

## REVIEW ARTICLE

# Para-prosthetic Leaks Following Mitral Valve Replacement: Case Analysis on a 20-year Period

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**Abstract: Background:** Mitral para-prosthetic leaks are rare but major complications of mitral heart valve replacements. When they must be re-operated, they are burdened with high mortality rates. We proposed to review our surgical experience in terms of approach and type of operation carried out.

**Methods:** Demographic, preoperative, intraoperative and postoperative characteristics of 34 patients benefited from a surgical treatment of mitral paravalvular leak, at the Brugmann University Hospital between 1996 and 2016, have been analysed retrospectively. We analysed the data to identify the risk factors of postoperative mortality. We then compared the data depending on the approach and the type of surgical treatment in order to compare the morbidity-mortality.

**Results:** The postoperative mortality rate was 11.7%. The presence of endocarditis and increase in lactate dehydrogenase were predictive factors of mortality. Cardiac complications and acute kidney failure were significantly more common in the deceased population. Direct mitral paravalvular leak suturing was more frequently performed on early apparition, anterior and isolated leaks, whereas a mitral heart valve replacement was most often performed to cure active primary endocarditis. The incidence of complications and mortality rates were identical according to the approach and the type of operation performed. A mitral para-prosthetic leak recurrence was observed in 33% of the cases.

**Conclusion:** Surgical treatment of mitral para-prosthetic leaks is accompanied by a high mortality rate. The operative strategy plays a major role and can influence the morbidity-mortality encountered in those patients.

**Keywords:** Mitral valve paravalvular leakage, mitral annulus, prosthetic valve, mitral valve replacement, early mitral para-prosthetic leak, late mitral para-prosthetic leak, morbidity.

## 1. INTRODUCTION

In Europe, the prevalence of valvular disease in the population comes close to 2.5% and increases with age. More than one in eight persons over 75 years suffers from either moderate or severe valvulopathy [1]. These statistics show that the increased degenerative heart valve disease cases are linked with the increase in life expectancy that has risen since the second half of the 20th century. When significant, valvulopathy can be treated by replacement or reconstruction of the valve (valvular plasty).

Each year, nearly 280 000 prosthesis are implanted over the world [2]. Mitral valvulopathy amounts to around 35% of

all cases of valvulopathy found in our countries [3]. Usually, reconstruction is considered by far to be the golden standard of surgical treatments for those patients. When irreparable, mitral valves are replaced by valvular prostheses.

A series of complications can be associated with these mitral prostheses. Among them, we count anticoagulation-linked hemorrhagic and thromboembolic complications [4, 5], structural deterioration of the prosthesis and, finally, mitral para-prosthetic leak (MPPL) [6-8].

- The para-prosthetic leak corresponds to a regurgitation between the prosthetic ring and the ring of the native valve. All matters of importance taken together, they are relatively common: 22-32% after mitral valve replacement (MVR) [7, 9]. The impact of those leaks varies according to their importance. The majority of them don't come with clinical consequences but some might cause them: Leaks of minor importance only

## ARTICLE HISTORY

Received: August 20, 2017  
Revised: October 19, 2017  
Accepted: November 03, 2017

DOI:  
10.2174/1573403X13666171110110344

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have a small hemodynamic impact on patients. They can lead to a hemolysis that sometimes requires to perform repeated blood transfusions thus justifying a re-operation. In the long run, they can induce in those patient, an acute kidney failure.

- Severe leaks have a major hemodynamic impact. They may cause congestive heart failure, thus requiring to be surgically revised [10]. They must be corrected as quickly as possible, as they tend to worsen with time. We consider that 1 to 2% of MPPL have significant hemodynamic consequences [11].

It is important to spot and treat para-prosthetic leaks when they may have dire consequences on the patients. The treatment can be done by complete resection of the valve and replacing it with a new prosthesis. When the leak is dim, we can "simply" directly close the paravalvular orifice [12, 13]. Those interventions are technically demanding and have a high mortality rate generally ranging from 3,7% to 22% [14, 15]. The approach to perform the interventions can be a sternotomy or a thoracotomy. The choice of either is usually determined by the approach previously used on the patient.

With this study, we suggest to review our surgical experience in the treatment of mitral para-prosthetic leaks. We will evaluate the morbidity and mortality of these interventions and we will try to identify the risk factors of postoperative mortality. We will examine the influence of the chosen approach as well as the type of operation performed on the morbidity-mortality and on the risk of recurrence of those leaks.

## 2. METHODS

### 2.1. Data sources and Search Strategy

We reviewed the literature on Pubmed and Science Direct, using the PICO method with the following keywords: paravalvular leakage, mitral valve periprosthetic leakage, mitral valve replacement, leak repair, early mitral paravalvular leak, late mitral paravalvular leak, morbidity, mortality and location of the leakage.

