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INCIDENCE AND RISK FACTORS FOR MITRAL PARAVALVULAR LEAK AND COMPARISON OF THE TREATMENT MODALITIES

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CONTENTS

ABREVIATIONS

2D – Two-dimensional

3D – Three-dimensional

BARC – Bleeding Academic Research Consortium

CABG – Coronary artery bypass graft surgery

GFR – Glomerular filtration rate

KDIGO – Kidney Disease Improving Global Outcomes

LV – Left ventricle

LVEF - Left ventricular ejection fraction

MVP – Mitral valve prosthesis

MVR – Mitral valve replacement

NYHA - New York Heart Association

PA – Pulmonary artery pressure

PVL – Paravalvular leak

RRT – Renal replacement therapy

SCr^{c} - Serum creatinine concentration

TEE – Transesophageal echocardiogram

TTE – Transthoracic echocardiogram

TV – Tricuspid valve

FOREWORD

“Go, talk to the people, widen your horizons, make new connections, explore, and ask questions. Otherwise, if you do not put your practice and thinking to the test, you will not excel, not improve”.

Prof. Vytautas Sirvydis

PREFACE

Some years ago together the colleague of mine and I observed the course of treatment in a number of very ill patients who came for redo surgery due to specific complications which potentially can occur after heart valve replacement. They were patients with prosthetic paravalvular regurgitation. Unfortunately, some did not survive the hardships of complex surgical treatment; others had to overcome severe postoperative complications. This clinical sequel can occur at any time of follow-up. Some put the blame on the original pathology for which the patients have been operated initially; others find fault with operative factors. Unfortunately, to date no definite answer to establish its cause has existed. Later rapid development of the transcatheter treatment modality for this complication emerged as an alternative to surgery at our hospital. Over five years, it has completely shifted the treatment for paravalvular leak (PVL) towards less invasive treatment option. This has driven our team to investigate the issues mentioned above and try to find answers in global literature and in our practice.

1. INTRODUCTION

1.1 Relevance of the research issue

The significance of mitral valve diseases spread is well known and not negotiable; they are the second-most common clinically significant form of valvular defect in adults [1]. The annual incidence of mitral valve disease in industrialized nations is estimated at around 2% to 3% of the overall population and higher in underdeveloped countries [2, 3].

Taking into account the aging population, especially in the West, mitral valve disease is the most common of the heart valve disorders, with a prevalence of more than 10% in people aged older than 75 years [4]. Globally, about a few hundred thousand people undergo mitral valve replacement (MVR) annually for any mitral valve disease [5]. Probably, millions of valves been implanted over the history of MVR [6]. The intentions and clinical ambitions of the mitral surgical interventions are to diminish symptoms, improve the quality of life, reduce the rate of progressive congestive heart failure associated readmissions, and potentially enhance long-term survival compared to natural history of the disease [7]. Unfortunately, a permanent accomplice to the surgical treatment is a great variety of complications; MVR is not an exception, and for instance, mitral PVL can become a serious obstacle on the path to achieve the targets mentioned above.

Surgical complications impair patients' recovery, postoperative psychosocial status and the quality of life; they also place a heavy burden on the physician's psychological well-being personally and impose considerable hardship for the health care system economics [8–1].

Mitral PVL is well-known complication after MVR, comprehensively presented in the scientific literature. Clinically significant mitral PVL can cause heart failure, hemolytic anemia or a combination of both [12]. Its reported incidence at follow-up can vary from 2% to 17% and sometimes

reported as high as 32% by intraoperative and early postoperative transesophageal echocardiography (TEE) findings [13–16]. Various risk factors for mitral PVL were described in global literature, such as failure to control the infection in patients with infective endocarditis, use of bioprosthesis, the continuous suture technique to implant the prosthesis, mitral annular calcification and others [13, 17-20]. Unfortunately, no definitive conclusion on this subject has been made yet. Medical treatment of mitral PVL delivers temporary relief [21]. For many years repeat surgery with cardiopulmonary bypass has been the only available effective therapy for the treatment of clinically significant PVL, despite significant mortality associated with severe perioperative morbidity [22, 23].

The recent accelerated advancement of transcatheter percutaneous treatment modalities for structural heart diseases and a great need to reduce postoperative morbidity and mortality in the treatment of mitral PVL has driven medical professionals along with the medical industry to introduce into clinical practice less invasive treatment. [24–26]. This less invasive treatment technique is catheter-based PVL closure.

Undeniably, during the past decade, this treatment option has gained global spread, and in some places has become a first-line treatment modality. Nevertheless, the comprehensive long-term outcomes of surgical or transcatheter interventions for this complication are largely unknown and there is a fundamental lack of data on this issue in global literature. This absence of comprehensive retrospective or prospective data originates from the deficit of uniform definitions to determine the significance of the disease, clinical endpoints to assess safety and efficacy, and appropriate single and composite endpoints to assess outcomes [27]. Additionally, many questions in the occurrence of mitral PVL and its treatment have not been extensively investigated globally and in Lithuania. Our research aims to establish true incidence of PVL after isolated MVR in the Lithuanian population, also to find the most relevant risk factors for its incidence. Besides that, we compare the

novel catheter-based transapical treatment procedure with a “purpose specific” device to conventional repeat cardiac surgery in the management of this dangerous complication.

1.2 Value and novelty of the research

Early and late outcomes after MVR, the incidence of PVL and the risk factors for its occurrence have never been comprehensively explored among the Lithuanian population. This research will help to establish the early and late results among patients after MVR, incidence and risk factor for mitral PVL appearance among the population who underwent isolated MVR at a high volume cardiac surgery center.

Infective endocarditis, the continuous suture technique to implant a prosthesis and mitral annular calcification are established risk factors for the development of mitral PVL in the literature [13, 17–20]. If the patient and treatment-related clinical risk factors for mitral PVL are managed in a timely manner and properly by applying evidence-based approach, the incidence of this undesirable complication can be reduced and the patients’ treatment outcomes improved. This can be achieved by avoiding clinical errors and the application of team-approach in decision-making during the operation and perioperative management of the patient [28-30]. Risk factors for mitral PVL found in the literature can be governed by adequate medical treatment and the improvement of the surgical skills and techniques within the framework of evidence-based literature. Thus, we hypothesize that change in practice in clinical decisions made by physicians and avoidance of errors during the treatment of the patients undergoing MVR can eliminate or reduce the incidence of various complications, including mitral PVL. To apply this in practice, firstly, the question of most relevant risk factors has to be answered. Taking into consideration the statement above, to establish risk factors for mitral PVL, we decided to widen the pool of the investigated disease-related risk factors compared to the ones found in contemporary literature. In addition, we made

the decision to investigate the physician as a risk factor for mitral PVL formation; previously it has not been investigated in the literature as a potential factor that influenced occurrence of mitral paravalvular dehiscence.

Another novelty of this research lies within the comparison of the treatment modalities for mitral PVL. Due to the previous lack of proper guidelines on PVL treatment and the widespread use of “off label” devices for paravalvular defects, scanty data for outcomes for mitral PVL treatment modalities is currently present in the literature. Despite the deficit of comprehensive prospective randomized data, the American Heart Association/American College of Cardiology has granted catheter-based PVL closure the Class IIa recommendation to apply in practice for high risk surgical patients [31, 32]. These recommendations based only on incontrovertible facts and statistics collected from case series and registries [31]. The available data are very heterogeneous where different devices to treat this complicated pathology are used, various access sites for the catheter entry employed, data on different valve prosthesis analyzed in the same paper and mostly short terms outcomes are presented [25, 33, 34]. Clinical trial principles and endpoint definitions for paravalvular leaks in surgical prosthesis were published only a little over a year ago [35]. A specifically designed and manufactured occlusion device for paraprosthetic defect closure was introduced into clinical practice a few years ago [36]. In the research we investigate and compare results of the conventional redo surgery with cardiopulmonary bypass versus surgical transapical catheter-based mitral PVL closure with a “purpose specific” device. According to the literature search we performed, such homogenous groups have not been compared yet.

The practical value is to prove that the novel technique of mitral PVL surgical treatment is safer and not inferior in terms of reduction of paravalvular regurgitation, compared to conventional re-do surgery with cardiopulmonary bypass. In addition, to demonstrate that transapical catheter-based mitral PVL

closure can be introduced into routine clinical practice with confidence and is feasible.

1.3 Aim of the research

The aim of this research is to establish, effectiveness and safety of the two treatment modalities for mitral PVL, thus compare conventional redo surgery with cardiopulmonary bypass versus surgical transapical catheter-based closure with “purpose specific” device.

1.4 Tasks of the research

1.4.1 To determine the incidence of the clinically significant mitral paravalvular leak among the patients following mitral valve replacement at tertiary hospital in the period from 2005 to 2017.

1.4.2 To establish the most relevant risk factors for mitral PVL occurrence among the patients following mitral valve replacement at tertiary hospital in the period from 2005 to 2017.

1.4.3 To establish early and late mortality rates among patients following mitral valve replacement at tertiary hospital in the period from 2005 to 2017.

1.4.4 To compare the early effectiveness and safety between conventional redo surgery with cardiopulmonary bypass and surgical transapical catheter-based closure with a “purpose specific” device for mitral PVL.

1.5 Theses to be defended

1.5.1 The incidence of the clinically significant mitral paravalvular leak among the patients following mitral valve replacement at tertiary hospital in the period from 2005 to 2017 does not differ from the data found in the literature.

1.5.2 The most relevant mitral PVL risk factors are related to mitral valve lesion etiology and perioperative surgical components related to the physician provided the treatment.

1.5.3 Surgical transapical catheter-based closure of mitral PVL with a “purpose specific” device from the point of regurgitation reduction of view is not inferior to conventional redo surgery with cardiopulmonary bypass.

1.5.4 Surgical transapical catheter-based closure of mitral PVL with a “purpose specific” device is safer in the early postoperative period compared to conventional redo surgery with cardiopulmonary bypass.

2. LITERATURE REVIEW

2.1 Method and design of the literature review

The literature search strategy combined two stages. PubMed and Google Scholar were the online search engines we used for all type of articles. The Cochrane Library was employed for systematic reviews or meta-analyses type of papers.

For the first part of the research, the following key words “mitral valve replacement results”; “mitral paravalvular/paraprosthetic leak incidence”; “mitral paravalvular/paraprosthetic leak risk factors” were used in various combinations. Overall, 583 articles were found. After the final selection, only 80 relevant to our research problem remained.

For the comparison of effectiveness and safety of mitral PVL treatment modalities, the following key words “mitral paravalvular leak surgical treatment”; “mitral paravalvular leak surgical catheter closure comparison” were used in various combinations. Overall, 324 articles were found. After the comprehensive selection, only 98 remained relevant. A manual review of all selected article abstracts was conducted, discarding not relevant papers, in total 57 publications were left. Narrowing down the literature pool to the publications in which conventional redo surgery is challenged by the catheter-based procedure, only five direct comparison publications and one meta-analysis remained.

Additional sources of literature or citations, especially historical ones (published before the year 2000) which were of the cornerstone value, were handpicked from the articles of a special relevant interest.

2.2 Mitral valve replacement

Since the very beginning of the cardiac valve surgery to the degree of its development as we know it nowadays, the course of many cardiac valve

diseases was profoundly influenced by various means of treatment. Availability of diverse cardiac surgical techniques and promising treatment modalities improved the pathway of serious heart diseases regardless of whether these means are curative or palliative [37].

Patients with significant mitral valve lesion can be treated medically. Unfortunately, often the effect is temporary and further delaying the surgery can turn patients with heart failure refractory to medical treatment. Clinical management of such patients is challenging and death or the need for surgery is almost unavoidable within ten years after the diagnosis [38, 39]. Medically treated patients with significant mitral valve pathology can have a ten-year survival rate as low as 27%, which produces surplus mortality, compared with the expected survival rate. The prognosis in medically and surgically treated patients is in favor of surgical treatment [40].

Regardless the mitral valve pathology, for many years MVR was the gold standard surgical treatment option in clinically significant cases [41]. Despite the development of the mitral valve repair techniques for degenerative mitral valve disease, MVR remains the treatment modality of choice for all types of mitral valve lesion etiology [42-44]. The main objectives and goals of surgical treatment modalities in patients with significant mitral valve lesion are to improve symptoms and the quality of life, reduce heart failure related hospitalizations, and potentially improve late and early survival [7].

MVR is a well-established and widely acknowledged safe procedure with low mortality rate; unfortunately, despite refinements in the design of artificial cardiac valve prostheses and surgical operative techniques it is not free from complications in the early or late postoperative period [15, 45].

2.3 Main complications following MVR

Wide variety of valve-related complications can occur after mitral replacement, substantially increasing patients' morbidity and mortality. Various acute and

late postoperative clinical issues after MVR that are related to the procedure can occur. These are acute and chronic heart failure, bleeding, stroke, thromboembolism, anticoagulant-related hemorrhage, prosthetic valve endocarditis, and valve dysfunction and often lead to serious disability or even death after surgical MVR [45]. As recommended by the Ad Hoc Liaison Committee for Standardizing Definitions of Prosthetic Heart Valve Morbidity released guidelines, morbidity is defined by structural valve deterioration, nonstructural dysfunction, valve thrombosis, embolism, bleeding event, operated valve endocarditis, repeat intervention on the valve [46]. In order to report in literature, any of morbidity related issues have to be determined by reoperation, autopsy, or clinical investigation. In MVR, structural valve deterioration refers to changes intrinsic to the valve prosthesis. It can be wear or erosion, fracture, poppet escape, calcification, leaflet tear, stent creep, and suture line disruption of a prosthetic valve component [47]. Nonstructural dysfunction refers to an issue that does not directly involve valve parts yet causes the dysfunction of mitral valve prosthesis (MVP) such as stenosis, regurgitation or hemolysis. These are entrapments by pannus, tissue, or suture, PVL, patient-prosthesis mismatch, inappropriate prosthesis positioning, and clinically important valve related anemia [48]. Valve thrombosis is a separate morbidity modality complication, defined as any thrombus attached to or near MVP that narrows blood flow path and interferes with prosthesis function [46]. Embolism is also separate morbidity modality that occurs in the absence of infection after the immediate perioperative period. Embolism can be present as a neurologic event or a non-cerebral embolism. A bleeding event is any episode of major internal or external bleeding that causes death, hospitalization, or permanent injury or necessitates transfusion [46]. Bleeding event can be presented according to the Bleeding Academic Research Consortium (BARC) criteria [49].

2.4 Mitral PVL

Another non-inferior by its significance complication in the early and late postoperative course after MVR, compared with mentioned previously is PVL. Mitral PVL is a challenging complication occurring usually after MVR that is associated with significant morbidity and mortality [14, 15, 50].

According to the guidelines for reporting mortality and morbidity after cardiac valve interventions mitral PVL is referred to morbidity caused by nonstructural dysfunction [46].

In addition, according to some authors in the literature and in practice, mitral paraprosthetic defect is a severe and well-described complication after MVR [51]. It forms an abnormal mitral paraprosthetic atrioventricular communication between the implanted prosthesis cuff structure and the cardiac tissue (usually mitral valve annulus) the prosthesis was attached to as a result of a lack of appropriate sealing [51, 52]. This abnormal connection causes mitral regurgitation, which result in systolic retrograde flow from the left ventricle (LV) to the left atrium [53].

Mitral PVL can be small, thus it can remain clinically silent, and patients follow a benign clinical pathway; larger mitral PVL subsequently will develop serious clinical consequences [54].

Patients with mitral PVL can present with severe congestive heart failure. It is determined by significant left atrioventricular (mitral) regurgitation which progresses insidiously, because the heart compensates for constantly increasing regurgitant volume by enlargement of the left atrium and subsequently causes LV overload and a dysfunction [54].

2.5 Incidence and risk factors for mitral PVL

Paravalvular leaks occur in patients who have undergone MVR, with a wide diversity of frequency depending on the literary source [21]. Several factors are

known to increase the risk of periprosthetic dehiscence, such as mitral annular calcification, infection, the suturing technique to implant the prosthesis the size and type of the prosthetic valve [21, 55, 56]. The early development of mitral PVL is considered to be associated with the technical aspects of the surgical implant, while late mitral PVL is a common consequence of suture dehiscence caused by endocarditis or gradual resorption of incompletely debrided annular calcifications [21]. O'Rourke et al. has reported that advanced age, smaller body size, and degenerative valve disease were predictive determinants of trivial and mild PVL after MVR surgery in the early postoperative period [16]. The recent study published by Hassanin et al. found that among the patients who underwent isolated MVR the incidence of mitral PVL in the early postoperative period was 3.25% [57]. Compared to the statement by O'Rourke et al. it can vary from 5% to 32% depending on the period of follow-up [16].

In the study by Ionescu et al. a comprehensive analysis by TEE was performed for patients undergoing MVR. An initial TEE was made on the operating table in the early stages after surgery; the second study was made two hours after surgery in the intensive therapy unit; then at discharge and follow-up annually, the authors found that 32% of all mitral prostheses had paraprosthetic jets of various degree of regurgitant significance in the early period [14]. It is noticeable that in their research, 41% of the valves implanted in continuous suture technique fashion had paravalvular leaks, compared with 7% of those with interrupted sutures ($p = 0.001$). At follow-up of 1.8 years, paraprosthetic jets were documented in ten (15%) patients out of the 67 [14].

In contrast, almost two decades ago, Genoni et al. found infective endocarditis to be the most important underlying valve etiology for paravalvular defect formation, which complies with previous studies [15, 17].

It is also worth mentioning that PVL influenced the course of clinical trials. Such an event occurred with the Artificial Valve Endocarditis Reduction Trial which was designed to evaluate the efficacy of the silver-coated sewing ring to

reduce prosthetic valve endocarditis, based on studies documenting the safety and efficacy of silver for antimicrobial protection [58, 59]. Unfortunately, study was prematurely terminated due to the higher incidence of severe PVL in the tested prosthesis group [60]. Initially, a silver-coated sewing ring of the prosthesis was the primary risk factor; later, a comprehensive analysis of all the factors influencing higher incidence of major paravalvular leaks was performed. Investigators found that a PVL event occurred in 5.8% of patients in whom valve implantation was performed by the suture technique with no pledget use versus only 1.7% of patients with pledgets for prosthesis implantation. Final multivariable model showed that only the suture technique without pledgets was an independent significant risk factor for major paravalvular regurgitation events in the study [61]. Nonetheless, the study was prematurely terminated and this potentially superior prosthesis did not make it to the market.

Despite the fact that causes and predictors of PVL are still controversial, in the milestone study by Hammermeister et al. the authors have found that a probability of developing mitral PVL at follow-up of 15 years is 17% for a mechanical prosthesis and 7% for bioprosthesis [13]. In the cross-sectional study Skudicky et al. reported a 31% incidence of mitral paraprosthetic jets after MVR with a mechanical valve, two-thirds of which had been secured with continuous sutures [62]. In contrast to the studies mentioned above, Bonnefoy and colleagues reported lower prevalence of paraprosthetic regurgitation. The investigators found regurgitant jets in 14% of studied patients with transthoracic echocardiography (TTE) and transesophageal echocardiography within one day after MVR [20].

The continuous suture technique described by Wada has gained its popularity among surgeons; later it was challenged by various groups of investigators [19, 63–66]. Some of the authors have found that interrupted suture technique can account for 5.1% of the leaks, while a continuous polypropylene suture technique resulted in nearly three times as much – 14.0% [66].

In the publication by Dhasmana et al. out of the 435 patients who underwent primary MVR, 25 (5.7%) developed periprosthetic leak in a follow-up period of 37 months. Following multivariate analysis, the Cox proportional hazards model indicated that only the use of a continuous polypropylene suture was the only relevant factor [19].

In the relatively recent study by Wasowicz et al. from Toronto, following immediate transesophageal echocardioscopy on the operation table, among 218 patients who underwent MVR, 29 (13%) developed mitral PVL of various degrees of regurgitation, while moderate or severe was found in 9 (4%) patients. After adjusting for covariates, the overall presence mitral PVL was associated with an increased risk of sepsis after surgery [67].

Taking into account all the facts mentioned above, the incidence, causes and predictors of mitral PVL were comprehensively investigated in literature; unfortunately, the results found, vary significantly and are controversial.

2.6 Diagnosis and indications for mitral PVL treatment

Diagnosis of mitral PVL initially is based on the clinical scenario and depends on the leading syndrome. The majority of cases with symptomatic PVL present with congestive heart failure due to volume overload, others do present with symptoms of hemolytic anemia resulted in a shear stress to the red blood cells [21].

To determine indications for mitral PVL surgical or catheter-based treatment, establishing the defect by means of echocardiography is not sufficient, it has to come along with the symptoms of heart failure or hemolytic anemia and be proven objectively.

Usually, if heart failure occurs, until patients begin to complain they present with a New York Heart Association functional Class of III or higher [12, 68]. Due to the ease of its application, the New York Heart Association’s functional classification is widely implemented in multiple clinical studies, various

practice guidelines and in day-to-day clinical practice [69, 70]. It is often used as indication for treatment therapy as well for prognostic purposes and assessment of outcomes, unfortunately due to possible different interpretations by various physicians and patients it is a subject to misinterpretation and bias, thus sometimes making it subjective and unclear [71, 72].

One of objective and gold standard tests to evaluate the severity of the heart failure symptoms is a cardiopulmonary exercise test as it assesses patients' aerobic functional capacity; unfortunately, it is time-consuming and imposes an additional logistic and financial burden. [71, 73]. An alternative easy to apply in practice is a six-minute walk distance test, as it is simple, almost costless and very objective in grading the severity of heart failure [74, 75]. In the systematic literature review by Yap et al. the authors found strong correlation between the New York Heart Association Class III and IV and the six- minute walking test performance [71]. In addition, as the recommendation made by Guyatt et al. a six-minute walk should be performed, as it is a useful assessment of functional exercise capacity and a proper measure of treatment outcome in patients with heart failure [76].

Blood biomarkers can also show the significance of heart failure. For instance, an N-terminal pro-B-type natriuretic peptide and B-type-natriuretic peptide have been shown to be useful in making heart failure diagnosis; these biomarkers can also be tested to support or reject diagnosis of heart failure [77].

To confirm the diagnosis of hemolysis, a series of laboratory tests should be performed [78]. A variety of laboratory markers to distinguish hemolytic anemia exists [79]. In the routine clinical setting, clinicians usually perform hemoglobin, lactate dehydrogenase, haptoglobin concentrations and reticulocyte count in the blood. [78, 80–82]. Hemoglobin is the most direct indicator of clinical severity in hemolytic anemia [83]. The level of hemoglobin concentration in mild forms of anemia can be close to normal

values and considered to be above 100 g/L. In moderate forms of disease, it shifts between 80 g/L and 100 g/L; severe hemolytic anemia is confirmed with concentrations between 60 g/L and 80 g/L, and if it is very severe, it should be under 60 g/L [84].

Reticulocytes are the index of bone marrow hemopoetic capabilities and are usually increased in the scenario of hemolysis [78]. Reticulocyte count may remain within the normal range in patients with a properly functioning prosthetic valve in mitral position, as this condition usually implies subclinical hemolysis with normal or slightly decreased hemoglobin levels, but it should rise in the setting of hemolysis related PVL [85].

Lactate dehydrogenase is an enzyme located in the cytoplasm and is physiologically measurable in the serum due to the physiological cellular cycle and it is represented by five isoenzymes [86]. Isoenzymes Lactate dehydrogenase-1 and Lactate dehydrogenase-2 are produced in the red blood cells and in hemolytic status; lactate dehydrogenase concentration is often increased, so a detailed analysis of isoenzymes may be useful to rule out extravascular hemolysis [87].

Haptoglobin is a glycoprotein produced by the liver; it acts as a scavenger by binding serum-free circulating hemoglobin released by hemolysis or normal erythrocyte life cycle hemolysis [78]. Free-circulating haptoglobin levels are usually is significantly decreased during hemolysis due to its binding to free hemoglobin [81].

Overall, the diagnosis of hemolytic anemia related to mitral periprosthetic defects should not be based exclusively on the laboratory test and echocardiography findings, but rather on a complete clinical picture [12, 88].

2.7 Heart failure mechanism in mitral PVL

In practice of cardiac surgeon or cardiologist mitral PVL in some patients is an unavoidable late or early complication after MVR surgery, thus the

understanding of its pathophysiology is a benchmark for successful treatment [89]. In normal physiology, the mitral valve provides a unidirectional flow from the left atrium to the LV in a smooth and efficient fashion; mitral prosthesis should perform the same or at least close to native mitral valve function [90]. In mitral paraprosthetic atrioventricular communication, abnormal regurgitant flow from the LV into the left atrium occurs [52]. The developing mechanism of heart failure in mitral PVL is the same as in chronic or acute mitral regurgitation and depends on its severity measured as effective regurgitant orifice area [91]. Any mitral regurgitation yielding volume overload of the left chambers of the heart induces heart failure. The driving force of regurgitation (left-ventricular systolic function) and left-atrial compliance affects this volume dramatically [92].

As most of mitral paravalvular regurgitation is chronic, a gradually enlarged left atrium is compliant, thus able to receive regurgitant backflow from the LV without significant pressure increase, initially yielding benign clinical course of the patient [93]. Patients are often completely asymptomatic, and may produce normal results during cardiopulmonary stress testing or other physical activity. This might be the evidence that the absence of symptoms is based upon true physiological compensation for the existing pathological state [94]. The chronic mitral regurgitation leads to an enlarged thin-walled LV chamber due to the volume overload [95]. Such remodeling leads to increased LV compliance and enhanced filling, the mechanism whereby the large diastolic volume of mitral regurgitation is accommodated at almost normal filling pressure [96]. This remodeling increases the total LV volume, so that normal ejection creates increased total stroke volume and maintains effective systolic stroke volume and cardiac output within normal range values [90]. Long-term progression of regurgitation can determine effective regurgitant orifice progressive increase caused by paravalvular lesions enlargement [97]. In other words, mitral paravalvular regurgitation is the same as other mitral regurgitation, is self-maintained, leads to atrial and mitral annular enlargement

and subsequently increases regurgitant volume and atrial pressure [93]. Nevertheless, mitral paravalvular regurgitation further increases atrial pressure, which leads to pulmonary hypertension and heart failure [98-100]. The progression of symptoms due to mitral paravalvular regurgitation will gradually lead to decompensation of congestive heart failure and poor prognosis [101, 102].

Moreover, the risk of congestive heart failure and cardiac death is directly related to the severity of regurgitation. Particularly, patients with higher regurgitant orifice are at increased risk of congestive heart failure more than four times higher than patients without it with an absolute rate of survival close to 70% at five years [103, 104].

2.8 Hemolysis in mitral PVL

Since the implantation of the first mechanical prosthesis in the mid-twentieth century, hemolysis has been recognized as a potentially serious complication following valve replacement [105]. This complication rarely seen nowadays with normally functioning mitral prostheses unless encountered in the setting of nonstructural prosthetic dysfunction, especially with PVL [106]. Intravascular hemolysis is often considered an unavoidable consequence of paraprosthetic regurgitation [107]. Hemolytic anemia as a consequence of mitral paravalvular regurgitation is well recognized, but less frequent complication than heart failure [108]. The incidence, pathophysiology, natural history, and management of this less frequent issue is poorly understood [107, 109].

Mild degrees of intravascular hemolysis are common among patients with normally functioning prosthetic valves and can be found in between 40% and 85% of the patients; fortunately, in most cases, this scenario with hemolysis is subclinical [110–112]. Nevertheless, in up to 15% of patients, hemolytic anemia can be severe enough and may cause either death or necessitate replacement of the prosthesis [113, 114].

Several mechanisms can contribute to the development of hemolytic anemia both with normal and with malfunctioning prosthetic valves. These pathophysiology mechanisms are related to the theories of shear stress, contact with foreign material, turbulence of the blood flow, pressure fluctuations and intrinsic abnormalities of the erythrocyte membrane [115].

Historically the mechanism of developing hemolysis was relatively small effective orifice area in a “ball-in-cage” prosthetic valve, with observed incidence between 6% and 15% [107, 116]. With the improvement of prosthetic valve models from “ball-in-cage” type to “tilting disc” and the development of bioprothetic valves with increased effective orifice area, the incidence of hemolysis with normally functioning valve prosthesis was significantly reduced [117]. The absence of severe degrees of hemolysis in normally functioning prosthetic valve relates to the use of a newer generation of prosthesis models [55]. Mecozzi et al. hypothesize that modifications of valve design can contribute to minimize the occurrence of hemolysis in mechanical prosthesis [85].

Other authors also state that hemolysis can be caused by imperfections in the design of old-generation prostheses, currently the development of PVL is more frequently the main reason [118].

Mechanical destruction of erythrocytes by intracardiac foreign bodies following a cardiac operation has been a well-known phenomenon since some authors reported that synthetic material of the prosthesis could cause hemolysis after repair of an endocardia1 cushion defect [119].

Some hypothesize that pathogenesis of the mechanical hemolysis after mitral replacement is the shearing stress generated between the foreign body surface of the synthetic cuff and erythrocyte; it destroys the membrane of the red blood cells [110, 120]. It has been experimentally demonstrated that a shearing stress of more than 3,000 dynes/cm^2 could increase the hemolysis significantly; it also been calculated that according to the Bernoulli's equation, stenosis with a

pressure gradient of 50 mmHg can generate a shearing stress of 4,000 dynes/cm^2 [121].

