Clin. Cardiol. 21, 387–392 (1998)

Evaluation of Hemolysis in Patients with Prosthetic Heart Valves

RAJIV MARAJ, M.D., LARRY E. JACOBS, M.D., ALFRED IOLI, RDMS, MORRIS N. KOTLER, M.D.

Echocardiography Laboratory, Division of Cardiology, Albert Einstein Medical Center, Temple University School of Medicine, Philadelphia, Pennsylvania, USA

Summary: The primary mechanism and most common cause of hemolytic disease in patients with prosthetic heart valves are mechanical trauma to red blood cells and paraprosthetic valvular regurgitation, respectively. Presenting features in patients with this condition include anemia, congestive heart failure, fatigue, jaundice, dark urine, and a regurgitant murmur. Various laboratory studies can be utilized to diagnose hemolytic anemia and to assess the severity of hemolysis. Transthoracic echocardiography, transesophageal echocardiography, and Doppler studies including color Doppler are useful imaging methods to assess valve function. Treatment is usually medical (oral iron); however, in patients with paravalvular regurgitation, surgery is often required to correct the anemia.

Key words: hemolysis, prosthetic valves, paraprosthetic valvular regurgitation, bioprosthetic valves, echocardiography, Doppler studies

Introduction

Valve-related complications lead to reoperation or cause death in a significant number of patients with prosthetic valves within 10 years of valve insertion.[1] One of the major complications of prosthetic valves is intravascular hemolysis. In 1975, Kloster reported the incidence of hemolysis in patients with prosthetic valves to be between 5 and 15%.[2] Dhasmana *et al.* reported an incidence of 7% in 1983.[3] A report in 1993 concluded that <4% of patients with hemolysis secondary to a prosthetic heart valve were anemic.[4] The reason for this downward trend may be due to improved surgical techniques and technology. This report reviews the pathophysiology, diagnostic studies, and management of this complication.

Pathophysiology of Hemolysis

Hemolytic anemia can be the result of congenital or acquired disorders (Table I). Mechanical trauma to red blood cells is the primary cause of hemolytic disease in patients with prosthetic heart valves.[2] One of the main mechanisms involved is thought to be turbulence of flow through the prosthesis which results in excessive shearing forces on the red blood cells.[2,5] Thus, any factor which causes an increase in turbulence is associated with a greater predisposition for hemolysis (Table II). In addition to turbulence, other mechanisms that may also contribute to hemolysis are shear stress, pressure fluctuations, intrinsic abnormalities of the erythrocyte membrane, interaction with foreign surfaces, and unfavorable flow characteristics of the valve.[2,6] An example illustrating one of these mechanisms is the finding that in patients with high transvalvular pressure gradients and in those with small valve prostheses (which are likely to result in higher pressure gradients) a greater incidence of hemolytic disease is present.[2] Furthermore, there are instances in which hemolysis decreases as a result of endothelialization of foreign surfaces of prosthetic valves, which decreases the interaction of the erythrocytes with these surfaces.[7] In patients with mechanical heart valves, the mechanical crushing effect of the valve also contributes to red cell trauma.[6]

Certain contributory factors may promote the hemolysis or aggravate the anemia. Iron-poor red cells resulting from iron deficiency exhibit increased fragility and are more prone to mechanical trauma. Folate deficiency resulting from hemolysis in turn leads to the inability of the bone marrow to produce red cells to compensate for those that have been destroyed. Chronic infection, for example in a patient with endocarditis, may inhibit erythropoiesis, thereby aggravating the anemia.[8] Hemorrhage, which may be related to anticoagulant therapy, may increase the need for erythrocyte production even further. The anemia per se may also accelerate the hemolysis since it would lead to both decreased blood viscosity and increased cardiac output, and both these factors increase turbulence of flow through the valve prosthesis.[2] Increased strenuous physical activity, has also been associated with increased hemolysis due to increased blood flow.[2]

Supported in part by Women's League for Medical Research, Albert Einstein Medical Center.

