and challenging, mainly due to the lack of accepted gold standard parameters for LA function.[118] Currently, the use of STE allows non-invasive functional quantification of myocardial longitudinal LA deformation during contractile, reservoir and conduit phases, which has been validated in healthy individuals in previous studies.[119] Nevertheless, measuring atrial strain is more challenging and time-consuming than assessing segmental LV function for a number of reasons. Firstly, the left atrium lies deeper in the thorax, hence further from the transducer. Moreover, LA myocardial wall is much thinner, with fewer speckles to undergo tracking as compared to LV, thus requiring more effort and attention to be manually tracked.

Our results showed that MR significantly impairs the indices of LA reservoir, conduit and contractile function. In agreement with Debonnaire *et al.*, who showed that LA strain parameters are considerably reduced in patients referred to surgery for MV replacement, our results confirm the detrimental effect of chronic MR on LA myocardial function.[72] The implantation of MitraClip© corrects LA reservoir and contractile function during the six-month follow-up period, but does not fully restore LA function as compared to healthy individuals.

LA reservoir function

Left atrial longitudinal systolic strain (LA-LSS) reflects passive stretching of the LA during LV systole, hence it has been used to predict LA reservoir function in our study population. In patients with mild MR, LA compensates for volume overload by increasing end-diastolic volume and accelerating atrial filling rate, thus enhancing reservoir capacity. However, in patients with severe MR, chronic volumetric burden triggers myocyte hypertrophy as well as alterations in the composition of extracellular matrix with excessive interstitial fibrosis, thus decreasing myocardial wall elasticity and resulting in a decline in LA reservoir function. Consistent with previous studies, STE revealed a prominently reduced baseline reservoir function in all study patients.[120] What is more, patients without preprocedural AF presented higher LA-LSS than patients with AF, indicating lesser degree of fibrosis and better preserved elasticity of atrial wall. Following PMVR, patients without LV remodeling and those without permanent AF showed considerable amelioration of LA reservoir function. These findings suggest substantial adaptive, yet irreversible LA remodeling in patients with LV remodeling and with preprocedural AF. However, regarding LA size, PMVR effectively reduced atrial volumes in all patients examined, clearly indicating a favourable atrial response to the procedure. These discrepancies underline the role of LA myocardial deformation assessment which has greater diagnostic power than LA volume measurement for the evaluation of LA reservoir function. Our results demonstrate that only myocardial strain specifically targets ultrastructural remodeling of the myocardial wall which is regarded to have important prognostic value in various heart diseases.[74]

LA conduit function

In patients with MR, passive LV filling is enhanced due to augmented atrioventricular gradient and reduced LV wall stiffness. Surprisingly, in our patients LA conduit function, which was assessed by left atrial early diastolic strain rate (LA-EDSR), manifested unusual impairment. Bauer *et al.* report that the conduit function might diminish with aggravating MR and concomitant declining LV function. Moreover, in decompensated stage of the disease, higher LV stiffness results in elevated LV filling pressure and, hence, greater atrial afterload which is consistent with incipient LV remodeling.[89] Moreover, due to excessive volume overload, the atrioventricular gradient is reversed, causing reduced transmitral flow. Our results demonstrate that PMVR did not essentially influence LA conduit function in either LVN or LVR patients,

suggesting discreet impairment of LV relaxation even in patients with apparently normal LV function.[121] However, in patients with preprocedural AF, the procedure enhanced LA conduit function, whereas patients with AF showed further deterioration in the conduit function. These findings reflect persistent alteration of LA compliance, which was also associated with AF recurrence and higher thromboembolic risk.[122]

LA contractile function

The LA pump function, represented by left atrial late diastolic strain rate (LA-LDSR), was impaired in patients with MR, which is attributable to combined effect of increased LA afterload resulting in overwhelmed Frank-Starling mechanism and deteriorated LA contractility. Mary-Albine *et al.* showed that chronic presence of regurgitant volume results in reduced contractile force of the LA primarily owing to myolysis (combined effect of muscle hypertrophy, necrosis and apoptosis) and disproportionate collagen synthesis and degradation leading to a loss of contractile apparatus.[123] Percutaneous mitral valve repair improves contractile function by immensely reducing LA afterload. Despite slight amelioration of LA pump function, the contractile force remains persistently impaired due to previously described irreversible histological changes in the LA wall.