According to other authors, the shearing stress is directly proportional to the square of the blood velocity that passes the stenosis area [122]. Consequently, paravalvular leakage following native MVR has a great potential to cause hemolysis. Due to left ventricular contractile force directly striking mitral PVL during systole, the shearing stress should be considered as great as the pressure gradient between the LV and the left atrium during systole [113].

In the fundamental study by Garcia et al. the geometry of the regurgitant paravalvular flow was classified into five patterns. The classification recognized “Fragmentation” jet that is divided by a solid structure. “Collision” jet occurs due to its sudden deceleration by a solid structure. “Acceleration” regurgitant jet occurs through a small orifice defect, with no direct impact on any solid structure. “Free” jet occurs through a large diameter of the defect and reaches the dome of the left atrium. “Slow deceleration” jet originates from a large eccentric orifice that is deflected in a curved trajectory along the atrial wall. After computer flow simulation they concluded that clinical hemolysis in patients with prosthetic mitral regurgitation is associated with distinct patterns of flow disturbance and are associated with high shear stress [115].

Following the comprehensive understanding of the pathophysiology mechanism of hemolytic anemia in mitral PVL and despite that the incidence is limited to a few percent, nonetheless it remains an indication for surgical treatment in clinically significant cases [16, 123].

2.9 Diagnosis confirmation with imaging modalities

Initial diagnosis of mitral paraprosthetic dehiscence can be challenging, and clinical presentation of patients mainly depends on the severity of regurgitation. It is basic knowledge that auscultation should be the first approach in patients with previously implanted prosthetic mitral valve and the

presence of new holosystolic murmur over left sternal border should trigger the suspicion of mitral paravalvular defect [124]. However, murmurs are frequently soft and can consequently be undetected by auscultation [68].

Therefore, clinical diagnosis in such a scenario is extremely unreliable; historically a number of attempts have been made to use non-invasive techniques in order to improve diagnostic accuracy [125]. Until the period of echocardiography a definitive diagnosis of mitral paraprosthetic leak were made by left ventriculography, although it can carry a significant risk [126].

Later, based on the study performed by Miller et al. echocardiographic findings alone became sufficient to recommend high-risk operation in a severely ill patient with mitral PVL [125].

In the current period, a diverse a pool of imaging techniques comes into play.

Already for quite some time a few imaging modalities, in particular echocardiography, have been the gold standard for the assessment of native cardiac valves as well prosthetic [124]. Following primary clinical diagnosis of mitral PVL, the first line approach to visualize the defect is to perform transthoracic echocardiography [127].

2.9.1 Transthoracic echocardiography

Initially, two-dimensional (2D) echocardiography imaging comprehensive evaluation should be done to assess the basic prosthetic valve characteristics with attention paid to a prosthetic valve leaflet morphology, mobility and its position in the sewing cuff [124].

The initial approach to identify mitral prosthetic regurgitation is similar to native mitral valve and requires the assessment of multiple color Doppler flow imaging [128].

Additional parameters regarding other echocardiographic indirect signs, such as the size of LV, hypertrophy of the cardiac chambers, systolic function,

pulmonary artery pressure, other valve morphology and function, should be assessed [129]. It should be imperative to compare the measurements obtained with previous examinations because variations in gathered echo data are the initial manifestation of suspected hemodynamically significant paraprosthetic valve regurgitation [130].

Although TTE has the ability to obtain regurgitant flow through color Doppler, it is extremely limited by the presence of acoustic shadowing generated by the prosthesis, and brings the potential to dissolve the severity of mitral paravalvular regurgitation [124].

It should be noted that negative TTE findings do not rule out the presence of mitral paravalvular regurgitation due to its low negative predictive value [131].

In cases of suspected mitral PVL on TTE, the evaluation of mitral prosthesis and its function must be followed by transesophageal echocardiography study to confirm or rule out the diagnosis [127].

2.9.2 Transesophageal echocardiography

Transesophageal echocardiography is highly sensitive and specific in detecting paraprosthetic mitral regurgitation and assessing it in detail. It should be the cornerstone tool in daily practice for precise assessment of mitral paraprosthetic regurgitation [131-133]. Often mitral paravalvular flow on color Doppler has a characteristic signature of jet which drives from the LV into the left atrium outside the sewing cuff of the prosthesis and often projects into the left atrium in an eccentric stream fashion [128]. Transesophageal four chamber, two-chamber and long chamber views allow detailed visualization of the left atrium and the prosthetic sewing cuff in order to identify paraprosthetic defects [124]. As mitral paravalvular regurgitation may be present at any location of the prosthesis circumference, thus it is imperative to inspect it in multiple planes [128].

It is also imperative to perform assessment with detailed scanning of the sewing ring using color Doppler in multiple angles. This should detect prosthetic mitral regurgitation and differentiate physiologic flows from pathologic ones and paravalvular from mechanical prosthesis “washing” regurgitation jets [134]. Once the mitral paravalvular regurgitation is identified TEE is also helpful for superior quality acquisition of other data related with regurgitation severity [135]. Transesophageal echocardiography examination and the use of off-axis views delivers better visualization of PVL stream throughout its entire channel, facilitating the alignment of continuous-wave Doppler utilizes continuous transmission and reception of ultrasound waves [124]. In addition to other parameters, evaluation of continuous-wave Doppler recording sets estimation and quantification of the severity of regurgitation [134]. Moreover, the role of TEE test in mitral paraprsthetic defects is essential to define the pinpoint origin and mechanism of regurgitation jet and to assess indirect signs of the severity of regurgitation [136]. For instance, systolic flow reversal in pulmonary veins has been correlated with the severity of mitral PVL [137]. The assessment of PVL can be challenging and requires integrative approach [128]. For mitral prosthetic regurgitation, qualitative color Doppler features are the initial approach used for assessing paravalvular regurgitation severity [138].

A variety of guidelines and expert statements has used a mild-moderate-severe grading scheme; the angiography uses a four-class scheme to report the severity of regurgitation. These have many downsides, since intermediate grades cannot be reliably determined. [139, 140]. To overcome this issue, in the recent expert statement the authors recommend to determine paravalvular regurgitation in accordance with the unifying five-class scheme where the grades of “trace”, “mild to moderate”, “moderate”, “moderate to severe” and “severe” are described in detail [138, 141]. The importance of detail and accurate evaluation of the severity of paraprosthetic regurgitation lies within the understanding the prognosis since patients with moderate to severe or

severe regurgitation are at greatest risk for two-year mortality and readmission to treat heart failure [142, 143].

Notably, TEE is not only essential to identify and establish the severity of paravalvular regurgitation, but it can also accurately identify the shape and size of the defect [144]. This is of paramount and fundamental significance in selecting the treatment strategy whether it is a catheter-based procedure or open-heart redo surgery [124].

Here three-dimensional (3D) TEE whose role is probably irreplaceable comes into play.

2.9.3 3D transesophageal echocardiography

Over the recent years' technical progress and immense contribution of medical professionals in echo imaging have allowed the development of 3D echocardiography to improve drastically diagnostic precision and to overcome limitations of 2D echocardiography, especially in the dynamic field of valvular heart disease. [124, 145, 146].

The use of multiplane transesophageal echocardiography views to reconstruct 3D images enabled the visualization of valvular anatomy from previously impossible orientations acquired with 2D echocardiography [147]. The ease and speed of data acquisition along with the ability to show cardiac structures using unique 3D images has determined rapid integration of 3D TEE into clinical practice and into diagnostic and treatment-guiding processes of mitral PVL [148, 149]. In the evaluation of prosthetic heart valves, 3D TEE, regardless the presence of color Doppler, provides outstanding results for diagnosis and description of all-type prosthetic valve dysfunction and particularly accurate for the diagnosis of mitral paravalvular defects, even sometimes compared with direct surgical inspection [124]. It is also worth mentioning that 3D TEE allows the evaluation of prosthetic valve details, such

as the sewing ring, mobility of the leaflet and the presence of any paravalvular defect etiological details such as vegetation, abscesses, dehiscence [149, 150].

Specifically, the 3D zoom modality can deliver facing forward views of the mitral valve and for the comfort to observe, the mitral valve image, can be viewed from the left atrial perspective, thus rotated to a “surgical view” position [145].

With 3D TEE dehiscence sites can be relatively easy to identify, paying particular attention to defect location, shape, size and area [150].

Full volume data acquisition provides wider angle images with higher temporal resolution, after data acquired, its sets can be rotated, manipulated and cropped to obtain optimal exposure of paravalvular defects [145].

Three-dimensional color flow can be used to confirm the presence of paravalvular orifice. [144]. In mitral valve dehiscence this tool provides incremental information regarding the exact anatomic characteristics of the dehisced area and information on the relationship between the dehiscence, mitral regurgitation jet and adjacent anatomical structures [150, 151]. Despite the fact that 3D TEE delivers comprehensive information and allows the assessment of mitral paravalvular defect in smallest detail it also has limitations. Proper and comprehensive assessment of the mitral prosthesis and its paravalvular defects can be challenging and technically demanding, because it requires high-quality image acquisition, to achieve expert level skills an echocardiographer has to undergo, a complete and extensive training process [124].

2.9.4 Cardiac computed tomography in mitral PVL

Despite echocardiography being the mainstream technique for prosthetic mitral heart valve evaluation, latest advances in computed tomography technology allowed adequate assessment of most present-day prosthetic heart valves and their pathology [152–154].

Even more, in the meta-analysis published three years ago, the authors showed that computed tomography delivered sufficient information about detecting etiology of valve obstruction and damage caused by infective endocarditis, without a clear superiority over echocardiography for the detection of periprosthetic regurgitation. [153].

In recent years, electrocardiography-gated computed tomographic angiography with 3D and four-dimensional reconstruction using volume-rendering techniques has settled well its serviceability as a legitimate technique to help physicians in the evaluation of mitral paravalvular regurgitation [124]. A recent study by Suh et al. compared computed tomography with 2D TEE showing very similar sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy in the revelation of mitral PVL [152]. Besides, it provides topographic evaluation of mitral PVL and can be very helpful in the planning of the catheter-based procedure [155]. Moreover, computed tomographic angiography is useful for describing distance of prosthetic separation from native cardiac structure, which results in mitral PVL, calcification and course of the defect channel [156].

Computed tomography-obtained data can be employed in 3D printing of the heart to assist the physician in better understanding the spatial relations between paravalvular defects and surrounding structures [157].

Despite all mentioned benefits, computed tomographic angiography has its drawbacks. These are artifacts from dense surrounding structures, such as metal parts of mechanical prosthetic valves or extensive calcifications, can limit defect size calculations. In addition, the use of intravenous contrast media puts patients with impaired renal function to the risk of development of contrast-induced nephropathy. Usually patients with dysfunctional prosthetic valves are older and there is less concern over radiation exposure. However, recent advances in computed tomography techniques allows scanning in markedly reduced parameters for ionizing radiation exposure and provides safe

evaluation even for younger patients [124, 138, 158, 159]. Due to the statement above, the role of cardiac computed tomography in the evaluation of mitral PVL in general is only complementary to the data obtained by TEE, thus the use of cardiac computed tomography should be balanced with associated risks and benefits gained [124].

2.9.5 Cardiovascular magnetic resonance

Current guidelines for management of valvular heart disease advice TTE as the cornerstone imaging modality to follow patients with heart varve regurgitation [32, 160, 161]. Despite that for more than 20 years now, cardiovascular magnetic resonance for medical professionals has become a tempting imaging technique for the evaluation of cardiac valvular heart disease [162, 163].

The important function of cardiovascular magnetic resonance in evaluation of the heart valve performance is the ability to accurately assess and quantify regurgitant volume [164]. It provides accurate and easily reproducible direct quantification of valvular regurgitation; for this reason, cardiovascular magnetic resonance has been recognized globally as the non-invasive gold standard for quantification of regurgitant volumes. [138, 164]. As cardiac magnetic resonance delivers unambiguous and direct assessment of regurgitant stream volume, which is the criterion of paramount importance for severity classification in mitral PVL [124, 165, 166]. This investigation tool can be especially beneficial to distinguish the severity of mitral regurgitation among patients in whom echocardiography results remain questionable, or in cases when there is significant disparity between the echocardiographic grading of regurgitation severity and clinical status of the patient [164]. Its other advantage for PVL assessment is the capacity to establish regurgitant volumes irrespective of the number of regurgitant jet or morphology [167].

Despite cardiac magnetic resonance persistently exhibited high accuracy and reproducibility of measurements, it also has technical and logistic limitations. It requires high-quality images and an experienced specialist also, prosthesis

associated and motion artifacts; various rhythm disturbances, compromise the accuracy of measurement and significantly affect the quality of investigation, not to mention increased costs and the irregular access to scanners [124, 166]. Until studies have showed this method's superiority in all cut point values evaluating mitral PVL over the conventional investigation methods, it will remain additional investigation or replacement when transesophageal echocardioscopy cannot be performed [124, 138].

2.9.6 Value of imaging techniques in mitral PVL

Since whenever imaging modalities began to play a significant role in diagnosis of mitral PVL, in comparison of noninvasive or semi-invasive diagnostic imaging technique most of the studies rely on true surgical findings during repeat surgery [152, 168].

Unfortunately, not many studies investigate the value of imaging modalities specifically for such relatively rare pathology as mitral PVL and even fewer compare them between or to surgical findings [134, 152, 169].

Despite that, few literary sources are available, most of them are only of a historical value and the findings cannot be applied in modern practice. Nevertheless, the value of TEE diagnosing mitral PVL has not changed over the years [128]. In the 1991 study by Khandheria et al. in in order to establish sensitivity and positive predictive accuracy comparison between TEE and surgical findings was performed and the authors found that sensitivity to establish mitral PVL by TEE was 96% with positive predictive accuracy at 98% [170]. In addition to TEE in diagnosis making of mitral PVL electrocardiogram-gated cardiac computed tomography has gained its advisable role [171]. In the recent study published by Young Joo et al. the authors have established sensitivity at 96.9%, specificity at 97.8%, positive predictive value at 96.9%, and negative predictive value at 97.8% for electrocardiogram-gated cardiac computed tomography. While for TTE sensitivity was 81.3%, specificity was 95.6%, positive predictive value was

92.9% and negative predictive value was 87.8%, TEE results were similar to computed tomography and were 96.2%, 95.8%, 96.2%, and 95.8% respectively [152]. Despite the statements mentioned above, the use of cardiac computed tomography in the evaluation of mitral PVL should be balanced between the associated risks and benefits gained and its role will remain advisory.

2.10 Treatment of mitral PVL

2.10.1 Medical therapy

Medical treatment of symptomatic mitral paravalvular regurgitation is to a great extent palliative not curative. [21]. In patients with symptoms of heart failure pharmacological management with loop diuretics for afterload reduction provide relief from the symptoms and signs of pulmonary and systemic venous congestion [172].

Unless contraindicated or intolerance occurs, addition of a low-dose of aldosterone antagonist should be prescribed for all patients with severe symptomatic heart failure [173].

In addition to medical therapy described above, as supported by randomized controlled trials patients with mild to severe symptomatic heart failure should be treated with angiotensin converting enzyme inhibitor combined with b-blocker, it is proven to reduce untimely mortality [174–176, 176–178].

In the paper by Shapira Y et al. in three patients with hemolytic anemia due to paraprosthetic regurgitation, relief was achieved in two with erythropoietin administration in deferring or obviating the need for repeat surgery; the third patient was refractory to treatment and had to undergo redo surgery [179].

To summarize, medical treatment in patients with clinically significant mitral paravalvular regurgitation will deliver interim relief of symptoms, either surgery or catheter-based closure will take place [21, 180]. The reduction of mortality due to progression of heart failure with medical treatment can be

achieved, but most likely temporary; in severe mitral paravalvular regurgitation corrective surgery should be undertaken [173, 181]. For those patients with clinically significant mitral PVL and having unacceptably high risk for redo surgery catheter-based therapy performed in the centers with expertise in the procedure should be advised [182].

2.10.2 Conventional redo surgery for mitral PVL

Up to one-tenth of the patients will require redo operation or catheter-based intervention for mitral PVL [183]. Conventional redo surgery for various issues has been around almost since MVR become available in the field of cardiac surgery [18, 184, 185]. Some authors report that previously elective/scheduled redo cardiac surgery with cardiopulmonary bypass for elective poppet replacement and strut debridement with valves were performed on a routine basis with a very low perioperative mortality rate [186].

In contrast to the patients with mitral PVL who are not experiencing symptoms of heart failure or hemolytic anemia in whom late outcomes are largely unknown; while for symptomatic ones the only definitive treatment modality was historically conventional redo surgery to the mitral valve [22, 50, 180].

Although transcatheter mitral PVL closure has emerged as a feasible and attractive alternative to conventional redo valve surgery; in many centers globally it is becoming the procedure of first choice [12, 25, 187]. Despite that conventional redo surgery historically was and currently remains the treatment of choice as it has been proven to reduce long-term mortality compared with conservative treatment [15, 188].

In contrast, four years ago the American College of Cardiology and American Heart Association Task Force on Practice Guidelines, released a statement that catheter-based PVL closure in centers with expertise in the procedure should be performed for patients at high risk for redo surgery and have favorable anatomy suitable for the procedure. [32, 189]. Nevertheless, conventional redo

surgery will remain in the armamentarium of treatment for mitral PVL for as long as such complication exists. This is due to the presence of various contraindications for catheter-based closure such as apical left ventricular aneurysm or thrombus; irreversibly high pulmonary hypertension; patients undergoing coronary artery bypass grafting or another valve surgery; more than one-third of prosthetic dehiscence; active endocarditis and failed catheter-based procedure [187, 190, 191].

Mitral valve PVL was and currently is the main cause of repeat interventions in patients after MVR [17, 192, 193]. Various debates took place whether to perform a high risk conventional redo operation for mitral PVL or not. The group from Ziurich in 2000 published by Genoni et al. revealed that results of conservative management of mitral PVL are poor, resulting in overall mortality of 26% at 134 months of follow-up, compared to 12% in surgically treated patients [15]. The authors also revealed that 30-day postoperative mortality for mitral valve reoperation was 6% [15]. In contrast, the report by Taramasso et al. showed 30-day mortality after conventional redo surgery for mitral PVL of 10.7%, with an overall actuarial survival rate of 39% at 12 years [194].

While the group from a Canadian cardiac center presented the paper by Bouhout et al. 30-day mortality was 8%, with the incidence of repeat intervention for bleeding at 8%. Acute renal failure with necessity for renal replacement therapy at 6%, postoperative stroke occurred in 2% and survival at one, five and 10 years was 82%, 71%, and 57% respectively [195].

Although a number of single center series have reported a dramatic reduction in operative mortality in repeat mitral valve conventional surgery during the last years, others still report 12% hospital mortality [196-199].

Such outcomes compared to natural course of significant paravalvular defects have resulted in general agreement that symptomatic patients with mitral PVL, despite significantly high early postoperative morbidity and mortality should be offered a corrective surgical procedure for mitral PVL [15].

Different causes for early and late postoperative mortality are named in the literature; those are advanced age at surgery, left ventricular dysfunction, urgent or emergent priority, increased heart failure status and pulmonary hypertension [196, 197, 199, 200].

Similar results for establishing risk factors for early and late mortality were detected from the multicenter European experience reporting hospital outcome undergoing redo mitral surgery [201]. In this multicenter experience following multivariable analysis the authors demonstrated that preoperative heart failure statement, acute infective endocarditis, preoperative LV performance and previous coronary artery bypass combined the use of antegrade and retrograde cardioplegia was associated with improved early survival [202].

As mentioned above high morbidity and mortality after redo surgery for mitral valve pathology occurs due to advanced age, deterioration of cardiac function, and limited other organ reserve, thus a necessity for conventional redo cardiac surgery has to be balanced against the potential benefits to the patient [196, 203].

Some report perioperative mortality as high as 22%, while others as low as 6% (who considered reoperation for mitral paravalvular defects to be low risk surgery) [15, 204, 205]. Nevertheless, there is no general definitive opinion on this subject. Generally, a variety of three surgical techniques is available to solve the issue of mitral PVL during conventional redo operation. If the defect is relatively small, “suture repair” can be employed, when dehiscence is substantially large the prosthesis is replaced with a new one or “patch repair” used [15, 27, 186]. According to different literary sources, “patch repair” or “suture repair” are used in up to three-quarters of the cases [15, 27]. Valve replacement is generally less frequent, except one literary source, where the vast majority of cases were treated in that manner [206–208]. The preference of treatment modality is left with the surgeon or specific center practice and usually depends on the size and complexity of mitral paravalvular defect.

Unfortunately, due to scanty data present on this subject in global literature, proper comprehensive comparison cannot be performed [209].

2.10.3 Catheter-based mitral PVL closure

In 1992 Hourihan et al. published first clinical experience with catheter-based PVL closure [210]. Eight years later, Moore et al. presented their single patient experience in a child with mitral PVL which was occluded with a coil. [211].

Then, a year later Eisenhauer et al. presented a successful case of prosthetic endocarditis induced severe mitral PVL. After adequate antimicrobial treatment the patient received catheter-based PVL closure with an occlusion device [212]. At the same time, Moscucci et al. performed another coil closure of the mitral PVL in a middle-aged male [213].

Then, a one of the first multiple patients clinical experience reports was published by Pate et al. where catheter-based mitral paravalvular defects closure was performed over a three-year period in nine patents; two types of occluders were employed with moderate success results [56].

Possibly, high rate of mortality and morbidity after conventional redo surgery, its burden on complicated postoperative care and rapid recent development various of catheter-based intracardiac procedures, have driven medical professionals alongside with the medical industry to introduce less invasive and possible better outcomes carrying treatment modality into clinical practice – catheter-based PVL closure [214].

Then the procedure popularity grown exponentially, various publications reporting mostly single center experiences, analyzing learning curve and risk factors for failure started to pour in to global medical literature [12, 188, 215, 216].

Since there were no guidelines to report outcomes and establish endpoints of the treatment, the data published was scanty and heterogeneous.

There was a global need of guidelines on how to report endpoints of the treatment as well morbidity and mortality related, subsequently a cornerstone document by the group of experts Clinical Trial Principles and Endpoint Definitions for Paravalvular Leaks in Surgical Prosthesis came to light a year ago [138].

Mitral paravalvular defects can be occluded by accessing prosthesis in a few routes, it can be accessed through the atrial septum so called percutaneous antegrade approach, then percutaneous retrograde transaortic approach and last but not least is the retrograde transapical approach, which can be surgical or percutaneous [217–219].

In general, the route selection is a choice of the surgeon, but it should be justified by the location of the mitral paravalvular defect, physicians' experience and mostly heart-team discussion [217, 220].

The retrograde approach can also be preferable as search and delivery catheters are not encountered with regurgitant blood flow [6].

Up to now, the results of larger patient series treated in transcatheter fashion for mitral paravalvular defects were analyzed only in a few papers and one recent literature meta-analysis [25-27, 207, 209, 221].

In the recent paper by Garcia et al. from HOLE (SpanisH real-wOrld paravalvular LEaks closure) registry, 333 cases of mitral catheter-based closure are presented. Unfortunately, only 30-day outcomes were presented, nonetheless all-cause mortality was 4.5%, and complications occurred in 19.8% [221]. Another downside of their paper as noted by Busu et al. is the definition of technical success of the treatment that described as the reduction of regurgitation by at least one degree, which is in conflict with recent recommendations that might have been influenced by other trials' inappropriate example [138, 209, 222].

Nevertheless, Garcia et al. reported that the technical success was delivered in 73.2% of cases [221]. The authors also state that an “off label” oblong device was associated with higher technical success rates in patients with mitral paravalvular regurgitation (HR 2.68, 95% CI 1.29 to 5.54, p=0.008), though it should be noted that this device was used in a vast majority (84.2%) of patients [209].

Wells et al. have presented reported early and one year results of 69 patients who were treated for mitral PVL in a catheter-based fashion; 30-day mortality was 7.1%, the occurrence of major complications 14%, rate of readmission 9% with the length of four-day stay. At one year, mortality rate was 16%, rate of readmission 23% and 9% underwent redo intervention in MVP [26].

At the end of 2017, investigators from the Montreal Heart Institute released their results in 69 patients who underwent catheter-based mitral paravalvular defect closure. In this study, procedural success in catheter-based procedure was achieved in only 55% of the cases with in-hospital death rate of 2.5% [27]. A composite of all-cause death or hospitalization for heart failure at one year was 44% and at three years of follow-up, it was 60%, adjusted by the Kaplan Meir estimator 47% and 70% respectively. While the rate of all-cause mortality was at 1 year 17% and at 3 years 31%, adjusted by the Kaplan Meir estimator 20% and 40% respectively [27]. Further analysis showed that a successful reduction of paravalvular regurgitation should be associated with lower rates of all-cause mortality and lower rate of composite all-cause death or hospitalization for heart failure [27].

The United Kingdom and Ireland registry results included 115 patients with mitral PVL. The authors revealed that in 60% of cases an “off label” oblong device was used, the overall hospital mortality was 3.9%, technical success or mild or less residual regurgitation was observed in 74.7% of the patients, and at follow-up of 110 days’ death occurred in 16%, only 6% required reintervention [25].

According to the study by Alkhouli et al. of Cano Clinic, the majority of patients (71%) were treated with an “off label” device, technical success was 70.1%, in-hospital morbidity and mortality were 7.7%, and 8.6% accordingly, the length of stay in hospital was 5.3 days, at follow-up of 4.0 years rate of reintervention was 11.3% [207]. To date, still scarce have been present in global literature. The results vary, for the reasons of various access sites used; a wide variety of devices is employed for closure of PVL and different understanding of procedural and technical success still exist. In general, it is promising treatment modality; unfortunately, it is too early to draw a definitive conclusion, since more studies are needed within the framework of recent recommendations [138].

3. METHODS

3.1 Study design and patients

This is a retrospective observational cohort study. The study was approved and permissions granted by the Vilnius Regional Biomedical Research Ethics Committee and State Data Protection Inspectorate. Research was performed into two stages. Every patient included into both stages of this research read and signed an informed consent form for the interventional procedure/operation approved by the hospital administration for either isolated MVR, conventional redo surgery for mitral PVL or transapical catheter-based closure of mitral PVL.

3.1.1 First stage: Incidence and risk factors for mitral PVL occurrence

For the first stage to establish clinically significant mitral PVL incidence and risk factors for its occurrence, we have selected patients who underwent primary isolated MVR from January 2005 until December 2017. To identify patients, we conducted automatic search for operation protocols in Vilnius University Hospital Santaros Klinikos electronic database ELI with the key

word in the title “mitral valve replacement”. A total of 1,308 patients corresponded to this primary search. Out of this cohort, we excluded patients who had had previous conventional MVR or repair surgery. Those undergoing concomitant aortic valve surgery were also ruled out, whereas that undergoing tricuspid repair surgery, coronary artery bypass grafting, arrhythmia ablation (Maze procedure) remained in the cohort. Patients who had significant absence of the variables were also excluded. In the final group for analysis, we had a cohort of 551 patients. This cohort of patients was analyzed as close as possible to the framework of guidelines for reporting mortality and morbidity after cardiac valve interventions [46]. The cohort of patients was investigated for preoperative clinical and demographic data, general and specific operative variables were analyzed. Early postoperative characteristics and complications where evaluated at 30 days or while in hospital. Mortality is presented as immediate, which is less than 72 hours after the indexed procedure, at 30 days or in hospital and overall at follow-up. Univariate followed by the Multivariate Cox Regression analysis was performed to establish most relevant patients, pathology and treatment-related risk factors for mitral PVL occurrence. To avoid any bias or personal influence on the results, the surgeons who performed MVR operations were coded in double blind fashion.

3.1.2 Second stage: A comparison of effectiveness and safety of mitral PVL treatment modalities

For the second stage of this research, to compare effectiveness and safety of mitral PVL treatment modalities, we retrospectively reviewed all patients who underwent conventional redo surgery or transapical catheter-based procedure for mitral PVL treatment from January 2005 until December 2017. In detail, the patient selection for this stage of the research is presented in Figure 1. Selection of the patients for this stage of the research is presented in detail in Figure 1. We conducted automatic search for operation protocols at Vilnius University Hospital Santaros Klinikos electronic database ELI, with the key word in the title “mitral paravalvular leak”. Eighty-six patients were identified

in this primary search. We excluded one patient who had active infective prosthetic endocarditis out of this cohort, one with the dehiscence of MVP more than one-third if the annulus perimeter and 11 patients who underwent mitral PVL transapical catheter-based closure with an “off label” devise (an occluder not designed for periprosthetic defect closure). Following this refined selection, we remained with a cohort of 73 patients. To compare effectiveness and safety of mitral PVL treatment modalities this cohort was divided into two groups and analyzed within the framework of recently published recommendations “Clinical Trial Principles and Endpoint Definitions for Paravalvular Leaks in Surgical Prosthesis” [138]. The group of patients underwent transapical catheter-based closure of mitral PVL with a “purpose specific” device was named “Catheter” and had 24 patients; while the other group of patients underwent conventional redo surgery for mitral PVL named “Surgical” had 49 patients. Preoperative clinical and demographic data, general and specific operative variables were investigated. These patients’ data were analyzed at baseline, perioperatively, at discharge, at six months and annually after the procedure. Early postoperative characteristics/complications were analyzed at 30 days or in hospital. Mortality is presented as immediate, at 30 days or in hospital and overall at follow-up. The effectiveness of the procedure was evaluated by prosthetic valve function and residual degree of regurgitation at discharge and annual follow-up. The safety was evaluated by occurrence of morbidity and mortality at in hospital and follow-up. Univariate followed by Multivariate Cox Regression analysis was performed to establish the most relevant patient, pathology and treatment-related risk factors for mortality at follow-up.