Address for reprints:

Larry E. Jacobs, M.D.
Director of Echocardiography
Albert Einstein Medical Center
363 Klein Professional Building
5401 Old York Road
Philadelphia, PA 19141, USA

Received: February 5, 1998
Accepted with revision: April 6, 1998

TABLE I Classification of the causes of hemolytic anemia

Congenital hemolytic disorders
Membrane defects (e.g., hereditary spherocytosis)
Abnormalities of red blood cell interior (enzyme defects, hemoglobinopathies, thalassemias)
Acquired hemolytic disorders
Sequestrational hemolysis (hypersplenism)
Immune hemolytic disorders
Alloimmune
Autoimmune
Drug induced (e.g., procainamide)
Paroxysmal nocturnal hemoglobinuria
Mechanical trauma (e.g., prosthetic heart valve hemolysis)
Direct toxic effect (e.g., malaria, clostridial infection, etc.)

TABLE II Factors involved in hemolysis

- Turbulence of blood flow
- Shear stress
- Pressure fluctuations
- Intrinsic abnormalities of erythrocyte membrane
- Interaction with prosthetic material
- Flow characteristics of valve

Paravalvular Regurgitation

The most common cause of significant hemolytic anemia in a patient with a prosthetic heart valve is paraprosthetic valve regurgitation.[2] This is defined as an abnormal retrograde flow of blood around the circumference of a prosthetic valve between the sewing ring and the annulus of the native valve.[9] The reported incidence of paravalvular regurgitation varies from 0.3 to 5% in some studies,[9] but has been reported to be as high as 7 and 13% in other studies.[3,10]

Various factors have been implicated in the causation of paravalvular regurgitation (Figs. 1, 2). Jindani *et al.*[9] reviewed possible contributory factors, and in their study infection was found to be an important factor occurring in 67% of patients with aortic valve replacement and 79% of patients with mitral valve replacement. Furthermore, the data suggest that patients with Marfan's syndrome are more susceptible to developing paravalvular regurgitation. This may be due to the fragmentation and disorganization of elastic fibers which are a hallmark of Marfan's syndrome.[11] In the same report, calcification was found in 47% of patients with aortic valve replacement and probably contributed to the development of both infection and paravalvular regurgitation.

From a surgical point of view, a study by Dhasmana *et al.*[3] concluded that paravalvular regurgitation in the absence of infection was strongly associated with technical factors, especially the use of small monofilament sutures (2–0) in a continuous suture technique and also with the presence of annular calcification. The regurgitation may result from the sutures having a cutting effect on the tissues and sewing rings and their tendency to break with the passage of time with resultant valve dehiscence. Also, sewing into calcified annular substance is difficult, and support for the suture is less stable compared with noncalcific tissue.[10]

Bioprosthetic Valves

Tissue failure due to structural changes is a major problem with regard to bioprosthetic valves, since these changes often lead to alterations in the hemodynamic profiles of the valves with resultant increases in turbulence and consequently hemolysis. In contrast to mechanical valves which are very durable,[12] most lasting at least 20 years, 10 to 20% of homograft bioprostheses and 30% of heterograft bioprostheses fail within 10 to 15 years of implantation and require replacement.[13] Youth, diabetes, pregnancy, and renal disease are all associated with increased rates of tissue valve failure. Patients under the age of 40 have a particularly high incidence of premature heterograft failure.[13]

In most patients with bioprosthetic valve failure, one finds regurgitation due to a tear or rupture of one or more of the valve cusps.[13] These cuspal tears most commonly involve the free edges of the cusps and possibly develop as a result of the breakdown of collagen at these sites.[14,15] In a study by Garcia

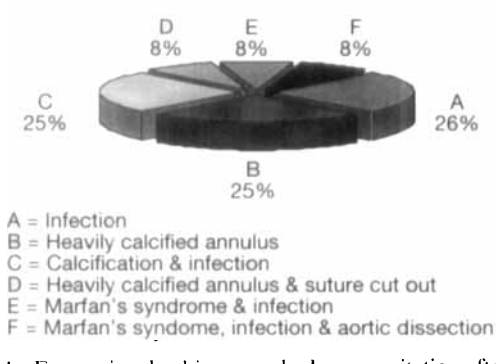

FIG. 1 Factors involved in paravalvular regurgitation after aortic valve replacement. *Source:* Ref. 9.

