

Surgical treatment of post-infarction papillary muscle rupture: systematic review and meta-analysis

Giulio Massimi^{1#}, Matteo Matteucci^{1,2#}, Mariusz Kowalewski^{1,3,4}, Daniele Ronco^{1,2}, Federica Jiritano^{1,5}, Cesare Beghi², Paolo Severgnini⁶, Roberto Lorusso^{1,7}

¹Department of Cardiothoracic Surgery, Heart and Vascular Centre, Maastricht University Medical Centre, Maastricht, The Netherlands;
²Department of Medicine and Surgery, Circolo Hospital, University of Insubria, Varese, Italy;
³Department of Cardiac Surgery, Central Clinical Hospital of the Ministry of Interior in Warsaw, Warsaw, Poland;
⁴Thoracic Research Centre, Collegium Medicum, Nicolaus Copernicus University, Innovative Medical Forum, Bydgoszcs, Poland;
⁵Department of Cardiac Surgery, University Magna Graecia of Catanzaro, Catanzaro, Italy;
⁶Department of Biotechnology and Sciences of Life, University of Insubria, Varese, Italy;
⁷Cardiovascular Research Institute Maastricht (CARIM), Maastricht, The Netherlands

Correspondence to: Matteo Matteucci, MD. Cardiothoracic Surgery Department, Heart & Vascular Centre, Maastricht University Medical Centre (MUMC), P. Debyelaan, 12, 6221 AZ Maastricht, The Netherlands. Email: matteomatteucci87@gmail.com.

Background: Papillary muscle rupture (PMR) is a rare but potentially fatal complication following acute myocardial infarction (AMI). Surgical treatment is considered the standard of care. This systematic review and meta-analysis aims to evaluate the early outcomes after surgical correction of post-AMI PMR.

Methods: Electronic databases were searched from January 1990 to December 2020. Studies reporting patients undergoing mitral valve surgery for post-AMI PMR were analysed. The primary outcome assessed was operative mortality. Differences were expressed as risk ratio (RR) with 95% confidence interval (CI) to assess the relationships between predefined surgical variables and clinical prognosis.

Results: A total of 1,851 adult patients, from 12 observational studies, were identified. Operative mortality was 21%. Meta-analysis revealed reduced operative risk in patients undergoing mitral valve repair (MVr) as compared to replacement (MVR) (RR, 0.33; 95% CI: 0.14 to 0.79; P=0.01), and an increased risk of operative mortality in patients with complete PMR (RR, 2.54; 95% CI: 1.12 to 5.74; P=0.03). No significant differences in terms of operative mortality were observed between patients with or without pre/perioperative intra-aortic balloon pump (IABP) support and between subjects who underwent mitral valve surgery with or without concomitant coronary artery bypass grafting (CABG).

Conclusions: Mitral valve surgery for post-AMI PMR carries a high operative mortality. Patients with complete PMR and subjects undergoing MVR have increased risks of operative mortality. The preoperative use of IABP and concomitant CABG seem not to influence the early postoperative course in this context.

Keywords: Papillary muscle rupture (PMR); mitral valve surgery; mitral regurgitation



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Introduction

Papillary muscle rupture (PMR) is an uncommon, but often catastrophic complication of acute myocardial infarction (AMI), with recent literature reporting an incidence between 0.05% and 0.26% (1). PMR usually occurs within a week after AMI, especially as an evolution of inferior

AMI (2). Despite mortality after surgical correction of PMR remarkably decreasing since the first successful mitral valve replacement (MVR) for PMR in 1965, the outcome of these subjects remains dismal (3). The poor results of medical treatment make surgical correction the standard of care for PMR (2). Although mitral valve repair (MVr)

^{*}These authors contributed equally to this work.

may lead to a better outcome due to greater preservation of post-operative left ventricular function, MVR is generally preferred in these high-risk patients (4). Since PMR is a rare event following AMI, most published series consist of single-center experiences with small sample sizes, and limited information regarding surgical results is available. We have therefore performed a systematic review and meta-analysis of the existing literature in order to provide a current perspective and summarize early post-operative outcomes and related predictors of the surgical correction of post-AMI PMR.