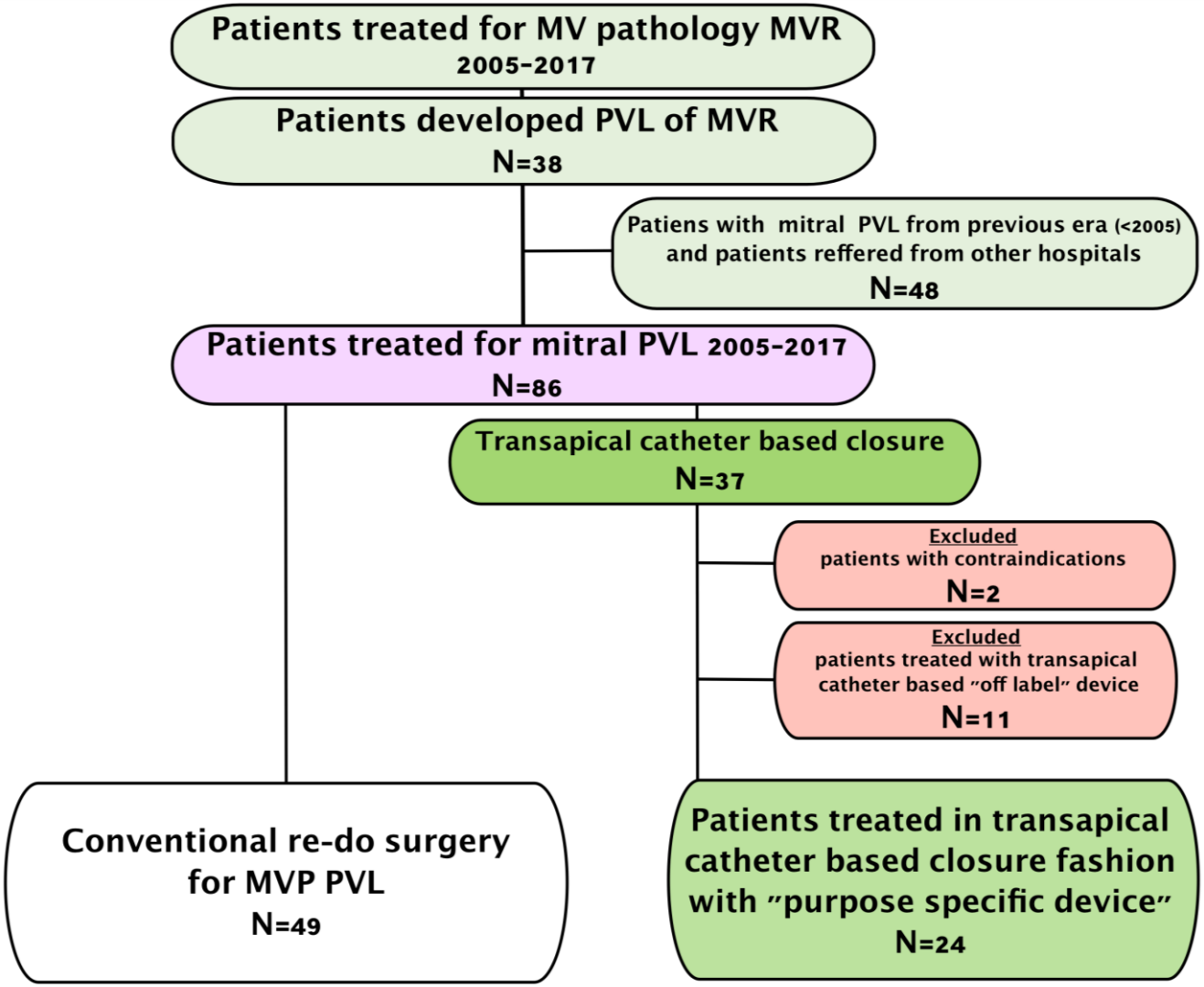

Figure 1. *Patients' selection pathway to compare effectiveness and safety of mitral PVL treatment modalities*

3.2 Statistical analysis

Statistical analysis was performed using the data collection and analysis software package SPSS 20.0 (IBM Corp., Armonk, NY, USA). The quantitative normality of continuous data was evaluated using the criteria of histograms, rectangular diagrams, and the Shapiro–Wilk test ($p < 0.05$). Quantitative data, distributed as normal are presented as a mean value ± standard deviation. The quantitative continuous data distributed outside the normal distribution were presented as the median and quartiles intervals. The categorical data were expressed as percentage. Freedom from moderate or severe residual paravalvular regurgitation, new or worsening hemolysis requiring transfusion, new or worsening prosthesis dysfunction and conversion to open surgery, mortality, stroke, rehospitalization for heart failure or treatment of hemolytic anemia were estimated using the Kaplan–Meier method. The censored data include patients who had follow-up terminated. *P*-value <0.05 is considered as statistically significant.

3.3 Establishment of the diagnosis of mitral PVL

All patients at the Vilnius University Hospital Santaros Klinikos after MVR are followed at 1, 4–6, 12 months and later annually in the outpatient cardiology clinic. Patients undergo routine cardiac physical examinations and are questioned for any clinical complains. Patients also undergo a routine electrocardiogram and TTE. In the scenario of mitral PVL suspicion, following initial diagnosis established by TTE, the shape, size and location of the defect is detailed using 3D TEE. The location of paravalvular defect described in a clock- adopted fashion [183]. The degree of paravalvular regurgitation is evaluated with 3D TEE with color Doppler and determined according to the unifying five-class scheme for paravalvular regurgitation severity [138, 141]. The prosthetic valve function and residual degree of regurgitation at follow-up was evaluated using transthoracic echocardiography. A 3D TEE with color Doppler at follow-up was performed in selected patients when the quality of TTE was not sufficient. To assess the indications and measure the response to

mitral PVL treatment in the “Catheter” group, a six-minute walk test was used to evaluate physical performance and individual patient success of those who presented with heart failure symptoms. The quality of life assessment has not been performed.

3.4 Establishment of the significance of mitral PVL

Five echocardiography specialists/cardiologists, using the combination of TTE and TEE imaging modalities, established a definitive diagnosis of mitral PVL. All of them have achieved accreditation by the European Association of Cardiovascular Imaging in TEE and TTE; moreover, each of those specialists’ yearly workload in performing TEE is over 200 cases. In order to maintain high quality imaging and two most experienced echocardiography specialists guide the transcatheter procedure.

As described in 2015 by Pibarot et al. and then suggested by Ruiz et al. in the "Clinical trial principles and endpoint definitions for paravalvular leaks in surgical prosthesis" to define the degree of paravalvular regurgitation we used the unifying 5-class scheme [138, 141]. This method was proposed to improve communication between members of various specialties of the heart team to dissolve misinterpretation between diversity of the grading schemes, and bring echocardiographic parameters closer to clinicians’ [138].

The unifying 5-class scheme defines degrees of mitral paravalvular regurgitation as trace, mild, mild-to-moderate, moderate, moderate-to-severe and severe.

3.4.1 Trace mitral PVL

In trace paravalvular regurgitation, structural parameters such as sewing ring motion, left atrium and LV size, the right ventricle size and function of the right ventricle and pulmonary artery pressures are usually within the normal range. Qualitative or semi quantitative Doppler parameters such as proximal flow convergence is absent. Color Doppler jet area is absent and mean pressure

gradient is normal. Diastolic pressure half-time is normal (<130 ms), vena contracta width is not measurable. Jet density measured with continuous-wave Doppler is incomplete or faint. Regurgitant jet profile measured with continuous-wave Doppler is parabolic. Pulmonary vein flow measured with pulsed waved Doppler has systolic dominance. The ratio between mitral valve flow and LV outflow tract flow is even (1:1). Circumferential extent of PVL across the perimeter of the mitral sewing cuff measured with color Doppler in trivial regurgitation should be not quantifiable. Quantitative Doppler parameters such as regurgitant volume should be less than 10 ml per systole and regurgitant fraction is under 15%. The effective regurgitant orifice area should measure less than 5 mm^2 [141].

3.4.2 Mild mitral PVL

Most of the parameters are similar to the trace regurgitation measurements. In mild paravalvular regurgitation, structural parameters such as sewing ring motion, the left atrium and LV and right ventricle size and function of the right ventricle as well pulmonary artery pressures are usually within the normal range. Qualitative or semi quantitative Doppler parameters such as proximal flow convergence is absent or minimal. The Color Doppler jet area is small, centrally oriented, usually less than 4 cm^2 or less than 20% of the left atrium area. The mean pressure gradient is normal. Diastolic pressure is normal (<130 ms) half-time, the vena contracta width is less than 2 mm. Jet density measured with continuous-wave Doppler is incomplete or faint. Regurgitant jet profile measured with continuous-wave Doppler is parabolic. Pulmonary vein flow measured with pulsed waved Doppler has systolic dominance. The ratio between the mitral valve flow and LV outflow tract flow is slightly increased. The circumferential extent of PVL across the perimeter of the mitral sewing cuff measured with color Doppler in mild regurgitation should be less than 5%. Quantitative Doppler parameters such as regurgitant volume should be less than 15 ml per systole and regurgitant fraction is under 15 %. Effective regurgitant orifice area should measure less than 5 mm^2 [141].

3.4.3 Mild-to-moderate mitral PVL

In mild-to-moderate paravalvular regurgitation, structural parameters such as sewing ring motion, the left atrium and LV and right ventricle size and function of the right ventricle as well pulmonary artery pressures are usually within the normal range. Qualitative or semi quantitative Doppler parameters such as proximal flow convergence is absent or minimal. Color Doppler jet area is small, centrally oriented, usually less than 4 cm^2 or less than 20% of the left atrium area. The mean pressure gradient is normal. Diastolic pressure half-time is normal (<130 ms), the vena contracta width is 2 mm to 3 mm. Jet density is measured with continuous-wave Doppler is variable. Regurgitant jet profile measured with continuous-wave Doppler is partial or parabolic. Pulmonary vein flow measured with pulsed waved Doppler has systolic dominance. Ratio between the mitral valve flow and LV outflow tract flow remains slightly increased. The circumferential extent of PVL across the perimeter of the mitral sewing cuff measured with color Doppler in mild-to-moderate regurgitation should be 5% to 10%. Quantitative Doppler parameters such as regurgitant volume should be 15 ml to 30 ml per systole and regurgitant fraction is under 15% to 30%. Effective regurgitant orifice area should be 5 mm^2 to 20 mm^2 [141].

3.4.4 Moderate mitral PVL

In moderate paravalvular regurgitation, structural parameters such as sewing ring motion should be normal or deviations should be insignificant. The left atrium and LV and right ventricle size should be normal or mildly dilated; the function of the right ventricle also can be normal or mildly decreased; while pulmonary artery pressures are usually variable. Qualitative or semi quantitative Doppler parameters such as proximal flow convergence are intermediate. Color Doppler jet area is variable. The mean pressure gradient is increased. Diastolic pressure half-time is normal (<130 ms), vena contracta width is 3 mm to 5 mm. Jet density measured with continuous-wave Doppler is dense. Regurgitant jet profile measured with continuous-wave Doppler is

partial or parabolic. Pulmonary vein flow measured with pulsed waved Doppler has systolic blunting. The ratio between the mitral valve flow and LV outflow tract flow should be intermediately increased. The circumferential extent of PVL across the perimeter of the mitral sewing cuff measured with color Doppler in moderate regurgitation should be 10% to 20%. Quantitative Doppler parameters such as regurgitant volume should be 30 ml to 45 ml per systole and regurgitant fraction is 30% to 40%. Effective regurgitant orifice area should be 20 mm^2 to 30 mm^2 [141].

3.4.5 Moderate-to-severe mitral PVL

In moderate-to-severe paravalvular regurgitation, structural parameters such as sewing ring motion should be normal or deviations should be insignificant. The left atrium and LV and right ventricle size should be normal or moderately dilated, the function of the right ventricle also can be normal or moderately decreased, while pulmonary artery pressures are usually moderately increased. Qualitative or semi quantitative Doppler parameters such as proximal flow convergence are intermediate. Color Doppler jet area is variable, while the mean pressure gradient is increased. Diastolic pressure half-time is normal (<130 ms), vena contracta width is 5 mm to 7 mm. Jet density measured with continuous-wave Doppler is dense. Regurgitant jet profile measured with continuous-wave Doppler is partial or parabolic. Pulmonary vein flow measured with pulsed waved Doppler has systolic blunting. The ratio between the mitral valve flow and LV outflow tract flow should be moderately increased. The circumferential extent of PVL across the perimeter of the mitral sewing cuff measured with color Doppler in moderate regurgitation should be 20% to 30%. Quantitative Doppler parameters such as regurgitant volume should be 45 ml to 60 ml per systole and regurgitant fraction is 40% to 50%. Effective regurgitant orifice area should be 30 mm^2 to 40 mm^2 [141].

3.4.6 Severe mitral PVL

In severe paravalvular regurgitation, structural parameters such as sewing ring motion can be variable. The left atrium and LV and right ventricle size should be moderately or severely dilated, the function of the right ventricle can also be moderately or severely decreased, while pulmonary artery pressures are usually severely increased (systolic pulmonary artery pressure >50mmHg). Qualitative or semi quantitative Doppler parameters such as proximal flow convergence is large, Color Doppler jet area is large (usually >8 cm2 or > 40% of left atrium area) or variable when wall impinging. The mean pressure gradient is higher than 5 mmHg. Diastolic pressure half-time is normal (<130 ms), vena contracta width is higher than **7** mm. Jet density measured with continuous-wave Doppler is dense. Regurgitant jet profile measured with continuous-wave Doppler is partial or parabolic. Pulmonary vein flow measured with pulsed-waved Doppler has systolic blunting. The ratio between the mitral valve flow and LV outflow tract flow should higher than 2.5. The circumferential extent of PVL across the perimeter of the mitral sewing cuff measured with color Doppler in moderate regurgitation should be higher than 30%. Quantitative Doppler parameters such as regurgitant volume should be more than 60 ml per systole and regurgitant fraction is higher than 50%. Effective regurgitant orifice area should be measured higher than 40 mm^2 [138, 141].

This grading scheme is not intended to replace the existing ones, but it can be applied as a scheme for the comprehensive clinical trials, may be simplified for the daily clinical use [138].

3.4.7 Monitoring residual mitral PVL at follow-up

All patients after mitral PVL closure at the Vilnius University Hospital Santaros Klinikos are followed at 1, 4–6, 12 months and later annually at the outpatient cardiology clinic. Patients undergo routine cardiac physical examinations and are questioned for any clinical complains. The prosthetic valve function and residual degree of regurgitation were evaluated using

transthoracic echocardiography. A 3D TEE with color Doppler at follow-up was performed in selected patients when the quality of TTE was not sufficient. To assess the indications and measure the response to mitral PVL treatment in the "Catheter" group, a six-minute walk test was used in order to evaluate physical performance and individual patient success of those who presented with heart failure symptoms. The quality of life assessment has not been performed.

3.5 Indications and contraindications for PVL treatment

All patients were assessed and discussed for the treatment modality at a heart team multidisciplinary meeting. Indications for the treatment either transapical catheter-based closure or conventional redo surgery were significant mitral PVL with symptoms of heart failure, symptomatic hemolytic anemia (hemoglobin less than 100 g/l or patients requiring red blood cell transfusions and all other reasons for anemia were excluded) or a combination of both [223]. Contraindications for the transapical catheter-based closure procedure were active prosthetic infective endocarditis and/or significant dehiscence of the mitral prosthesis (more than 1/3 of the prosthesis annular perimeter).

3.6 Endpoints of mitral PVL treatment

Primary endpoints after treatment were the absence of death, moderate or severe residual regurgitation, new or worsening hemolysis, and new or worsening prosthesis dysfunction, conversion to open surgery in catheter-based closure patients, stroke and readmission for heart failure or treatment of hemolytic anemia. [138]. Secondary endpoints were the absence of acute kidney injury (creatinine increase by 150% or higher compared with the baseline), and bleeding according to the BARC criteria (life-threatening or disabling and major bleeding) [49]. Acute kidney injury was assessed in accordance with the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines therapy [224]. The continued intended safety and performance of the device for the patients treated in transapical catheter-based

fashion was evaluated by the absence of occluder migration, embolization, detachment, fracture, worsening of hemolysis, or systemic emboli related to device thrombosis, erosion of bioprosthetic leaflet or surrounding tissue, transvalvular pressure gradient increase by more than 10 mmHg, reduction of paravalvular insufficiency without producing central valvular incompetence or stenosis [138]. Following this analysis, the aim is to compare effectiveness and safety of the both mitral PVL treatment modalities, conventional re-do surgery with cardiopulmonary bypass versus surgical transapical catheter-based closure with a "purpose specific" device.

3.7 Conventional surgery technique of MVR

With the patient under general anesthesia in supine position, surgery is undertaken through median sternotomy. After median sternotomy is performed, the pericardium opened in an inverted "T" letter fashion. Prior the cannulation intravenous heparin (300U per kg of the patient body) is administered, aiming for activated clotting time above 400 seconds. Aortic bi-caval cannulation is employed for cardiopulmonary bypass. Cardioplegia solution can be delivered antegrade into aortic root, retrograde into the coronary sinus or both. The surgeon makes the choice; it also depends on the presence or absence of significant coronary pathology. After the initiation of the cardiopulmonary bypass, the aorta is cross-clamped at the level of the distal ascending aorta and cardioplegia solution is delivered into coronary circulation. The exposure of the mitral valve is achieved through either left atriotomy below the Waterson groove or a transatrial incision [225]. When the complete asystole in diastole is achieved, mitral valve is exposed, in transatrial incision approach. If the exposure of the mitral valve is not sufficient, the incision is continued towards the dome of the left atrium. The valve is inspected for structural changes, presence of severe calcification and main lesion is identified. Native diseased mitral valve can be excised completely, or only anterior leaflet can be excised while posterior is left intact or complete chordal preservation technique can be employed [226]. Previously it was

believed and later proven by experimental observation and clinical experience studies that the retention and preservation of the mitral tensor apparatus at MVR, results in a better LV function postoperatively [227, 228]. The decision whether to perform chordal preservation is left for the surgeon's preference. Following valve excision, the mitral valve orifice is measured with an appropriately chosen prosthesis sizer. The choice of the prosthesis type (biologic or mechanical) is made during the discussion with the surgeon preoperatively or if the patient is not compliant with medical treatment the physician makes the choice. In general, two techniques to implant the prosthesis can be employed; it is either continuous or interrupted suture techniques. The surgeon based on the clinical judgement makes the preference. In general, when severe calcification of the mitral annulus is present, the continuous suture technique should not be used. MVR in a continuous suture technique fashion is described below. A double needle armed suture (size 2-0 monofilament polypropylene, some surgeons use size 2–0 ethylene terephthalate polyfilament) buttressed with a felt pledget is passed through mitral annulus posterior to anterolateral commissure. Suture is then passed through prosthetic sewing ring, and valve is lowered into native mitral annulus position. Using few throws, suture line is carried over the anterior aspect of the mitral annulus towards the posteromedial commissure, passing stitches from annulus to sewing ring and taking proper bites. Care should be taken to avoid damage to the underlying noncoronary cusp of the aortic valve. Suture is held on tension at the A2 aspect of the mitral annulus, midway across the distance to posteromedial commissure. The other end of the same suture, having been placed through the mitral annulus, is put into prosthetic sewing ring and continued from the annulus to the sewing ring. Using few throws, suture line is carried over the posterior aspect of the mitral annulus towards the posteromedial commissure, passing stitches from the annulus to sewing ring and taking proper bites. Care should be taken avoiding damage to the underlying circumflex artery. This end of the suture is held on tension as at the A2 aspect of the mitral annulus. A second double needle armed suture is begun

just posterior to posteromedial commissure. Both ends are carried with few throws in each direction, first anteriorly toward A2 and then posteriorly towards P2 aspects of the annulus, then approached to the opposite sutures tie with previously held ends. Knots will lie behind leaflet guards of bi-leaflet mechanical prosthesis in the setting of antianatomical position [229]. When the replacement of the mitral valve is complete, LV vent is placed through the prosthesis into the cavity of the ventricle, incisions of the atrial septum and right ventricle are sutured, cardiac chambers de-airing procedure is performed and aortic cross clamp is removed. After rewarming the patient and hemodynamics being stable cardiopulmonary bypass is terminated. Hemostasis is achieved with the protamine sulfate. Then median sternotomy is closed. All patients after MVR surgery are transferred to the intensive therapy unit and closely monitored for hemodynamic instability and postoperative bleeding.

3.8 Conventional redo surgery technique for mitral PVL

The procedure carried out in a standard cardiac surgery operating room with a cardiopulmonary bypass machine. Standard cardiac monitoring for adult redo surgery was applied. With the patient under general anesthesia in supine position, surgery was undertaken through redo median sternotomy. After redo median sternotomy was performed, a dissection of the adhesion undertaken, care should be taken to avoid damage to the heart or great vessels. Prior the cannulation of the great vessels, intravenous heparin (usually 300U per kg of the patient body weight) is administered, aiming for activated clotting time above 400 seconds. Cardiopulmonary bypass is established with aorto-bicaval cannulation. In case where a patent's internal mammary to the left anterior descending artery graft is present, or complications such as bleeding (due to damage to the heart or adjacent structures) occurred, cardiopulmonary bypass is initiated via the femoral artery and vein. Usually, for prompt access, the femoral vessels are surgically exposed before redo-sternotomy. After the initiation of the cardiopulmonary bypass, the aorta is cross-clamped at the level of the distal ascending aorta. Myocardial protection from ischemia is achieved

with antegrade or retrograde delivery of hyperkalemic cold blood cardioplegia and moderate systemic body temperature hypothermia. Following complete asystole, MVP was exposed through the right atriotomy and atrial septotomy, if the exposure of the mitral prosthesis was not sufficient, the incision continued towards the dome of the left atrium. The prosthetic valve is inspected for structural dysfunction, thrombosis also for pannus formation, and then PVL is identified. The decision on the mode of paravalvular defect repair is usually made by the surgeon's preference. Usually it is based on the size of the defect. If the defect is relatively small, "suture repair" can be employed. When the defect is substantially large the prosthesis is replaced with a new one. It is important that care should be taken when placing the sutures for defect repair or removing the prosthesis from the posterior aspect of the mitral annulus to avoid the circumflex artery damage. Damage can cause perioperative myocardial infarction with undesirable postoperative clinical sequel. When the repair of the defect or replacement of the prosthesis is complete incisions of the atrial septum and right ventricle are sutured, the cardiac chambers deairing procedure is performed and aortic cross clamp is removed. After rewarming the patient and hemodynamics being stable cardiopulmonary bypass is terminated. Hemostasis is achieved with the pharmacological support of the protamine sulfate (medication that is used to reverse the effects of heparin). Then median sternotomy is closed. All patients after redo surgery for mitral PVL surgery are transferred to the intensive therapy unit were closely monitored for hemodynamic instability and postoperative bleeding. After the extubation patients with mechanical prostheses receive oral anticoagulant treatment with warfarin from the second postoperative day. All patients receive antibiotics at induction of anesthesia and post-operatively for 48 hours, antibiotic treatment is prolonged in some patients where clinically indicated.

3.9 Surgical transapical catheter-based mitral PVL closure procedure

The procedure is carried out in a hybrid operating room. It has to be equipped with a fixed angiographic imaging system that supports high-quality interventional imaging and complex open and minimally invasive surgeries. It also has to have a hybrid-operating table, wall mounted video display monitor, surgical and interventional lighting, anesthesia and a cardiopulmonary bypass machine, physiologic/hemodynamic monitor, and a contrast media injector. Moreover, finally yet importantly is the cardiac ultrasound technology with the capability to perform real time 3D transesophageal cardiac ultrasound. All this technology allows physicians to perform procedures using real-time image guidance, and to assess its effectiveness and manage perioperative complications, in a single encounter.

For this procedure, standard cardiac surgery monitoring for adult redo surgery is applied. This includes continuous electrocardiogram, temperature, continuous pulse oximetry, end-tidal capnography, and fraction of inspired oxygen monitoring. The invasive arterial blood pressure monitoring through radial artery catheter is granted; this access also allows arterial blood sampling when necessary. Peripheral and central venous access (through the right internal jugular vein with multi-lumen central venous catheter.) is used to monitor central venous blood pressure and administer fluids and intravenous drugs. Self-adhesive external pads are attached to the patients back before draping to ensure prompt electrical cardioversion in case life threatening arrhythmia occurs. Prior to skin incision TTE is performed to identify the location of the apex and skin is marked. With a patient in supine position, under general anesthesia and endotracheal intubation, left anterolateral small (5–7 cm in length) thoracotomy is performed at the projection of the apex of the LV. With a help of a rigid metallic Finochietto rib retractor intercostal space is widened for the convenience of surgical maneuvers. Shown in Figure 2.

The pericardium identified and opened, care must be taken not to incise the myocardium (in redo surgery the pericardium can be severely adhered to the myocardium). Blunt dissection of the adhesions is performed. If the left lung lower lobe gets “in the way” a wet swab is used “to push” it into the pleura beyond the incision. Stay sutures (use size 2-0 ethylene terephthalate polyfilament) are placed to the edges of the pericardium and it is hinged to the skin under the retractor. Two “U” shape sutures (use size 2-0 monofilament polypropylene) reinforced with two felt pledgets each are placed and secured with the tourniquets perpendicular to each other at the apex of the heart. Shown in Figure 3. Following these surgical maneuvers, a rigid metallic Finochietto rib retractor is removed.

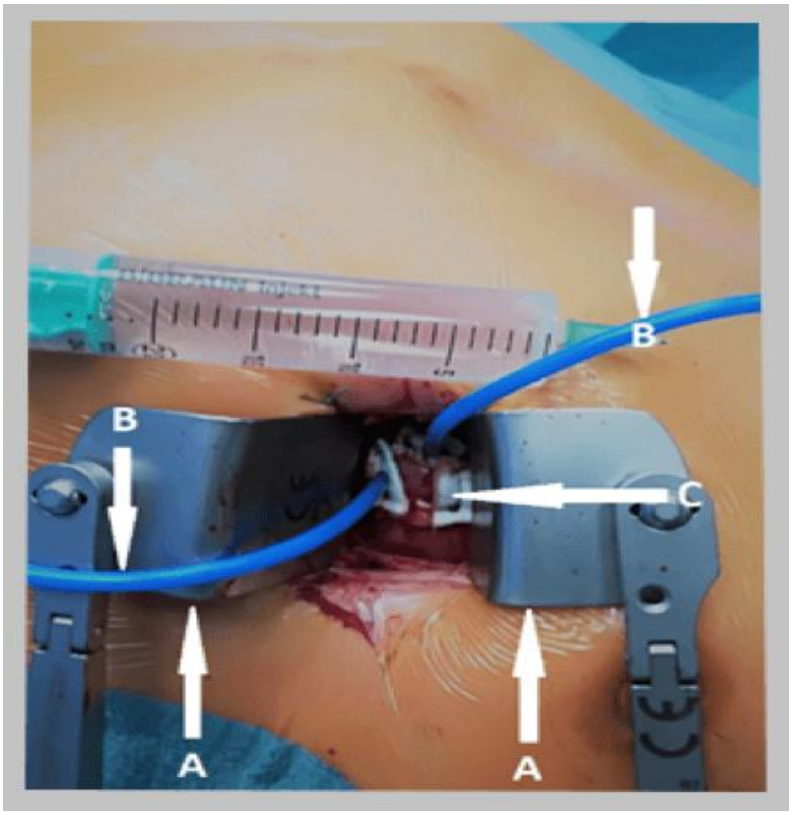

Figure 2. *Overall view of the operative field while retractor is in place. A - Finochietto retractor blades spreading the intercostal space; B – tourniquets securing two “U” shape sutures placed perpendicular to each other at the apex of the heart; C – Pledgets for suture reinforcement*

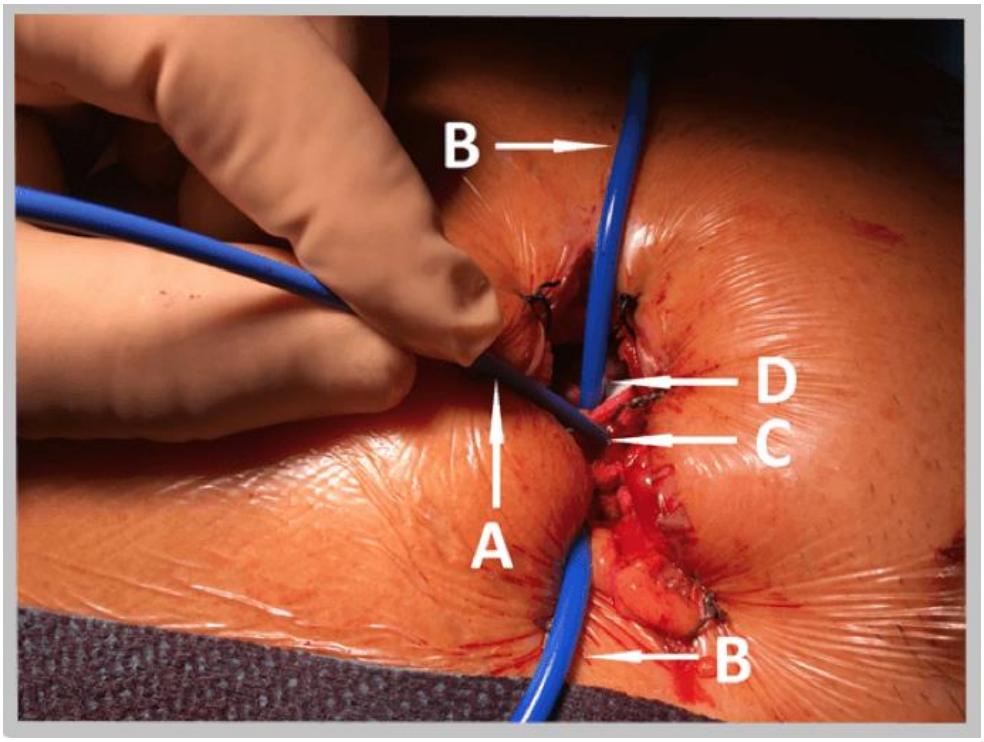

Figure 3. *Overall view of the operative field after Finochietto retractor removed. A – Delivery catheter introduced in to the LV. B – Tourniquets securing the "U" shape sutures at the apex of the heart. C – Entry site of the delivery catheter into the LV. D – "U" shape sutures perpendicular to each other, reinforced with pledgets on the apex of the LV.*

Anticoagulation is achieved by administering intravenously heparin (150 units/kg) aiming for activated clotting time of 250 to 300 seconds. A needle puncture between four pledgets is performed and the guidewire introduced in the LV with subsequent short catheter sheath insertion, showed in Figure 4.