### 2.2. Methods

This study has been submitted to the ethics committee of Brugmann University Hospital, which issued a favourable review (with reference CE 2016/17). We identified in retrospect every patient that benefited from a surgical treatment of MPPL in the hospital between 1996 and 2016 to gather the following data: demographics, preoperative, intraoperative and postoperative characteristics. Demographics charted the age, body mass index, left ventricular ejection fraction, systolic pulmonary artery pressure, the New York Heart Association class (NYHA), the presence of chronic obstructive pulmonary disease, hypertension, diabetes, atrial fibrillation and chronic renal failure (Table 1). The characteristics of the last MVR included the different types of prosthesis used, the associated procedures, the initial mitral valve disease (rheumatic, degenerative or endocarditis) and the presence of multiple MVR (Table 2). Preoperative data included level of lactate dehydrogenase, hemoglobin level, operative indication and presence of endocarditis (Table 3). Perioperative data included the time span of the Cardiopulmonary

**Table 1. Patients' demographics.**

-	General population	Deceased	Non-deceased	p Value
Age in years	54 (75-19)	52 (75-42)	54 (75-19)	0.87
Sex ratio M : F	2,4 : 1	2 : 1	2,5 : 1	
BMI (kg/m <sup>2</sup> )	21,9 ± 3,3	20,4 ± 3,1	22 ± 3,2	0.22
LVEF	60,9 ± 8,9	60 ± 7	64 ± 9	0.68
SPAP	64,2 ± 14,3	64 ± 15	65 ± 14	0.82
NYHA	3 ± 0,5	3,1 (2,4-3,7)	3 (2,8-3,2)	0.92
Euroscore II	5,5 ± 2,9	7,5 ± 1,08	5,1±0,55	0.08
<b>Risk factors</b>				
Smoking	2 (6%)	0	2 (7%)	0.99
Hypertension	4 (12%)	1 (17%)	3 (11%)	0.55
Diabetes	7 (21%)	1 (17%)	6 (22%)	0.64
Atrial fibrillation	24 (71%)	5 (83%)	19 (68%)	0.63
CRF	3 (9%)	0	3 (11%)	0.98
Period 1	16	3 (18.75%)	13 (81.2%)	0.99
Period 2	18	3 (16.6%)	15 (83.3%)	

Age are expressed as median (extreme values), risk factors are expressed as absolute number (percentage) and other values as mean ± standard deviation. BMI body mass index, LVEF left ventricular ejection fraction, SPAP systolic pulmonary artery pressure, NYHA New York heart association, CRF chronic renal failure.

**Table 2. Characteristics of the last mitral valve replacement.**

-	General Population	Deceased	Non-deceased	p Value
<b>Initial mitral valve disease</b>				
Rheumatic	27 (79%)	4 (67%)	23 (82%)	0.56
Degenerative	4 (12%)	0	4 (14%)	
Endocarditis	3 (9%)	2 (33%)	1 (4%)	
Isolated MVR	18 (53%)	3 (50%)	15 (54%)	
<b>Prosthesis type</b>				
St-Jude	15 (44%)	3 (50%)	12 (43%)	
Starr	11 (32%)	2 (33%)	9 (32%)	
Carbomedics	5 (15%)	0	5 (17%)	
Duromedics	2 (6%)	1 (17%)	1 (4%)	
Bioprosthesis	1 (3%)	0	1 (4%)	
History of AVR	16 (47%)	3 (50%)	13 (47%)	0.98
History of TA	12 (35%)	3 (50%)	9 (32%)	
Redo of MVR	16 (47%)	4 (67%)	12 (43%)	0.38
<b>Number of MVR</b>				
1	18 (53%)	2 (33%)	16 (57%)	
2	13 (38%)	3 (50%)	10 (36%)	
3	1 (3%)	0	1 (4%)	
4	1 (3%)	0	1 (4%)	
5	1 (3%)	1 (17%)	0	

Results are expressed as absolute number (percentage). MVR mitral valve replacement, AVR aortic valve replacement, TA tricuspid annuloplasty.

**Table 3. Preoperative data.**

-	General population	Deceased	Non-deceased	p Value
Endocarditis	10 (29%)	4 (67%)	6 (21%)	0.04
<b>Type of endocarditis</b>				
Primary	4 (12%)	2 (33%)	2 (7%)	0.15
Secondary	2 (6%)	1 (17%)	1 (4%)	0.35
Non active	4 (12%)	1 (17%)	3 (10%)	0.92
LDH	3055 ± 2148	5145 ± 1455	2600 ± 2016	0.01
Hb	9,63 ± 2,4	8,6 ± 2,2	9,8 ± 2,5	0.31
<b>Operative indication, n (%)</b>				
Hemolytic anemia	9 (27%)	1 (17%)	8 (29%)	0.92
Hemodynamic instability	12 (35%)	1 (17%)	11 (39%)	0.64
Combination of both	13 (38%)	4 (66%)	9 (32%)	0.15

Results are expressed as mean ± standard deviation or absolute number (percentage). LDH lactate dehydrogenase, Hb haemoglobin.

**Table 4. Perioperative data.**

	General population	Deceased	Non-deceased	p Value
CPB time (min)	134 ± 48,7	193 (132-253)	119 (105-133)	<0.01
ACC time (min)	77,7 ± 40,4	130 ± 41	67 ± 32	<0.01
VF time (min)	51,9 ± 21,8	72 ± 24	45 ± 17	0.13
Concomitant procedures	13 (39%)	3 (50%)	10 (37%)	0.63
Aortic valve surgery	5 (15%)	2 (33%)	3 (11%)	
Tricuspid valve surgery	10 (30%)	3 (50%)	7 (26%)	
Coronary artery bypass grafting	1 (3%)	0	1 (4%)	
Overall length of the intervention (hours)	5,4 ± 1,4	7 ± 1,4	5 ± 1,2	0.02

Results are expressed as mean ± standard deviation or absolute number (percentage). CPB cardiopulmonary bypass, ACC aortic cross clamp, VF ventricular fibrillation.