Methods

This systematic review and meta-analysis was registered with PROSPERO (ID: CRD42020163077) and was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (5).

Data sources, search strategy and selection criteria

PubMed, Embase and the Cochrane central register of controlled trials (CENTRAL) were screened for studies published from January 1, 1990 to the end of December 2020. The search terms were: "papillary muscle rupture" OR "mitral chordal rupture" OR "acute mitral regurgitation" OR "mechanical complication" AND "myocardial infarction" OR "surgical treatment". The literature was limited to articles published in English. Studies which provided the outcomes for adult patients (>18 years old) who underwent surgical correction of post-AMI PMR were included. Articles were excluded if they included: (I) animal studies; (II) PMR not AMI-related (e.g., post-traumatic); (III) studies including <20 surgical patients; (IV) duplicate publications from the same center reporting overlapping patient data. Case reports and systematic reviews were not considered. Reference lists were reviewed manually and cross-checked for other relevant reports.

Data extraction and endpoint selection

Two independent reviewers (G Massimi and M Matteucci) selected the studies for inclusion and extracted articles, as well as patient characteristics of interest and relevant outcomes. A standardised form was used to extract data of interest. Discrepancies were resolved by discussion and adjudication by a third reviewer (R Lorusso). The primary

outcome being assessed was operative mortality, defined as any death, regardless of cause, occurring within 30 days after surgery (in or out of hospital) or after 30 days but during the index hospitalization subsequent to the surgery. Secondary endpoints were the following in-hospital postoperative complications: stroke, major bleeding, renal failure requiring renal replacement therapy (RRT), and low cardiac output syndrome (LCOS). Long-term follow-up and out-of-hospital complications were not considered.

Quality assessment

Two authors (G Massimi and M Matteucci) independently assessed the trials' eligibility and risk of bias. Risk of bias at the individual study level was appraised with ROBINS-I (Risk Of Bias In Not-randomized Studies of Interventions), a tool used for assessment of bias (the selection of the study groups; the comparability of the groups; the ascertainment of either the exposure or outcome of interest) in cohort studies included in a systematic review and/or meta-analysis (6). Any divergences were resolved by a third reviewer (R Lorusso).

Statistical analysis

Pooled risks ratios (RRs) were reported with 95% confidence intervals (CIs). The Cochran's Q test and I² test were all performed to judge the heterogeneity among the studies included in the meta-analysis. Heterogeneity was considered to be significant at P<0.1 for the Q statistic. An I² value of less than 50% indicates low heterogeneity, values between 50% and 75% suggest moderate heterogeneity, and I² greater than 75% was considered high heterogeneity. Sensitivity analysis was carried out by successively excluding the low-quality studies to assess the stability of the outcome. Potential publication bias was evaluated by constructing a funnel plot. The plot was estimated visually, and asymmetry in the funnel plot suggested possible publication bias. Review Manager 5.3 software, developed by the Cochrane Collaboration (http://tech.cochrane.org/revman/), was used for statistical computations. A value of P<0.05 was considered statistically significant.

Results

We identified 3,023 reports, reviewed 62 full text articles, and identified 12 studies that met explicit inclusion criteria (4,7-17), enrolling a total of 1,851 patients. Of the 12

Table 1 Baseline characteristics of studies and patients									
Author (ref.)	Year of publication	Study period	dy period Country		Age* (years)	Male (n)	Shock (n)	Inotropes (n)	IABP (n)
Fujita (14)	2020	2014–2017	Japan	196	74	119	140	-	159
Kilic (15)	2020	2011–2018	USA	1,342	66	911	759	582	764
Sultan (11)	2018	2011–2017	USA	24	62	15	-	-	14
Ternus (7)	2017	2000–2014	USA	22	70	16	15	-	15
Bouma (9)	2014	1990–2012	The Netherlands	48	65	34	31	26	21
Schroeter (13)	2013	2002–2010	Germany	28	63	22	15	-	12
Russo (16)	2008	1980–2000	USA	54	70	40	-	-	-
Chevalier (10)	2004	1985–2002	France	37	-	-	-	-	-
Chen (17)	2002	1978–2000	UK	33	64	20	-	26	17
Tavakoli (4)	2002	1988–1998	Switzerland	21	62	-	21	-	11
Figueras (8)	1997	1979–1995	Spain	24	-	-	-	-	-
Kishon (12)	1992	1981–1990	USA	22	68	15	15	-	13
Total [%] or (± SD)) –	-	-	1,851	66 (±4)	1,192 [67]	996 [59]	634 [44]	1,026 [59]