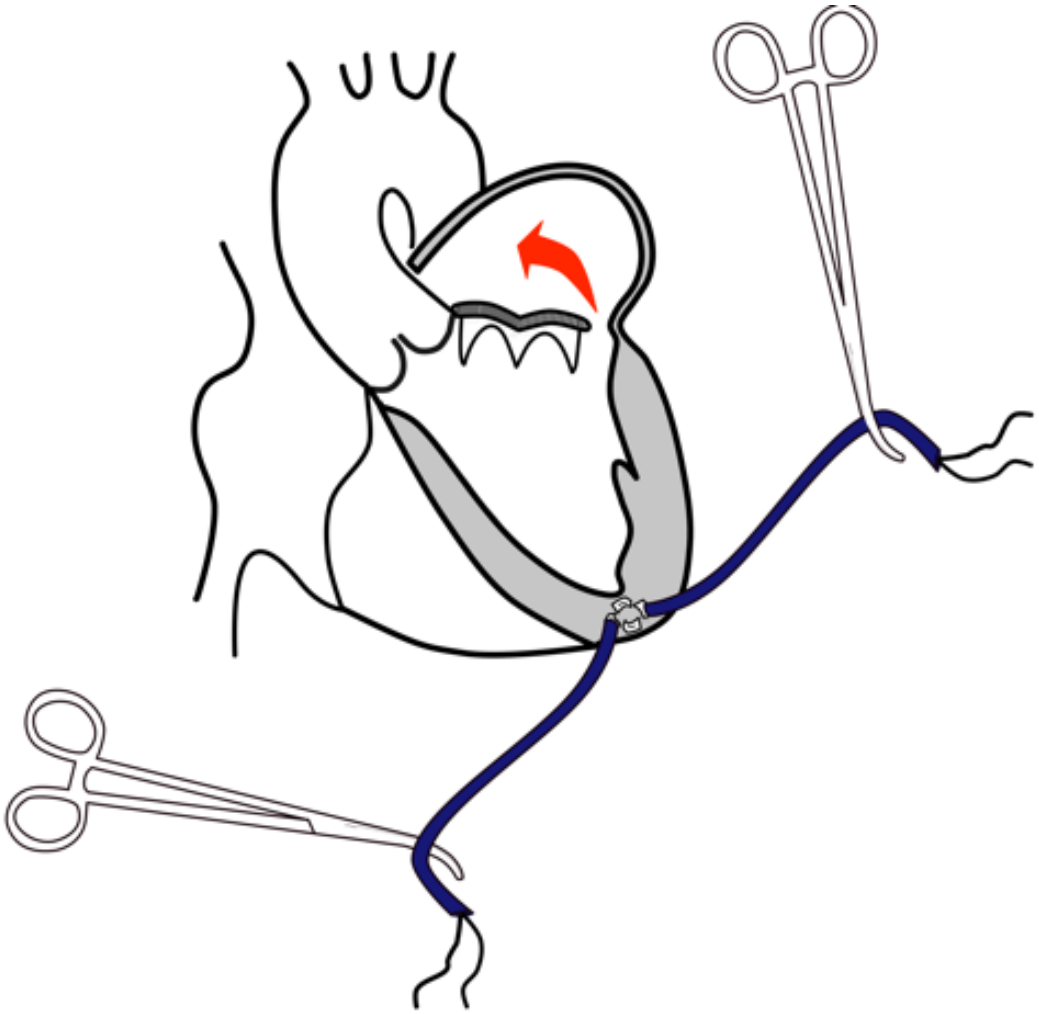

Figure 4. *Schematic view of the procedure initial steps, prior LV needle puncture.*

Two “U” shape sutures reinforced with pledgets are placed and secured with tourniquets perpendicular to each other at the apex of the heart. Paravalvular regurgitation is shown with the red arrow at the posterior aspect of the mitral prosthesis. Following catheter sheath insertion, tourniquets are gently tightened for hemostasis. Real time 3D TEE is performed identifying and confirming the exact location, detailed size, depth and shape of the mitral paravalvular defect. Fusion of fluoroscopy and real-time 3D TEE can be employed, if technology accessible, as it is a useful method in catheter-based PVL closure via the transapical approach. The operating table and C-arm are oriented for the transesophageal probe to be visible in the fluoroscopy field; this maneuver

allows the fusion software navigation system to “recognize” the transesophageal probe and co-register its position with the table and angulation of the C-arm. When co-registration is “successful”, the C-arm and transesophageal probe can be manipulated with the fused images maintained. Hydrophilic guidewire is used to pass through the defect with the help of a guidance catheter [230]. Shown in Figure 5.

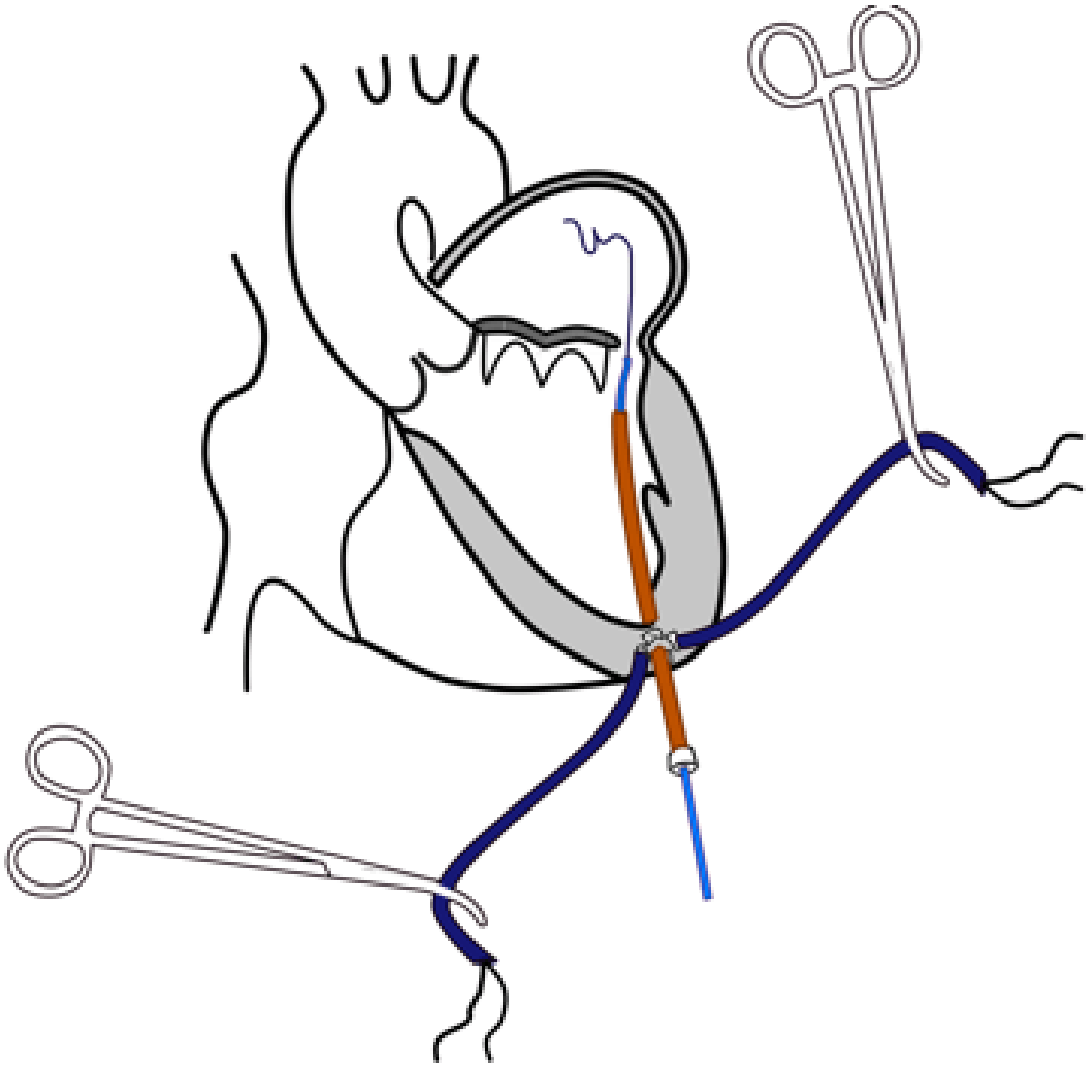

Figure 5. *Hydrophilic guidewire passed through the PVL with the help of a guidance catheter.*

The guiding catheter is advanced through the leak and hydrophilic guidewire replaced with stiff wire. The delivery sheath is chosen according to the size of the occluder. Guidance catheter is removed and delivery sheath advanced through the defect. Under control of real-time 3D TEE and fluoroscopy PVL closure device is deployed stepwise, first the distal (atrial) disc. Following the controlled orientation of the device distal disc is released from the delivery sheath. Shown in Figures 6 and 7.

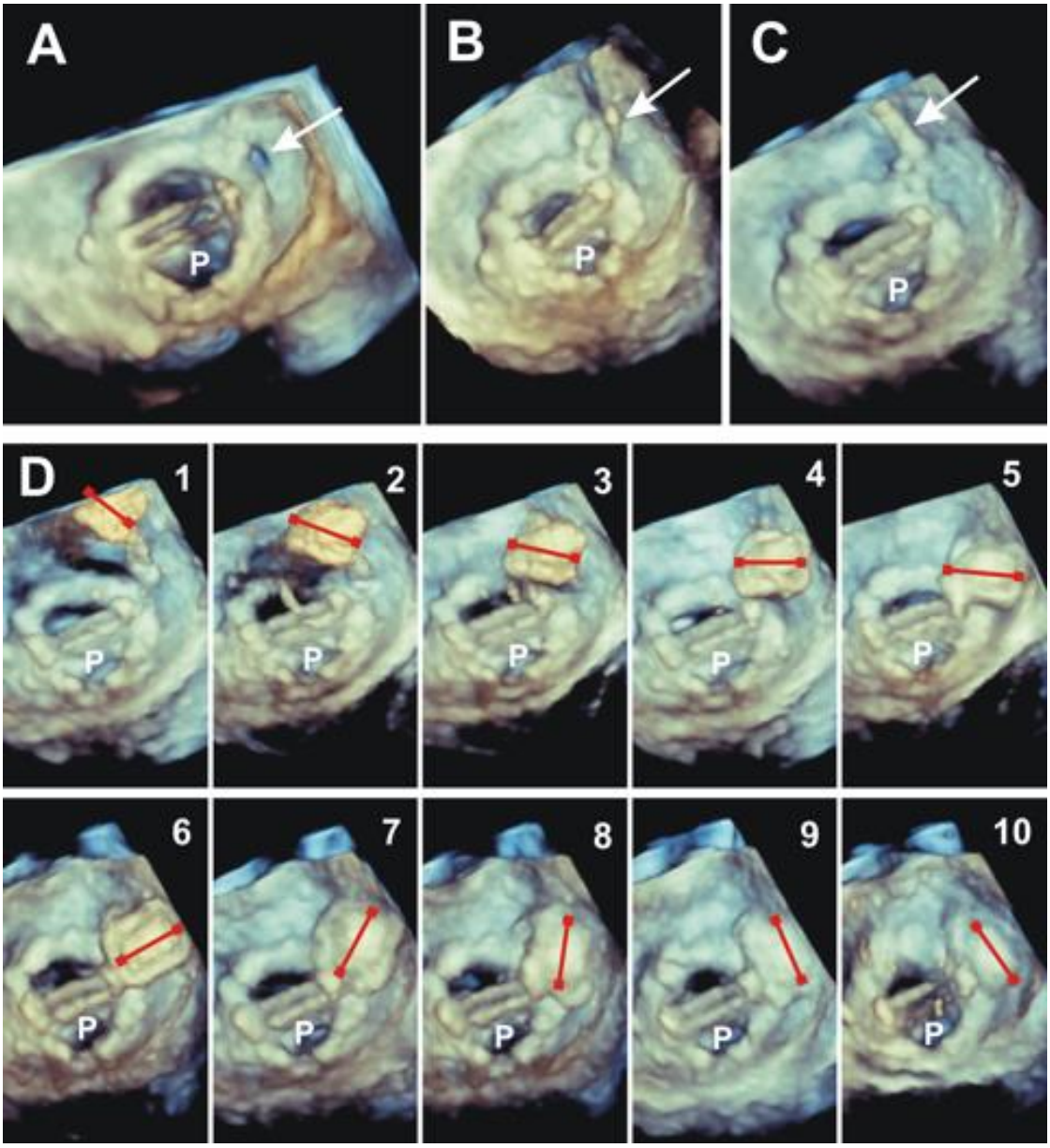

Figure 6. *3D TEE view of the prosthesis from the left atrium and orientation of the occluder. A-prosthesis with PVL at 2 o'clock. B - guidewire crossing the PVL. C - delivery sheath crossing the PVL. D (images from 1 to 10) - gradual rotation of the occluder until its proper position. Red line - longitudinal axis of the occluder.*

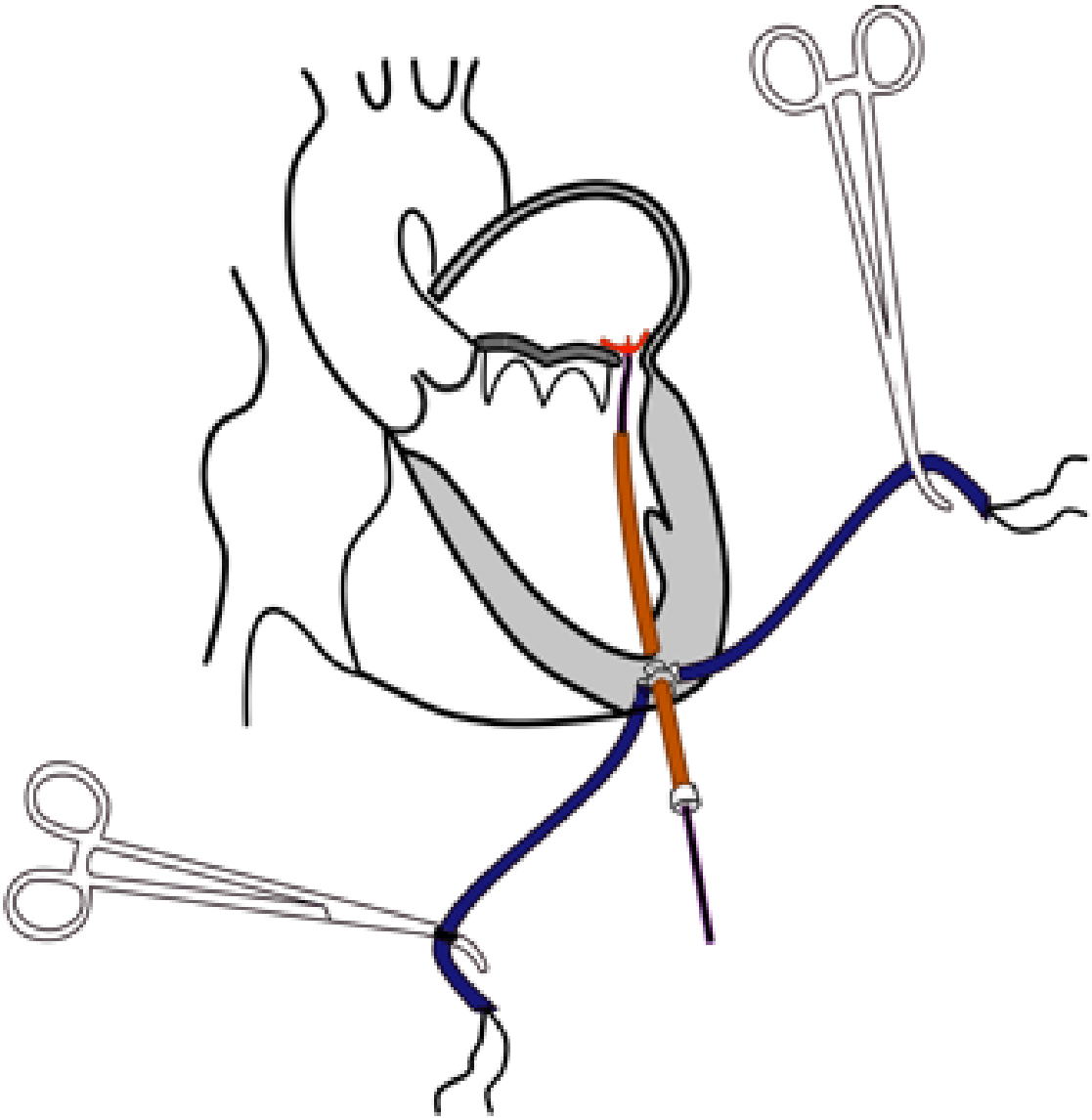

Figure 7. *Deployment of the PVL closure device (red), the distal (atrial) disc released from delivery sheath.*

Following full expansion of the both proximal and distal occlusion device discs, the function of the prosthetic valve is checked for its interference with the occluder. Shown in Figure 8.

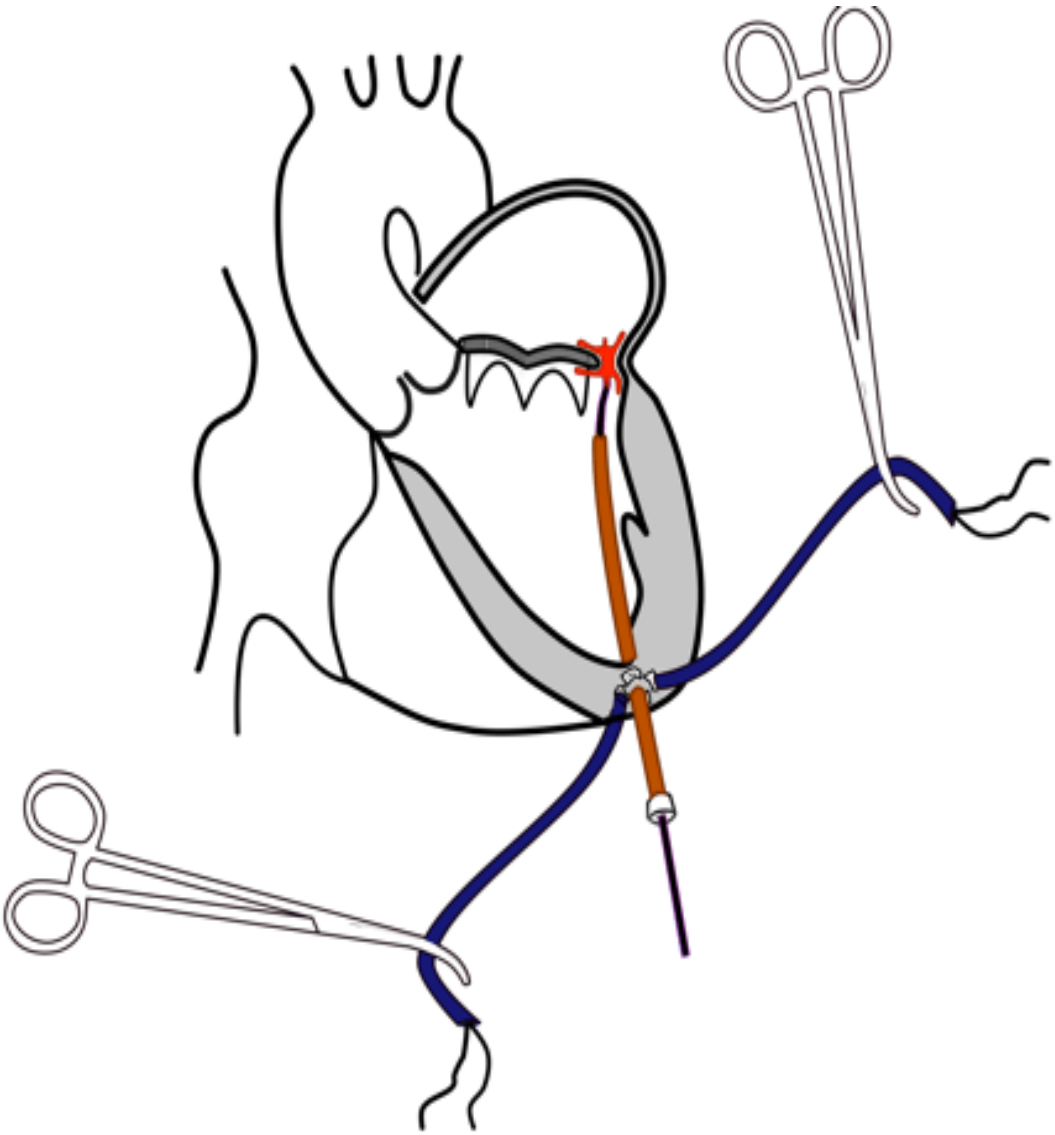

Figure 8. *Deployment of the PVL closure device (red), the proximal (ventricular) disc released from delivery sheath.*

If performance of the valve prosthesis not compromised, position, orientation and hemodynamic effect of the closure device are checked, if paravalvular regurgitation is significantly reduced or not present, the device is detached from the delivery system. Following a successful PVL closure, catheters and sheaths removed from the LV and protamine sulfate administered. “U” shape sutures securely tightened and the pericardium closed with three or two interrupted sutures, leaving communication between the pleural cavity and pericardial space. The pleural cavity drained with one drain, usually inserted

one or two intercostal spaces bellow the incision. Thoracotomy closed in a routine fashion. Showed in Figure 9.

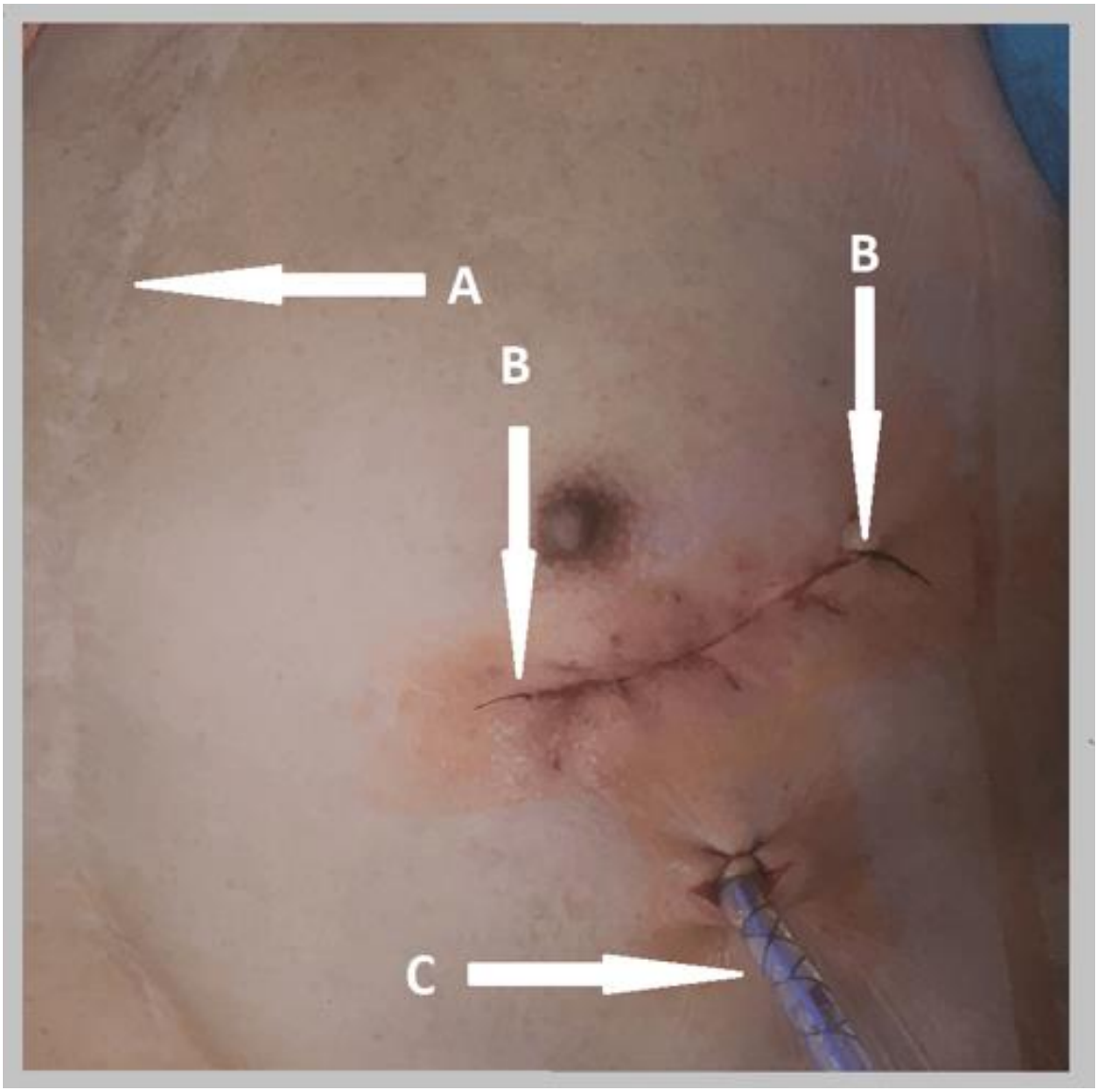

Figure 9. *Overall view of the postoperative field after thoracotomy is closed. A – Previous sternotomy scar. B – The margins of the thoracotomy (approximately 5 cm). C – Pleural drain inserted one intercostal space below the thoracotomy.*

Patients transferred to a cardiac intensive therapy unit and monitored for bleeding and hemodynamic instability. Patients are usually extubated within four hours after operation if no complications occur.

3.10 “Purpose specific” device for PVL closure

The purpose specific occluder explicitly designed and manufactured for PVL closure has obtained CE mark approval on October 7, 2014. The occluder has two discs interconnected by bundle of wires. The device is made of a Nitinol braided wire mesh and is available in square and rectangular disc designs. Shown in Figure 10.

