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Diagnosis and Treatment of Mechanical Hemolysis after Mitral Repair in Adult

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ABSTRACT

Background: Mitral repair has been widely used in the treatment of secondary mitral lesions in recent years. Hemolytic anemia is known to be a rare complication after mitral repair. This study aimed to investigate the diagnosis and treatment of mechanical hemolysis after mitral repair in adults.

Methods: In this retrospective study, we reviewed the medical records of patients undergoing mitral repair complicated with mechanical hemolysis at our institution between August 2006 and May 2020.

Results: Twenty-four patients undergoing mitral repair complicated with mechanical hemolysis were included in the study. They were divided into two groups: the reoperation group (patients who underwent reoperation; N = 18) and the conservative treatment group (patients who received symptomatic treatments, including blood transfusion, diuresis, alkalization of urine, liver protection, hemodialysis, and oral metoprolol; N = 6. All patients in the reoperation group underwent mitral valve replacement. There were six hospital deaths, all in the conservative treatment group. Seventeen of eighteen patients (94.4%) completed follow up. Fifteen of seventeen survivors (88.2%) were in NYHA class I and 11.8% (2/17) in NYHA class II at the last time follow up.

Conclusions: Hemolysis is a sign of failure of mitral repair. Reoperation is the best choice once the hemolysis has been diagnosed. Reoperation should be carried out as soon as possible.

INTRODUCTION

Mitral repair has been widely used in the treatment of secondary mitral lesions in recent years. Hemolytic anemia is known to be a rare complication after mitral repair. Most of the literature involve case reports. Insufficient experience of doctors with the diagnosis and treatment of mechanical hemolytic anemia after mitral repair easily leads to misdiagnosis and mistreatment [Rose 1954; Pollet 2008; Cerfolio 1997; Dilip 1992; Weill 2015; Naik 2016]. This study aimed to investigate the diagnosis and treatment of mechanical hemolysis after mitral repair in adults.

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PATIENTS AND METHODS

Study population eligibility/inclusion criteria: All patients undergoing mitral repair complicated with mechanical hemolysis at our institution between August 2006 and May 2020 were included in the retrospective study. The diagnosis of mechanical hemolytic anemia was based on the clinical manifestations, lab investigation, and echocardiographic findings. Early mortality was defined as death before hospital discharge or within 30 days of mitral repair. Patients who were not complicated with mechanical hemolysis were excluded from the study.

Variables investigated: Variables were evaluated, including gender, age, weight, total bilirubin, hemoglobin, blood urea nitrogen, serum creatinine, ICU retention time, intubation time, findings in reoperation, multiple organ failure, and death.

Surgical technique, mitral valve repair (first surgery): Mitral valve repair was performed via median sternotomy under a standard cardiopulmonary bypass established by ascending aortic and both venae cavae. Moderate hypothermia and cold blood cardioplegia for myocardial protection were used. Surgical approach was through the right atrium. Mitral valve repair techniques are defined based on the leaflets involved in the repair as posterior, anterior, bi-leaflet, or ring annuloplasty alone. Commissuroplasty is classified as a bi-leaflet repair. Posterior leaflet repair includes posterior leaflet triangular resection/plication, cleft closure, and repair with a prosthetic ring. For patients with anterior leaflet prolapse with or without ruptured chordae, the surgical techniques included artificial chordae, chordal shortening, and chordal transposition. A ring annuloplasty was performed in all patients. According to surgeons' preference, either a rigid ring such as Meditronic Duran AnCore ring or a flexible ring such as Carpentier-Edwards Physio was used. The ring size was determined by measuring the area of the anterior leaflet with prosthetic sizers provided by its manufacturers. We routinely utilized intraoperative transesophageal echocardiography (TEE) in all patients.

Surgical technique, mitral valve replacement (second surgery): The patients in the reoperation group all underwent mitral valve replacement after hemolysis diagnosis. The reoperation was carried out under general anesthesia and mild

hypothermia cardiopulmonary bypass, through the median incision of the original sternum. Cold histidine tryptophane ketoglutarat solution crystal cardioplegia solution (Custodiol; Dr F Ko¨hler Chemie GMBH, Alsbach, Germany) was used. Mitral valve replacement with mechanical prosthetic valves was performed through the atrial septal incision.