*, mean value. Ref., reference; n, number; y, years; IABP, intra-aortic balloon pump; SD, standard deviation.

articles included, all were observational and retrospective in design. Ten studies were considered to have adequate criteria to be included in the meta-analysis. The PRISMA flow chart depicting the study selection process is presented as Figure S1.

Risk of bias

A summary of the risk of biases of included studies is reported in Table S1. Overall, quality assessment revealed a significant risk of bias, in particular due to confounding and selection bias. Analysis of the funnel plots showed symmetry and suggested no significant risk of publication bias or big/small study effect (Figures S2,S3).

Baseline and operative characteristics

Mean age of the patients was 66±4 years, and men accounted for 67% of cases. All subjects had acute severe mitral regurgitation caused by post-infarction PMR. The rate of individuals in cardiogenic shock was 59% (909/1,679 patients) at the time of operation, with 44% (634 patients) requiring inotropic support. Severe left ventricular systolic dysfunction (LVEF <30%) was present in one

third of the patients (531/1,608). Pre- or perioperative IABP was inserted in almost 60% of subjects. Detailed characteristics of studies and patients are listed in *Table 1*. The rupture involved the postero-medial papillary muscle in 77% (182/235) of cases, and the rupture was partial or incomplete (head rupture) in 54% of subjects. Patients most commonly underwent MVR; MVr was performed in only 18% (319/1,792) of cases. Mean duration of cardiopulmonary bypass (CPB) was 147±31 minutes. Fifty-seven percent of patients had concomitant coronary artery bypass grafting (CABG) at the time of mitral valve surgery. Postoperative IABP support was necessary in almost two-thirds of the patients. Operative data is shown in *Table 2*.

Postoperative outcomes

Overall, the total number of early deaths was 392, representing an operative mortality rate of 21%. Post-operatively, kidney dysfunction requiring RRT occurred in 13% of subjects, whereas major bleeding requiring re-intervention and stroke occurred in 16% and 5% of cases, respectively. Mean hospital length of stay was 18.9± 11.3 days. The most common cause of postoperative death was LCOS (45%). Surgical outcomes are outlined in *Table 3*.

Table 2 Operative data									
Author (ref.)	A-L PMR (n)	P-M PMR (n)	Head rupture (n)	Body rupture (n)	MVR (n)	MVr (n)	CPB* time (m)	Conc. CABG (n)	IABP (n)
Fujita (14)	-	-	-	-	176	20	156	60	-
Kilic (15)	-	-	-	-	1,071	271	162	796	-
Sultan (11)	6	18	15	9	17	7	171	13	-
Ternus (7)	12	10	12	10	-	-	-	-	-
Bouma (9)	5	42	28	20	38	10	178	24	24
Schroeter (13)	11	11	-	-	25	3	151	19	20
Russo (16)	6	48	-	-	41	13	89	42	39
Chevalier (10)	6	31	12	25	-	-	-	-	-
Chen (17)	-	-	-	-	31	2	-	20	21
Tavakoli (4)	-	-	-	-	19	2	-	19	-
Figueras (8)	-	-	-	-	24	0	-	8	-
Kishon (12)	0	22	15	7	21	1	121	17	-
Total [%] or (± SD)	46^ [20]	182 [77]	82 [54]	71 [46]	1,463 [82]	329 [18]	147 (±31)	1,018 [57]	104 [64]

^{*,} mean value; ^, in the remining 3% of cases, the rupture involved both A-L and P-M papillary muscles. Ref., reference; A-L, anterolateral; P-M, postero-medial; PMR, papillary muscle rupture; n, number; MVR, mitral valve replacement; MVr, mitral valve repair; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; Conc., concomitant; IABP, intra-aortic balloon pump; m, minutes; SD, standard deviation.