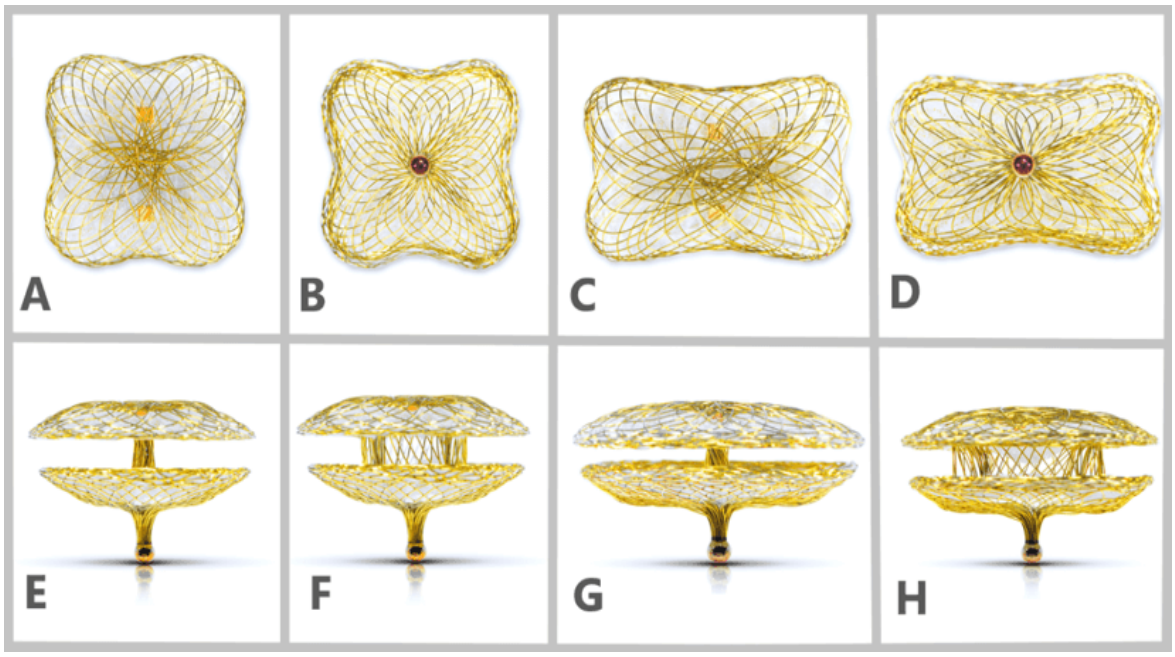

Figure 10. *Pictures of the purpose specific device (Occlutech® PLD occluder). Image belongs to Occlutech International AB, all copyrights reserved. A – Square shape, view at the distal disc; B – Square shape, view at the proximal disc, red is a welded ball (hub); C – Rectangular shape, view at the distal disc; D – Rectangular shape, view at the distal disc, red is a welded ball (hub); E – Square shape, with a Twist type of connector, side view; F – Square shape, with a Waist type connector, side view; G – Rectangular shape, with a Twist type connector, side view; H – Rectangular shape, with a Twist type connector, side view.*

Inside each disc, two thin polyethylene terephthalate patches are inserted, which helps to ensure immediate closure of paravalvular defect right after the implantation of the device. In addition, two radiopaque gold markers on the distal disc are present; it indicates the location of the disc frame, as well enhances radiographic visibility of the device, and allows accurate deployment

across the defect and its proper orientation. Discs are connected by an ellipsoid or circularly shaped bundle of wires. Depending on the shape of the connecting part, the occluder for PVL closure comes in two shapes – Waist and Twist. Waist type devices have a wide connecting part and should be chosen for oblong or crescent shape shallow defects. Twist type devices have a narrow connecting part and should be employed for defects, which are oval and/or "deeply" channeled. Devices with square discs are intended for circular PVL closure, while rectangular device designs are predetermined for crescent shaped leaks. The purpose specific occluders for PVL are available in different sizes ranging from 3 mm to 7 mm in square designs and from 4 mm × 2 mm to 18 mm×10 mm in rectangular designs. Both rectangular and square designs of the device have less surface area by one-third as compared to similar sized analogues. This reduces the possibility of mechanical interference with a prosthetic valve and minimizes device overlap in case multiple occluders are needed to close the defect. Moreover, due to the specific waist designs, it has no radial strength, but it has an intrinsic clamping force that keeps the prosthetic valve and tissue in close proximity to each other after PVL closure. The occluders wire braiding ends in a welded ball (hub) on the proximal side of the device; it serves for the "jaws" like grabbing system to attach. To connect an occluder to the delivery cable, the handle is pulled back to open the "jaws" located at the distal end of the wire. Shown in Figure 11.

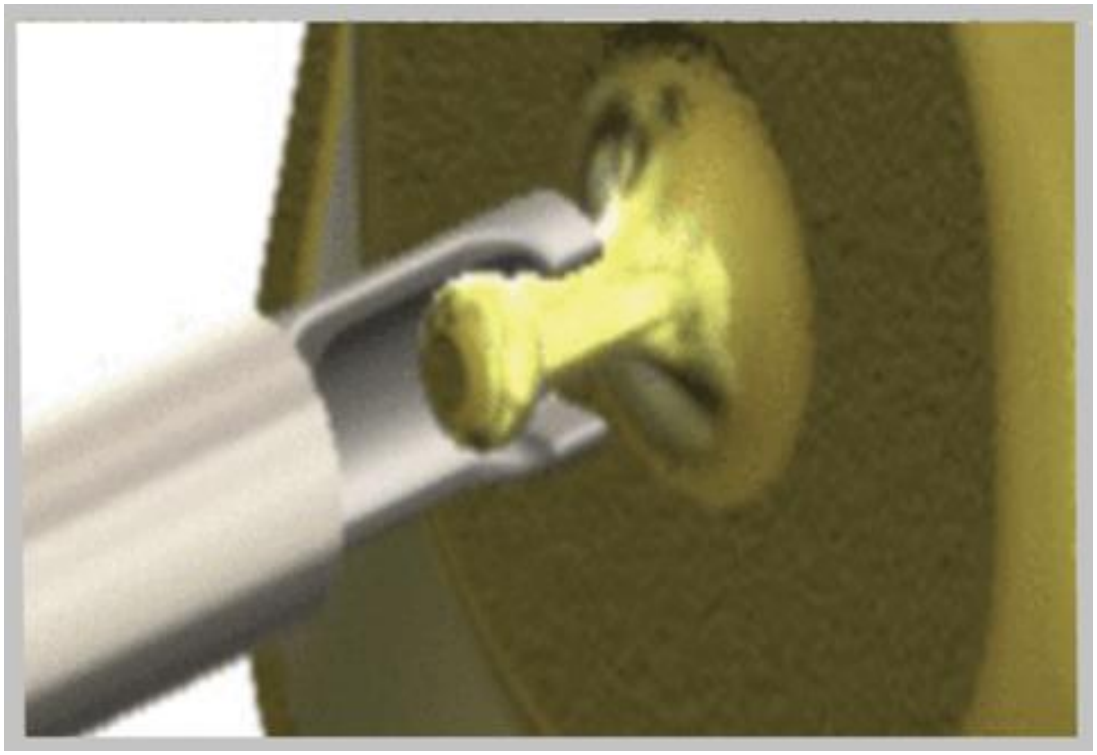

Figure 11. *"Jaws" like grabbing-releasing system of the delivery cable holding the hub of the occluder. Image belongs to Occlutech International AB, all copyrights reserved.*

Release of the handle causes the jaw to close around the ball adapter thus attaching the pusher wire to the device. Once attached, the connection is secured by means of actuating a screw-locking mechanism on the handle of the delivery cable to prevent accidental or premature release of the device. After the occluder has been positioned optimally in the deployment area, the device can be disconnected from its delivery cable by loosening the locking mechanism and releasing the handle.

3.11 Translation of PVL into the occluder

As the purpose specific device comes in various sizes and shapes, its purpose is to fit a variety of paravalvular defects which also can come in various shapes and sizes. Dimensions of the paravalvular defect can change over time; occluder selection is made during the procedure. The choice is made in accordance with dimensions of the mitral paravalvular dehiscence channel and cross sectional area, established following multi-planar reconstruction of 3D TEE data set. Shown in Figure 12.

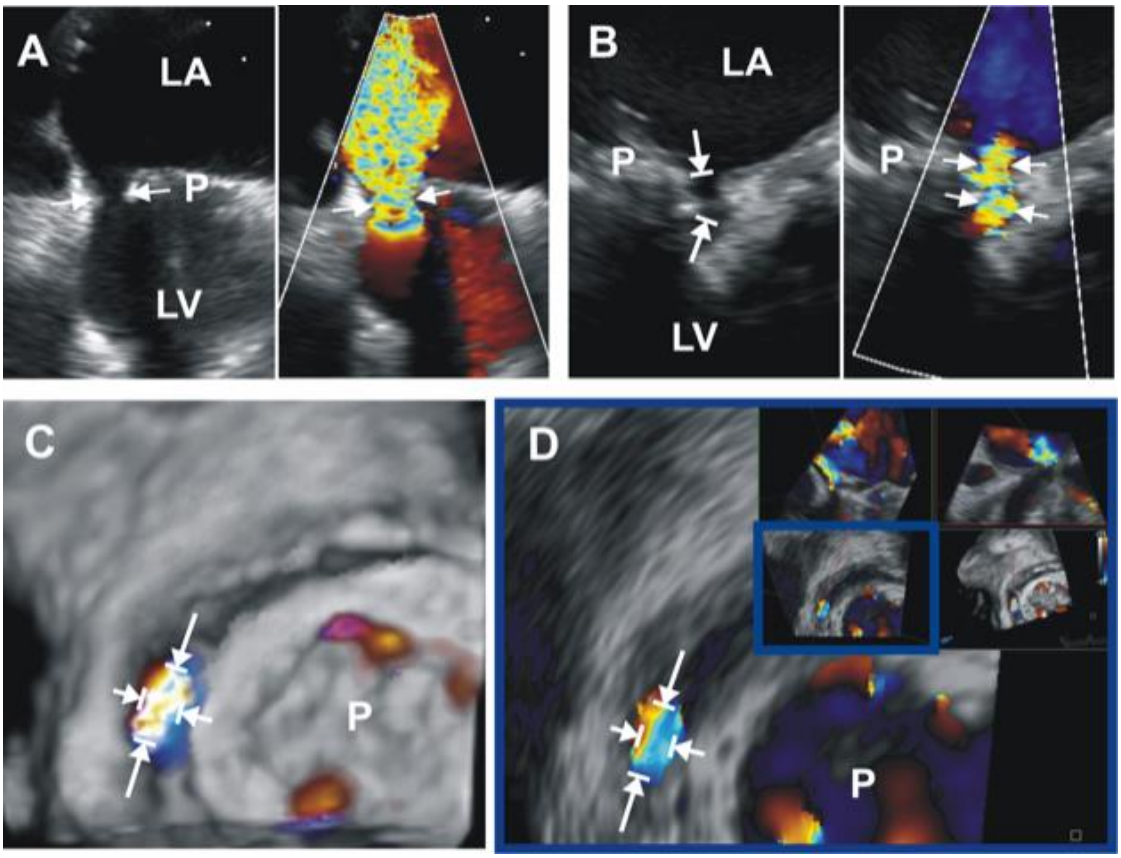

Figure 13. *Measurement of the dimentions of the PVL from 2D and 3D images. A and B - 2D longitudinal view of the PVL. C and D - 3D view of the PVL from LA. P - mitral prosthesis. Arrows point to the margins of the PVL.*

The "purpose specific" occluder for PVL closure comes in two shapes Waist and Twist. In selection of the device our opinion does not differ from other authors; Waist type device should be chosen for oblong or crescent shape shallow defects. To prevent occluder from bending or folding after deployment in the defect, it should not be oversized in comparison to cross sectional measurements of the defect [31, 34]. Bending or folding of it can cause significant residual regurgitation. Twist type should be employed for defects which are oval and/or "deeply" channeled. In an ideal scenario, the discs connecting part should have a snug fit to the defect, thus it has to match or be as close as possible to the defect cross sectional measurements. In the case of failure to occlude complex defects with a single plug, a multiple plug approach should be attempted or the Hopscotch technique to occlude paravalvular defect can also be exercised [220, 231].

4 RESULTS

4.1 Preoperative characteristics of the patients who underwent MVR

Following the refine search, we ended with a cohort of 551 patients. The detailed preoperative demographic and clinical characteristics of the patients underwent MVR are presented in Table 1. Median age of the cohort was 64 (55–71) years. Patients had median body surface area of 1.89 (1.74 mm – 2.04) m^2. Two hundred eighteen (40%) patients were male and 333 (60%) were female. A vast majority – 549 (99.6%) – of patients underwent elective MVR. Forty-seven (8.5%) patients were operated with infective endocarditis vegetation, l70 (12.7%) had only mitral stenosis, 251 (45.6%) had only regurgitation, while 183 (33.2%) patients underwent surgery for combined mitral stenosis and regurgitation. Half of the patients, 283 (51.5%) were found to have rheumatic heart disease. Seventy-two (13.1%) patients developed mitral valve lesion due to chordal rupture, while 53 (9.6%) patients underwent MVR for ischemic etiology. Forty-seven (8.5%) were victims of infective endocarditis, 41 (7.4%) patients were found to have calcific degeneration of the mitral valve, 34 (6.2%) patients of the cohort had degenerative mitral valve regurgitation, 15 (2.7%) were patients in whom mitral valve regurgitation was secondary due to dilative cardiomyopathy. Five patients (0.9%) had congenital pathology of some sort of the mitral valve. Great part of the patients 439 (79.7%) were in NYHA class III, 26 (4.7%) patients were severely symptomatic and presented with NYHA class IV and 86 (15.6%) patients were less symptomatic NYHA class II. Concerning concomitant cardio vascular pathology, 117 (21.2%) patients had significant coronary artery disease, with previous intervention or planed coronary artery bypass grafting. Twenty-five (4.5%) patients had previously documented cerebrovascular event with residual impairment. Ninety-six (17.4%) had presented with previously implanted permanent pacemaker for various conduction disturbances. More

than half 309 (56%) patients had preoperative atrial fibrillation. The kidney function of the cohort was rather good; with a mean serum creatinine, concentration of 88 (72-106) μmol/L. Serum creatinine concentration over 200 μmol/L was only in nine (1.6%) patients. In terms of the cardiac performance, 266 (48%) patients had preserved LV, with LV ejection fraction above 55%. Mildly abnormal LV with ejection fraction between 45% and 55% were observed in 194 (35%) patients, moderately abnormal LV with ejection fraction above 30% and under 45% was seen in 81 (15%) patients and a relatively small number – 10 (2%) – patients had severely abnormal LV with ejection fraction under 30%. End diastolic diameter of less than 50 mm was in 147 (26.7%) cases; 257 (47%) patients were with dimensions between 51 mm and 60 mm. Moderately enlarged LV with dimensions between 61 mm and 70 mm were in 127 (23%) patients, while severely enlarged when end diastolic diameter of the LV met dimensions over 71 mm was in 20 (3.6%) patients. Severe pulmonary hypertension with systolic pressure above 55mmHg was observed among 106 (19.2%) patients (Table 1).

Table 1. *Preoperative demographic and clinical characteristics of the patients underwent MVR.*

Clinical variables	**N (%) / median [Q1-Q3]**
Number of patients	551 (100%)
Age, years	64 (55-71)
Body surface area, m^2	1.89 (1.74-2.04)
Gender	
Male	218 (40%)
Female	333 (60%)
Type of surgery	
Elective	549 (99.6%)
Urgent/Emergency	2 (0.4%)
Mitral valve lesion	
Infective endocarditis vegetation	47 (8.5%)
Mitral stenosis	70 (12.7%)
Mitral regurgitation	251 (45.6%)
Mitral stenosis combined with regurgitation	183 (33.2%)
Mitral valve lesion etiology	
Rheumatic	283 (51.5%)
Chordal rupture	72 (13.1%)
Ischemic	53 (9.6%)
Infective endocarditis	47 (8.5%)
Calcific degeneration	41 (7.4%)
Degenerative	34 (6.2%)
Dilative cardiomyopathy	15 (2.7%)
Congenital	5 (0.9%)
NYHA	
II	86 (15.6%)
III	439 (79.7%)
IV	26 (4.7%)
Concomitant pathology	
Coronary artery disease	117 (21.2%)
Previous cerebrovascular event	25 (4.5%)
Previous permanent pacemaker	96 (17.4%)
Peripheral vascular disease	1 (0.2%)
Preoperative atrial fibrillation	309 (56%)
Serum hemoglobin concentration < 100 g/L	20 (3.6%)
Serum creatinine concentration, µmol/L	88 (72-106)
Serum creatinine concentration >200 µmol/L	9 (1.6%)
LV function	
Severely abnormal (LVEF < 30%)	10 (2%)
Moderately abnormal (30% ≤ LVEF < 45%)	81 (15%)
Mildly abnormal (45% ≤ LVEF < 55%)	194 (35%)
Good (LVEF ≥ 55%)	266 (48%)
LV end diastolic diameter	
≤ 50 mm	147 (26.7%)
≥51 mm ≤ 60 mm	257 (47%)
≥ 61 mm ≤ 70 mm	127 (23%)
≥ 71mm	20 (3.6%)
PA pressure >55mmHg	106 (19.2%)

4.2 General operative characteristics of MVR operations

General operative characteristics of the MVR operations are presented in Table 2. Two surgeons performed half of the mitral valve replacements: Surgeon B performed MVR in 157 (28.5%) patients. Surgeon Z operated on 103 (18.7%) patients. Another two surgeons have done one fifth of all mitral valve replacements in our cohort. Surgeon P had 67 (12.2%) patients and Surgeon F operated on 45 (8.1%) patients. Surgeon L performed MVR in 39 (7.1%) cases; Surgeon K had 25 (4.5%) cases. Moreover, a group of surgeons in whose practice MVR is a rare procedure or those in training; every surgeon in that group performed fewer than 25 cases during the observed period; thus that group was named Surgeon D. performed the remaining fifth part of all operations. In total Surgeon D carried out a total of 112 (20.9%) MVR procedures.

In terms of concomitant procedures, only tricuspid valve repair was performed in two thirds of the cohort, 350 (63.5%) patients. Alongside MVR, a coronary artery bypass grafting with tricuspid valve repair has been done to 69 (12.5%) patients. Mitral replacement with surgical ablation for atrial fibrillation (MAZE procedure) has only been performed in 4 (0.4%) patients. Mitral replacement with surgical ablation for atrial fibrillation (MAZE procedure) and tricuspid valve repair was done in 43 (7.8%) patients. Moreover, 53 (9.6%) patients had only isolated mitral replacement without any concomitant procedure.

In our cohort, the mean duration of cardiopulmonary bypass was 158 (12–194) minutes. Cardiopulmonary bypass was rather quick and less than 60 minutes was in two patients. Two hundred and eight patients (38%) had cardiopulmonary bypass during surgery in between one and two hours. In 242 (44%) cases, duration of cardiopulmonary bypass was between 120 minutes and 180 minutes. Sixty-eight (12%) patients had cardiopulmonary bypass for more than three but less than four hours; 31 (6%) patient in whom surgery had

technical and clinical challenges experienced cardiopulmonary bypass for more than four hours.

Mean aortic cross clamp duration was 99 (66–163) minutes. Almost one-third, 149 (27%) patients had aorta cross clamped under 60 minutes; two thirds 329 (60%) cases had aorta cross clamped between one and two hours. In 66 (12%) patients, it was between two and three hours. Seven patients (1%) had aorta being cross-clamped over three hours. The mean duration of the surgery was 275 (190–445) minutes.

Table 2. *General operative characteristics of the MVR operations.*

Variable	**N (%) / median [Q1-Q3]**
Number of operated patients by surgeon	
Surgeon B	157 (28.5%)
Surgeon Z	103 (18.7%)
Surgeon P	67 (12.2%)
Surgeon F	45 (8.1%)
Surgeon L	39 (7.1%)
Surgeon K	25 (4.5%)
Surgeon D	115 (20.9%)
Concomitant procedure	
Isolated mitral replacement	53 (9.6%)
Mitral replacement with Tricuspid repair	350 (63.5%)
Mitral replacement with CABG	32 (5.8%)
Mitral replacement with CABG and Tricuspid repair	69 (12.5%)
Mitral replacement with MAZE	4 (0.4%)
Mitral replacement with MAZE and Tricuspid repair	43 (7.8%)
Cardiopulmonary bypass duration, min	158 (12-194)
≤ 60min	2 (0%)
≥ 61 min ≤ 120 min	208 (38%)
≥ 120 min ≤ 180 min	242 (44%)
≥ 181 min ≤ 240 min	68 (12%)
≥ 241 min	31 (6%)
Aorta cross clamp duration, min	99 (66-163)
≤ 60min	149 (27%)
≥ 61 min ≤ 120 min	329 (60%)
≥ 120 min ≤ 180 min	66 (12%)
≥ 180 min	7 (1%)
Operation duration, min	275 (190-445)
≥ 61 min ≤ 120 min	48 (9%)
≥ 120 min ≤ 180	245 (44%)
≥ 181 min ≤ 240 min	142 (26%)
≥ 241 min≤ 300 min	61 (11%)
≥ 301 min	55 (10%)

MAZE - type of heart surgery for atrial fibrillation, "MAZE" refers to the series of lesions arranged in a maze-like pattern in the atria

4.3 Specific operative characteristics of MVR operations

Specific operative characteristics of the MVR operations are presented in detail in Table 3. Two-thirds 371 (67.3%) patients received mechanical prosthesis, while another third 180 (32.7%) patients have been implanted with biologic mitral valve prosthetic valve. Most of the 347 (63%) patients received a prosthesis of 29-millimeter diameter; 118 (21%) patients received a prosthesis of 27-millimeter diameter, while 81 (15%) patients got a prosthesis of 31-millimeter diameter, while 81 (15%) patients got a prosthesis of 31-millimeter diameter. In five (1%) patients, the mitral valve annulus was small enough to fit only 25-millimeter prosthetic valve. In three hundred and filthy-five (64.4%) cases prosthesis was implanted in the interrupted suture technique fashion. In 196 (35.6%) of the patients MVP was sewn employing the interrupted suture technique. The mitral valve was approached through atrial septotomy only in 150 (27.2%) patients; atrial septotomy with a left atrium dome incision was used in 401 (72.8%) cases. Due to acute postoperative cardiac failure, an aortic balloon pump was introduced in 64 (11.6%) patients. For the same reason when an aortic balloon pump was not efficient enough, extracorporeal mechanical support was implicated in seven (1.3%) patients. Severe intraoperative bleeding occurred in 15 (3%) cases. Thirty-four (6%) patients, due to unstable hemodynamics or severe bleeding failed to come off cardiopulmonary bypass in the first attempt.

Table 3. *Specific operative characteristics of the MVR operations.*

Variable	N (%) / median [Q1-Q3]
Prosthesis type	
Biologic	180 (32.7%)
Mechanical	371 (67.3%)
Prosthesis size	
25 mm	5 (1%)
27 mm	118 (21%)
29 mm	347 (63%)
31 mm	81 (15%)
Suture technique to implant prosthesis	
Continuous	196 (36%)
Interrupted	355 (64%)
Technique to access the mitral valve	
Atrial septotomy only	150 (27.2%)
Atrial septotomy with left atrium dome/ septal superior	401 (72.8%)
Intraoperative unplanned procedures	
Intraortic balloon pump	64 (12%)
Extracorporeal mechanical support	7 (1%)
Severe intraoperative bleeding	15 (3%)
Failure to come off from cardiopulmonary bypass in the first attempt	34 (6%)

4.4 Early postoperative characteristics following MVR

Early postoperative characteristics, complications and mortality following MVR in detail are presented in Table 4. There were 18 (3.3%) patient deaths immediately (within 72 hours) after the operation. Fifty-nine (10.7%) patients expired either in hospital or within 30 days after MVR. Permanent stroke with various degree of permanent disability occurred in 19 (3.4%) of the cases observed. Due to the conduction disturbances, 61 (11.1%) patients received a permanent pacemaker. Fifty-one (9.3%) patients developed severe acute kidney failure with a need of renal replacement therapy. Resternotomy for various reasons was performed in 67 (12.2%) cases. Forty (7%) patients received surgical revision for bleeding. Five (1%) developed deep sternal wound infection, 6 (1%) suffered repeat sternotomy due to cardiopulmonary resuscitation, 16 (3%) patients underwent resternotomy for mechanical circulatory support initiation and six (1%) underwent rewiring of the sternotomy for the flail sternum. Red blood cells were transfused to 182 (33%)

patients, fresh frozen plasma in 145 (26.3%) cases and 112 (20.3%) patients received platelets transfusion. Aortic counter pulsation balloon pump insertion was performed in 64 (11.6%) patients. Overall, median intensive therapy unit stay was three (2–6) days, while length of hospital stay was 14 (12–20) days.

Table 4. *Early patient's postoperative characteristics/complications and mortality after MVR.*

Variables	**N (%) / median [Q1-Q3]**
Immediate procedural mortality	18 (3.3%)
Hospital (30 days) mortality	59 (10.7%)
Permanent stroke	19 (3.4%)
Postoperative implantation of permanent pacemaker	61 (11.1%)
Postoperative renal replacement therapy	51 (9.3%)
Resternotomy/revision	67 (12.2%)
Reason for resternotomy/revision	
Bleeding	40 (7%)
Deep sternal wound infection	5 (1%)
Cardiopulmonary resuscitation	6 (1%)
Need for mechanical circulatory support	16 (3%)
Flail sternum	6 (1%)
Need for blood products transfusion	
Red blood cells	182 (33%)
Fresh frozen plasma	145 (26.3%)
Platelets	112 (20.3%)
Need for aortic balloon pump insertion	64 (11.6%)
Need for mechanical circulatory support	21 (3.8%)
Length of postoperative intensive therapy unit stay, days	3 (2-6)
Length of hospital stay, days	14 (12-20)

4.5 Incidence of mitral PVL and mortality

Among the population analyzed (551 patients), clinically significant, necessitating additional attention from medical professionals mitral paravalvular defects were established in 31 (6.8%) patients. Most of the mitral paravalvular leaks (77 %) were diagnosed within the first year of follow-up, the remaining 23% occurred later. Immediately (≤72 h after procedure) after MVR 81 (3.3%) patients died, in hospital or within 30 days after the operation 59 (10.7%) patient died. A Kaplan-Meier survival function showed five-year survival at 75% and 10-year survival at 62%; see Figure 13.

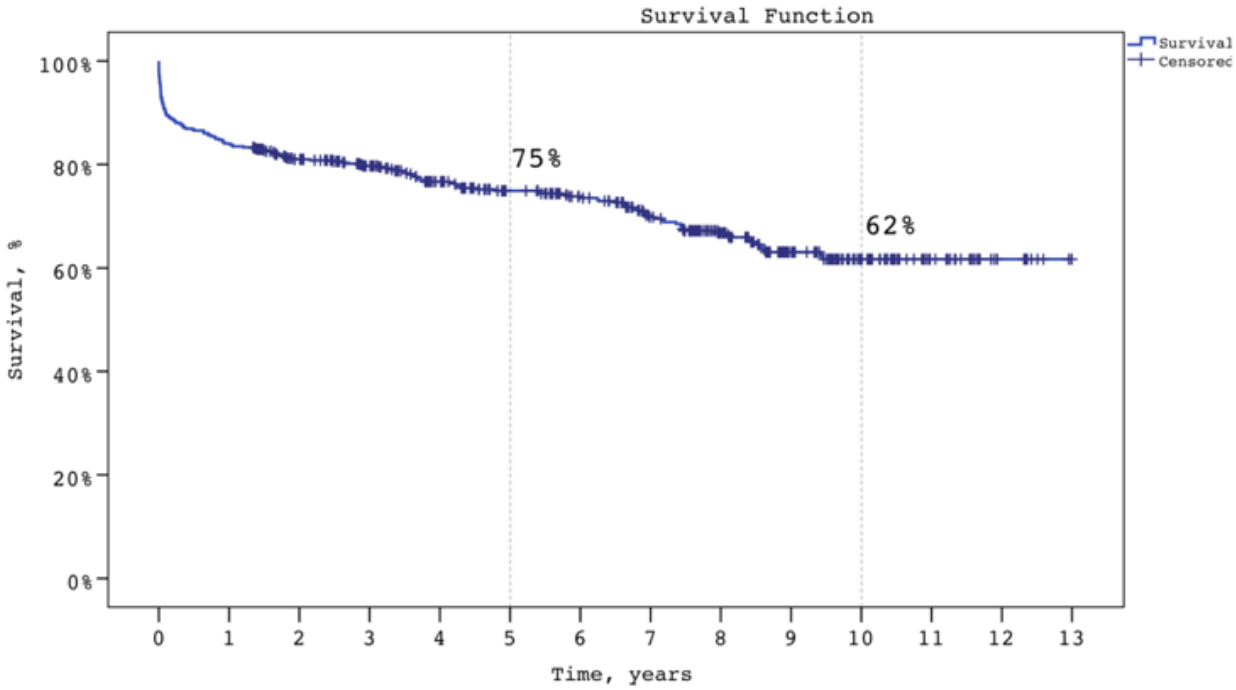

Figure 14. *Kaplan-Meier survival functions for the cohort of 551 patients after MVR.*

4.6 Analysis of risk factors associated with PVL occurrence after MVR

We performed a simple univariate analysis of factors associated with PVL occurrence after MVR, presented in detail in Table 5. Every factor, which in our opinion and the ones found in the literature can have influenced the occurrence of mitral PVL, were included into the initial analysis (whether PVL was present or not). Following the analysis performed, mitral PVL was met more frequently in male patients (55%) compared to females (*p*-value = 0.04). The surgeon as a risk factor was found to be important as well. In the PVL occurrence group 39% of patients had mitral valve replaced by a specific surgeon (*p*-value = 0.001). In the subgroup of cases were mitral PVL was present mean LV end diastolic diameter was 5.9 cm (5.3–6.4 cm), contrary to PVL absence group it was 5.5 cm (5–6 cm), (*p*-value = 0.013). The continuous suture technique to implant the prosthesis was also found to be a potential cause for mitral PVL formation among the patients who developed the lesion in 53% was implanted in a continuous suture technique fashion (*p*-value = 0.023).