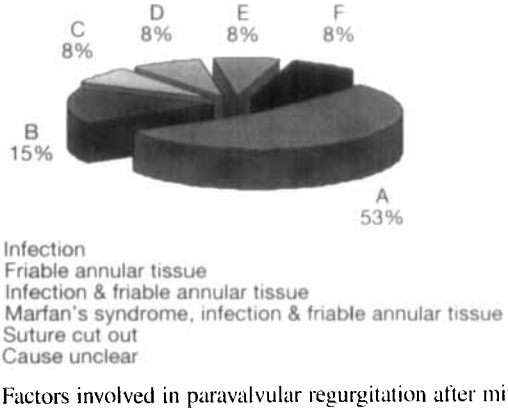

FIG. 2 Factors involved in paravalvular regurgitation after mitral valve replacement. *Source:* Ref. 9.

et al.,[16] certain conditions of regurgitant flow were associated with high shear rates and hence higher rates of hemolysis. Contributing factors included rapid acceleration, collision with a solid wall, and fragmentation (defined as a regurgitant jet that is divided by a solid structure in its path).

Bioprosthetic tissues that have been implanted in the human heart undergo a complex, time-dependent process of structural change that finally results in dysfunction of the valve.[17] Increased cuspal calcification is the main reason for the failure of porcine and other bioprosthetic tissues.[17, 18] Various methods have been investigated to reduce this calcification, some showing positive short-term results.[19]

An Approach to a Patient with a Prosthetic Valve Presenting with Hemolytic Anemia

Clinical Clues for the Detection of Hemolysis

In a patient presenting with hemolytic anemia, one factor to be considered is the duration of time that has elapsed following valve replacement. This is particularly important in patients with bioprosthetic valves since porcine valve failure is rare (1%) in the first 5 years post replacement, increases to 20–30% within 10 years, and approximates 50% in 15 years.[20]

Patients with prosthetic valve failure and laboratory evidence of hemolysis present most often with one or more of the following features: congestive heart failure, fatigue, dark urine, and shortness of breath.[7, 21–24] Enzenauer *et al.*[23] conducted a chart and literature review of 15 patients who had porcine xenograft valve failures with hemolysis. The relative frequencies of the presenting features in this study are shown in Figure 3. These findings emphasize that one should suspect hemolysis in a patient with a prosthetic valve presenting with anemia, congestive heart failure, jaundice, dark urine, and a cardiac murmur.

Valve dysfunction may be suggested by a change in the intensity or quality of a previously audible sound, the appearance of a new murmur, or a change in the characteristics of a preexisting murmur.[3] The examining physician should be particularly alert to the development of any regurgitant murmur which may suggest a paraprosthetic leak.[25]

Laboratory Studies in a Patient with Suspected Hemolytic Anemia

One of the ways to approach the problem of hemolysis in a patient with a prosthetic valve is to direct studies toward one of four goals:[23] (1) Demonstration of the presence of anemia; (2) determination of the presence and severity of hemolysis; (3) evaluation of deficiency states secondary to iron loss or accelerated hematopoiesis; and (4) consideration of factors contributing to increased hemolysis, particularly dysfunction of the prosthesis.

Specific laboratory studies (Table III) that are helpful are a hematocrit or hemoglobin determination, serum lactate dehydrogenase (LDH) levels, reticulocyte count, peripheral blood smear examination for schistocytes (Fig. 4), serum haptoglobin level, and serum iron and folic acid levels.[2, 13, 23, 26] The severity of the hemolysis can be assessed by analyzing the above laboratory studies[2] (Table IV).

A hematocrit or hemoglobin determination would establish the presence or absence of anemia. However, the absence of anemia does not exclude the presence of significant hemolysis since compensation for increased red cell destruction may occur for a considerable period of time before the patient develops overt anemia.[2]

TABLE III Laboratory studies used in the diagnosis of hemolytic anemia

- Hemoglobin/ hematocrit
- Serum lactate dehydrogenase level
- Reticulocyte count
- Serum haptoglobin level
- Serum iron & folic acid levels
- Blood smear examination for schistocytes

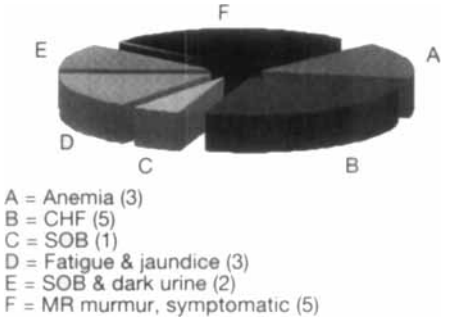

FIG. 3 Presenting features in patients with hemolytic anemia secondary to prosthetic valves (number of patients in parenthesis). CHF = congestive heart failure, SOB = shortness of breath, MR = mitral regurgitation. Source: Ref. 23.

