Reoperation for hemolytic, anaemia complicating mitral valve repair

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Abstract

Objective: To identify the possible cause(s) of hemolysis after mitral valve repair for mitral regurgitation (MR) and to evaluate the late outcome of surgical treatment. Methods: We reviewed all patients who had reoperation after valve repair for mitral regurgitation. Ten patients had reoperation because of hemolytic anaemia. The diagnosis of hemolysis was made by decreased serum haptoglobin, elevation of serum lactate dehydrogenase (LDH), and schistocytosis. No other causes of anaemia or hemolysis were identified in these six men and four women (ages 35–84 years; median 59 years). Interval between initial mitral valve repair and reoperation ranged from 40 to 165 days (median 87 days), and prior to reoperation, red cell transfusions (range 2–12 units; median 5 units) were required in all patients. Seven patients were symptomatic: two complained of easy fatigability and five were severely limited. Transesophageal echocardiogram during hemolytic evaluation showed only mild MR in two patients, moderate in five, moderately severe in two and severe in one. Results: Etiology of hemolysis was suggested from echocardiography and confirmed at reoperation. In one patient, an eccentric MR jet struck a pledget of a commissural annuloplasty. In the remaining nine patients, the regurgitant jet struck a non-endothelialized portion of the annuloplasty ring (Carpentier-Edwards n = 5; Duran n = 2; Cosgrove-Edwards n = 2). Seven patients had prosthetic replacement and three patients had re-repair. There were no operative deaths and all patients had resolution of hemolytic anaemia. Conclusions: Relatively minor degrees of regurgitation after mitral valve repair can produce hemolytic anaemia which is manifested within the first few postoperative months. Most patients are highly symptomatic because of anaemia. The mechanism of red cell destruction is a high velocity eccentric stream of blood impacting on a small area of a prosthetic ring or pledget. This process retards endothelialization of the ring. Reoperation with re-repair or mitral valve replacement is safe and effectively relieves the hemolysis. © 1997 Elsevier Science B.V.

Keywords: Hemolytic anaemia; Mitral valve repair

1. Introduction

Hemolytic anaemia is a recognized but rare complication of prosthetic replacement of the mitral valve often associated with perivalvular leak. It has been described, although less frequently, as a complication of mitral valve repair. The incidence, pathophysiology, natural history, and management of this unusual problem is poorly understood [1–13]. We reviewed our experience with patients who required reoperation at the Mayo Clinic because of mechanical hemolysis from residual mitral regurgitation (MR) after mitral valve repair.

2. Material and methods

Between January 1986 and July 1995, ten patients required reoperation after previous mitral valve repair because of mechanically induced hemolytic anaemia from residual mitral regurgitation. Patients with previous mitral valve commissurotomies, congenital mitral valve disease, regurgitation from cardiac or valvular masses, or previous balloon mitral valvuloplasties were excluded from the study. During this time interval,
1095 mitral valve repairs were performed at our Clinic. Patients’ Clinic charts, hospital progress notes, operative notes, and laboratory tests were examined. Follow-up was obtained from records of the patient’s most recent Mayo Clinic visit, letters from home physicians, and telephone calls. Information received at follow-up included the patient’s current functional status, their mitral valve competency as determined by their latest echocardiogram, and any subsequent morbidity or mortality.

Operative mortality is defined as any death occurring prior to hospital dismissal or within 30 days of the operative procedure. Late mortality is defined as any subsequent death. Late complications are defined as those that occurred after hospital dismissal. All objective data is expressed as a range with a median.

3. Results

3.1. Initial mitral valve repair

There are six men and four women whose age ranged from 35 to 84 years with a median of 59 years. Patient characteristics are shown in Table 1. Initial mitral valve repair was performed from March 1985 to April 1995, and indications were severe MR in all 10 patients. Initial mitral valve repair was the first median stereotomy for all patients. Six of the ten patients had their initial repairs performed at the Mayo Clinic and four were done elsewhere. The type of initial repairs are shown in Table 2. As seen, nine of the ten repairs included a prosthetic annuloplasty ring. Three patients underwent four concomitant cardiovascular procedures which were: coronary artery bypass grafting in two, and ligation of a left atrial appendage and closure of a patent foramen ovale in one each. Four patients had intraoperative, transesophageal echocardiographic (TEE) evaluation of their mitral valve after repair. Two patients had none to trivial MR and two had mild residual MR. Seven of the ten patients had dismissal transthoracic echocardiograms which assess the MR as none to trivial in two, mild in four, and moderate in one patient.