Table 5. *Univariate analysis of risk factors associated with PVL occurrence.*

Variable	PVL present, N (%) / median [Q1–Q3]	PVL absent, N (%) / median [Q1–Q3]	*p* - value
Male gender	21 (55%)	197 (38%)	0.04
Mitral valve lesion			
Infective endocarditis vegetation	5 (13%)	42 (8%)	0.290
Mitral stenosis	4 (11%)	66 (13%)	0.676
Mitral regurgitation	20 (53%)	231 (49%)	0.364
Combined lesion	9 (24%)	174 (34%)	0.196
Mitral valve lesion etiology			
Rheumatic	16 (42%)	268 (52%)	0.228
Chordal rupture	3 (8%)	69 (14%)	0.327
Ischemic	8 (21%)	45 (9%)	0.013
Calcific degeneration	4 (11%)	37 (7%)	0.453
Infective endocarditis	5 (13%)	42 (8%)	0.290
Degenerative	1 (2.6%)	33 (6.4%)	0.347
Dilative cardiomyopathy	1 (2.6%)	14 (2.7%)	0.972
Congenital	0 (0%)	5 (1%)	0.541
LV function			
LVEF < 30%	1 (2.8%)	8 (1.7%)	0.622
30% ≤ LVEF < 45%	6 (17%)	70 (15)	0.73
45% ≤ LVEF < 55%	*14 (39%)*	168 (35%)	0.631
LVEF ≥ 55%	15 (42%)	235 (49%)	0.405
Left ventricle diameter, cm	5.9 (5.3-6.4)	5.5 (5-6)	0.013
Number of patients per the surgeon			
Surgeon B	10 (26%)	161 (29%)	0.683
Surgeon Z	15 (39%)	88 (17%)	0.001
Surgeon P	1 (2.6%)	66 (13%)	0.063
Surgeon F	4 (11%)	41 (7.9%)	0.582
Surgeon L	3 (7.9%)	36 (7%)	0.839
Surgeon K	1 (2.6%)	24 (4.7%)	0.559
Surgeon D	4 (11%)	107 (20.9%)	0.125
Surgical procedure			
Isolated MVR	3 (7.9%)	50 (9.7%)	0.709
MVR with TV repair	26 (68%)	324 (63%)	0.882
MVR CABG	2(5.3%)	30 (5.8%)	0.585
MVR with CABG and TV repair	5 (13%)	64 (12.5%)	0.515
MVR with MAZE	0 (0%)	4 (0.8%)	0.902
MVR with MAZE and TV repair	2 (5.3%)	41 (8%)	0.545
Suture technique			
Continuous	20 (53%)	176 (34%)	0.023
Interrupted	18 (47%)	337 (66%)	0.023

MAZE - heart surgery for atrial fibrillation, "MAZE" refers to the lesions in a maze-like pattern in the atria.

Further, we performed the univariate Cox proportional hazards model for the factors associated with mitral PVL occurrence; presented in detail in Table 6. Following outcomes were established. Male gender; body surface area; body surface area when ≥2 m^2; the continuous suture technique; specific surgeon; ischemic mitral valve lesion etiology; LV end diastolic diameter with various hazard ratio and confidence interval, where statistically significant risk factors for mitral PVL formation at any time of follow-up.

Table 6. *Univariate Cox proportional hazards model for the factors associated with PVL.*

Variable	Odds ratio	95% Confidence interval	*p* - value
Male gender	1.935	1.020 – 3.668	0.043
Body surface area	5.867	1.471 – 23. 405	0.012
Body surface area, ≥2 m^2	2.268	1.189 – 4.311	0.013
Continuous suture technique	1.871	0.989 – 3.540	0.054
Surgeon B	1.07	0.524 – 2.185	0.854
Surgeon Z	2.989	1.565 – 5.709	0.001
Surgeon P	0.268	0.048 – 1.51	0.136
Ischemic mitral valve lesion	2.763	1.263 – 6.047	0.011
Left ventricle diameter	1.679	1.139 – 2.476	0.009

B, P, Z – coding of the surgeons

Nonetheless, as the defect can occur at any time of follow-up univariate Cox Regression analysis for the factors associated with mitral PVL occurrence was performed. Subsequently, leaving the specific surgeon with Hazard ratio of 2.631, 95% Confidence interval 1.311 – 5.279 (*p*-value = 0.006) and ischemic mitral valve lesion etiology with Hazard ratio of 2.343, 95% Confidence interval 1.020–5.383 (*p*-value = 0.045) being the only statistically significant risk factors for mitral PVL formation, in detail presented in Table 7.

Table 7. *Univariate Cox Regression analysis for the factors associated with mitral PVL.*

Variable	Odds ratio	95 % Confidence interval	*p* - value
Male gender	1.235	0.557 – 2.736	0.603
Body surface area	2.969	0.625 –14.097	0.171
Continuous suture technique	1.825	0.914 – 3.641	0.081
Surgeon Z	2.631	1.311 – .279	0.006
Ischemic	2.343	1.020 – 5.383	0.045
LVEDD	1.439	0.891 – 2.323	0.136

LVEDD - Left ventricular end diastolic diameter, **Z** – Coding of the surgeon

This was confirmed by Multivariate Cox Regression analysis, the specific surgeon, Hazard ratio 3.327, 95% Confidence interval 1.733–6.389 (*p*-value = 0.000305), while ischemic mitral valve lesion etiology, Hazard ratio 2.343, 95% Confidence interval 1.166–2.575, and (*p*-value = 0.0071), see Table 8.

Table 8. *Multivariate Cox Regression analysis for the factors associated with mitral PVL.*

Variable	Odds ratio	95 % Confidence interval	*p* - value
Surgeon Z	3.327	1.733 – 6.389	0.000305
Ischemic	2.343	1.166 – 2.575	0.0071

Z – Coding of the surgeon

4.7 Preoperative characteristics of the patients who underwent mitral PVL treatment

A detailed description is presented in Table 9. A total of 73 patients underwent conventional re-do surgery or transapical catheter-based procedure for mitral PVL treatment from January 2005 until December 2017. To compare the effectiveness and safety of mitral PVL treatment modalities this cohort was divided into two groups. A group of patients underwent transapical catheter-based closure of mitral PVL with “purpose specific” device was named “Catheter” and had 24 (33%) patients, while a group of patients underwent conventional re-do surgery for mitral PVL named “Surgical” had 49 (67%) patients. Overall mean age was 64 (58–68) years, patients in the “Catheter” group were two years younger than in “Surgical”, 66 (61–69) versus 64 (57–67) years, without statistical significance. In total 36 (49%) were male, in the

"Catheter" group 14 (58%), among the patients in the "Surgical" group 22 (45%) were male gender. The vast majority of patients have presented electively. Overall only four (5%) patients were operated urgently, one (4%) in the "Catheter" and 3 (6%) patients in the "Surgical" group. Among all the patients mean time from initial MVR was 58 (13–177) months, 36 (13–177) months in the "Catheter" and 60 (14–179) months in the "Surgical" group; this difference of 24 months between the groups had no statistical significance. Nine (12%) patients had previously undergone surgical treatment for mitral PVL, 4 (17%) in the "Catheter" and five (10%) in the "Surgical" groups. Overall, mean perioperative mortality risk according to the European System for Cardiac Operative Risk Evaluation was 7.4% (5%–10.6%), 6.0% (3.9%–10.6%) for "Catheter" group of patients and 8.0% (5.8%–11.1%) for "Surgical" group (*p*-value = 0.07). The Society of Thoracic Surgeons Risk for mortality for both groups of patients was 1.95 (1.28–2.9), for "Catheter" patients it was 1.8 (1.4–2.4) and for "Surgical" patients it was 1.98 (1.4–3.2), without reaching statistical significance. Hemolysis was found in 28 (38%) in all patients, among patients in the "Catheter" group there were 13 (68%) patients and 15 (31%) cases in the "Surgical" group (*p*-value = 0.05). Anemia, when patients presented with Hemoglobin concentration less than 100 g/L was observed in 19 (26%) in the overall population, whilst nine (38%) patients where anemic in the "Catheter" group and 10 (20%) in the "Surgical" group (*p*-value = 0.12). Mean serum creatinine concentration was 88 (76–110) μmol/L in all patients, and did not differ between the groups. Cardiac performance was evaluated by assessing the LV function and pulmonary artery pressure; these two variables also showed no statistical significance. Mechanical prosthesis was seen more frequently in the "Surgical" group, 45 (92%) patients versus 17 (71%) patients in the "Catheter" patients. There were also two (8%) patients in the "Catheter" group with paravalvular regurgitation near the mitral annuloplasty ring after mitral valve repair, while no such patient was seen in the "Surgical" group.

Among all of the patients only three (4%) had hemolytic anemia as the only indication for mitral PVL closure. Two (8%) patients were in the “Catheter” group and one (2%) among surgical patients (*p*-value = 0.2). Heart failure as the only indication for the treatment was present in 45 (62%) patients among the whole population treated, while in the “Catheter” group of patients it was seen in 11 (46%) and 34 (68%) in the “Surgical” patients (*p*-value = 0.05). A combination of heart failure and hemolytic anemia as an indication for treatment did not differ between the patients of the two groups. Most 57 (78%) cases had one paravalvular defect, 14 (58%) patients had one leak in the “Catheter” group and 43 (88%) patients in the “Surgical” group (*p*-value = 0.004). Seven (29%) cases had two paraprosthetic defects in the “Catheter” group and there were 5 (10%) such patients in the “Surgical” group (*p*-value = 0.04).

Table 9. *Preoperative characteristics of the patients with mitral PVL.*

Clinical variables	All patient N (%) / median [Q1-Q3]	"Catheter" N (%) / median [Q1-Q3]	"Surgical" N (%) / median [Q1-Q3]	*p*-value
Number of patients	73(100%)	24 (33%)	49 (67%)	
Age, years	64 (58-68)	66 (61-69)	64 (57-67)	0.08
Gender, male	36 (49%)	14 (58%)	22 (45%)	0.97
Presentation, elective	69 (96%)	23 (96%)	46 (94%)	0.73
Time form MVR, months	58 (13-177)	36 (13 -177)	60 (14 -179)	0.8
Previous PVL closure	9 (12%)	4 (17%)	5 (10%)	0.43
NYHA				
II	8 (11%)	5 (21%)	3 (6%)	0.06
III	54 (74%)	16 (67%)	38 (77%)	0.32
IV	11 (15%)	3 (12%)	8 (16%)	0.67
EuroSCORE II, %	7.4 (5.0-10.6)	6.0 (3.9-10.6)	8.0 (5.8-11.1)	0.07
STS risk of mortality, %	1.95 (1.28-2.9)	1.8 (1.4-2.4)	1.98 (1.4-3.2)	0.32
Coronary artery disease	12(16%)	3(13%)	9 (18%)	0.525
Hemolysis	28 (38%)	13 (68%)	15 (31%)	0.05
Anemia Hb < 100g/L	19 (26%)	9 (38%)	10 (20%)	0.12
SCr[c], µmol/L	88 (76-110)	86 (74-110)	88 (77-105)	0.42
Left ventricle function				
LVEF < 30%	3 (4%)	1 (4%)	2 (4%)	0.97
LVEF 31– 44%	24 (33%)	9 (38%)	15 (31%)	0.56
LVEF 45 – 54%	28 (38%)	6 (25%)	22 (45%)	0.1
LVEF ≥ 55%	18 (25%)	8 (33%)	10 (20%)	0.23
PA pressure >55mmHg	26 (36%)	9 (38%)	17 (35%)	0.45
Prosthetic valve type				
Bioprosthesis	9 (12%)	5 (21%)	4 (8%)	0.12
Mechanical	62 (85%)	17 (71%)	45 (92%)	0.019
Annuloplasty ring	2 (3%)	2 (8%)	0 (0%)	0.04
Indications for PVL closure				
Hemolytic anemia	3 (4%)	2 (8%)	1 (2%)	0.2
Heart failure	45 (62%)	11 (46%)	34 (69%)	0.05
Both	25 (34%)	11 (46%)	14 (29%)	0.144
Number of PVL per patient				
1defect	57 (78%)	14 (58%)	43 (88%)	0.004
2defects	12 (16%)	7 (29%)	5 (10%)	0.04
3defects	4 (5%)	3 (13%)	1 (2%)	0.24
Degree of PVL regurgitation				
Moderate	22 (30%)	4 (17%)	17 (35%)	0.11
Severe	51 (70%)	20 (83%)	32 (65%)	0.11

EuroSCORE - European System for Cardiac Operative Risk Evaluation**; STS** - Society of Thoracic Surgeons**, SCr[c] –** Serum creatinine concentration.

4.8 Topographic location, dimensions and shape of mitral PVL

The data are presented in detail in Table 10 and Figure 14. Overall, there were 93 paravalvular defects in total. In the "Catheter" group of patients, there were 37 (40%) defects, while the remaining two-thirds of the defects were among the "Surgical" cases. Seventeen (18%) paravalvular defects were observed at A1, 10 (11%) at the A2, 15 (16%) at A3, 8 (9%) at P1, 33 (36%) at P2, five (5%) defects were at P3 aspects of the mitral valve annulus. One (1%) defect was located at the P1/A1 (anterolateral) commissure and four (4%) were observed at P3/A3 (posteromedial) commissure of the mitral annulus. One-third of all paravalvular defects was located exactly at the P2 aspect of the mitral annulus, and distributed evenly between both groups, 13 (35%) in the "Catheter" group of patients and 20 (36%) among the "Surgical" patients. Surprisingly, no defects were seen at the A2 aspect of the mitral valve annulus in the "Catheter" patients, while among the patients in the "Surgical" group in 10 (18%) cases defects were observed at that location. What is also worth mentioning is that over 40% of all defects are located at the anterior aspect of the mitral annulus.

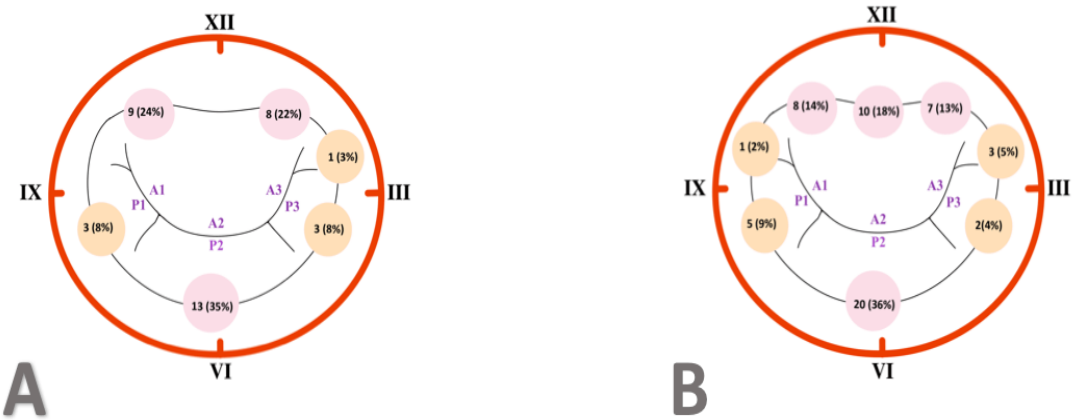

Figure 15. *Distribution of PVLs along the perimeter of the mitral valve, presented in a clock adopted fashion [183]. A – Distribution of the periprosthetic defects in the "Catheter" group; B - Distribution of the periprosthetic defects in the "Surgical" group. III, VI, IX and XII – represent hours of the clock; A1, A2, A3, P1, P2, P3 – mitral valve scallops (segments). N (%) – number of defects and fraction in the cohort of patients.*

Table 10. *Morphological and topographic description of the PVL.*

	All patients N (%) / median [Q1-3]	"Catheter" N (%) / median [Q1-3]	"Surgical" N (%) / median [Q1-3]	*p*-value
Number of PVLs	93 (100%)	37 (40%)	56 (60%)	0.049
PVL location				
A1	17 (18%)	9 (24%)	8 (14%)	0.392
A2	10 (11%)	0 (0%)	10 (18%)	0.013
A3	15 (16%)	8 (22%)	7 (12%)	0.425
P1	8 (9%)	3 (8%)	5 (9%)	0.890
P2	33 (36%)	13 (35%)	20 (36%)	0.954
P3	5 (5%)	3 (8%)	2 (4%)	0.342
A1/P1	1 (1%)	0 (0%)	1 (2%)	0.414
A3/P3	4 (4%)	1 (3%)	3 (5%)	0.537
PVL shape				
Crescent	28 (30%)	8 (22%)	20 (36%)	0.244
Oval	65 (70%)	29 (78%)	36 (64%)	0.244
PVL size				
Length, mm	6 (4-10)	5 (4-8)	10 (3-15)	0.112
Width, mm	4 (3-5)	4 (3-4)	3 (3-6)	0.646

4.9 General operative characteristics in redo surgery for mitral PVL

General operative characteristics in conventional redo surgery for mitral PVL in detail are presented in Table 11. Surgeons B and Z operated 31 (63%) patients. The remaining 18 (36%) cases received redo surgical service from Surgeons F, L and D and distributed evenly.

The mean duration of cardiopulmonary bypass was 137 (93–163) minutes. Twenty-four (41%) patients had duration of cardiopulmonary bypass between one and two hours, 22 (45%) cases were on cardiopulmonary bypass machine for a period between two and three hours. Two (4%) patients had to withstand

perfusion between three and four hours and four (8%) underwent redo surgery for more than four hours. Almost respectively to duration of cardiopulmonary bypass time, was the duration of myocardial ischemia represented by aortic cross clamp time. Mean aorta cross clamp time in all redo surgical patients was 65 (45–105) minutes, 20 (41%) cases had myocardial ischemia under 60 minutes. Twenty-four (49%) patients had aorta cross-clamped between one and two hours, in three (6%) patients, it was between two and three hours and in 2 (4%) patients it exceeded a period of three hours. The mean duration of the surgery was 270 (240–350) minutes. Fifth teen (30%) patients underwent surgery in between three and four hours, in 12 (24%) cases it was four to five-hour surgery; 22 (45%) patients spent under surgery more than six hours on the operating table.

Table 11. *General operative characteristics in redo surgery for mitral PVL.*

Variable	N (%) / median [Q1-Q3]
Number of operated patients by surgeon	
Surgeon B	21 (43%)
Surgeon Z	10 (21%)
Surgeon F	7 (14%)
Surgeon L	5 (10%)
Surgeon D	6 (12%)
Cardiopulmonary bypass duration, min	137 (93-163)
≤ 60min	1 (2%)
≥ 61 min ≤ 120 min	24 (41%)
≥ 120 min ≤ 180 min	22 (45%)
≥ 181 min ≤ 240 min	2 (4%)
≥ 241 min	4 (8%)
Aorta cross clamp duration, min	65 (45-105)
≤ 60min	20 (41%)
≥ 61 min ≤ 120 min	24 (49%)
≥ 120 min ≤ 180 min	3 (6%)
≥ 180 min	2 (4%)
Operation duration, min	270 (240-350)
≥ 181 min ≤ 239 min	15 (30%)
≥ 201 min≤ 299 min	12 (24%)
≥ 300 min	22 (45%)

4.10 Specific operative characteristics of redo surgery for mitral PVL

Specific operative characteristics and complications of redo surgery for mitral PVL are presented in detail in Table 12. Forty-five (92%) patients had a mechanical mitral valve, only 4 (8%) presented with biologic prosthesis, 46 (94%) patients underwent surgery through the conventional redo median sternotomy, while in three (6%) patients MVP was approached through right thoracotomy. More than in two-thirds (69%) of the cases PVL was treated by suture repair when in remaining third (31%) prosthesis replacement was

modality of treatment. Right ventricle damage on resternotomy occurred in two (4%) cases, damage to other structures adjacent to the heart such as a lung or innominate vein occurred in 4 (8%) patients. The operation was complicated with severe heart failure among seven (14%) patients. Heart failure was managed with the support of intraortic balloon pump in five (10%) patients, one (2%) required extracorporeal mechanical support. Severe intraoperative bleeding was documented among six (12%) patients.

Table 12. *Specific operative characteristics of the redo surgery for mitral PVL.*

Variable	**N (%) / median [Q1-Q3]**
Prosthesis type	
Biologic	4 (8%)
Mechanical	45 (92%)
Approach	
Right thoracotomy	3 (6%)
Median restenotomy	46 (94%)
Technique employed to correct paravalvular defect	
Prosthesis replacement	15 (31%)
Suture repair	34 (69%)
Intraoperative complication	
Right ventricle damage	2 (4%)
Damage to other structures	4 (8%)
Severe heart failure	7 (14%)
Complete atrioventricular block	2 (4%)
Intraoperative unplanned procedures	
Intraortic balloon pump	5 (10%)
Extracorporeal mechanical support	1 (2%)
Severe intraoperative bleeding	6 (12%)

4.11 Specific operative characteristics for catheter-based procedure

Specific operative characteristics for transapical catheter-based procedure with a “purpose specific device are presented in Table 13. It should be noted that the median length of the paravalvular defects was five (4 – 8 mm) mm, while the width was four (3 – 4 mm) mm. A majority 29 (78%) if the periprosthetic defects were crescent shaped, only fifth, eight (22%) leaks were oval. Occluder devices were deployed in 17 (71%) patients with biologic MVP, while five (21%) of cases had mechanical prosthetic mitral valve. Interestingly, two (8%) patients, had periprosthetic leakage after mitral valve repair with a rigid annuloplasty ring. Median number of one (1-2) devices were deployed per patient. Median fluoroscopy time was 1377 (518–1806) seconds.

Table 13. *Specific operative characteristics for catheter-based procedure.*

Variable	N (%) / median [Q1-Q3]
Paravalvular leak size	
Length, mm	5 (4-8)
Width, mm	4 (3-4)
Paravalvular leak shape	
Oval	8 (22%)
Crescent	29 (78%)
Type of the prosthesis	
Mechanical	5 (21%)
Biologic	17 (71%)
Annuloplasty ring	2 (8%)
Number of closure devices per patient	1 (1-2)
Fluoroscopy time, s	1377 (518-1806)
Severe intraoperative bleeding	0 (0%)

4.12 Immediate postoperative data following mitral valve PVL treatment

Immediate postoperative data following mitral valve PVL treatment in detail described in Table 14. Immediately (within first 72 hours after procedure or surgery), none of the patients died in the “Catheter” group, while five (10%) expired in the “Surgical” group of patients. All-cause procedural mortality at 30 days or in hospital after operation in the “Surgical” group occurred in nine (18%) patients, none in the “Catheter” group. There were eight (16%) patients who suffered from myocardial infarction within first 72 hours and 9 (18%) at 30 days after the index procedure among the “Surgical” patients, there were none patients who had this complication in the “Catheter” group. Three (6%) patients suffered ischemic cerebrovascular event in the “Surgical” group while being in hospital or at 30 days after operation. Their serum creatinine concentration increased more than three times postoperatively compared to the baseline or they required renal replacement therapy; no such patients were found in the “Catheter” group. Life-threatening or disabling bleeding (Type 5, 3b and 3c by the BARC criteria) occurred in the “Surgical” group of patients in nine (18%) patients, none among the “Catheter” ones (*p*-value = 0.03). Postoperatively seven (14%) patients developed sepsis in the “Surgical” group, none in the “Catheter” (*p*-value = 0.05). The “Surgical” patients compared to the “Catheter” group lost more blood in the first 24 hours after surgery. It was 675 (600–1550) milliliters versus 135 (100–250) milliliters respectively (*p*-value = 0.001). The patients in the “Surgical” group due to higher postoperative morbidity spent more time in the intensive therapy unit than those in the “Catheter” group, 3 (2–8) days versus one (1–1) day respectively (*p*-value = 0.001). The same statistically significant difference was in hospital stay: the “Surgical” patients spent 10 (8–13) days, while the “Catheter” patients 15 (12–21) days (*p*-value = 0.001).

Table 14. *Immediate postoperative data and complications of the patients after mitral valve PVL treatment.*

Variable	All patients N (%) / median [Q1-3])	"Catheter" N (%) / median [Q1-3])	"Surgical" N (%) / median [Q1-3])	*p* - value
Number of patients	73 (100%)	24 (33%)	49 (67%)	
Immediate procedural mortality (≤72 after procedure)	5 (7%)	0 (0%)	5 (10%)	0.15
Procedural mortality (at 30 days or in-hospital)	9 (12%)	0 (0%)	9 (18%)	0.025
Myocardial infarction (≤72 h after procedure)	8 (11%)	0 (0%)	8 (16%)	0.036
Myocardial infarction (within 30 days or in hospital)	9 (12%)	0 (0%)	9 (18%)	0.025
Stroke (within 30 days or in hospital)	3 (4%)	0 (0%)	3 (6%)	0.22
Acute kidney injury according to KDIGO	19 (26%)	5 (21%)	14 (28%)	0.48
Stage 1 (SCr[c] increased 1.5-2 times baseline)	7 (10%)	2 (8%)	5 (10%)	0.8
Stage 2 (SCr[c] increased 2-3 times baseline)	4 (6%)	3 (13%)	1 (2%)	0.07
Stage 3 (SCr[c] increased >3 times baseline or RRT)	8 (11%)	0 (0%)	8 (16%)	0.04
Bleeding according to BARC	16 (22%)	2 (8%)	14 (28%)	0.05
Life-threatening or disabling bleeding	9 (12%)	0 (0%)	9 (18%)	0.03
Major bleeding	2 (3%)	1 (4%)	1 (2%)	0.6
Major access site complications	12 (16%)	1 (4%)	11 (22%)	0.05
Surgical revision	6 (8%)	1 (4%)	5 (10%)	0.4
Drainage, ml/24h	200 (100-500)	135 (100 -250)	675 (600-1550)	0.001
Hospital stay, days	13 (10-19)	10 (8-13)	15 (12-21)	0.001
Intensive therapy unit stay, days	2 (1-4)	1 (1-1)	3 (2-8)	0.001

4.13 Results of mitral PVL treatment at discharge from hospital

Overall, 64 (88%) patients out of 73 were discharged from hospital. Forty patients (82%) out of 49 were discharged alive from hospital in the "Surgical" group, while all patients went home from the "Catheter" group. According to residual paravalvular regurgitation, overall complete seal of the defect, either by means of catheter-based closure, "suture repair" or valve redo replacement in the "Surgical" group, overall was achieved in 55 (86%) of discharged patients. In the "Catheter" group, a complete closure was achieved in 19 (79%) of cases, while in the "Surgical" group 30 (90%) patients were released from hospital with a completely competent MVP. Mild mitral paravalvular regurgitation (clinically not significant) was observed in five (8%) cases, among patients in the "Catheter" catheter group there were four (17%) and one (2.5%) in the "Surgical" one. Severe mitral PVL was seen in three (4%) patients in both groups; one (4%) female in the "Catheter" group and two (4%) patients in the "Surgical" group. Results of mitral PVL treatment at discharge from hospital are presented in detail in Table 15.

Table 15. *Results of mitral PVL treatment in both groups of patients at discharge.*

Clinical variables	All patient N (%) / median [Q1-Q3]	"Catheter" N (%) / median [Q1-Q3]	"Surgical" N (%) / median [Q1-Q3]	*p*-value
Number of patients at discharge	64 (88%)	24 (100%)	40 (82%)	0.025
Degree of residual PVL				
None	55 (86%)	19 (79%)	36 (90%)	0.23
Mild	5 (8%)	4 (17%)	1 (2.5%)	0.04
Moderate	1 (2%)	0 (0%)	1 (2.5%)	0.43
Severe	3 (4%)	1 (4%)	2 (4%)	0.88

4.14 Long term results of mitral PVL treatment

Overall, follow-up was available in all discharged patients, median duration for both groups was three (1.5–8.5) years, the "Catheter" group of patients were followed for 1.9 (0.97–2.23) years, while the "Surgical" ones were followed statistically for more a longer period – it was six (2.87–9.3) years (*p* – value = 0.001).

Overall mortality at follow-up was 29%, two patients (8%) expired in the "Catheter" group and 19 (39%) among the "Surgical cases; (*p* – value = 0.007). Reoccurrence of significant paravalvular regurgitation requiring readmission occurred in five (8%) patients for both groups, one (4%) patient in the "Cather" group and 4 (10%) cases in the "Surgical" group; two were discharged with severe leak and two were newcomers. Reoccurrence of mitral leak among the "Surgical" cohort was causing moderate regurgitation in one (2.5%) patients and severe in three (7.5%). All four later underwent catheter-based procedure. Long-term results of mitral valve paravalvular treatment in both groups of patients are presented in Table 16.

Table 16. *Long-term results of mitral valve PVL treatment in both groups of patients.*

Clinical variables	**All patient N (%) / median [Q1-Q3]**	**"Catheter" N (%) / median [Q1-Q3]**	**"Surgical" N (%) / median [Q1-Q3]**	***p*-value**
Follow-up, years	3 (1.5-8.5)	1.9 (0.97-2.23)	6 (2.87 – 9.3)	<0.001
Overall mortality	21 (29%)	2 (8%)	19 (39%)	0.007
Reoccurrence of PVL	5 (8%)	1 (4%)	4 (10%)	0.4
Moderate	1 (2%)	0 (0%)	1 (2.5%)	0.43
Severe	4 (6%)	1 (4%)	3 (7.5%)	0.6

4.15 Technical success in the “Catheter” group

There were no periprocedural strokes. All devices were successfully delivered and positioned, the delivery systems were withdrawn with no complications, no periprocedural impingement between the device and MVP occurred. There was no immediate conversion to full sternotomy. Failure to reduce PVL to a mild or lesser degree occurred in one patient; otherwise, technical success was achieved in 23 (96%) cases.

4.16 Device success in the “Catheter” group

No occluder migration, detachment, fracture, no embolization due to thrombosis or endocarditis occurred. Device success was achieved in 21 (88%) patients. Failure to treat PVL occurred in one patient (described above). In another patient, PVL was reduced from severe to mild. Unfortunately, worsening anemia developed requiring four units of red blood cells transfusion weekly. This patient underwent redo surgery with an occluder removal and prosthesis replacement. The third patient had excessive postoperative bleeding requiring surgical revision.