6. Study limitations

Two-dimensional echocardiography has shown limitations regarding interobserver reproducibility and potential inadequate acoustic windows particularly in heart failure patients with pleural effusion and pulmonary oedema. The most crucial technical restriction of speckle-tracking echocardiography is its dependency on the frame rate as well as on the image resolution which could not be obtained in all patients undergoing PMVR (19 patients had to be excluded from the study). In addition, MR grading after a double-orifice valve had been created makes MR quantification by means of colour Doppler echocardiography (to define *vena contracta* width) an arduous challenge. Moreover, functional MR is known to be fluctuant and load-dependent, therefore, its measure is difficult to standardize.[97] Patient clinical recovery was evaluated exclusively in terms of NYHA functional class improvement. In large clinical trials, the effectiveness of the results was defined by a combined effect of MR reduction, NYHA functional class improvement, change in six-minute walk test distance and data retrieved from quality-of-life questionnaires. The latter time-consuming measures were not carried out in our study. Another limitation of the study was the number of patients involved, however comparable with previous studies. Further larger studies with longer follow-up periods and with the use of more accurate three-dimensional techniques are needed to confirm the beneficial hemodynamic long-term effects of percutaneous mitral valve repair and prognostic role of speckle-tracking-derived strain parameters.

7. Future prospects

Future studies regarding reverse remodeling of the left heart chambers would benefit greatly from better non-invasive imaging modalities and serial haemodynamic measurements. Three-dimensional echocardiography, a promising and reliable technique for the assessment of intracardiac volumes, has been used to assess patients before, during and after percutaneous mitral valve repair. Some studies demonstrated significant correlation between 3D direct volumetric and 3D speckle-tracking methods for ventricular volume quantification which implies the interchangeable role of 3D echocardiography for more precise assessment of LV and LA volumes. Unfortunately, 3D echocardiography was not performed in the present study, but it could be implemented in the future.

8. Concluding remarks

Two-dimensional echocardiography plays a fundamental role in the diagnosis and treatment of patients with mitral regurgitation. Being easily accessible, it is a valuable tool for patient screening and for the evaluation of valve lesion, providing insight into the pathophysiology of MR and allowing careful patient selection for interventional treatment. Speckle-tracking echocardiography represents a sensitive and reliable tool supplying additional information on the myocardial function and detecting subtle changes in LV function. The timing of percutaneous mitral valve repair using the MitraClip© device in patients with chronic mitral regurgitation is crucial for the feasibility of the procedure. Present study supports established complexity of LV myocardial function such as coordinated longitudinal contraction, circumferential shortening and radial thickening. Prompt interventional treatment i.e. before left ventricular adaptations become irreversible and myocardial function becomes severely impaired, demonstrated notable amelioration of myocardial contractility which was associated with considerable increase in effective forward flow measured in LVOT. Most importantly, the amelioration of LV performance predates changes in LVEF, providing not only accurate diagnostic, but compelling prognostic information. Improvement of myocardial function extends beyond left ventricle to left atrium, thus defining global recovery of the left heart when volume overload has been reversed. The results confirm the hypothesis that patients without LV remodeling exhibit major improvement in myocardial contractility, whereas no benefit is expressed in the presence of irreversibly altered LV geometry. Therefore, in the era of rapidly developing technologies, medical devices such as MitraClip© should be primarily offered to patients who will benefit from them the most.