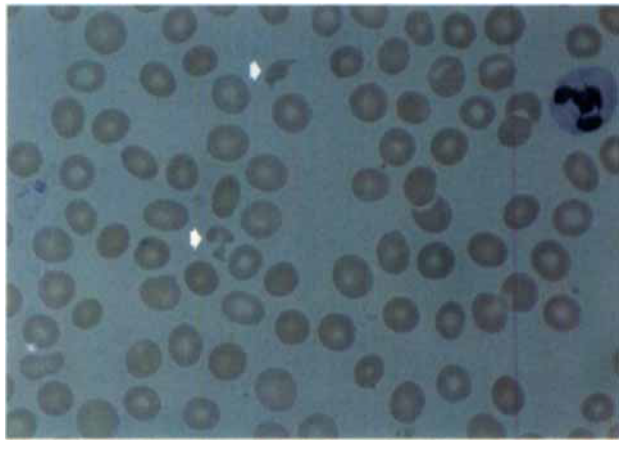

FIG. 4 Peripheral smear from a patient with hemolysis secondary to a prosthetic valve leak showing schistocytes (arrows).

TABLE IV Assessment of severity of hemolysis

	Hemolysis[a]		
	Mild	Moderate	Severe
Lactate dehydrogenase	<500 units	>500 units	>>500 units
Haptoglobin	Decreased	Absent	Absent
Reticulocytosis	<5%	>5%	>>5%
Schistocytosis	<1%	>1%	>>1%

[a] > = greater than, >> = much greater than, < = less than, << = much less than. Reprinted from Ref. No. 2 with permission.

In patients with hemolytic anemia, studies have demonstrated an excellent relationship between serum LDH levels and red cell survival.[2, 23, 27, 28] Levels of LDH are often elevated in patients with intravascular hemolysis and change rapidly with the degree of hemolysis. Serum LDH levels can therefore be utilized as simple and sensitive screening tests for intravascular hemolysis.[2]

The reticulocyte count is increased in patients with hemolytic disease. This is a nonspecific but fairly accurate indicator of the severity of the problem. Also, studies have shown that the number of schistocytes in the peripheral blood of patients with artificial heart valves is directly related to the severity of hemolysis.[2, 29]

Free hemoglobin resulting from intravascular hemolysis binds rapidly to plasma haptoglobin, and the resultant complex is cleared by the reticuloendothelial system. This results in decreased haptoglobin levels. Thus, serum haptoglobin levels are a good index of intravascular hemolysis and are useful as a screening test.[2]

In addition to the above investigations, serum iron and folic acid levels should be determined. These levels may be decreased because of increased erythropoiesis.[2]

Assessment of Prosthetic Valve Dysfunction

Imaging methods to assess valve function: Cinefluoroscopy is a simple, rapid and inexpensive technique for evaluating prosthetic valve function and is particularly useful for assessing leaflet motion and gross motion of the sewing ring. In paravalvular regurgitation, cineradiographic studies show abnormal rocking motion of the prosthesis and provide useful confirmation of the presence but not the amount of regurgitation.[10] Two-dimensional transthoracic echocardiography is especially useful in assessing the function of bioprosthetic valves.[13] In contrast, mechanical valves are often difficult to visualize because of intense echo reverberations from the mechanical leaflets.[13]

Doppler echocardiography has been found to be extremely useful for evaluating patients with suspected prosthetic valve dysfunction. Doppler echo measures the direction and velocity of blood flow and is particularly useful for detecting regurgitation through or around prosthetic valves.[30] Pulsed and continuous-wave Doppler are possibly more sensitive than color Doppler in detecting the presence of prosthetic valvular regurgitation. In contrast, color Doppler is superior to pulsed and continuous-wave Doppler in the semi-quantitative assessment of the severity of regurgitation and has practically supplanted conventional Doppler.