4.17 Procedural success in the “Catheter” group

All patients were discharged from hospital. Median intensive therapy unit stay was one (1–1) day, mean hospital stay was 10 (8–13) days. A complete closure of mitral PVL intraoperatively and at discharge (none or trivial residual paravalvular regurgitation) was achieved in 19 (79%) patients, reduction to mild in four (17%) patients; in one patient (4%) the reduction of paravalvular regurgitation was not achieved. The reduction of paravalvular regurgitation to a mild or lesser degree was achieved in 23 (96%) patients. A six-minute walk increased from 264 ± 108 meters on admission to 313 ± 120 meters (95% Confidence interval 20–77 meters) (p–value = 0.02) at thirty days after the procedure. Relief from anemia was achieved in seven (78%) out of nine patients.

4.18 Individual patient success in the “Catheter” group

Individual patient success at one-year follow-up was achieved in 20 (83%) patients treated. Individual patient success at one-year follow-up was not achieved in four patients. First is the patient in whom we failed to reduce mitral paravalvular regurgitation (later this patient expired 12 months after procedure). Another patient died due to uncontrolled sepsis, caused by a hemodialysis catheter (patient was in chronic renal failure preoperatively, which progressed in a few months). Third was a patient with worsened anemia. Fourth was a patient who suffered severe bleeding from a fractured rib.

4.19 Bleeding in the “Catheter” group

Postoperatively in the first 24 hours after the procedure, median blood loss was 135 ml, interquartile range from 100 ml to 250 ml. One patient bled 1450 ml in the first 24 hours (BARC Type 3b), and required re-exploration. Another patient bled due to a heparin overdose, lost 500 ml of blood in the first 24 hours (BARC Type 3a), and was managed medically. In three patients, postoperative bleeding was BARC Type 2 and they were treated with packed red blood cell transfusions. Five patients (21%) bled with accordance of the BARC criteria; no mortalities due to bleeding occurred. No bleeding events occurred at follow-up after discharge. Bleeding comparison between the groups is shown in Figure 15.

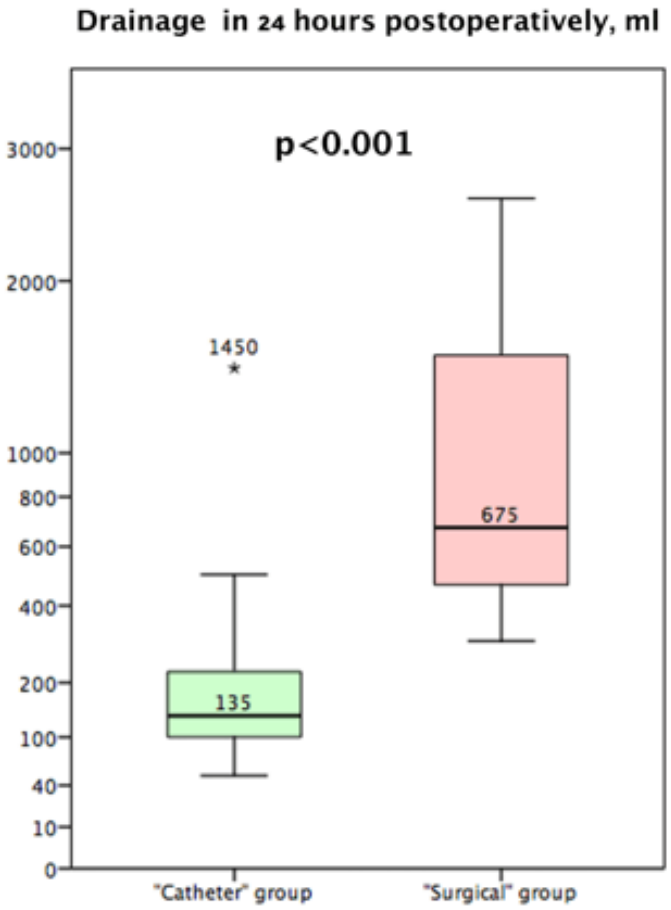

Figure 16. *Box plot of postoperative drainage in first 24 hours. The boxes contain 50% of the data. The upper edge of the box indicates the 75th percentile of the data set and the lower edge, the 25th percentile. The range of the middle two quartiles is the interquartile range. The line in the box indicates the median value. The ends of the vertical lines indicate the minimum and maximum data values. The star represents wild outlier. The values presented in mililtres per first 24 hours after operation.*

4.20 Acute kidney injury in the “Catheter” group

In accordance with the KDIGO clinical practice guidelines, acute kidney injury occurred in five (21%) patients, Stage 1 occurred in 2 (8%); Stage 2 occurred in three (13%); none of the patients developed acute kidney injury at Stage 3 and none required renal replacement therapy.

4.21 Access-site related complications in the “Catheter” group

An access site related complication occurred in one patient (4%). This occured due to a surgical retractor blade injury to the rib with subsequent severe bleeding requiring surgical revision. There was no wound infection in accordance with the ASEPSIS scoring system or CDC definitions of nosocomial surgical site infections [232, 233].

4.22 Description of the patient who required surgical exploration

A 75-year-old male presented with symptoms of heart failure due to mitral PVL. The 3D TEE confirmed presence of a crescent shape paravalvular defect at the A3 aspect of the mitral annulus with dimensions of 10 mm x 4 mm. He underwent a surgical transapical catheter-based mitral PVL uneventful closure. On the fourth postoperative hour, immediately after extubation, the patient lost 1000 ml of blood. Emergency revision was performed. A bleeding source was a rib fracture, possibly caused by the rib retractor blade. The patient’s further postoperative course was uneventful.

4.23 Description of the patient with failed reduction of PVL

A 60-year old female underwent mitral replacement with bi-leaflet mitral prosthesis 32 years ago. The patient failed previous redo surgery for PVL twice. As mitral PVL persisted, she was referred to a surgical transapical catheter-based procedure. She was suffering from heart failure and anemia. Her 3D TEE showed the defect at the P2 aspect of the mitral annulus (dimensions were 4 mm x 10 mm crescent in shape with surgical suture crossing the defect

in the middle). Multiple attempts to deploy occluders of various sizes and shapes were undertaken. The best intraoperative result was achieved with a combination of 4mm x 2 mm rectangular Waist and 4 mm x 4 mm square plugs with moderate residual regurgitation. Unfortunately, severe paravalvular regurgitation was present at discharge. She was referred to redo surgery again. The plan was abandoned because of severe pulmonary hypertension, severe tricuspid regurgitation, poor kidney function, chronic lung disease treated with bronchodilators and a history of unsuccessful two redo MVR surgeries (EuroSCORE II – 19.4%). The patient expired due to the progression of heart failure 12 months after an unsuccessful PVL closure.

4.24 Description of the patient with worsened anemia

A 57-year-old man with a previous history of moderate aortic stenosis developed infective endocarditis with an abscess on the aortic mitral curtain. He underwent uneventful replacement of both valves with a bi-leaflet mechanical prosthesis. Two months after surgery he presented with severe hemolytic anemia. His 3D TEE revealed mitral PVL. The defect was 8x5 mm at 2 o'clock (A3), oval shape, causing severe regurgitation, another defect 2 mm in diameter was at 6 o'clock (P2), and causing trivial regurgitation. The patient underwent a surgical transapical catheter-based mitral PVL closure procedure. An attempt to close the defect with 8 mm x 4 mm waist device failed to reduce regurgitation. A significant reduction of regurgitation was achieved with a 12 mm x 5 mm waist rectangular occluder. The real time 3D TEE showed presence of mild regurgitation located next to the device. No impingement of the occluder with prosthesis or incomplete expansion of the discs was observed. The defect at 6 o'clock was considered too small and was left intact. As the treatment result was acceptable, the team decision to terminate the procedure was reached. Although PVL regurgitation was reduced from severe to mild, the patient developed worsening anemia on the seventh postoperative day, requiring four units of red blood cells transfusion weekly. All other possible causes of anemia were excluded. Despite a high

perioperative risk, he underwent redo surgery with the removal of the defect closure device and both mechanical aortic and mitral prosthesis replacement with tissue prosthesis and was discharged from hospital on the 40th postoperative day.

5 DISCUSSION

5.1 Incidence of mitral PVL

The natural history of the significant mitral valve disease was dramatically influenced in a positive way by MVR, which aims to improve patients' survival and symptoms. Unfortunately, this surgery is not free of complications. One is mitral PVL, and if left untreated, it can significantly impair patients or even cause unnecessary premature mortality. Despite the fact that in the literature the incidence and risk factors for its development described by many authors, as a part of this research we sought to determine incidence of mitral PVL and factors affecting its occurrence in the population within our scope. Unfortunately, the number of patients in the cohort of the first stage could have been larger; a significant proportion of cases were dropped out, simply due a high degree of incompleteness or missing retrospectively analyzed clinical data. Nevertheless, we addressed the literature to look at the number of patients in the reported papers. To establish the incidence of mitral PVL, various cohorts by the amount of cases were analyzed in the literature available. Studies with a smaller cohort of patients were also available, for example, Skoularigis et al. evaluated 119 patients after MVR, to determine the incidence of the PVL [55]. For instance, in the cornerstone publication by Ionescu et al. cited globally, an incidence in mitral periprosthetic defects of 117 patients was investigated [14]. Dhasmana et al. in 1983 published an analysis of 435 patients, which were followed up to 69 months after primary MVR without native infective endocarditis [19]. From the perspective of very early (first 24 postoperative hours) incidence of mitral PVL, Bonnefoy et al. have performed a study on a relatively small group of 77 consecutive cases who underwent MVR with a mechanical prosthesis [20]. Fortunately, some authors analyzed a larger cohort of patients, for instance Ho Young et al. investigated a cohort of 1,202 cases, which were followed for 20 years [50]. Genoni et al. the group from Ziurich analyzed 618 cases after MVR for the same reason [15]. In our opinion, retrospective research of a cohort

consisting of 551 patients to evaluate the true incidence of mitral paravalvalvular leak after isolated MVR is sufficient.

According to the demographical presentation, our cohort of patients analyzed in did not differ from the populations analyzed in the literature available. It applies to the preoperative clinical data and operative variables. It means that our analyzed population who underwent MVR had similar characteristics, compared to the data available in the literature.

The rate of mitral paravalvular regurgitation varies dramatically across the studies published; this variability depends on the period of follow-up in each study, on the decade study was published, also on the prevalence of the surgical suture technique employed to implant the prosthesis and more.

Dhasmana et al. back in 1978 released a publication with an incidence of mitral PVL at 7.1% [19]. In the study published by Ionescu Marian et al. experience with biologic mitral prosthesis is analyzed in 250 patents with follow-up of 11 years, the authors showed that the overall PVL developed in seven patients overall, which brings its incidence to 2.8% [234]. In contrast, Adrian et al. was looking at all degrees of mitral PVL during intraoperative, early postoperative and follow-up echo studies and reported 32% early incidence of mitral paravalvular regurgitation while at follow-up of 1.8 years, the authors report the prevalence of periprosthetic regurgitation being 15% [14]. Skudicky et al. presented a 31% prevalence of mitral paraprosthetic jets after MVR consistent with findings of Ionescu Adrian [62]. In the paper by Bonnefoy et al. paravalvular regurgitant jets were diagnosed in 14% of patients investigated within one day after MVR [20]. In the recent study, published in 2015, Ho Young, et al. established incidence of early significant mitral paravalvular defects at 1.9%, while late incidence was 6.2% and overall at 8.1% [50]. Karl Hammermeister et al. performed a milestone study for evaluation of valvular prosthetic performance; the authors subjected 181 patients who underwent MVR, between 1977 and 1982 to randomization in the operating theater, either

to receive disc mechanical prosthesis or a porcine bioprosthetic valve. After mean follow-up of 15 years, the incidence of mitral paravalvular regurgitation was 17% in the mechanical prosthesis arm of the study and 7% among patients with bioprosthesis [13]. To conclude, the incidence of the mitral paravalvular regurgitation at follow-up can be as high as 17%. Our findings showed that the prevalence of mitral PVL among the population we analyzed, at median follow-up of 5.5 years is 6.8 %; this does not conflict with the findings in the global medical literature, even lower than in most of the published experiences.

5.2 Risk factors for mitral PVL

Many factors in the literature available are known to increase the risk of mitral PVL formation; those are mitral annular calcification, infection, suturing technique, and the size and type of the prosthetic implant, even the race of the patient [19, 204].

In 1983, the group of the authors lead by Kirklin and Kouchoukos used simple contingency and table methods for patient and treatment related factors including a surgeon, which influenced the occurrence of PVL, followed by univariate and multivariate analyses, initially using logistic regression, then the Cox proportional hazards model. Following such comprehensive analysis, they concluded that the use of the continuous suture technique, mitral annular calcification, left ventricular hypertrophy, and people of the black race were independent risk factors for this complication to occur [19]. Later another group of investigators put the “blame” on the continuous suture technique; they found that 41% of the valves implanted with continuous sutures had periprosthetic leaks, compared with 7% of those with interrupted sutures [14]. In the publication by Ho Young et al. age, male gender and redo MVR were associated with major mitral periprosthetic leak during follow-up [50]. We performed analysis of all factors potentially influenced mitral PVL occurrence, presented in detail in Table 5. We initially used simple contingency and table methods, followed by univariate and multivariate analyses to answer the

question on most relevant risk factors. After univariate analysis, we found that the body surface area ≥2 m2, the continuous suture technique to implant the prosthesis, the specific surgeon, ischemic etiology of the mitral valve lesion and LV end diastolic diameter were predictors for mitral PVL to occur. Multivariate Cox regression analysis revealed that most significant risk factors for developing mitral PVL in our population were the specific surgeon performed MVR and ischemic mitral valve lesion etiology.

Bringing this chapter to the conclusion, none of the literary sources previously named variables of ischemic mitral etiology and the surgeon as independent and most significant risk factors for mitral paravalvular dehiscence formation. On the subject of ischemic mitral valve lesion etiology, we hypothesize that continuous negative left ventricular remodeling with the surgically fixed prosthesis in mitral position can further enlarge mitral valve annulus, subsequently disrupting the suture line between the prosthesis and native tissues of the mitral annulus. On the subject of a surgeon as a risk factor, many papers have been written discussing a surgeon's performance, its improvement, and quality and performance control; but it is not the subject of this research [248-253]. To carry discussion on, if a specific surgeon can cause a higher incidence of mitral PVL, further analysis of the factors within, such as experience, surgical techniques, yearly operative workload, etc. have to be analyzed, and this might be a subject of another analysis.

5.3 Early and late mortality and morbidity following MVR

Immediate procedural mortality after MVR was 3.3% in hospital or 30 days was 10.7%. The main causes of this were permanent stroke striking at the rate of 3.4% at 30 days, a high rate of sternotomy at the incidence of 12.2% for the reasons of bleeding, deep sternal wound infection, cardiopulmonary resuscitation, need for mechanical circulatory support and flail sternum. The Kaplan-Meier survival function showed a 5-year survival at 75% and 10-year survival at 62%.

The recent publication released by Shintyan et al. analyzed the outcomes of 2727 patients who underwent isolated mitral replacement in the period from 1997 to 2006. In hospital or at 30 days mortality was 2.7% in patients who received biologic mitral prosthesis and 0.8% – mechanical prosthesis; the incidence of stroke at 30 days in their population was 0.8% for patients with bioprosthesis and 1.1% in patients with a mechanical one. Actuarial 15-year survival was 74.3% after bioprosthetic versus 80.8% receiving a mechanical prosthesis [235]. Another study by Bakaeen et al. analyzed patients who underwent MVR from 2000 to 2013, presented 30-day mortality at a rate of 3.5% with mortality rate at 10 years of follow-up at 37%. The rate of resternotomy was 3.9%, stroke 1.9% and median stay in hospital for 10 days [236]. The Society of Thoracic Surgeons released the paper in 2016 analyzing 61,201 patients from 867 centers who underwent isolated MVR operations with various concomitant procedures; they reported three-year outcomes with overall mortality, which was 2.9% [237]. In the previously mentioned study by Hammermeister et al. published 30 years ago, 30-day mortality was observed in 6.5% of patients in a mitral bioprosthetic valve group and 9.1% in a mechanical valve group [238]. In 2003, Thourani et al. released the paper comparing MVR versus repair; in hospital mortality in the MVR arm of patients was 6.9%, and overall 10-year survival was 46% [239].

One of the findings of this research is high early postoperative mortality after MVR. In nowadays comparison, the immediate and 30-day mortality results following MVR analyzed in our cohort are higher compared to the literature. The reasons of high incidence of intraoperative complications and high postoperative morbidity were not investigated in this study. In summary, further studies of this cohort are needed to investigate the true underlying reasons behind this variation and to identify contingency in order to improve the care of the patients undergoing MVR. Since the results of long-term survival in our population are similar to the ones available in the literature, this

outcome variable can be improved by the reduction of the immediate and 30-day mortality results.

5.4 General considerations about catheter-based mitral PVL closure

Until the recent development and widespread use of catheter-based closure procedures for paraprosthetic dehiscence, repeat surgical treatment was the only effective treatment modality [15, 240]. Despite its improved survival compared with conservative management, redo surgery for mitral paravalvular defects can carry high morbidity and mortality, also a high rate of the reoccurrence of this complication is noted [13, 15, 22]. The high rate of mortality and morbidity following conventional redo surgery, a burden on complicated postoperative care as well rapid development of various catheter-based intracardiac procedures have driven medical professionals alongside with the medical industry to introduce into clinical practice less invasive and possibly better outcomes carrying treatment modality – catheter-based PVL closure. Initially, it was performed with variety "off label" products. Recently a new device for paravalvular defect closure has been developed and introduced into clinical practice. Up to date, only a few studies of mitral PVL treated by the surgical transapical catheter-based approach have been published [241, 242]. A few years ago at Vilnius University Hospital Santaros Klinikos, catheter-based transapical mitral paravalvular defect closure with an "off label" device was introduced into practice. The evidence in the literature has determined our choice of a surgically open transapical access site. Some authors have demonstrated low incidence of adverse procedural events with transapical access site compared with other access sites for mitral PVL closure; they conclude that the transapical approach could be considered as a first line therapy [194, 218]. Other authors state that this approach allows access to defects in all anatomic locations of the mitral prosthesis [25]. Furthermore, analysis by Jelnin et al. showed that a planned transapical approach resulted in shorter fluoroscopy and procedural times compared with converted and

combined trans-septal procedures [219]. In addition, at our center at the time of the initiation of the catheter-based treatment of mitral PVL a transapical procedure to correct mitral regurgitation was already in practice [243]. This experience was easily translated into the mitral paraprosthetic defect closure procedure. The open surgical transapical approach was also chosen for the reason of the controlled surgical closure of the ventricular puncture and avoidance of damage to the coronary arteries. Consistently with other investigators we found that this access site delivers a high rate of successful periprosthetic defect closure in mitral position; it is also practical and feasible. A “purpose specific” occluder was introduced into our clinical practice soon after the European CE mark approval was granted. Each paravalvular defect is unique in shape, geometry, size and its proximity to prosthesis. To fit such a wide variety of defects the manufacturer offers devices in various sizes and shapes. Oblong devices can fit the defect more accurately; in the paper by Calvert et al., its use was associated with less residual regurgitation and more improved heart failure symptoms at follow-up [25]. According to the literature, technical success of patients treated in transapical fashion for mitral PVL closure can vary from 91% to 100% [12, 68, 241, 244]. In our group it has been achieved in 23 (96%) patients. Failure to reduce mitral periprosthetic mitral regurgitation in one (4%) patient occurred due to the tortuous anatomy of the defect (crescent shape with surgical suture material crossing it in the middle). Retrospectively, analyzing the periprocedural events of this patient, it could have been helpful to attempt implanting two small square occluders in the Hopscotch technique fashion [231]. We found almost no reports in the recent literature where device success of catheter-based mitral PVL closure is presented as recommended by the recent expert statement [138]. Device success in our group at 30 days and follow-up was achieved in 21 (88%) patients, compared to the results of 83 % presented recently by Aydin et al. or 86% reported by Smolka et al. bringing our device success rate similar to the results reported previously [241]. We failed to achieve device success in three patients due to the impossibility of reducing paravalvular regurgitation in one

patient, bleeding event in another and worsened anemia in the third (described in detail above). A bleeding event occurred in a frail octogenarian due to the use of a rigid metallic Finochietto rib retractor and overspread of the intercostal space; this caused rib fracture and damage to the intercostal neurovascular bundle; this complication is well described as a complication of small thoracotomy [245]. Some authors promote avoidance of rib fracture during thoracotomy as a potential for postoperative chest wall hemorrhage or hemothorax [245, 246]. Potentially, with the use of the atraumatic plastic soft tissue retractors the rate of bleeding due to trauma to the ribs can be avoided. Unfortunately, due to the additional cost of the procedure, we are very limited in the use of additional "expensive" materials such as a soft tissue retractor. To minimize the risk of rib fracture with a sequel of bleeding we minimized the use of a rigid Finochietto retractor only for pericardial adhesion dissection and its hitching to the skin. Later, for the entire procedure we remove the rib spreader (Figure 3).

In the third patient, a failure to treat hemolysis despite reduction of paravalvular regurgitation to a mild degree has also been previously described by Smolka et al. and other authors [34, 56]. The understanding of the hemolysis mechanism in those patients is difficult. As stated by Kliger et al. some patients after catheter-based paravalvular defect closure continue to be transfusion-dependent, as hemolysis can occur from blood shunting through the device and typically should resolve within six months after complete endothelialization [21]. The exacerbation of hemolytic anemia could have happened due to device oversize in comparison to the defect, which later led to its bending and residual mild regurgitation. Following this experience found in the literature, we attempted to manage our patient with red blood cell transfusions with no improvement for five weeks; so patient had redo surgery with both valves replacement and the device removal. Unfortunately, no significant epithelization was present on the device (Fig 15). In our opinion, such patients can be managed in two ways: firstly, redo surgery, secondly, redo

catheter-based removal of occluders with reattempts for complete closure [216].

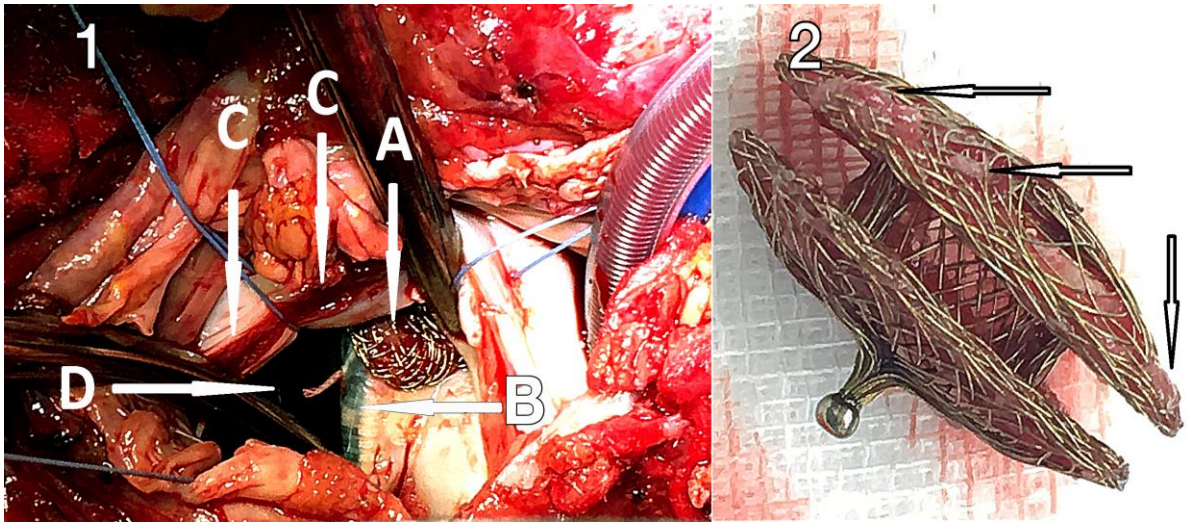

Figure 17. *Intraoperative pictures of the PLD occluder in patient with worsened anemia. 1: PLD occluder at the mitral valve annulus. A – PLD occluder in situ at the A2 aspect of the mitral valve annulus, B – cuff of the mitral valve prosthesis, C – interatrial septum, D – left atrium. 2: PLD occluder removed. Arrows point to "islands" of the epithelium.*

5.5 “Catheter” versus “Surgical” treatment of mitral PVL

Up to date only five papers have exist where “Surgical” treatment is compared to the catheter-based modality and included 848 patients [209]. Unfortunately, none of the publications compares such a homogenous group of catheter-based procedure to the conventional redo surgical group as in our cohort. In contrast to other authors, our patients treated through the same access site, all patients had surgically controlled left thoracotomy for the entry into the LV. Only a device specifically designed for the treatment of paravalvular defect closed the defects in our catheter-based PVL closure group of patients. It is also worth mentioning that the same dedicated team of cardiac surgeon, interventional cardiologist and an expert echocardiographic imaging specialist treated the catheter-based group of patients. Some can argue that one team approach may compromise the reproducibility of the procedure. Since mitral PVL complication is relatively rare, to maintain good results, the same team performs its treatment at our center. Thus if the procedure is performed by various specialists, procedures results can be compromised by the low volume of performed procedures. For the prospective of translating the experience to other, during the procedure, trainees from all parts of the team are always present. Also in comparison to other authors, we had no significant differences between the groups of patients concerning preoperative clinical and demographic data.

Alkhouli et al. published the comparison of 195 patients who underwent catheter-based treatment for mitral PVL and 186 cases that had redo surgery [207]. In contrast to our group of patients in the catheter-based group, in Alkhouli et al. group mitral paravalvular defects were approached in three different routes: transseptal without venoarterial rail, transseptal with venoarterial rail and transseptal with tranapical rail. None of the patients in their cohort was treated in tranapical approach fashion. What is also worth mentioning is that this group used three different devices which are “off label” for PVL closure.

Technical success differs between our and Alkhouli et al. groups of the surgical cohorts 90% versus 95.5%, respectively. Comparison of technical success between our catheter-based patients and Alkhouli et al. group, was higher in our group – 96% versus 70.1%. Hospital mortality among patients treated surgically was lower among patients in Alkhouli et al. group compared to our surgically treated patients, 7.7% versus 18% respectively. While in our catheter-based group of patients had a hospital mortality rate of 0%, Alkhouli et al. it was 3.1%. Hospital length stay did not differ between surgical patients in Alkhouli et al. and our patients, 14 versus 15 days respectively. In contrast, our catheter-based patients stayed 10 days in hospital, while in Alkhouli et al. the same cohort stayed 5.3 days. It can be related to the fact that our patients had to recover from a surgical trauma of thoracotomy, which the patients in Alkhouli et al. group did not experience. Our cohort of patients' hospital and intensive therapy unit stay is represented in Figure 16.

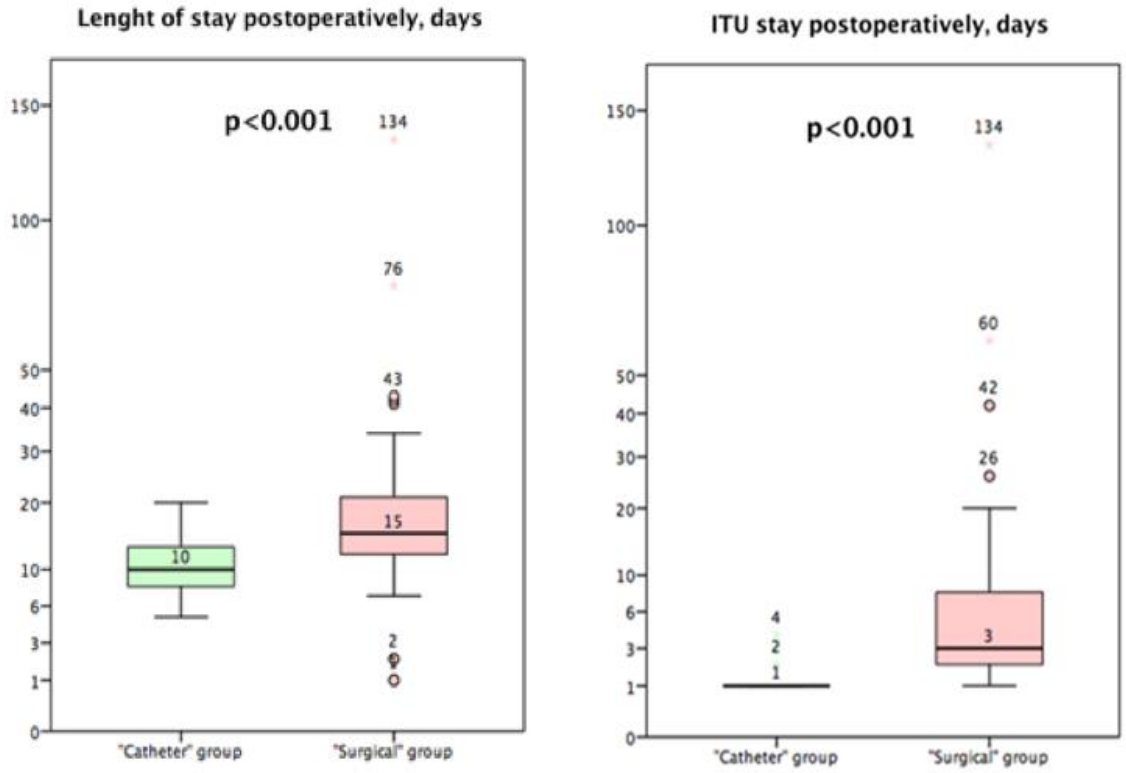

Figure 18. *Box plot ITU and hospital stay for patients treated for PVL. The boxes contain 50% of the data. The upper edge of the box indicates the 75th percentile of the data set and the lower edge – the 25th percentile. The range of the middle two quartiles is the interquartile range. The line in the box indicates the median values. The ends of the vertical lines indicate the minimum and maximum data values. The circle represents outlier values. The star represents wild outlier.*

mortality in their group was in surgical arm 6.9% and in catheter-based group 7.1%. In Wells et al. patients in the catheter-based group of patients stayed a shorter time at hospital than our treated cohort. Wells et al. surgical and catheter-based patients in hospital were treated 8 and 4 days respectively. However, at one year, Wells et al. found no difference in mortality, readmission, or repeat intervention between patients surgical and the catheter-based groups [26].