Follow up: All survivors discharged from hospital were followed up to the end date of the study (May 2020). All patients were investigated with electrocardiogram, X-ray chest film, and echocardiogram in the outpatient clinic once every three months. At the last time of follow up, the patients were interviewed in the outpatient clinic or contacted by telephone.

Data analysis: SPSS version 24.0 software (IBM SPSS Inc, Chicago, III) was used to perform all analysis. Paired t tests were used to make comparisons of preoperative and postoperative continuous variables. We used the Kaplan-Meier method to estimate survival rates. The chi-square test, the Kruskal-Walls test, or the Wilcoxon rank-sum test, as appropriate, to be used to evaluate relationships between the preoperative variables and selected intraoperative and postoperative variables. P-values less than 0.05 were considered statistically significant.

Ethical aspects: The experiment protocol for involving humans was in accordance with national guidelines and approved by the Medical Ethics Committee of The People's Hospital of Guangxi Zhuang Autonomous Region, and The Medical Ethics Committee of The People's Hospital of Guangxi Zhuang Autonomous Region gave the authors approval to waive the need for patient consent for publishing data in the study about the patients.

RESULTS

Patient characteristics: Twenty-four patients undergoing mitral repair complicated with mechanical hemolysis were included in the study. They were divided into two groups: the reoperation group (patients who underwent reoperation; *N* = 18) and the conservative treatment group (patients who received symptomatic treatments, including blood transfusion, diuresis, alkalization of urine, liver protection, hemodialysis, and oral metoprolol; *N* = 6. All patients in the reoperation group underwent mitral valve replacement. There were six hospital deaths, all in the conservative treatment group. Table 1 shows the comparison of characteristics of the reoperation group and the conservative treatment group. (Table 1)

Color Doppler echocardiography showed residual mitral regurgitation with eccentric regurgitation area of 3.6-20.88 cm^2. The interval between the first surgical procedure and the diagnosis of hemolytic anemia was 1-58 days (median 12 days), and the interval between the diagnosis of hemolytic anemia and the reoperation was 5-21 days (median 10.5 days). The interval between the two operations was 8-67 days (median 22 days).

Operative results of second surgery: The operative data of the second surgery is shown in Table 2. (Table 2) There were six hospital deaths, all in the conservative treatment group died from multiple organ failure, and no death in the reoperation group.

In the reoperation group, all patients recovered well after the mitral valve replacement and were discharged from hospital, with the hemoglobin uria disappeared, urine recovered clear, symptoms of anemia and jaundice quickly subsided, and general condition significantly improved. Table 3 shows the comparison of clinical data between pre-second surgery and post-second surgery 1 week later in the reoperation group. (Table 3) Findings in reoperation (second surgery) included leakage around artificial valve ring, new rupture of tendon, laceration of suture, and formation of mitral valve vegetation, tearing of leaflets. (Table 4) Regurgitation after mitral repair is given in Figure 1. (Figure 1)

Follow-up results: 94.4% (17/18) patients completed follow up. The mean follow-up duration was 42.1±28.2 months. No late death occurred. 88.2% (15/17) survivors were in NYHA class I and 11.8% (2/17) in NYHA class II at the last time follow up.

DISCUSSION

In 1997, Mayo Clinic reported that 10 cases of adult mitral repair were complicated with hemolysis (the incidence was 0.9%). There were 1,348 patients who underwent mitral repair at our institution from August 2006 to May 2020 retrospectively, and mechanical hemolysis were diagnosed after mitral repair in 24 patients. The incidence of hemolysis after

Table 1. Comparison of characteristics of the reoperation group and the conservative treatment group

Variables	Reoperation Group (*N* = 18)	Conservative Treatment Group (*N* = 6)	*P*-value
Male, n (%)	11 (61.1%)	3 (50%)	0.633
Age (years)	40.39±3.39	45.0±2.59	0.107
Weight (kg)	59.94±1.17	58.83±2.51	0.040
Total bilirubin (μmol/L)	103.28±10.61	113.07±6.37	0.089
Hemoglobin (g/L)	79.44±1.40	74.33±3.24	0.442
blood urea nitrogen (mg/L)	25.62±0.82	23.47±1.77	0.540
serum creatinine (μmol/L)	407.89±19.31	308.67±18.10	0.141