3.2. Reoperation

Patient symptoms leading to re-evaluation consisted of progressive fatigue soon after hospital discharge after mitral valve repair in seven patients. Table 3 illustrates the patients’ characteristics at time of hospital re-admittance. Of the three patients who were not functionally impaired, two noted discolored urine and the third patients’ hemolysis was discovered during evaluation for a persistently low hemoglobin.

All patients required transfusions of packed red blood cells prior to reoperation. The median number of units transfused was five with a range of 2–12. All patients underwent extensive hematological evaluation which revealed low serum haptoglobin, elevated serum lactate dehydrogenase (LDH), and schistocytosis in each. Urinary hemosiderin and an elevated unconjugated bilirubin were present in the eight and four patients who had these tests performed, respectively. Bone marrow aspirates performed in seven patients demonstrated erythroid hyperplasia. Echocardiography as shown in Table 2 was performed in all patients immediately prior to reoperation. Nine of the ten patients had MR that was less than severe, yet most were significantly clinically ill.

The median time between operations was 87 days with a range of 40–165 days. Reoperation was performed through a median stereotomy and standard left atriotomy in eight patients and transeptally in two because of the need for concomitant right atrial procedures. The initial repairs were intact in eight patients and disrupted in two. The causes of residual MR in the eight patients with intact repairs included newly ruptured chordae to leaflets that were not repaired at initial operation in three, a redundant non-previously repaired anterior leaflet in two, and indeterminable in three. Causes of MR in the two patients with disrupted repairs were dehiscence of the annuloplasty ring and breakdown of a chordae shortening procedure to the anterior leaflet in one patient each.

The etiology of the mechanical hemolysis was suggested by preoperative transesophageal echocardiogram (TEE) and confirmed by visual inspection of the valve. In nine patients one or more regurgitant jets of blood struck a nonendothelialized portion of the annuloplasty ring. In the one patient who had a previous commissural annuloplasty the eccentric jet of blood was directed against a pledget.

As seen in Table 2, seven patients had mitral valve replacement (four mechanical and three tissue prostheses) and three had re-repair. Two patients had concomitant procedures at reoperation. One had closure of a
Table 2
Patient characteristics

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Type of initial MVR</th>
<th>No. unit trans blood</th>
<th>Degree of residual MR prior operations</th>
<th>Days between operations</th>
<th>Type second MV procedure</th>
<th>Findings at reoperations; causes hemolytic anaemia</th>
<th>Initial repair intact?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C-E ring</td>
<td>12</td>
<td>Moderate</td>
<td>165</td>
<td>Rerepaired; excised part of ring, Kay annuloplasty</td>
<td>2. Jets blood against non-endothelialized part of ring</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>C-E ring</td>
<td>5</td>
<td>Moderately severe</td>
<td>45</td>
<td>Starr-Edwards no. 4</td>
<td>Jet blood against non-endothelialized part of ring</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>C-E ring, shorten chord and leaflet</td>
<td>2</td>
<td>Mild</td>
<td>95</td>
<td>27 mm St. Jude</td>
<td>Jet blood against non-endothelialized part of ring</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>Duran ring, plication ant leaflet</td>
<td>2</td>
<td>Mild</td>
<td>115</td>
<td>27 mm Intact medtronic porcine</td>
<td>Jet blood against non-endothelialized part of ring</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>Duran ring, plication ant leaflet, shorten chord and leaflet</td>
<td>7</td>
<td>Moderate</td>
<td>96</td>
<td>27 mm C-E</td>
<td>Jet blood against non-endothelialized part of ring</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>Reed annuloplasty</td>
<td>4</td>
<td>Moderate</td>
<td>89</td>
<td>25 mm St. Jude</td>
<td>Jet against a non-endothelialized pledget</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>C-E ring, wedge resect and leaflet</td>
<td>2</td>
<td>Moderate</td>
<td>84</td>
<td>Rerepaired, 32 mm C-E ring</td>
<td>Jet blood against non-endothelialized part of ring</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>Cosgrove-Edwards ring, shorten chord post leaflet</td>
<td>8</td>
<td>Severe</td>
<td>40</td>
<td>31 mm C-E valve</td>
<td>Jet blood against non-endothelialized part of ring</td>
<td>Yes</td>
</tr>
<tr>
<td>9</td>
<td>C-E ring wedge resect post leaflet</td>
<td>5</td>
<td>Moderately severe</td>
<td>58</td>
<td>Rerepaired with Duran ring 27 mm, plication ant leaflet, shortening of chordae to ant leaflet</td>
<td>Jet blood against non-endothelialized part of ring</td>
<td>Yes</td>
</tr>
<tr>
<td>10</td>
<td>Cosgrove-Edwards ring</td>
<td>4</td>
<td>Moderate</td>
<td>67</td>
<td>29 mm St. Jude</td>
<td>3. Jets blood against non-endothelialized part of ring</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Patient characteristics prior to mitral valve reoperation