Millan et al. presented outcomes of 163 patients who underwent treatment for mitral periprosthetic defects surgically or in the catheter-based fashion. In his cohort of patients, analyzed surgical treatment was applied to 98 patients and

catheter-based procedure was performed in 65 cases. The majority of patients – 99.3% – treated by redo surgery in their group had no or minimal paramitral regurgitation at discharge compared to our surgical patients: it was achieved in 96% of cases. Residual paravalvular regurgitation higher than mild in catheter-based patients of Millan et al. group was noted in 50% of this cohort, while among our patients treated in the catheter-based fashion it was 4%, due to failure to reduce PVL in one patient. Again, hospital mortality in our catheter-based group was 0%, while in publication by Millan et al. same group had 2.5% hospital mortality rate. Comparing redo surgery, in Millan et al. surgical patient's hospital mortality was 6.6%, while in our surgical patents it was 18% [27]. The remaining two comparative studies consisted of smaller cohorts. Angulo-Llanos et al. reported results of 67 patients treated for mitral PVL. In patients who underwent catheter-based treatment, paramitral defects were approached in three ways anterograde (transeptal), retrograde (transaortic) and in a transapical route. Similarly, to previously presented authors, Angulo-Llanos et al. had employed an "off label" device to treat mitral paravalvular regurgitation. In-hospital mortality among the surgical group of patients in Angulo-Llanos et al. publication was 30.6%, compared to our surgical cohort – 18% of patients who died in hospital. In contrast, the catheter-based patients in Angulo-Llanos et al. cohort had in hospital mortality at the rate of 9.8%; compared to our patients in the same group it was 0%. The authors also present their cohorts mortality at two-year follow-up, which was 54.3% among surgical patients versus 39.2% in catheter-based group [208]. Our patients treated for mitral PVL, both Kaplan-Meier survival curves for mortality and Kaplan-Meier survival curves for composite of death, anemia (Hb < 100 g/L) and residual mitral PVL higher than mild are presented in Figures 17 and 18 respectively.

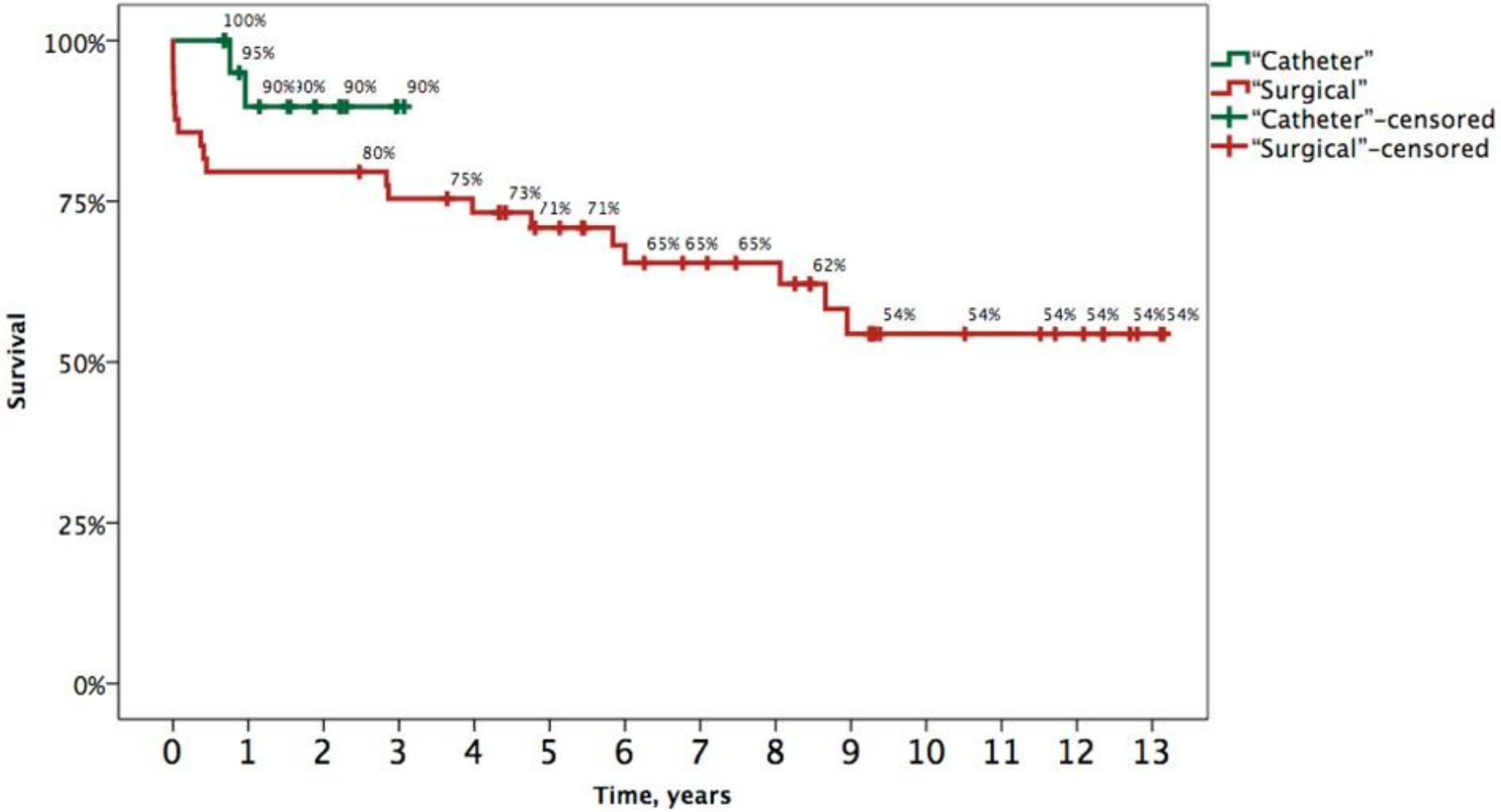

Figure 19. *Kaplan-Meier survival curve for mortality after mitral PVL treatment.*

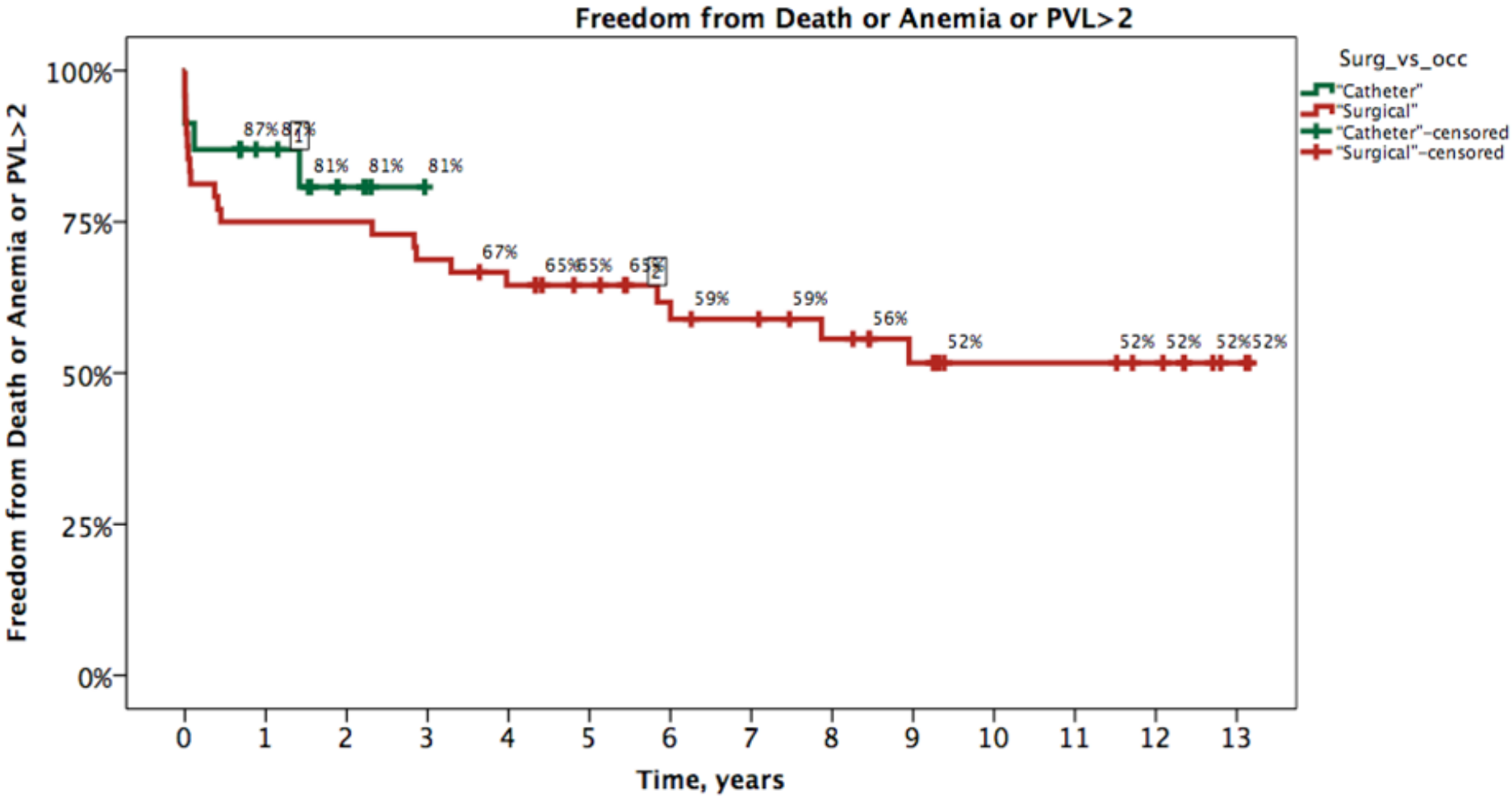

Figure 20. *Kaplan-Meier survival curve for the composite of death, anemia (Hb < 100 g/L) and residual mitral paravalvular regurgitation higher than mild.*

In contrast to other authors and our results, Pinheiro et al. presented a smaller cohort, a comparison of 21 patients with mitral paravalvular leak, 13 of them underwent redo surgery and eight patients catheter-based mitral PVL closure. In their cohort, there were no deaths during the hospitalization in the catheter-based group of patients, while in-hospital mortality among surgical patients was 8%. In addition, it is worth mentioning hospital stay: surgical patients stayed in hospital for 30 days, while the catheter-based patients for 32 days [247].

The results of our cohort of patients treated for mitral PVL presented in this manuscript and compared with the scientific literature showed that conventional re-do surgery with cardiopulmonary bypass for mitral PVL carries higher early postoperative morbidity, which translates into unacceptably high in hospital mortality, if compared to catheter-based transapical mitral PVL closure with a “purpose specific” device. Similar results presented in the most respected sources in the literature. In addition, we found that from the perspective of mitral paravalvular regurgitation reduction, catheter-based closure of mitral PVL with a “purpose specific” device is not inferior to conventional redo surgery.

5.6 Research limitations

This research has several limitations. Firstly, this is a retrospective study of a single center practice in both stages of the research, except for prospectively enrolled patients for mitral PVL treatment in the “Catheter” group of patients.

Secondly, the number of patients in the cohort of the first stage could have been larger; unfortunately, a significant proportion of cases were dropped out, simply due a high degree of incompleteness or missing clinical data. This also influenced our failure to report morbidity and mortality after conventional isolated mitral replacement within the framework of guidelines. Nevertheless, this stage of the research provides the largest and the most comprehensive series of patients analyzed after MVR for this specific purpose in Lithuania.

Thirdly, the lack of randomized data globally, to compare results of different treatment modalities for mitral PVL, limits our comparison to the experiences in the comprehensive literature and weakens the conclusion of the present research.

Fourthly, the small number of patients aggravates the comparison of the treatment modalities for mitral PVL the comparison of the treatment modalities for mitral PVL. Thus, further inclusion of the patients needed to prove or deny superiority or inferiority of treatment between both methods.

Fifthly, we have found no sources in the literature were the patients treated in catheter-based fashion for mitral PVL were as homogenous as ours were. Mostly, catheter-based groups in the global literature are heterogonous in terms of variety of access sites employed, and devices to close the defect used. Thus, a comparison of our catheter-based closure patients to the cohorts found in the literature is more of a comparison between apples and oranges.

6 CONCLUSIONS

The prevalence of mitral paravalvular leak among the population we analyzed at median follow-up of 5.5 years is 6.8 % and this does not conflict with the findings in the global medical literature.

The most relevant risk factors for the development of mitral PVL among our analyzed population were the surgeon who performed MVR and ischemic etiology of the mitral valve lesion.

Immediate procedural mortality after MVR among our analyzed population was 3.3%, in hospital or 30 days was 10.7%. Five-year survival was 75% and 10-year survival was 62%.

Surgical transapical catheter-based closure of mitral paravalvular leak with “purpose specific” device is not inferior compared to conventional redo surgery with cardiopulmonary bypass in the effectiveness of mitral PVL reduction. Surgical transapical catheter-based closure of mitral paravalvular leak with a “purpose specific” device is safer in the early postoperative period compared to conventional redo surgery with cardiopulmonary bypass.

7 PRACTICAL RECOMMENDATIONS

Currently, the first line of treatment should be transapical catheter-based closure with a “purpose specific” device for patients with clinically significant mitral paravalvular leak.

Conventional redo surgery should remain as an alternative reserve, in case of catheter-based closure failure or for the patients with contraindications for catheter-based procedure.

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APPENDIX

List of publications

1. Zorinas A, Janusauskas V, Davidavicius G, Puodziukaite L, Zakarkaite D, Kramena R, Cypiene R, Bilkis V, Rucinskas K, Aidietis A, Onorato EM. Fusion of real-time 3D transesophageal echocardiography and cardiac fluoroscopy imaging in transapical catheter-based mitral paravalvular leak closure. Postępy w Kardiologii Interwencyjnej/Advances in Interventional Cardiology. 2017;13(3):263-268. doi:10.5114/aic.2017.70200.

2. Zorinas A, Janušauskas V, Davidavičius G, Šimakauskas R, Puodžiukaitė L, Zakarkaitė D, Bilkis V, Čypienė R, Samalavičius R, Onorato E, Aidietis A, Ručinskas K. Retrospective analysis of single-center early and midterm results of transapical catheter-based mitral paravalvular leak closure with a purpose-specific device. Advances in Interventional Cardiology/Postępy w Kardiologii Interwencyjnej. 2018;14(2):167-175. doi:10.5114/aic.2018.76408.

3. Onorato EM, Zorinas A, Janusauskas V, Davidavcius G, Zakarkaite D, Kramena R, Bilkis V, Rucinskas K, Samalavicius R, Aidietis A. Occlutech® Paravalvular Leak Device (PLD). In Transcatheter Paravalvular Leak Closure. Singapore: Springer; 2017. p. 55-77.

List of international presentations

1. Zorinas A, Janusauskas V, Simkauskas R, Rucinskas K, Aidietis A. “Surgical vs. catheter-based paravalvular mitral valve leak closure (transapical approach). Early results: Single center experience”. At the 25th Anniversary Congress of the World Society of Cardiothoracic Surgeons being hosted by the Royal College of Surgeons of Edinburgh, September 2015.

2. Zorinas A, Bilkis V, Simakauskas R, Janusauskas V, Rucinskas K, Davidavicius G, Zakarkaite D, Aidietis A. “Catheter-based mitral valve paravalvular leak closure. Early results”. At the 16th International Society for Minimally Invasive Cardiothoracic Surgery (ISMICS) Annual Scientific Meeting, June 2016.

3. Zorinas A, Janusauskas V, Simkauskas R, Bilkis V, Rucinskas K, Aidietis A. “Mitral paravalvular leak. Retrospective comparison of surgical treatment modalities in 50 patients. Single centre experience”. At the 26th Anniversary Congress of the World Society of Cardiothoracic Surgeons, September 2016.

4. Zorinas A, Janusauskas V, Puodziukaite L, Davidavicius G, Zakarkaite D, Kramena R, Bilkis V, Samalavicius RS, Rucinskas K, Aidietis A. “Mitral paravalvular leak closure in elective patients with purpose manufactured device: early clinical experience”. At the 66th ESCVS International Congress of the European Society for CardioVascular and Endovascular Surgery, May 2017.

5. Zorinas A, Janusauskas V, Puodziukaite L, Simakauskas R, Davidavicius G, Bilkis V, Kramena R, Zakarkaite D, Cypiene R, Samalavicius RS, Rucinskas K, Aidietis A, Onorato EM. “Conventional Redo Surgery Vs Catheter-based Trans-apical Procedure in Mitral

Paravalvular Leak Treatment". At the 27th Anniversary Congress of the World Society of Cardiothoracic Surgeons, September 2017.

Vilnius Regional Biomedical Research Ethics Committee Approval

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LEIDIMAS
ATLIKTI BIOMEDICININĮ TYRIMĄ

2017-07-04 Nr.158200-17-934-436

Tyrimo pavadinimas:
Prievožtuvinių fistulių susidarymo priežasčių nustatymo ir skirtingų gydymo metodų palyginamasis tyrimas pacientams po širdies vožtuvų operacijų

Protokolo Nr.:	MVPPVF2017
Versija:	1.0
Data:	2017-06-19
Pagrindinis tyrėjas:	**Kęstutis Ručinskas**
Įstaigos pavadinimas:	VUL Santaros klinikos
Adresas:	Santariškių g. 2, Vilnius
Leidimas galioja iki:	**2022-12**

Leidimas išduotas Vilniaus regioninio biomedicininių tyrimų etikos komiteto posėdžio (protokolas Nr. 158200-2017/07), vykusio 2017 m. liepos 4 d. sprendimu.

Pirmininkas Saulius Vosylius

State Data Protection Inspectorate Research Approval

VALSTYBINĖ DUOMENŲ APSAUGOS INSPEKCIJA

Viešajai įstaigai Vilniaus universiteto
ligoninės Santaros klinikoms
(per E. pristatymo informacinę sistemą ir el. paštu
kestutis.raciukas@santa.lt)

SPRENDIMAS
DĖL LEIDIMO VIEŠAJAI ĮSTAIGAI VILNIAUS UNIVERSITETO LIGONINĖS SANTAROS KLINIKOMS ATLIKTI ASMENS DUOMENŲ TVARKYMO VEIKSMUS

2017 m. spalio 27 d. Nr. 2R-[illegible](2.6-1.)
Vilnius

Valstybinė duomenų apsaugos inspekcija (toliau – Inspekcija), išnagrinėjusi Viešosios įstaigos Vilniaus universiteto ligoninės Santaros klinikų 2017-10-05 Pranešimą dėl išankstinės patikros Nr. SR-5997 (toliau – Pranešimas) (Inspekcijoje gauta 2017-10-06, reg. Nr. 1R-7363) dėl asmens duomenų tvarkymo mokslinio medicininio tyrimo tikslu,

n u s t a t ė,

kad Pranešime nurodyti asmens duomenų tvarkymo veiksmai atitinka Lietuvos Respublikos asmens duomenų teisinės apsaugos įstatyme nustatytus asmens duomenų tvarkymo ir duomenų subjektų teisių įgyvendinimo reikalavimus bei numatytus fizikinės organizacinės ir techninės duomenų saugumo priemonės.

Valstybinė duomenų apsaugos inspekcija, vadovaudamasi Lietuvos Respublikos asmens duomenų teisinės apsaugos įstatymo 33 straipsniu, Valstybinės duomenų apsaugos inspekcijos direktoriaus 2016 m. birželio 22 d. įsakymo Nr. 1T-23 patvirtinių Išankstinės patikros atlikimo taisyklių 12 ir 19.2 punktais,

n u s p r e n d ž i a

Viešajai įstaigai Vilniaus universiteto ligoninės Santaros klinikoms išduoti leidimą atlikti Pranešime nurodytų asmens duomenų apie sveikatą tvarkymo mokslinės medicininio tyrimo **„Prievožtovinių fistulių susidarymo priežasčių nustatymo ir skirtingų gydymo metodų palyginamasis tyrimas pacientams po širdies vožtuvų operacijų“ (Protokolo Nr. MVPPVF2017)** tikslu veiksmus.

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Direktoriaus pavaduotoja,
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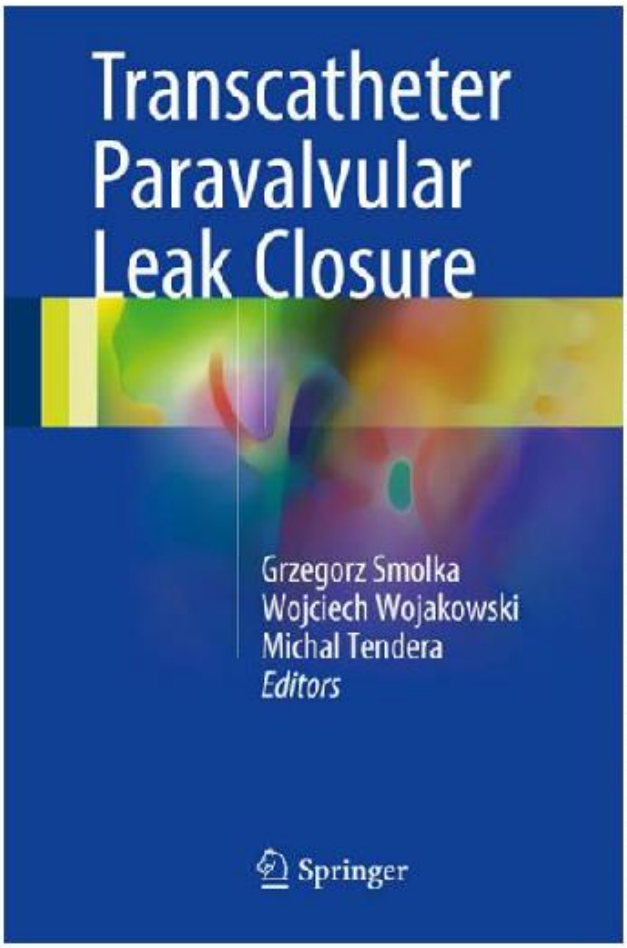
Chapter "Occlutech® Paravalvular Leak Device (PLD)" in a book "Transcatheter Paravalvular Leak Closure" (front pages of the book and chapter)



Chapter 4

Occlutech® Paravalvular Leak Device (PLD)

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4.1 Background

Since the first reported use of the double-umbrella Rashkind device [1] in 1992, transcatheter paravalvular leak (PVL) closure has been performed extensively by many centers around the world.

A surprising number of different devices including atrial septal defect occluders, duct occluders, muscular ventricular septal defect occluders, and, more recently, vascular plugs [2–11] have been used to close aortic or mitral paravalvular leaks.

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Publication "Retrospective analysis of single-center early and midterm results of transapical catheter-based mitral paravalvular leak closure with a purpose-specific device" (front page)

ADVANCES IN INTERVENTIONAL CARDIOLOGY
Postępy w Kardiologii Interwencyjnej

Original paper

Retrospective analysis of single-center early and midterm results of transapical catheter-based mitral paravalvular leak closure with a purpose-specific device

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Abstract

Introduction: Due to the recent lack of definitions to establish the severity of paravalvular leak (PVL) and endpoints for its treatment, the effectiveness and safety of a new device for PVL closure have not been comprehensively analyzed.

Aim: To analyze a single center's experience of mitral PVL closure in a surgical transapical catheter-based fashion with a purpose-specific device.

Material and methods: This is a retrospective cohort study of patients following transapical catheter-based mitral PVL closure with a purpose-specific device. Data were analyzed at baseline, perioperatively, at discharge, at six months and annually after the procedure.

Results: Nineteen patients underwent surgical transapical catheter-based mitral PVL closure with the Occlutech PLD Occluder. Mean follow-up time was 20 ±7 (range: 9–33) months. The patients' mean age was 64 ±7 years, and 11 (58%) were male. Technical, device and individual patient success at follow-up was achieved in 18 (95%), 16 (84%) and 16 (84%) patients respectively. Median intensive therapy unit stay was one day (1–4) and mean hospital stay was 11 ±4 days. A reduction of paravalvular regurgitation to a mild or lesser degree was achieved in 18 (95%) patients. There were no strokes or myocardial infarctions at follow-up. There were no deaths at 30 days after the procedure. One (5%) patient expired due to progression of heart failure 12 months after surgery. None of the patients required immediate conversion to full sternotomy.

Conclusions: Surgical transapical catheter-based mitral PVL closure with the Occlutech PLD Occluder is a safe and clinically effective treatment.

Key words: heart failure, transcatheter closure, mitral regurgitation, paravalvular leak, prosthetic heart valve.

Introduction

In 1992 Hourihan *et al.* published the first clinical experience with catheter-based paravalvular leak (PVL) closure [1]. Since then various adjunctive devices have been used to treat heart failure and/or hemolytic anemia caused by mitral PVL: the Rashkind and Cuaso double umbrella device, Gianturco coils, Amplatzer Vascular Plug II and III, Amplatzer Duct Occluder, Amplatzer Septal Occluder, and the Muscular Ventricular Septal Defect Occluder were employed to occlude mitral paravalvular defects. Due to a lack of definitions to establish disease severity and endpoints for the safety and efficacy of PVL treatment there is currently an absence of outcomes for PVL treatment modalities in the literature [2]. Available data are very heterogeneous, with different devices being used, various access sites being employed for different valve prostheses, and mostly short-term outcomes are presented [3–5]. The specifically designed and manufactured Occlutech PLD Occluder for PVL closure has been introduced into clinical practice.

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Publication "Fusion of real-time 3D transesophageal echocardiography and cardiac fluoroscopy imaging in transapical catheter-based mitral paravalvular leak closure" (front page)

ADVANCES IN INTERVENTIONAL CARDIOLOGY
Postępy w Kardiologii Interwencyjnej

Short communication

Fusion of real-time 3D transesophageal echocardiography and cardiac fluoroscopy imaging in transapical catheter-based mitral paravalvular leak closure

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Introduction

Real-time 3D transesophageal echocardiography (TEE) with cardiac fluoroscopy X-ray imaging is well introduced into practice and is used to monitor and assist catheter-based cardiac operations [1–6].

Cardiac fluoroscopy imaging is useful to monitor and control delivery tools into the desired site of the heart during transcatheter closure of paravalvular defects [3, 7, 8]. Fluoroscopy is superior to 3D TEE in visualization of the catheters, wires, devices, and calcified and metallic structures. The main disadvantages of fluoroscopy are the inability to determine the three-dimensional anatomy of intracardiac tissues, exposure to radiation and the need for contrast media.

3D TEE is a standard method to visualize intracardiac structural pathology and measure its hemodynamic significance. It is also used to control intracardiac manipulation of various instruments as well as paravalvular leak closure devices [8]. 3D TEE provides spatial intracardiac anatomy imaging in multiple planes, but its advantages are limited by echo shadowing, which reduces visualization of the catheters and metallic structures. Also experienced personnel are needed to achieve high quality 3D imaging and guide the procedures [7].

Merging these two imaging techniques combines the advantages of fluoroscopy and 3D TEE during paravalvular leak closure. As to date there are no studies comparing mitral paravalvular leak closure with or without fusion technology, we hypothesize that periprocedural fusion of cardiac fluoroscopy and real-time 3D TEE may make intracardiac procedures more controlled, precise and easier. Also it may reduce patients' and professionals' exposure to radiation [7].

We present three cases of transapical catheter-based mitral paravalvular leak closure. All patients were treated with devices specifically designed and manufactured by Occlutech Holding, Switzerland for paravalvular leak closure. The Occlutech® Paravalvular Leak Device represents a novel device with unique rectangular- and square-shaped designs. Occlutech® Paravalvular Leak Device was CE marked in 2014 and is the first transcatheter device indicated and approved for aortic and mitral PVL closure. Procedures were performed with the assistance of fusion (EchoNavigator system, Philips Medical Systems, Netherlands) of cardiac fluoroscopy imaging (Philips AlluraClarity, Philips Medical Systems, Netherlands) and real-time 3D TEE (Philips Epiq7, Philips Medical Systems, Netherlands).

Procedure description

The procedure was carried out in a hybrid operating room. Standard cardiac surgery monitoring was used. Prior to surgical draping, two self-adhesive external defibrillator pads were applied to the patient's back. With the patient in a supine position under general anesthesia and single lumen endotracheal intubation, left anterolateral thoracotomy (5–6 cm) was performed at the level of the left ventricle apex (preoperative TEE guidance). The pericardium was identified and opened. Blunt dissection of the adhesions was performed. Stay sutures were placed at both edges of the pericardium and hinged to the edges of the skin under the retractor. Two "U" shape sutures reinforced with Teflon pledgets

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