9. List of Tables

10. List of Figures

11. Abbreviations

2D – two-dimensional

3D – three-dimensional

ACEI – angiotensin-converting enzyme inhibitor

ACCESS-EUROPE – an observational study of the MitraClip© system in Europe

AF – atrial fibrillation

AO – aortic root

APLAX – three-chamber view

A4C – apical four-chamber view

A2C – apical two-chamber view

CRT – cardiac resynchronization therapy

ECG – electrocardiography

EuroSCORE – European System for Cardiac Operative Risk Evaluation

EVEREST – Endovascular Valve Edge-to-Edge Repair Study

GLS – global longitudinal strain

IVSd – interventricular septum thickness, end-diastolic

MR – mitral regurgitation

MV – mitral valve

NYHA – New York heart Association

LA – left atrium / left atrial

LAV – left atrial volume

LAVi – left atrial volume index

LA-LSS – left atrial longitudinal systolic strain

LA-EDSR – left atrial early-diastolic strain rate

LA-LDSR – left atrial late-diastolic strain rate

LV – left ventricle / left ventricular

LVEF – left ventricular ejection fraction

LVEDd – end-diastolic left ventricular diameter

LVEDs – end-systolic left ventricular diameter

LVEDV – left ventricular end-diastolic volume

LVESV – left ventricular end-systolic volume

LVM – left ventricular mass

LVMi – left ventricular mass index

LVN – patient without left ventricular remodeling / normal ventricular geometry

LVR – patient with left ventricular remodeling

LVOT – left ventricular outflow tract

MR – mitral regurgitation

MV – mitral valve

NYHA – New York heart Association

PMVR – percutaneous mitral valve repair

PSS – peak systolic strain

PWTs – posterior wall thickness, end-systolic

ROI – region of interest

RWT – relative wall thickness

RV – right ventricle / right ventricular

STE – speckle-tracking echocardiography

sPAP – systolic pulmonary artery pressure

TAPSE – tricuspid annular plane systolic excursion

TTE – transthoracic echocardiography

TEE – transesophageal echocardiography

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13. Affidavit

I, Oskar Galuszka, certify under penalty of perjury by my own signature that I have submitted the thesis on the topic ***The role of echocardiography for evaluation of left ventricular and left atrial function in patients undergoing percutaneous mitral valve repair using MitraClip.*** I wrote this thesis independently and without assistance from third parties, I used no other aids than the listed sources and resources.

All points based literally or in spirit on publications or presentations of other authors are, as such, in proper citations (see "uniform requirements for manuscripts (URM)" the ICMJE www.icmje.org) indicated. The sections on methodology (in particular practical work, laboratory requirements, statistical processing) and results (in particular images, graphics and tables) correspond to the URM (s.o) and are answered by me. My interest in any publications to this dissertation correspond to those that are specified in the following joint declaration with the responsible person and supervisor. All publications resulting from this thesis and which I am author correspond to the URM (see above) and I am solely responsible.

The importance of this affidavit and the criminal consequences of a false affidavit (section 156,161 of the Criminal Code) are known to me and I understand the rights and responsibilities stated therein.

Date Signature

14. Curriculum vitae

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

15. Publications and Presentations

- ***Circulating exosomal microRNAs predict functional recovery after MitraClip repair of severe mitral regurgitation.*** Kasner M, Gast M, **Galuszka O**, Stroux A, Rutschow S, Wang X, Dohmen P, Skurk C, Landmesser U, Poller W, Gross M. *Int J Cardiol*. 2016 Apr 7;215:402-405
- ***Left ventricular remodeling and myocardial mechanics obtained by 2D strain for prognostic evaluation of clinical improvement in heart failure patients undergoing percutaneous mitral valve repair.*** Article in Journal of the American College of Cardiology 67(13):345 · April 2016
- ***Left atrial volume and function in patients with chronic mitral regurgitation undergoing percutaneous mitral valve repair.*** Poster presented at Heart Failure 2015 – 2nd World Congress on Acute Heart Failure, Seville
- ***Improvement of LV function beyond ejection fraction in patients undergoing edge-to-edge mitral valve repair.*** Poster presented at EuroEcho-Imaging Congress 2015, Seville
- ***Left atrial reverse remodeling in patients with mitral regurgitation following percutaneous mitral valve repair: an echocardiographic study.*** Free Lecture at 82. Annual Meeting of the German Cardiac Society 2016, Mannheim
- ***Improvement of left ventricular function beyond ejection fraction in patients undergoing percutaneous mitral valve repair: a two-dimensional speckle-tracking study.*** Free Lecture at 82. Annual Meeting of the German Cardiac Society 2016, Mannheim
- ***The improvement of right ventricular function following percutaneous mitral valve repair using MitraClip system: a two-dimensional speckle-tracking study.*** Poster presented at 82. Annual Meeting of the German Cardiac Society 2016, Mannheim