<table>
<thead>
<tr>
<th>Preoperative disability</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>7</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>5</td>
</tr>
<tr>
<td>Shortness of breath at rest</td>
<td>5</td>
</tr>
<tr>
<td>Angina</td>
<td>1</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>3</td>
</tr>
<tr>
<td>Moderately severe impairment</td>
<td>2</td>
</tr>
<tr>
<td>Severe impairment</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 3

patent foramen ovale which was undiagnosed at initial mitral valve repair performed elsewhere and another had a tricuspid valve repair performed for severe tricuspid regurgitation. Cardiopulmonary bypass time ranged from 56 to 212 min with a median of 100 min. Aortic cross-clamp time ranged from 29 to 99 min with a median of 67 min.

There were no operative deaths. The length of hospital stay ranged from 7 to 87 days with a median of 10 days. Non-fatal complications occurred in three patients (30%). One patient required a pacemaker for third-degree heart block, one required a tracheostomy for respiratory failure and hemodialysis because of renal failure. The third patient developed a sternal wound infection.

During this same time period we have identified two additional patients who had documented cases of mechanically induced hemolytic anaemia from residual MR who did not require reoperation because of hemolytic anaemia. Both had persistent mild hemolysis and did not require red blood cell transfusion postoperatively, yet both eventually came to reoperation at 4 and 5 years after initial mitral valve repair because their residual MR progressed to severe. Reoperation cured the mild hemolysis in both patients.

4. Follow-up

Follow-up was 100% complete and ranged from 2 months to 8 years with a median of 2.5 years. At the time of last assessment, all patients except one denied functional impairment.

Echocardiographic follow-up was complete in all patients. All of the seven patients with prosthetic valves have none to trivial MR at last examination. In the three patients who underwent re-repair, echocardiogram demonstrated none to trivial MR at 5 and 8 years post op in two patients and mild MR at 2 years in one. Two of the three patients who underwent re-repair are currently alive. One patient died 5 years post re-repair due to cryptogenic hepatic failure.

There were no late complications. Late deaths have occurred in three patients. One patient is mentioned above. The second died 1 year after reoperation from sudden death. He did not undergo postmortem examination. The third patient died four months after reoperation from renal failure.

5. Discussion

Hemolytic anaemia is an uncommon but well-recognized complication of mitral valve replacement where small periprosthetic leaks create a high velocity of blood flow adjacent to the sewing ring of a prosthesis. As seen in this study, a different pathophysiologic mechanism is responsible for hemolysis after mitral valve repair. In our patients, relatively small leaks were directed at prosthetic annuloplasty rings, so the pathophysiologic substrate includes an eccentric direction of the high velocity jet as well as a prosthesis.

An important finding in our review was the short median interval between initial valve repair and reoperation for hemolysis. It is reasonable to assume that many patients had hemolysis very early after repair, and it is possible that intraoperative transesophageal echocardiography might identify patients at risk for this complication. Thus, surgeons should be aware of directional residual regurgitant jets as well as volume of valve leakage.

Lack of endothelialization of the prosthesis may contribute to development of hemolytic anaemia after mitral valve repair, but it is difficult to know whether it is primary or secondary. Lack of endothelialization was a uniform finding in our patients, and it suggests that the high velocity jet of blood discourages fibrous incorporation of the Dacron or felt prosthesis. We speculate that small eccentric leaks that develop late after mitral valve repair do not lead to hemolysis because the surface of the annuloplasty rings and felt-buttressed sutures are covered by neo-intima.