**Table 5. Postoperative outcomes.**

	General Population	Deceased	Non-deceased	p Value
Hospital length of stay (days)	23 ± 18,9	24 ± 19,5	23 ± 18,9	
ICU stay (days)	5,1 ± 4	5 ± 4	5,4 ± 4,5	
Length of intubation (hours)	34 ± 36,3	36 ± 39,2	33,9 ± 36,3	
Length of inotropic support (hours)	45,8 ± 50,4	132 ± 46	29 ± 29	<0.01
Days post drain ablation	3 ± 2	3,4 ± 2,2	3 ± 2	
Drain 24h in mL	748 ± 638	809 ± 696	748 ± 638	
Drain total in mL	1523 ± 1415	1696 ± 1623	1523 ± 1415	
<b>Complications</b>				
Revision for bleeding	4 (12%)	0	4 (15%)	0.99
Recurrence of MPPL	11 (33%)	1 (17%)	10 (37%)	0.64
Respiratory complications	6 (18%)	2 (33%)	4 (15%)	0.28
Cardiac complications	7 (21%)	6 (100%)	1 (4%)	<0.01
Acute renal failure	4 (12%)	3 (50%)	1 (4%)	0.01
Sepsis	3 (9%)	2 (33%)	1 (4%)	0.07

Results are expressed as mean ± standard deviation or absolute number (percentage). ICU intensive care unit, MPPL mitral para-prosthetic leak.

Bypass (CPB), the time span of the aortic cross clamping or ventricular fibrillation, the concomitant procedures and the overall length of the intervention (see Table 4). Postoperative data included the length of hospitalisation, Intensive Care Unit (ICU) stay, intubation, inotropic support and drainage, blood loss in 24 hours and in total and the various complications (cardiac, respiratory, acute renal failure, revision for bleeding, recurrence of MPPL and sepsis) experienced by the patients (see Table 5). The diagnosis of MPPL was obtained by cardiac ultrasonography. The MPPL was defined as early when detected straight away in postoperative monitoring or in a 30-day delay. After those 30 days, the MPPL is considered as late. This was done to find out if they were present right after the replacement or if they appeared afterwards. The mitral valve annulus was divided into clock-

like sections. Locating 12 at the middle of the anterior valve, we identified leaks as anterior when located between 9 and 3, and as posterior when located between 3 and 9. Endocarditis was active when the histological examination of the mitral annulus showed the presence of inflammatory tissue rich in leukocytes. Whenever the results of this examination did not appear in the medical records of the patients, the association of positive blood cultures and presence of echography vegetation's revealed the diagnosis. We categorized active endocarditis between primary and secondary. They were primary if the MPPL diagnosis was obtained after or at the same time as the endocarditis' and secondary if they were diagnosed before. Finally, endocarditis were non active or sequelar on patients whose endocarditis was treated medically or surgically. When they were mentioned in medical records, blood

cultures were negative (at least to common germs) at the moment of the diagnosis.

With this data, we compared the deceased and non-deceased sub-groups to identify predictive risk factors. We also evaluated the data according to the approach and the type of operation carried out. The operative indication lies on the identification of a hemolysis causing significant and refractory anemia or on the presence of a hemodynamically significant valve failure for the patient.

### 2.3. Surgical Treatment of the Leakage

Interventions were carried out by the same surgical team.

They were operated under CPB, with aortic clamping or ventricular fibrillation.

They followed a standardised protocol for anaesthesia, CPB monitoring and myocardial protection [16].

The surgical approach consists of operation through median sternotomy or right thoracotomy. The choice of the approach was as follows: a thoracotomy was preferred in patients who underwent multiple sternotomies or when the surgical act was isolated to the mitral valve whereas a sternotomy was preferred in cases of primo-redo or associated surgical acts such as aortic valve surgery. This strategy had to be adapted for patients who underwent several sternotomies requiring associated surgical acts. During the two decades of the study, surgical technique and myocardial protection in cardiac surgery improved. We divided the period in two decades and compared the mortality between the two periods.

Actually, either a thoracotomy or sternotomy could be chosen according to the number of previous surgeries and the nature of the associated surgical acts. A thoracotomy or a sternotomy could also be performed on patients who underwent a primo-redo with an isolated surgical act.

The surgical treatment of the leak involves of a replacement of the mitral heart valve or leakage repair with U-shaped polyester 2/0 sutures leaning on polytetrafluoroethylene (PTFE) pads. In general, mitral heart valve replacement was preferred when the leaks were numerous or in the presence of an active endocarditis. When leaks were isolated and of small size, we stitched a U-shaped suture leaning on PTFE pads.

In the intraoperative stage, the surgeon documented the degree of calcification of the mitral annulus, the presence of a lesion suspected to be a prosthetic endocarditis and the location of the MPPL on the mitral annulus.

We considered a recurrence of MPPL when it occurred in the follow-up period. It was early if detected in the 30 first days. Afterwards, the recurrence was considered as late. Postoperative mortality includes all the casualties occurring in the 30 day span after the intervention. Overall in-hospital mortality was defined as death within 30 days of surgery or during the same hospital admission.