With color Doppler, it is possible to assess the severity of mitral prosthetic valve regurgitation by expressing the regurgitant jet area as a ratio of the dependent chamber area. This corresponds well with standard angiographic estimation of severity. Maximum jet area/left atrial area percent ratios of ≤20%, 20–40%, and >40% denote mild, moderate, and severe regurgitation, respectively. Prosthetic aortic regurgitation can also be assessed. The proximal jet width, measured at the point of its origin from the aortic valve and expressed as a percent ratio of the left ventricular outflow tract diameter measured at the same point, grades regurgitation as mild (1–24%), moderate (25–46%), moderately severe (47–64%) and severe (65% or more).[31]

Transesophageal echocardiography (TEE) provides an unobstructed view of the atria and the mitral valve. Since there is no obstruction by the lungs, sternum, or ribs, stable and distinct images can be obtained which are of a higher resolution than those obtained by transthoracic echo.[13] Thus, in a patient with prosthetic mitral valve dysfunction, TEE is very useful and should be performed.[3] Furthermore, in a study by Chen *et al.*,[32] TEE was found to be more accurate than transthoracic echocardiography and auscultation in the detection of paravalvular leaks. Even mild paravalvular leakage and physiologic regurgitant jets can be detected. In patients with paravalvular regurgitation, a TEE would demonstrate a turbulent eccentric jet originating outside the prosthetic sewing ring or may show a paravalvular gap between the annulus and sewing ring[33] (Figs. 5–8). This jet would have a high flow velocity. In

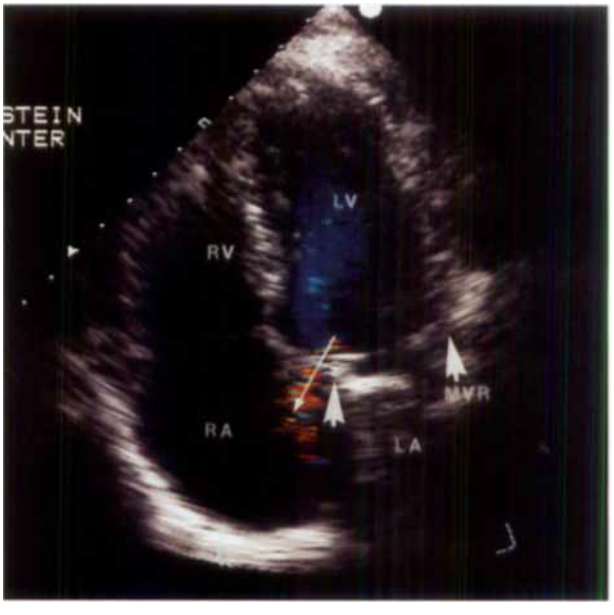

FIG. 5 Transthoracic echocardiographic view of mitral valve prosthesis. Color-flow Doppler demonstrates mild paravalvular regurgitation. Small arrows show regurgitant jet. Arrowheads outline the area of the suture ring. LA = left atrium, LV = left ventricle, RA = right atrium, RV = right ventricle.

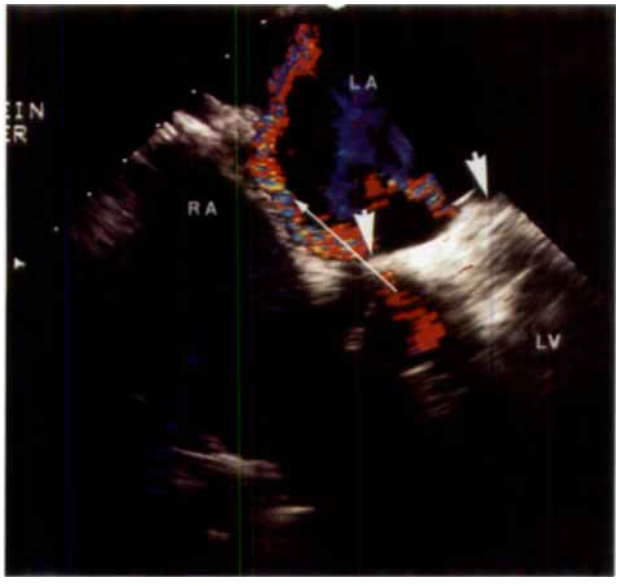

FIG. 6 Transesophageal echocardiographic view of mitral valve prosthesis. Color-flow Doppler demonstrates moderate paravalvular regurgitation. Small arrows show regurgitant jet. Arrowheads outline the area of the suture ring. Abbreviations as in Figure 5.