Table 2. Comparison of clinical results between the reoperation group and the conservative treatment group

Variables	Reoperation Group (*N* = 18)	Conservative Treatment Group (*N* = 6)	*P*-value
Mortality, n (%)	0	6 (100%)	0.000
Intubation time (hours)	40.61±5.89	235.83±19.17	0.000
ICU retention time (days)	3.73±0.23	9.82±0.80	0.000

mitral repair at our institution was 1.8% (24/1348), which is higher than those reported. The reasons maybe included the artificial grafts with rough surface used to fold the posterior mitral annulus in early years [Pollet 2008; Cerfolio 1997; Demirsoy 2008]. The six hospital deaths in the conservative treatment group are very unfortunate. They did not undergo reoperation (second surgery) for various reasons, including doctors' insufficient understanding of mechanical hemolysis after mitral repair, not enough money of families of patients, and so on.

It is believed that the abnormal high velocity of mitral regurgitation beam impinging on the area of the artificial valve ring or gasket is the cause of red blood cell destruction and hinders the endothelialization of the surface of the artificial valve ring. It was reported that 19% of 145 cases of reoperation after mitral repair had severe mechanical hemolysis [Garcia 1996; Abe 2010; Yeo 1998].

The residual regurgitation of mitral valve with high shear force is currently recognized as an important cause of postoperative hemolysis. The high shear force can be caused by the annular leakage of the artificial valve, the impact of blood flow on the rough surface of the artificial material, the turbulence formed by the reflux beam, and the special reflux beam types (impact, acceleration, split type). When the shear force increases beyond the maximum stress that the erythrocyte membrane can bear, it will lead to cell breakage [Ishida 2015; Lee 2020; Ishibashi 2005; Qian 2010; Chan 2014]. Some researchers have conducted in vitro experiments and found that when the shear force reaches 50-450 PA, it can lead to red blood cell destruction, and when the flow rate cross valve is 5 m/s, the shear force of blood flow on the aortic wall can be as high as 870 PA. Mechanical hemolysis after mitral repair has nothing to do with the degree of residual regurgitation, mainly with the speed of regurgitation. The flow beams of regurgitation were divided into five types: impact type, acceleration type, segmentation type, slow deceleration type, and central type. The impact type, acceleration type, and segmentation type of regurgitation beams are closely related to the mechanical hemolytic anemia, while the slow deceleration type and central type of regurgitation beams cause little damage to the red blood cells. It is believed that the implantation of artificial valve rings and the existence of residual regurgitation may be the pathogenesis of mechanical hemolysis after mitral repair. It is reported that hemolytic symptoms disappeared in one patient after removal of the artificial valve ring [Vahidkhah 2016; Vahanian 2012; Suri 2006].

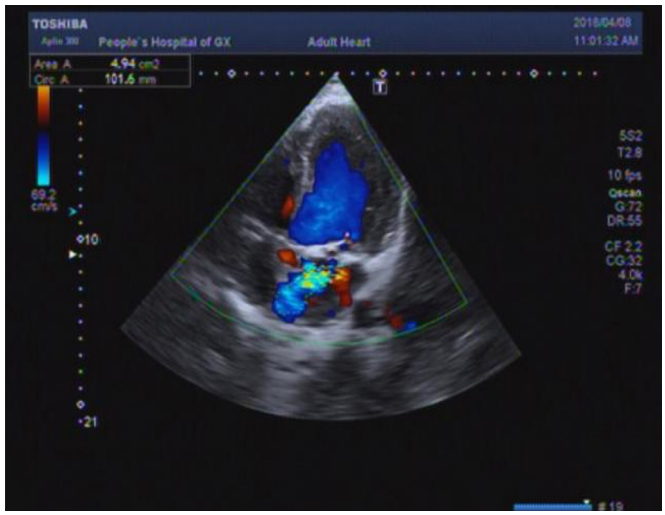
There are many causes of mechanical hemolysis after mitral repair: whiplash-like movement of broken tendon and suture, leakage around artificial valve ring, rough surface of artificial material not covered by endothelium, eddy current, and high shear stress caused by reflux beam [Warnes 1980; Eishi 2001; Nakaoka 2017; Cerfolio 1996].