### 2.4. Statistical Analysis

The statistical analyses were carried out with the SPSS software (SPSS Inc v.23, Chicago, IL). A Kolomogorov-Smirnov test was carried out to check the normality of the distribution of continuous variables. Comparisons between

continuous variables were performed using the Student t-test or the Mann-Whitney U test. A Fisher test was carried out to compare the qualitative variables. A p-value of less than 0,05 was considered statistically significant.

## 3. RESULTS

This retrospective study focused on 34 patients. The average age of patients was 53,3 years ( $\pm 13,8$ ). Postoperative mortality was 11.7% and the overall in-hospital mortality was 18%. Six patients died in total. Two died in the few hours following surgery: one underwent a non-reducible ventricular tachycardia evolving into a ventricular fibrillation (second surgery) and the other one died in the MOF caused by a massive haemorrhage (sixth surgery). One patient presented myocardial failure on irreversible pulmonary arterial hypertension (third surgery) at day 4. Another one died in the MOF induced by recurrence of MPPL (fourth operation) at day 19. Finally, two patients died in sepsis (third surgery for both) at days 37 and 43. We retrospectively performed a Euroscore II in all the patients (Table 1). The mean value was 5,5%. On average, the Euroscore II was higher in the deceased population compared to the non-deceased, but this result failed to reach statistical significance ( $p=0,08$ ).

A patient's surgery failed since the intervention couldn't lead to the surgical paravalvular cleaning due to the lack of access allowing the placement on femoral to femoral artery bypass. It was then the fourth reopening of the chest wall and only a thoracic approach under safety CPB was conceivable.

The demographics of the general population, as well as those of the deceased and non-deceased sub-groups are presented in Table 1. The comparative mortality between the first and the second decade was of 18.7% and 16.6% ( $p=0.99$ ), respectively.

Among all the demographic data taken into account, none was predictive about the mortality rate of the patients.

The characteristics of the last MVR of the general population and the deceased and non-deceased sub-groups are charted in Table 2. Deceased and non-deceased patients present the same characteristics of the last MVR.

The preoperative data of the general population as well as that of the deceased and non-deceased patients are charted in Table 3. Deceased patients present a higher incidence of endocarditis and a higher value of lactate dehydrogenase.

The perioperative data of the general population as well as that of the deceased and non-deceased patients are presented in Table 4. Deceased patients presented a higher CPB, ACC and overall length of the intervention time as compared to non-deceased patients.

The postoperative data of the general population as well as that of the deceased and non-deceased patients are charted in Table 5. Deceased patients present a higher length of inotropic support, cardiac complications and acute renal failure incidence. Sepsis tends to be more frequent in the deceased patients.

The average interval time between the last MVR and the diagnosis of the MPPL is close to 10 years (118 months) with a maximal interval of 30 years. We observe that 23,5% of the MPPL have been diagnosed in the first year after

MVR. The cumulative incidence of the time of appearance of MPPL is illustrated in Fig. (1).

The number of early (30 days) MPPL after the last MVR is 7 (21%). 5 of them (72%) are anterior, one (14%) is posterior and one (14%) is found on multiple areas of both anterior and posterior sections of the annulus. They result in one case (14%) in the presence of symptoms of heart failure, in 5 cases (72%) in the presence of hemolytic anemia, and in one case (14%), with a combination of both.

We registered 27 cases of late MPPL after the last MVR (79%). 6 of them (22%) were anterior, 13 (48%) were posterior and 6 (22%) involved both anterior and posterior sections of the annulus. The examination of medical records failed to locate 2 leaks. They resulted in 11 cases (41%) in the presence of symptoms of heart failure, 5 cases (18%) in the presence of hemolytic anemia and 11 cases (41%) with a combination of both.

Data of patients who benefited from a direct repair versus from a MVR are charted in Table 6.

The data of the patients according to the approach chosen are presented in Table 7.

Every patient who underwent a thoracotomy got a ventricular fibrillation. Likewise, all the patients who have un-

dergone sternotomy benefited from myocardial protection with induced cardioplegia.

Among the patients that have undergone a thoracotomy, 4 of them (31%) received associated surgical acts. For two of them, it consisted in a second redo, while for the other two, it was the third. Among the patients who underwent sternotomy, we observed that 5 of them (25%) received associated surgical acts. Among them, one patient got an aortic and tricuspid valve replacement and 4 others did not get concomitant procedures.

For a second redo, we noted that sternotomy or thoracotomy could be performed independently of any associated surgical act. After the second redo, the approach has exclusively been performed through a thoracotomy.

An MPPL recurrence was observed on 11 patients (33%). As previously seen, the recurrence rate stayed the same whatever the approach and treatment were performed (see Tables 6 and 7). Endocarditis, either active or not, did not account as predicative factors of recurrence. The patients who underwent several redos did not present a higher risk than those who underwent a first redo. Among 11 cases of recurrence, 7 (64%) happened along the postoperative follow-up and 4 (36%) appeared after a while, between 1 and 6 years later. Moreover, 4 (36%) required a reintervention. 3 of them belonged to the belated leakage category.



Fig. (1). Cumulative incidence of the time of appearance of mitral para-prosthetic leaks.

Table 6. Data of the patients according to the type of operation performed.