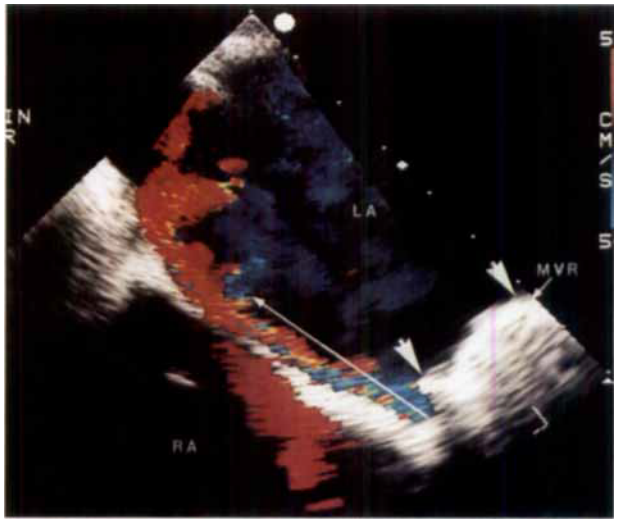

FIG. 7 Transesophageal echocardiographic view of St. Jude mitral valve prosthesis. Color-flow Doppler demonstrates moderate par-avalvular regurgitation. Small arrows show regurgitant jet. Arrowheads outline the area of the suture ring. Abbreviations as in Figure 5.

contrast, physiologic jets are characterized by centralized retrograde flow with two or four parallel regurgitant jets of low flow velocity.[32] However, TEE has been reported to be limited in its ability to detect aortic prosthetic valve obstruction or regurgitation, especially when a mitral prosthesis is present.[13]

Magnetic resonance imaging is another modality which can be used to assess valve dysfunction but has not been found to be useful for assessing prosthetic valve structure. Also, since this imaging modality is more expensive and time consuming than echocardiography, it has a limited role to play.[13]

Cardiac catheterization is useful for measuring transvalvular pressure gradients from which a calculation of the effective orifice area can be made. It is also useful for visualizing and quantifying valvular or paravalvular regurgitation. The disadvantage of using cardiac catheterization is that the catheter may become entrapped in a mechanical valve or may disturb the hemodynamics of a valve. Consequently, it is indicated only when the information obtained by noninvasive methods is inconclusive.[13]

Treatment

Medical treatment is effective in the majority of patients with hemolytic disease caused by prosthetic valves. Oral iron therapy is indicated in those with evidence of significant iron loss even in the absence of anemia.[2]

Blood transfusion may be necessary to correct refractory anemia, after which oral iron therapy is usually sufficient to maintain a satisfactory hematocrit level. It is important to bear in mind that whenever anemia is refractory to vigorous iron therapy, the possibility of folate deficiency should be considered and, if present, should be treated.[13]

There is widespread agreement among echocardiographers and surgeons that severe paravalvular regurgitation should be corrected immediately.[33] The management of patients with mild and moderate paravalvular regurgitation is controversial. Movsowitz *et al.*[33] conducted a clinical and echocardiographic follow-up of eight patients with mild and moderate mitral paravalvular regurgitation detected by TEE at the time of valve replacement surgery. It was found that the patients with moderate paravalvular regurgitation deteriorated clinically and echocardiographically over time. A third of the patients

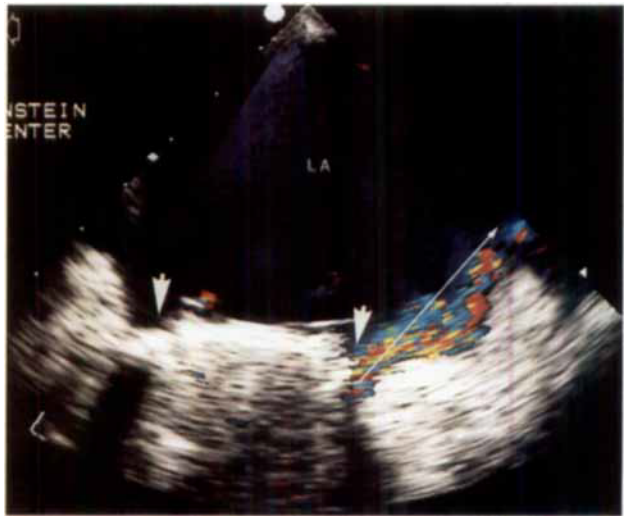

FIG. 8 Transesophageal echocardiographic view of St. Jude mitral valve prosthesis. Color-flow Doppler demonstrates mild paravalvular regurgitation. Small arrows show regurgitant jet. Arrowheads outline the area of the suture ring. Abbreviations as in Figure 5.

