Hemolysis Associated With Prosthetic Heart Valves

A Review

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Abstract: Hemolysis is one of the potentially serious complications of prosthetic heart valves. It is usually associated with either structural deterioration or paravalvular leak. Mild, compensated hemolysis associated with mechanical heart valves is not uncommon even in the current era. Severe hemolysis is rare, however, and usually reflects paravalvular leak. The use of transesophageal echocardiography–guided operative techniques may help prevent or minimize early postoperative paravalvular leakage. There is a gamut of available therapeutic approaches—medical, transcatheter, and surgical—to this complication and therapy should be tailored to the individual patient. Novel pharmacological agents include erythropoietin and pentoxifylline. Several reports described the feasibility of transcatheter closure of paravalvular leak with coils or devices, but their effect on hemolysis is unpredictable. Surgery remains the treatment of choice in severe cases.

Key Words: prosthetic heart valve, hemolysis, paravalvular leak, percutaneous closure

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Hemolysis is one of the potentially serious complications of prosthetic heart valves.[1] It is usually associated with either structural deterioration or paravalvular leak. Its main mechanism is a turbulent flow through the valve or between the sewing ring and the native ring. The first case of valve-related hemolysis was described by Rose et al in 1954, in a prosthetic valve prototype.[2] The reported rate of significant hemolysis has decreased from 5% to 15% in the 1960s and 1970s[3,4] to less than 1% in the 1990s, with the introduction of improved valve models.[5–7] However, a certain degree of mild, compensated, hemolysis is still observed in a large proportion of patients. Subclinical hemolysis was reported in 51.2% of 170 patients with St. Jude Medical valves and 17.8% of 80 patients with Medtronic-Hall valves; none of the patients had anemia.[6] Greater hemolysis was associated with double-valve versus single-valve replacement and with mitral position ($P < 0.01$) and aortic position ($P < 0.01$). In another study, subclinical hemolysis was detected in 26% of 172 patients with bileaflet mechanical valves (53 CarboMedics, 119 Sorin Bicarbon) and 5% of 106 patients with biologic valves (15 St. Jude Medical Toronto SPV, 19 Baxter Perimount, and 72 Medtronic Mosaic) ($P < 0.001$), with no cases of clinically significant hemolysis.[7] Investigations using carbon monoxide levels revealed that the mean erythrocyte lifespan (normal value, 122 ± 23 days) was somewhat short in patients with biologic valves (103 ± 15 days) and even shorter in patients with mechanical valves (98.8 ± 23 days).[8]

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MECHANISMS OF HEMOLYSIS

Older-generation valve models were associated with a high rate of hemolysis. In some cases, this was associated with structural valve deterioration. For example, the disc of the Beall valve was subject to wear and tear[9] and the fully covered Starr-Edwards valve was prone to tears in the cloth cover.[10] Hence, new-onset hemolysis in a patient who was formerly free of hemolysis should raise the suspicion of structural valve deterioration. Structural deterioration is extremely rare in the current valve models. Therefore, the main mechanism for valve-associated hemolysis in current models is paravalvular leak. The occurrence of paravalvular leakage in the early postoperative period can be minimized by the routine intraoperative use of transesophageal echocardiography (TEE) for quality control. Figure 1 shows an intraoperatively detected paravalvular leak that required a second pump run for correction. Late paravalvular leak is usually caused by suture dehiscence, which is more likely to occur in patients with heavy annular calcification[11–14] or localized infection,[15] or with the application of certain surgical techniques.[16–19] It is usually visualized by echocardiography; TEE is mandatory if peri-mitral leak is suspected. The degree of hemolysis is not necessarily proportional to the amount of regurgitation. The irregularity of the leaking site as well as the colliding angle may play important roles: a central jet causes less hemolysis than an eccentric jet that hits the opposite wall.[20] Occasionally, the periprosthetic jet strikes the ridge separating the left pulmonary vein from the left atrial appendage, resulting in a significant hemolysis.[21] Biologic valves are rarely associated with mechanical hemolysis, except in the presence of a paravalvular leak, but structural deterioration may occasionally cause intravascular hemolysis.[22,23]

DIAGNOSIS

The clinical presentation of valve-related hemolysis depends on the degree of anemia and the associated leak, and may vary from an asymptomatic state to pallor, weakness, and signs of congestive heart failure. Brisk hemolysis may be associated with hemoglobinuria. The hallmark of mechanical hemolytic anemia is the appearance of fragmented erythrocytes in the peripheral blood smear. Accompanying findings include reticulocytosis, low haptoglobin levels, elevated lactic dehydrogenase (LDH), indirect hyperbilirubinemia, and urinary excretion of hemosiderin (and occasionally free iron). The anemia is due to the failure of the bone marrow to compensate for the shortened lifespan of the erythrocytes. Chromium-51 labeling for the measurement of erythrocyte life span has been recently replaced by expiratory carbon monoxide concentration.[8]