Preoperative Data	MPPL Suturing (n=19)	MVR (n=14)	p Value
Endocarditis	6 (32%)	4 (29%)	0.96
<b>Type of endocarditis</b>			
Primary	0	4 (29%)	0.02
Secondary	2 (11%)	0	0.32
Non active	4 (21%)	0	0.11
Early MPPL	7 (37%)	0	0.02
<b>Perioperative data</b>			
CPB time (min)	117 (97-136)	157 (126-189)	0.03
ACC time (min)	55 (39-72)	107 (74-140)	<0.01
VF time (min)	(23-65)	(30-90)	0.99

(Table 6) Contd...

Preoperative Data	MPPL Suturing (n=19)	MVR (n=14)	p Value
<b>Location of the MPPL</b>			
Anterior	10 (53%)	1 (7%)	0.02
Posterior	7 (37%)	6 (43%)	0.71
Ant + Post	2 (10%)	5 (36%)	0.07
Isolated MPPL	17 (89%)	8 (57%)	0.04
<b>Postoperative outcomes</b>			
Mortality	3 (16%)	3 (21%)	0.93
<b>Complications</b>			
Recurrence of MPPL	6 (32%)	5 (36%)	0.93
Respiratory complications	2 (11%)	4 (29%)	0.36
Cardiac complications	3 (16%)	4 (29%)	0.71
Acute renal failure	2 (11%)	2 (14%)	0.63
Sepsis	0	3 (21%)	0.06

Results are expressed as absolute number (percentage) or median value (extreme values). MVR mitral valve replacement, MPPL mitral para-prosthetic leak, CPB cardiopulmonary bypass, ACC aortic cross clamp, VF ventricular fibrillation.

**Table 7. Data of the patients according to the approach chosen.**

Characteristics of the Last MVR	Thoracotomy (n=13)	Sternotomy (n=20)	p Value
Redo of MVR	10 (77%)	5 (25%)	<0.01
<b>Concomitant procedures</b>			
AVR	3 (23%)	5 (25%)	0.92
TA	0	5 (25%)	0.13
TA + AVR	3 (23%)	0	0.05
<b>Perioperative data</b>			
CPB time (min)	144 (124-163)	126 (99-154)	0.12
ACC time (min)	-	78 ± 40	
VF time (min)	52 ± 22	-	
Repair vs MVR ratio	1,4 : 1	1,5 : 1	0.92
Concomitant procedures	4 (31%)	9 (45%)	0.48
Primo-redo	3 (23%)	15 (75%)	<0.01
<b>Postoperative outcomes</b>			
Mortality	3 (23%)	3 (15%)	0.65
<b>Complications</b>			
Recurrence of MPPL	5 (38%)	5 (25%)	0.46
Respiratory complications	2 (15%)	4 (20%)	0.92
Cardiac complications	3 (23%)	4 (20%)	0.72
Acute renal failure	1 (8%)	3 (15%)	0.98
Sepsis	2 (15%)	1 (5%)	0.54

Results are expressed as absolute number (percentage) or median value (extreme values). MVR mitral valve replacement, AVR aortic valve replacement, TA tricuspid annuloplasty, CPB cardiopulmonary bypass, ACC aortic cross clamp, VF ventricular fibrillation, MPPL mitral para-prosthetic leak.

#### 4. DISCUSSION

The postoperative mortality after surgical treatment of the MPPL was 11,7%. In the reviewed literature, the mortality rate was variable and usually fluctuated from 3.7% to 22%. For example, Jindani *et al.* reported a mortality rate similar to ours [14]. Even though it was predictable, we noticed that among our patients, the presence of active or inactive endocarditis was a predictive factor of mortality. Indeed, endocarditis is an established risk of post-operative mortality in mitral valve surgery [17]. This is why several previous studies investigating postoperative outcome after the surgical correction of paraprosthetic leaks excluded patients with active endocarditis [15, 18, 19]. They, therefore, obtained better results on mortality. Surgery for active infective prosthetic valve endocarditis continues to be challenging and can lead to an overall in-hospital mortality of 28.4 % [20]. Thus, it is clear that the high rate of endocarditis observed in our patients explains the high mortality rate we noted.

We noted that high level of lactate dehydrogenase (LDH) was highly predictive of the mortality risk. Hemolysis, which is one of the causes that could explain the increase of LDH is not however, more common in deceased patients. We can conclude that high levels of LDH in the deceased population mean something other than hemolysis. All the deceased patients presented cardiac complications - mainly that of low output - and 50% suffered from acute renal failure due to this low cardiac output. The increase in LDH in these patients thus surely reflects the general hemodynamic, and especially hepatic, consequences of the cardiac pathology. These patients therefore suffered from a significantly higher cardiac decompensation. It is interesting to note that LDH has never been studied as a predictive factor of mortality in cardiac surgery.

Patients included at the beginning of our study did not have a systematic measurement of the troponins, at that time, hence the predictive value of mortality was not calculated. In cardiac surgery patients, several studies have described the kinetics of cardiac troponin elevation in the plasma. It has been shown that cardiac surgery *per se* induces an increase in the plasma level of cardiac troponins, even in the absence of ischemic myocardial damage and would be the result of a cardiac surgical trauma [21]. However, several studies suggest that an increased postoperative troponin release post cardiac surgery can be associated with mortality [22]. As for the BNP, unfortunately, this is not refunded in our country. They are not systematically carried out, far from it, and it is impossible for us to collect them in our patients.