Although hemolytic anaemia occurs infrequently after mitral valve repair, its importance has been under emphasized. Six patients with hemolysis in this series had initial valvuloplasty at our Clinic, and during the same time interval 1095 patients had valve repair for mitral regurgitation (incidence, 0.55%). However, in a previous review from our institution of 49 patients having reoperation after mitral valve repair, hemolysis was the second most common indication for reoperation (14%), and this exceeded the incidence of reoperation due to left ventricular outflow obstruction, infection, or valve stenosis. In that report, 16 of the 49 (33%) patients had an eccentric jet detected by preoperative echocardiography, and only six of these patients had hemolytic anaemia. Five of these six patients were noted to have at least mild MR at hospital dismissal from initial mitral valve repair. Therefore, it appears that residual MR immediately following valve repair...
may prevent complete endothelialization of the prostheteic ring and may be another contributing factor to hemolytic anaemia.

Hemolytic anaemia should be considered in any patient who, after mitral valve repair, has functional impairment out of proportion to the severity of residual MR. Hematological evaluation should be performed testing for evidence of hemolysis and anaemia. Trans-esophageal echocardiogram should be performed to detect an eccentric regurgitant jet of blood that transthoracic echocardiography might miss. If the anaemia and or hemolysis is severe enough to require repeat transfusion or continued symptoms despite treatment, reoperation should be performed and the option of re-repair kept open.

The present series includes only patients with mechanical hemolysis who had an operation, and this surely underestimates the overall incidence of hemolysis after mitral valve repair. Low levels of hemolysis that do not lead to severe anaemia might not be detected during routine follow-up, and it is possible that hemolytic anaemia may improve with time if the direction of the regurgitant jet changes and/or the prosthetic ring or felt pledget becomes endothelialized. Thus, when mechanical hemolysis is first discovered in a patient with minimal functional impairment an initial trial of medical therapy seems prudent with afterload reducing agents to minimize mitral regurgitation, and iron, folate, and vitamin B12 supplementation to correct anaemia. However, when medical treatment is unsuccessful, reoperation should not be delayed.

The indications for reoperation because of hemolytic anaemia after mitral valve repair are severity of hemolysis based on the inability to adequately treat the anaemia or symptoms of fatigue, continued requirement for red blood cell transfusions, or progression of residual mitral regurgitation to severe. In patients who require repeated transfusion reoperation should be performed immediately after the diagnosis has been established.

The mechanism of hemolysis makes its resolution unlikely, since residual mitral regurgitation after mitral valve repair either remains constant or increases with time but rarely, if ever, decreases. In 80% of our patients, the initial repair was intact at reoperation, and mitral regurgitation was not severe. Interestingly, in several of the case reports in the literature [6,7,9,12] and in nine of our ten patients an annuloplasty ring was used and was the nidus of hemolysis, presumably providing the anvil for destruction. Other causes of hemolysis described include loose ends of chordae tendineae [5] and torn or loose sutures [5,8].

Re-repair can be performed in selected patients. In this series, three of the ten patients (30%) underwent re-repair as compared to six out of the 42 in our previous report (14%). (This excludes two of the seven patients in that previous report with hemolytic anaemia who underwent re-repair). The main indication for reoperation in that report was recurrent severe mitral regurgitation. The residual mitral regurgitation in patients with hemolytic anaemia is often only mild to moderate, the anatomy of the valve may be favorable for repair. Most previous case reports, however, describe mitral valve replacements at reoperation. Some valves that are replaced are probably re-repairable but because the patient is undergoing reoperation weeks or months after his first repair a prosthetic valve is often chosen because of its more predictable outcome.

Acknowledgements

We would like to thank Dr. James J. Morris for contributing patients to this paper.

References

Appendix A. Conference discussions

Dr A. Carpenter (Paris, France): Everyone involved in valve repair, one day had to face the problem of hemolytic anaemia, which is quite different than the hemolytic anaemia we see in reconstructive surgery of congenital malformations. Usually they tend to disappear, whereas in this particular group after valve repair they do not tend to disappear. I have a lot of questions, but I would like to ask the audience to ask the questions that I am ready to ask. Who would like to ask questions?

Dr A. Alsanei (Riyadh, Saudia Arabia): I enjoyed your presentation very much. We have the same problem back home. Have you looked at the heart rate, or did you try to bring the heart rate down with Inderal because occasionally you can get away with it with some patients, especially the ones with one to two-plus MR. If you put them on Inderal you break the vicious circle, hemolysis, anaemia, and tachycardia and so on. So if you bring the heart rate down, we have found that sometimes you buy some time and you get away with it especially if the mitral regurgitation jet hitting the ring. If you reduce the heart rate, this will reduce the jet of MR and will give chance to the ring to endothelize.