Operative mortality

Operative mortality was significantly increased in patients with complete (body rupture) PMR as compared to partial or incomplete PMR (head rupture) (RR, 2.54; 95% CI: 1.12 to 5.74; P=0.03; $I^2=0\%$) (Figure 1), with early death rates of 31.5% (17/54) and 10.9% (6/55), respectively. Subjects undergoing MVr had a reduced risk of operative mortality (RR, 0.33; 95% CI: 0.14 to 0.79; P=0.01; I^2 =53%) (Figure 2) as compared to those undergoing MVR. Operative mortality rate was 24.3% (322/1,326) and 5.7% (18/314) for MVR and MVr respectively. There was no significant difference in the risk of operative mortality between patients with or without pre/peri-operative IABP support (RR, 2.62; 95% CI: 0.56 to 12.17; P=0.22) and between subjects undergoing mitral valve surgery with or without concomitant CABG (RR, 0.61; 95% CI: 0.36 to 1.06; P=0.08), with moderate heterogeneity among studies $(I^2=54\% \text{ and } I^2=64\%, \text{ respectively})$ (Figures 3,4). Mortality rates were 20% (182/906) in patients with concomitant CABG, 22.2% (136/612) in no-CABG patients, and 35.3% (18/51) and 14.9% (7/47) for pre/peri-operative IABP support versus no-IABP respectively.

Sensitivity analysis

Analysis performed by successively deleting the studies at highest risk of bias did not reveal any change in direction nor magnitude of the treatment effect.

Discussion

PMR is a rare but serious mechanical complication of AMI. It occurs in less than 1% of patients sustaining AMI (1), and accounts for 5% of infarct-related deaths (1). Most ruptures develop within seven days after AMI, but a delayed rupture may also occur (2). Post-AMI PMR is usually characterized by pulmonary edema and cardiogenic shock, ultimately leading to multiorgan failure and death (18). Early diagnosis and prompt management are therefore paramount to ensure successful treatment and patient survival. Immediate surgical correction is considered the optimal and most rational treatment for acute post-AMI PMR; however, even for patients who are treated surgically, mortality is high, ranging between 9% and 45% (7,8). Real-world results in the modern era indicate that no major improvements have been observed in the last two decades (18), highlighting

Table 3 Main postoperative complications and outcomes								
Author (ref.)	Stroke (n)	RRT (n)	Major bleeding (n)	LCOS (n)	H stay* (d)	Operative mortality (n)	Cardiac cause (n)	Other cause (n)
Fujita (14)	16	35	-	-	28	50	-	-
Kilic (15)	70	161	-	-	16	268	-	-
Sultan (11)	0	2	2	-	19	3	3	0
Ternus (7)	-	-	-	-	-	2	2	0
Bouma (9)	0	7	8	-	19	12	10	2
Schroeter (13)	-	16	6^	16	8	11	-	-
Russo (16)	-	-	-	16	20	10	8	2
Chevalier (10)	-	-	-	-	-	8	-	-
Chen (17)	-	-	-	-	-	7	-	-
Tavakoli (4)	1	3	-	-	-	4	2	2
Figueras (8)	-	-	-	-	-	11	4	7
Kishon (12)	-	-	-	-	_	6	4	2
Total [%] or (± SD)	87 [5]	224 [13]	16 [16]	32 [39]	18 (±7)	392 [21]	33 [69]	15 [31]

^{*,} mean value; ^, re-thoracotomy for unclear reason. Ref., reference; n, number; RRT, renal replacement therapy; LCOS, low cardiac output syndrome; H, hospital; d, days; SD, standard deviation.

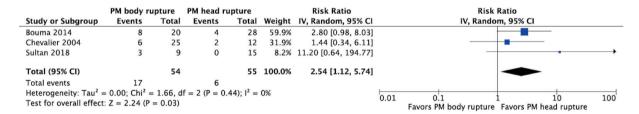


Figure 1 Forest plots of comparison of PM body (complete) rupture versus head (partial) rupture. Outcome of interest: operative mortality. CI, confidence interval; PM, papillary muscle.