The NYHA class, which is a classic risk factor of mortality in cardiac surgery, is high in all our patients. Thus, it cannot be considered as discriminatory any longer.

The mean value of the Euroscore II was 5,5%. This predicted operative mortality is lower than the mortality rate we observed. This might be due to the fact that this score does not take into account the number of previous surgeries performed on the patients. As mentioned previously, all of our deceased patients have experienced multiple surgeries beforehand.

We observed a longer ACC and CPB in the deceased patients. The duration of ACC and CPB is directly related to

the complexity of the procedure and its heaviness. This heaviness seems to be correlated with the presence of endocarditis. Three out of four patients who died within 30 days of the procedure had endocarditis. It is obvious that in the presence of an infection, the mitral valve is systematically replaced and the mitral ring must be debrided and eventually thoroughly reconstructed.

We wished to distinguish two types of leaks according to the time of their appearance:

- Early leaks are those we imputed to the surgery and which are often present from the intervention. They are generally minor [23] and tend to heal with time [7, 9]. According to our experiment, we noticed that early leaks mostly cause anemia. They are indeed highly hemolyzing. First, because the valve annulus is not yet endothelialised in the days following the operation and, secondly, because they are generally of a small caliber with a larger pressure gradient and high velocity. All have been treated with direct surgical sutures. It is also interesting to note that 72% of the early leaks happen in the anterior section of the mitral annulus. This area carries thus a higher risk of perioperative problems. One of the possible explanation comes from the fact that the visibility of this area is less clear during the surgical approach of the heart valve and thus becomes a technical difficulty when implanting the prosthesis [15]. Those technical difficulties can thus cause the MPPLs, which will then appear during the intervention or right after.
- Late leaks are those that can occur several years later. Their etiology is the endocarditis as well as dehiscence on a poor valve healing that we can encounter, for example, in multiple cases of redos of MVR. Even though this case was not considered in this study, the use of a Silzone type prosthesis (St Jude Medical) also constituted a contributing factor. Those finned valves, available in the market from 1997 to 2000, included a valvular annulus on which a metallic silver deposit bonded. Silver nanoparticules have increased antibacterial properties due to their crystalline structure and their small volume-surface ratio. They also have a cytotoxic effect, notably on fibroblasts [24]. These prostheses were, therefore, used to reduce the incidence of infections to the maximum but also to fight the pannus development. However, some studies have proved that there was a higher risk to develop MPPLs with this type of prostheses because of their inhibitory effect on fibroblastic growth that would then alter the healing [25]. Our study reveals that 93% of the posterior leaks appear after a while. It is therefore true that in the long term, this area is at risk of developing a MPPL. Kunzelman *et al.* report that the distribution of collagen fibers around the mitral annulus is not consistent both quantitatively and qualitatively. The central layer of the annulus consists of dense collagen fibers; the fibrosa, which is thinner in the posterior area. This indicates that the anterior leaflet could better resist traction forces [26]. As far as we know, there is no study in the existing literature analysing the delay in the occurrence of MPPL with its



location. For Hwang *et al.*, all MPPLs taken into account, most often appear in the posterior area (46.1%), anteriorly (24.1%), then medially (20.7%) and finally edgeways (1,7%). The remaining 10.4% concerns simultaneously various areas [6].

We report an average appearance timeframe of 118 months (almost 10 years) between the last MVR and the date of the diagnosis. The maximal interval listed is of 30 years. Nair *et al.* report a maximal timeframe of 5 year with a follow-up lasting up to 10 years post MVR [27]. Genoni *et al.* report a maximal timeframe of 23 years with an average duration of 4 months [28]. Hwang *et al.*, for their part, report an average timeframe of 136 months and a maximal timeframe of 250 months (21 years) but do not take early leaks into account [6]. Lastly, De Cicco *et al.* observe an average timeframe of 67 months with a maximal period of 12 years. Therefore, timeframes are rather fluctuant. Our high average interval can be explained by the fact that many of our patients are referred from abroad. The date of the diagnosis may thus have been delayed. Moreover, the patients did not always benefit from a regular ultrasound follow-up after the last MVR because of the limited access to health care.

Another interesting observation concerns the approach used in the surgical treatment of the MPPL. It turns out that it is mainly the number of redo that influences the choice between a sternotomy and a thoracotomy. Thoracotomy is preferred in cases of multi-redo to avoid sternal adhesions that may have formed, especially with the aorta. This approach is usually more complex but it reduces the risks in patients treated by redo valve surgery. It has been shown that this technique has multiple advantages such as less postoperative bleeding, reduced need for blood transfusion and the absence of sternal wound infection [29].

We observe no difference in the incidence of complications or of mortality between those two groups. The strategy adopted therefore seems to be the good one. Furthermore, we noticed that the approach does not modify the strategy of the treatment of the leakage. Miura *et al.* recently compared these types of approaches with patients benefitting from a mitral and/or tricuspid valve surgery and who underwent one or several sternotomies in the past. They did not note any difference in the postoperative morbidity-mortality either [30]. Sharony *et al.* also made the comparison but, this time, on patients benefitting from a redo with only one surgical act (aortic or mitral). They showed a comparable hospital mortality, CPB and aortic clamp time between the two groups. In addition, they demonstrated fewer wound complications, less blood transfusion requirements and shorter hospital stays for patients who underwent thoracotomy [31].