Dr R.J. Cerfolio: Ten patients and the two others that I mentioned parenthetically. We have attempted afterload reduction with beta blockers in three patients. They have also received Vitamin B-12 and folate. We have observed no resolution of the hemolytic process in any of these patients.

Dr A. Carpentier: I would be strongly opposed to this treatment because it will give only a temporary solution. Obviously, there are three conditions, there is a high-velocity jet, eccentric, in contact with rough surface. He did not mention the high velocity. And, of course, you can reduce the velocity of the jet by, reducing cardiac contraction, but this is not the way to solve the problem. The only way is to reoperate these patients.

Dr O. Alfieri (Brescia, Italy): Do you have any occasion of spontaneous subsiding of the hemolytic anemia?

Dr R.J. Cerfolio: No.

Dr O. Alfieri: So you do not advise to wait at all? That is the diagnosis and that is the conclusion of it.

Dr R.J. Cerfolio: There may be a subset of patients who have mild hemolysis, and we are aware of two such patients. Their mild hemolysis has continued for 4 and 5 years after initial mitral valve repair, respectively, but they have not required any red blood cell transfusion and are asymptomatic. In those patients who have hemolytic anaemia severe enough to lead to symptoms of fatigue or those patients that require transfusion, reoperation has uniformly been required.

Dr A. Carpentier: You mentioned that you had in all of the cases eccentric jet, in contact with a rough surface, and I just added high-velocity jet, which is important. If you have a low cardiac output, you may not have this hemolytic anaemia. This is why in some patients it appears after some time. However, I was a little bit disappointed not to hear from you the different lesions you have found, whether ring detachment, whether a hole at the level of the annulus, or whether a leak at the commissure, because these are usually the three conditions. Could you identify in your series which ones?

Dr R.J. Cerfolio: We had one slide on reoperative findings that showed that the repair was intact in eight patients and dehisced in two. Because of time constraints, we could not elaborate further. Two patients had dehiscence of the annuloplasty ring. In the other eight patients, the recurrence of the residual mitral regurgitation was due to several different factors, usually redundancy of the leaflet that was not initially repaired. The numbers are too low to be able to identify any specific type of residual lesion that was more likely to lead to mitral regurgitation causing hemolytic anaemia.

Dr A. Carpentier: Yes. Three conditions are necessary, eccentric, in contact with surface, and high-velocity jet. The reason I mentioned the problem of the lesions is because when you identify the lesions they are usually easily corrected. So I strongly recommend you to correct the lesion once it is identified, because, in my experience, I do not remember a single case in which I was not able to re-repair by just a stitch, a very simple stitch or two or three stitches at the location of the leak itself. And it can be so easily identified that it is a waste of time and effort to replace. So I strongly recommend you to re-repair these patients, although, as he said very well, they look very sick, and for a very limited mitral valve insufficiency, as he said very well.

Dr R.J. Cerfolio: Patients who got re-repaired, and I think some of the other seven patients could have been re-repaired well based on the description of the valve. However, I think the reason they were replaced was because the patient was coming back to re-reoperation so early after their first attempted repair and wanted a procedure with a more predictable outcome.

Dr A. Carpentier: Particularly important are the leaks at the commissure, and just by placing a so-called magic stitch at the commissure, you solve the problem, because one cause of the hemolytic anaemia is quite often in rheumatic valvular disease a commissurotomy which extends too far away and too close to the prosthetic ring.

Dr G. Merin (Jerusalem, Israel): I have a technical point. You mentioned that all of your cases have been operated very soon after the first intervention, and I would like to mention that our experience has also been that if you have to do these repairs, you should rather do them early than late. But in cases where you have combined with revascularization, we found it extremely useful to do it through a right thoracotomy, not using any cross-clamp or any cardioplegia, but mildly hypothermic bypass to avoid all of the technical difficulty and bleeding of early intervention following a previous one, especially when it is combined with a coronary bypass.

Dr R.J. Cerfolio: Well, I think that the surgical approach to a right thoracotomy should be kept as an option and used in selected patients. All ten patients in this series were approached via a median sternotomy.

Dr A. Carpentier: This is usually the recommended approach, but it permits me to again emphasize the need for an early reoperation, because this hemolytic anaemia, it is not going to disappear anyway. So there is no need to wait. The earlier the reoperation, the easier the approach, and then the median sternotomy is certainly the approach of choice. After one or two months, then with all the additions, there are two options.