with mild paravalvular regurgitation deteriorated over time. This study therefore supported the view that moderate paravalvular regurgitation should be corrected at the time of valve replacement surgery if this can be performed without high operative risk. Because some cases will progress, mild paravalvular regurgitation should probably also be repaired if this can be performed at low risk.

In those with a contraindication to repeat surgery, beta blockers may reduce the magnitude of hemolysis. Although the exact mechanism is unclear, it is thought that beta blockers reduce the shearing stress between the erythrocytes and the foreign material by slowing the velocity of the circulation, thereby reducing the hemolysis.[34]

Conclusion

Hemolytic anemia remains one of the major complications in patients with prosthetic valves. Ongoing research is important for the further improvement of existing valve designs and to aid in the development of new valves that will lead to a lower incidence of this complication

References

1. Schoen FJ: The first step to understanding valve failure: An overview of pathology. *Eur J Cardiothorac Surg* 1992;6(Pt 1):50–53
2. Kloster FE: Diagnosis and management of complications of prosthetic heart valves. *Am J Cardiol* 1975;35:872–885
3. Dhasmana JP, Blackstone EH, Kirklin JW, Kouchoukos NT: Factors associated with periprosthetic leakage following primary mitral valve replacement: With special consideration of the suture technique. *Ann Thorac Surg* 1983;35:170–178
4. Amidon TM, Chou TM, Rankin JS, Ports TA: Mitral and aortic paravalvular leaks with hemolytic anemia. *Am Heart J* 1993; 125:266–268
5. Rodgers BM, Sabiston DC Jr: Hemolytic anemia following prosthetic valve replacement. *Circulation* 1969;39(Pt 1):155–161
6. Rao KMS, Learoyd PA, Rao RS, Rajah SM, Watson DA: Chronic hemolysis after Lillehei-Kaster valve replacement. *Thorax* 1980; 35:290–293
7. Myers TJ, Hild DH, Rinaldi MJ: Hemolytic anemia associated with heterograft replacement of the mitral valve. *J Thorac Cardiovasc Surg* 1978;76:214–215
8. Walsh JR, Starr A, Ritzmann LW: Intravascular hemolysis in patients with prosthetic valves and valvular heart disease. *Circulation* 1969;39(Pt 1):135–140
9. Jindani A, Neville EM, Venn G, Williams BT: Paraprosthetic leak: A complication of cardiac valve replacement. *J Cardiovasc Surg* 1991;32:503–508
10. Kastor JA, Buckley MJ, Sanders CA, Austen WG: Paravalvular leaks and hemolytic anemia following insertion of Starr-Edwards aortic and mitral valves. *J Thorac Cardiovasc Surg* 1968;56: 279–288
11. Pyeritz RE: Genetics and cardiovascular disease. In *Heart Disease: A Textbook of Cardiovascular Medicine* (Ed. Braunwald E), p. 1643. Philadelphia: W.B. Saunders Company, 1992
12. Grunkemeier GL, Rahimtoola SH: Artificial heart valves. *Ann Rev Med* 1990;41:251–263
13. Vongpatanasin W, Hillis LD, Lange RA: Prosthetic heart valves. *N Engl J Med* 1996;335:407–416
14. Ishihara T, Ferrans VJ, Boyce SW, Jones M, Roberts WC: Structure and classification of cuspal tears and perforations in porcine bioprosthetic cardiac valves implanted in patients. *Am J Cardiol* 1981;48:665–678
15. Schoen FJ, Levy RJ: Pathology of substitute heart valves: New concepts and developments. *J Cardiol Surg* 1994;9(Pt 1):222–227
16. Garcia MJ, Vandervoort P, Stewart WJ, Lytle BW, Cosgrove DM III, Thomas JD, Griffin BP: Mechanisms of hemolysis with mitral prosthetic regurgitation. *J Am Coll Cardiol* 1996;27:399–406