The incidence of complications and mortality rate were also identical according to the type of surgical treatment. We noted that we tend to favour sutures when the leaks are isolated, early and anterior. However, we tend to perform MVR to treat primary active endocarditis. This operative strategy, more aggressive on those patients, allows us to reduce the incidence of complications and mortality that is normally higher in active endocarditis. Abdel-Hady *et al.* report a morbidity-mortality rate higher for patients who underwent MVR. However, this study includes only anterior and isolated leaks of small caliber [12].

The recurrence rate of MPPL all along the follow-up period is 33%. We notice that it is neither influenced by the approach nor by the type of surgical treatment performed. In a similar manner to Genoni *et al.* no recurrence risk factor could be identified. They report a recurrence rate of 22% [28]. As seen previously, 36% required a surgical revision. Those reinterventions mainly concerned late recurrences (75% of the cases). Early recurrences indeed rarely (14% of the cases) led to a significant hemolytic anemia or to a hemodynamically substantial valvular failure for the patient that would have justified a revision surgery.

Our study is subject to the classic limitations of a retrospective study (discontinuation of the follow-up, unavailability of certain data, *etc.*). Our sample group was relatively small and heterogeneous. Due to the small number of patients in our study, we could not proceed to a multivariate regression analysis taking into account the predictive factors of mortality. Another limitation concerns the length of the period that is taken into account (from 1996 until 2016). Hence some results like the length of the hospitalisation and ICU stay may not be up-to-date in comparison with current values.

## CONCLUSION

Surgical treatment of mitral para-prosthetic leaks is heavy and burdened with a high mortality rate. There are few predictive factors of mortality. The only identified factors are the presence of endocarditis and an increase in lactate dehydrogenase in deceased patients, which attest the hemodynamic instability induced by the pathology. Furthermore, the quality of the results is highly linked to the strategy we can adopt regarding the approach and the type of surgical treatment. This strategy must be evaluated individually for each MPPL according to the number of redo and associated surgical acts as well as its characteristics.

## LIST OF ABBREVIATIONS

CPB	=	Cardiopulmonary Bypass
ICU	=	Intensive Care Unit
LDH	=	Lactate Dehydrogenase
MPPL	=	Mitral Para-prosthetic Leak
MVR	=	Mitral Valve Replacement
NYHA	=	New York Heart Association
PTFE	=	Polytetrafluoroethylene

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Brugmann University Hospital Institutional Review Board. Individual consent was waived by the committee because of the retrospective nature of the study.

## CONSENT FOR PUBLICATION

Not applicable.

## CONFLICT OF INTEREST

All collaborators who contributed to the conception, collection of data, and writing of this manuscript were included as authors. All the authors disclose any financial or other competing interests. No source of funding is declared for any author.

## ACKNOWLEDGEMENTS

MD conceived the study, and participated in its design and coordination. He participated in literature search, data collection, data analysis, data interpretation, and wrote the manuscript. PW conceived the study, and participated in its design and coordination. He participated in literature search, data analysis, data interpretation, and provided the critical revision. All authors read and approved the final manuscript.