Table 3. Comparison of clinical data between pre-second surgery and post-second surgery in the reoperation group (*N* = 18)

Variables	Preoperation	Postoperation	*P*-value
Total bilirubin (μmol/L)	103.28±10.61	28.17±1.01	0.000
Hemoglobin (g/L)	78.17±1.37	92.21±4.21	0.003
Blood urea nitrogen (mg/L)	25.62±0.82	13.35±0.57	0.000
Serum creatinine (μmol/L)	407.89±19.31	282.50±25.55	0.000

Table 4. Findings in reoperation (second surgery)

Variables	*N*
Leakage around artificial valve ring	8
New rupture of tendon	6
Laceration of suture	3
Formation of mitral valve vegetation, tearing of leaflets	1



Regurgitation after mitral repair.

Diagnosis of mechanical hemolytic anemia after mitral repair: Mechanical hemolysis often occurs immediately after mitral repair. Jaundice, hemoglobin uria, anemia, and the mitral regurgitant flow with high shear stress found by the echocardiography post operation, are helpful to the diagnosis. However, the diagnosis of hemolytic anemia after mitral repair has its particularity. The clinical manifestations and echocardiographic findings are important for the diagnosis. If the patient meets the following conditions, the presence of mechanical hemolytic anemia should be considered: (1) progressive anemia; (2) no history of hemolysis before mitral repair; (3) soy urine after operation; (4) residual mitral regurgitation found by echocardiography. Transthoracic echocardiography and transesophageal echocardiography are important for the diagnosis of mechanical hemolysis after mitral repair [Aoyagi 2007; El Sabbagh 2018; Tsang 2019; Matsunaga 2018].

Treatment strategy: In the second operation, mitral valve replacement was performed to eliminate regurgitation, turbulence, shear stress, rough surface of reflux beam, whiplash movement of ruptured chordae tendineae, and other factors leading to the destruction of red blood cells. The root causes of organ damage (lung, kidney, liver, heart, etc.) were eliminated, and the occurrence and development of multiple organ failure were blocked. Before the second operation, perfect preoperative preparations were performed, including correction of hypoproteinemia and anemia, alkalization of urine and so on to place the patient in a better state to increase the tolerance to surgery and prevent multiple organ failure. During the operation, the suture should be accurate to prevent perivalvular leakage. After operation, sufficient oxygen supply, tissue perfusion, and good circulation should be maintained. Proper diuresis, if necessary, and hemodialysis were used to prevent multiple organ failure.

Drug therapy did not eliminate the causes of hemolysis and could not prevent and reverse the development of hemolysis and multiple organ failure. Finally, the patient died of multiple organ failure.

Do not hesitate to perform reoperation if the following situations occur: 1) Drug treatment effect is not good; 2) Symptoms are progressively aggravated; 3) Repeated transfusion of red blood cells is needed; 4) Hemodynamic instability caused by reflux occurs; and 5) Organ function damage, such as renal failure, occurs. Once the patients who need repeated transfusion of red blood cells are diagnosed with mechanical hemolytic anemia, they need immediate surgery without delay [Acharya 2013]. We also believe that patients with hemolytic anemia in the early stage after mitral repair tend to rapidly progress, often accompanied by renal function damage. Our experience is that the earlier hemolysis occurs, the more severe the condition and the higher reoperation mortality will be. The earlier the operation was performed after diagnosis, the better. Once the diagnosis is made and other causes of hemolysis are excluded, medical treatment will be invalid. Reoperation should be carried out as soon as possible. Emergency operation should be considered for severe patients. Good results can be achieved by mitral valve replacement [Lam 2004].

CONCLUSIONS

The implantation of artificial ring and the existence of residual mitral regurgitation may be the pathogenesis of mechanical hemolysis after mitral repair. Hemolysis is a sign of failure of mitral repair. Reoperation is the best choice once the hemolysis has been diagnosed. Reoperation should be carried out as soon as possible. Emergency operation should be considered for severe patients. Good results can be achieved by mitral valve replacement.

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