	MV Re	pair	MV Replacement		Risk Ratio		Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	I IV, Random, 95% CI		
Bouma 2014	0	10	12	38	8.4%	0.14 [0.01, 2.21]]		
Fujita 2020	4	20	46	176	33.5%	0.77 [0.31, 1.90]] —		
Kilic 2020	13	271	255	1071	43.9%	0.20 [0.12, 0.35]] —		
Russo 2008	1	13	9	41	14.2%	0.35 [0.05, 2.51]]		
Total (95% CI)		314		1326	100.0%	0.33 [0.14, 0.79]			
Total events	18		322						
Heterogeneity: $Tau^2 = 0.37$; $Chi^2 = 6.38$, $df = 3$ (P = 0.09); $I^2 = 53\%$						5	0.01 0.1 1 10 100		
Test for overall effect: $Z = 2.50$ (P = 0.01)							Favors MV Repair Favors MV Replacement		

Figure 2 Forest plots of comparison of MV repair versus MV replacement. Outcome of interest: operative mortality. CI, confidence interval; MV, mitral valve.

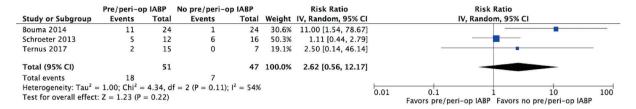


Figure 3 Forest plots of comparison of pre/peri-operative IABP support versus no-IABP support. Outcome of interest: operative mortality. CI, confidence interval; IABP, intra-aortic balloon pump.

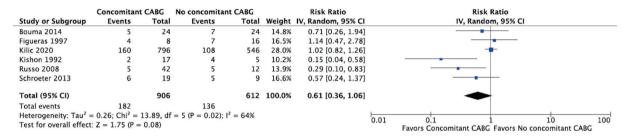


Figure 4 Forest plots of comparison of concomitant CABG versus no-CABG. Outcome of interest: operative mortality. CI, confidence interval; CABG, coronary artery bypass grafting.

that careful evaluation is required to understand potential areas for improvement. This systematic review provides an overview of published evidence on the characteristics and outcomes after surgical treatment of post-AMI PMR.

Posteromedial PMR is far more common than anterolateral PMR (2) given the coronary anatomy and arterial blood supply of the papillary muscles (3). Indeed, the anterolateral papillary muscle has a dual blood supply from the left anterior descending and left circumflex coronary arteries, whereas the posteromedial papillary muscle has a single blood supply from the posterior descending artery (2). In this review, ruptures involved mostly the posterior papillary muscle (77%), which supports previous observations.

PMR may be complete (usually occurring at the base of the papillary muscle) or partial occurring at one of the tips (heads) of a papillary muscle. Partial PMR can lead to varying degrees of mitral insufficiency, whereas complete PMR causes prolapse of both the anterior and posterior leaflet and subsequently, severe mitral regurgitation. Our results showed a significantly higher frequency of operative mortality in complete PMR (body rupture) than partial PMR. While partial rupture occurred slightly more frequently than complete rupture, patients were more likely to have worse conditions and preoperative hemodynamic

instability in complete PMR, which is also consistent with the literature (9-11).

Despite alternative approaches, such as MitraClip, having been increasingly proposed to treat patients with post-AMI PMR (19,20), retrospective studies have shown that the in-hospital mortality rate in patients undergoing surgery is remarkably better (21), mainly in subjects with preoperative hemodynamic instability and cardiogenic shock. The operative mortality in the current study was relatively low, when compared to the early mortality of patients undergoing surgery for other post-infarction mechanical complications, such as ventricular septal rupture (VSR) (22) (21% versus 38%, respectively).

PMR can be addressed with either MVr in select patients, or MVR. When post-infarction PMR is complete, repair is often not feasible because of necrotic and friable infarcted tissue. Mitral regurgitation secondary to partial or incomplete PMR, with limited adjacent tissue damage, is often amenable to a reliable and durable repair. In this review, MVR was carried out in almost 85% of cases. Moreover, we observed a higher operative mortality rate after MVR. A possible explanation for this is the critical illness status of patients in whom MVR was undertaken. MVR is usually reserved for subjects with complete PMR or partial/incomplete PMR and compromised hemodynamic

stability at surgery in order to reduce CPB, ischemic times, and related risks (10-12).