## REFERENCES

- [1] Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: A population-based study. *Lancet Lond Engl* 2006; 368(9540): 1005-11.
- [2] Pibarot P, Dumesnil JG. Prosthetic heart valves: Selection of the optimal prosthesis and long-term management. *Circulation* 2009; 119(7): 1034-48.
- [3] Iung B, Baron G, Butchart EG, et al. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. *Eur Heart J* 2003; 24(13): 1231-43.
- [4] Ruel M, Kulik A, Lam BK, et al. Long-term outcomes of valve replacement with modern prostheses in young adults. *Eur J Cardio-Thorac Surg Off J Eur Assoc Cardio-Thorac Surg* 2005; 27(3): 425-33; discussion 433.
- [5] Brennan JM, Edwards FH, Zhao Y, et al. Long-term safety and effectiveness of mechanical versus biologic aortic valve prostheses in older patients: Results from the society of thoracic surgeons adult cardiac surgery national database. *Circulation* 2013; 127(16): 1647-55.
- [6] Hwang HY, Choi J-W, Kim H-K, Kim K-H, Kim K-B, Ahn H. Paravalvular leak after mitral valve replacement: 20-year follow-up. *Ann Thorac Surg* 2015; 100(4): 1347-52.
- [7] Ionescu A, Fraser AG, Butchart EG. Prevalence and clinical significance of incidental paraprosthesis valvar regurgitation: A prospective study using transoesophageal echocardiography. *Heart Br Card Soc* 2003; 89(11): 1316-21.
- [8] Kim GJ, Lee JT, Lee YO, Cho JY, Oh T-H. Outcomes of non-pledgeted horizontal mattress suture technique for mitral valve replacement. *Korean J Thorac Cardiovasc Surg* 2014; 47(6): 504-9.
- [9] O'Rourke DJ, Palac RT, Malenka DJ, Marrin CA, Arbuckle BE, Plehn JF. Outcome of mild periprosthetic regurgitation detected by intraoperative transesophageal echocardiography. *J Am Coll Cardiol* 2001; 38(1): 163-6.
- [10] Noble S, Ibrahim R, Basmadjian A, Müller H, Lerch R, Roffi M. Fuite paravalvulaire après chirurgie cardiaque: Quelle place pour l'approche percutanée ? *Rev Médicale Suisse* 2010; 24(251): 1154-8.
- [11] Movsowitz HD, Shah SI, Ioli A, Kotler MN, Jacobs LE. Long-term follow-up of mitral paraprosthesis regurgitation by transesophageal echocardiography. *J Am Soc Echocardiogr Off Publ Am Soc Echocardiogr* 1994; 7(5): 488-92.
- [12] Abdel-Hady M, Farouk AE-D, Abdelrahman A, Osama A, Fathy A. Surgical intervention for moderate anterior paravalvular leakage after mitral valve replacement. Is it always necessary to replace the valve? *J Egypt Soc Cardio-Thorac Surg* 2012; 20(3): 43-8.
- [13] Choi J-W, Hwang HY, Kim K-H, Kim K-B, Ahn H. Long-term results of surgical correction for mitral paravalvular leak: Repair versus re-replacement. *J Heart Valve Dis* 2013; 22(5): 682-7.
- [14] Jindani A, Neville EM, Venn G, Williams BT. Paraprosthesis leak: A complication of cardiac valve replacement. *J Cardiovasc Surg (Torino)* 1991; 32(4): 503-8.
- [15] De Cicco G, Russo C, Moreo A, et al. Mitral valve periprosthetic leakage: Anatomical observations in 135 patients from a multicentre study. *Eur J Cardio-Thorac Surg Off J Eur Assoc Cardio-Thorac Surg* 2006; 30(6): 887-91.
- [16] Marinakis S, Van der Linden P, Tortora R, Massaut J, Pierrakos C, Wauthy P. Outcomes from cardiac surgery in Jehovah's witness patients: Experience over twenty-one years. *J Cardiothorac Surg* 2016; 11(1): 67.
- [17] Jones JM, O'kane H, Gladstone DJ, et al. Repeat heart valve surgery: Risk factors for operative mortality. *J Thorac Cardiovasc Surg* 2001; 122(5): 913-8.
- [18] Akins CW, Bitondo JM, Hilgenberg AD, Vlahakes GJ, Madsen JC, MacGillivray TE. Early and late results of the surgical correction of cardiac prosthetic paravalvular leaks. *J Heart Valve Dis* 2005; 14(6): 792-9; discussion 799-800.
- [19] Taramasso M, Maisano F, Denti P, et al. Surgical treatment of paravalvular leak: Long-term results in a single-center experience (up to 14 years). *J Thorac Cardiovasc Surg* 2015; 149(5): 1270-5.
- [20] Musci M, Hübler M, Amiri A, et al. Surgical treatment for active infective prosthetic valve endocarditis: 22-year single-centre experience. *Eur J Cardiothorac Surg* 2010; 38(5): 528-38.
- [21] Lasocki S, Provenchère S, Bénessiano J, et al. Cardiac troponin I is an independent predictor of in-hospital death after adult cardiac surgery. *Anesthesiology* 2002; 97: 405-411.
- [22] Van Geene Y, Van Swieten HA, Noyez L. Cardiac troponin I levels after cardiac surgery as predictor for in-hospital mortality. *Interact Cardiovasc Thorac Surg* 2010; 10(3): 413-6.
- [23] Waşowicz M, Meineri M, Djaiani G, et al. Early complications and immediate postoperative outcomes of paravalvular leaks after valve replacement surgery. *J Cardiothorac Vasc Anesth* 2011; 25(4): 610-4.
- [24] Hemmerlein JB, Trerotola SO, Kraus MA, Mendonca MS, Desmond LA. *In vitro* cytotoxicity of silver-impregnated collagen cuffs designed to decrease infection in tunneled catheters. *Radiology* 1997; 204(2): 363-7.
- [25] Schaff HV, Carrel TP, Jamieson WRE, et al. Paravalvular leak and other events in silzone-coated mechanical heart valves: A report from AVERT. *Ann Thorac Surg* 2002; 73(3): 785-92.
- [26] Kunzelman KS, Cochran RP, Murphree SS, Ring WS, Verrier ED, Eberhart RC. Differential collagen distribution in the mitral valve and its influence on biomechanical behaviour. *J Heart Valve Dis* 1993; 2(2): 236-44.
- [27] Nair SK, Bhatnagar G, Valencia O, Chandrasekaran V. Effect of valve suture technique on incidence of paraprosthesis regurgitation and 10-year survival. *Ann Thorac Surg* 2010; 89(4): 1171-9.
- [28] Genoni M, Franzen D, Vogt P, et al. Paravalvular leakage after mitral valve replacement: improved long-term survival with aggressive surgery? *Eur J Cardio-Thorac Surg Off J Eur Assoc Cardio-Thorac Surg* 2000; 17(1): 14-9.
- [29] Murzi M, Solinas M, Glauber M. Is a minimally invasive approach for re-operative mitral valve surgery superior to standard re-sternotomy? *Interact Cardiovasc Thorac Surg* 2009; 9(2): 327-32.
- [30] Miura T, Tanigawa K, Matsukuma S, et al. A right thoracotomy approach for mitral and tricuspid valve surgery in patients with previous standard sternotomy: Comparison with a re-sternotomy approach. *Gen Thorac Cardiovasc Surg* 2016; 64(6): 315-24.
- [31] Sharony R, Grossi EA, Saunders PC, et al. Minimally invasive reoperative isolated valve surgery: early and mid-term results. *J Card Surg* 2006; 21(3): 240-4.