17. Turina J, Hess OM, Turina M, Krayenbuehl HP: Cardiac bioprostheses in the 1990s. *Circulation* 1993;88:775–781
18. Valente M, Minarini M, Maizza AF, Bortolotti U, Thiene G: Heart valve bioprosthesis durability: A challenge to the new generation of porcine valves. *Eur J Cardiothorac Surg* 1992;6(Pt 1):82–90
19. Arbustini E, Jones M, Moses RD, Eidbo EE, Carroll RJ, Ferrans VJ: Modification by the Hancock T6 process of calcification of bioprosthetic cardiac valves implanted in sheep. *Am J Cardiol* 1984; 53:1388–1396
20. Hammermeister KE, Sethi GK, Henderson WG, Oprian C, Kim T, Rahimtoola A: Comparison of outcomes in men 11 years after heart-valve replacement with a mechanical valve or bioprosthesis. *N Engl J Med* 1993;328:1289–1296
21. Magilligan DJ Jr, Fisher E, Alam M: Hemolytic anemia with porcine xenograft aortic and mitral valves. *J Thorac Cardiovasc Surg* 1980;79:628–631
22. Schaer DH, Cheng TO, Aaron BL: Hemolytic anemia and acute mitral regurgitation caused by a torn cusp of a porcine mitral prosthetic valve 7 years after its implantation. *Am Heart J* 1987;113:404–406
23. Enzenauer RJ, Berenberg JL, Cassell PF Jr: Microangiopathic hemolytic anemia as the initial manifestation of porcine valve failure. *South Med J* 1990;83:912–917
24. Brown MR, Hasaniya NWMA, Dang CR: Hemolytic anemia secondary to a porcine mitral prosthetic valve leaflet dissection. *Ann Thorac Surg* 1995;59:1573–1574
25. DeSilvey DL: Long-term management of prosthetic valves. *Heart Dis Stroke* 1993;2:493–496
26. Skoularigis J, Essop MR, Skudicky D, Middlemost SJ, Sareli P: Frequency and severity of intravascular hemolysis after left-sided cardiac valve replacement with Medtronic Hall and St. Jude medical prostheses, and influence of prosthetic type, position, size and number. *Am J Cardiol* 1993;71:587–591
27. Thompson ME, Lewis JH, Porkolab FL, Hasiba U, Spero JA, Wilson J, Snyder M: Indexes of intravascular hemolysis, quantification of coagulation factors, and platelet survival in patients with porcine heterograft valves. *Am J Cardiol* 1983;51:489–491
28. Febres-Roman PR, Bourg WC, Crone RA, Davis RC Jr, Williams TH: Chronic intravascular hemolysis after aortic valve replacement with Ionescu-Shiley xenograft: Comparative study with Bjork-Shiley prosthesis. *Am J Cardiol* 1980;46:735–738
29. Eyster E, Rothchild J, Mychajliw O: Chronic intravascular hemolysis after aortic valve replacement. *Circulation* 1971;44:657–665
30. Kotler M, Jacobs LE, Movsowitz HD, Ioli AW: Noninvasive evaluation of normal and abnormal prosthetic valve function. In *Textbook of Echocardiography and Doppler in Adults and Children* (Eds. Sutton MGSJ, Oldershaw PJ, Kotler MN), p. 277–322. Cambridge: Blackwell Science, 1996
31. Nanda NC, Cooper JW, Mahan EF III, Fan P: Echocardiographic assessment of prosthetic valves. *Circulation* 1991;84(Pt 1): 228–239
32. Chen Y, Kan MCJ, Lin W, Chang M, Hu W, Hwang D, Lee D, Hwang S, Chiang BN: Detection of prosthetic mitral valve leak: A comparative study using transesophageal echocardiography, transthoracic echocardiography, and auscultation. *J Clin Ultrasound* 1990;18:557–561
33. Movsowitz HD, Shah SI, Ioli A, Kotler MN, Jacobs LE: Long-term follow-up of mitral paraprosthetic regurgitation by transesophageal echocardiography. *J Am Soc Echocardiol* 1994;7:488–492
34. Okita Y, Miki S, Kusuhara K, Ueda Y, Tahata T, Yamanaka K: Propranolol for intractable hemolysis after open heart operation. *Ann Thorac Surg* 1991;52:1158–1160