The impact of concomitant CABG on the outcomes of patients undergoing cardiac surgery for post-AMI mechanical complication remains unclear. In our previous meta-analysis, we did not find any significant protective effect of simultaneous CABG in addition to septal defect repair in the setting of post-AMI VSR (22). Similarly, in this study, concomitant CABG did not influence early survival. Further analysis is needed to determine the importance of simultaneous CABG in the context of mitral valve surgery for post-AMI PMR.

Pre-operative hemodynamic instability and cardiogenic shock are frequent scenarios after the occurrence of post-AMI PMR, making the use of IABP effective and generally accepted by current guidelines (23). Such an approach may therefore be helpful in improving the hemodynamic stability of patients and allow postponement of surgical intervention. In the current review, IABP was used in almost half of PMR patients prior to surgery. However, similar to the findings reported in several other studies (3,9,13), our analysis showed no significant difference in the risk of operative mortality between patients with or without pre/peri-operative IABP support. A possible explanation for this is the critical illness status of patients in whom the decision of IABP insertion was made.

In patients with extremely or very compromised pre-operative hemodynamic stability, more aggressive mechanical circulatory support (MCS), such as extracorporeal membrane oxygenation (ECMO), has been shown to be a useful strategy for the treatment of post-AMI PMR in the setting of univentricular or biventricular failure, either preoperatively as a bridge to surgery, or postoperatively following mitral valve operation (24). ECMO allows circulatory support, providing time and hemodynamic stability for diagnostic workup and surgical intervention planning, while reversing organ damage. This improvement occurs at the expense of a high rate of device-related complications (25), so patient selection and the single center's experience are important to achieve satisfactory results. The literature relating to the use of ECMO in the context of PMR is limited to successful case reports and as part of small observational studies (13-15) depicting the utility of ECMO as a way of stabilizing inoperable or high-mortality surgical candidates. However, the lack of specific information in the ECMO subgroup prevented us from exploring this issue.

Limitations

The retrospective nature of the reports included represents the major limitation of this review. Retrospective studies are subject to confounder bias, possibly affecting the conclusive power of our meta-analysis. The pooled occurrence rates for complications and mortality were based on heterogeneous data and should be treated with considerable reserve. Individual and institutional experience is crucial in determining the likelihood of the success of PMR surgery. This is therefore an important current subgroup analysis, limited by the number of included studies, and should be viewed with caution. Better results observed with mitral valve repair and concomitant CABG may not be reflected in centres experienced with early mitral valve replacement and high-risk percutaneous coronary interventions (PCIs). Although our analysis revealed no evidence of significant reporting bias, such bias still remains a possibility, with potentially more favourable results being reported from large-volume expert centres that may not be representative of all institutions. Trends in characteristics and outcomes in this review are largely driven by the Society of Thoracic Surgeons (STS) registry (15); the value in this study is that the more geographically diverse data presented here does not substantially differ in findings from the large STS dataset published by Kilic et al. Two national registries provided data for this review (14,15), with the potential risk of patients overlapping accounting for less than 2.5% of the population (7,11). As the timeline of the study period is fairly long, progress in management and operative strategies may have changed over time, limiting our qualitative analysis. Another important limitation of the current review is the considerable amount of missing data. Finally, because this study is limited to operative outcomes, it does not provide information on the durability of surgical PMR procedures.

Conclusions

Mitral valve surgery for post-AMI PMR is associated with high operative mortality (21%). The findings of the present meta-analysis seem to indicate that the risk of operative mortality is higher in the presence of complete PMR and in subjects undergoing MVR. Our results also suggest that concomitant CABG during PMR correction and the pre/peri-operative use of IABP do not improve early survival. More aggressive pre- or post-operative MCS use might presumably be of some help in unstable patients

with a high risk of surgery, in an attempt to improve outcomes. However, more data and studies are warranted to conclusively indicate the actual potential and role of such an approach in post-AMI PMR.

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Footnote

Conflicts of Interest: Prof. RL is a a consultant for Medtronic, Getinge and LivaNova, and Member of the advisory board of Eurosets and Fresenius/Xenios. The other authors have no conflicts of interest to declare.

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