QUANTIFICATION OF HEMOLYSIS

There is no standard system for quantifying mechanical hemolytic anemia. Elevated levels of LDH, a high degree of red blood cell fragments, high urinary iron concentration, and the need

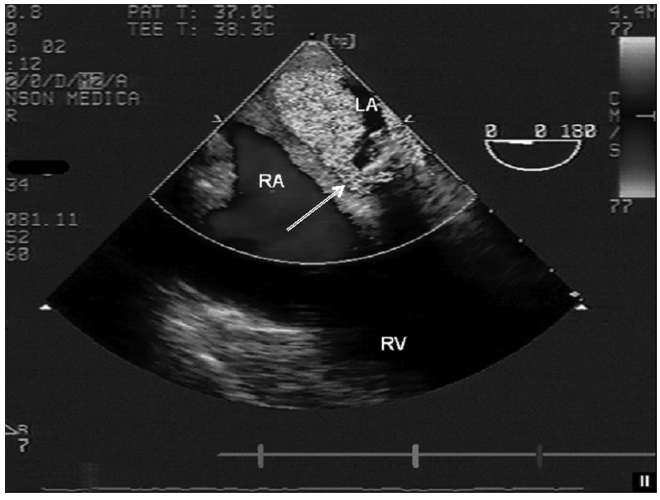

FIGURE 1. Intraoperative TEE showing paraseptal perivalvular leak (arrow) due to a torn knot. The leak was detected during weaning from bypass. LA indicates left atrium; RA, right atrium; RV, right ventricle.

for frequent red blood cell transfusions are markers of greater hemolysis.[24,25]

TREATMENT

Oral Medications

There are a few reports on the effect of β-adrenergic blockers in patients with mechanical hemolysis associated with prosthetic heart valves.[26–28] The suggested mechanism of action is a reduction of the shearing forces acting on the erythrocytes.

Iron supplementation is often required to counteract the urinary iron loss in cases of hemoglobinuria and hemosiderinuria. Clinicians should check for folic acid deficiency, which needs to be corrected by folate supplementation.

Pentoxifylline has recently been found to reduce prosthetic-valve-related hemolysis, probably by improving erythrocyte deformability. Golbasi et al,[29] using a placebo-controlled design, reported a reduction in hemolysis parameters in 60% of 20 patients treated with pentoxifylline 400 mg TID compared with 5% in the placebo arm. Moreover, hemolysis was abolished in 6 of the 9 patients with very high LDH (>1500 U/dL).

Surgery

The recently published European guidelines on the management of valvular heart disease recommend reoperation for paravalvular leak if it is related to endocarditis, if it causes severe symptoms, or if the hemolysis is severe enough to warrant repeated blood transfusions (class I recommendation, level of evidence C).[30] The surgical risk at reoperation is higher than for the first operation and is in the order of 10%.[31–36] Replacing the valve does not necessarily ameliorate hemolysis, especially after several operations on the same valve.[37] Nevertheless, surgery is the gold-standard definitive therapy in this setting.

Percutaneous Closure

During the last 15 years, several reports have described the percutaneous closure of paravalvular leaks with coils or devices that were originally designed for other purposes (such as ventricular septal defect or patent ductus arteriosus). This practice was introduced by Hourihan et al[38] in 1992, who successfully closed 2 periaortic leaks. Some of the technical aspects are detailed below and reflect the results of pioneering groups in this field.[39–42]

The procedure is guided by both fluoroscopy and TEE, and it is usually performed under general anesthesia to allow for continuous TEE. In cases of a peri-mitral defect, an attempt is usually made to cross the defect antegradely via a trans-septal approach. A diagnostic catheter (preferably right Judkins or Multipurpose) is advanced toward the leak. Thereafter, a hydrophilic wire is advanced through this catheter and used to cross the leak. The catheter is then advanced through the leak. The hydrophilic wire is exchanged with a stiff wire and the sheath is advanced over the wire (the dilator is remounted if necessary). Once it crosses the leak, the device is advanced and deployed. Contrast injection can be performed to delineate the size and shape of the defect, although some centers prefer TEE sizing to reduce radiation exposure. Periaortic leaks are usually approached in a retrograde fashion through the femoral artery. A coronary diagnostic catheter is advanced toward the leak, which is then crossed with a hydrophilic wire, followed by a pigtail catheter. After the injection of contrast material to delineate the size and shape of the defect, the pigtail catheter is exchanged with a designated delivery sheath, and the designated device is deployed across the leak site. It may be advisable to use a device that is at least one size greater than the minimal diameter of the hole. In general, patent ductus arteriosus occluders are more suitable for narrow and elongated holes and ventricular septal defect occluders, for wide and short tunnels. Amplatzer devices were employed in most of the studies in the literature, although other devices and coils were reported as well.

Clear contraindications for percutaneous closure of perivalvular leak are active infection, vegetations, or thrombi (either at the leaking site or elsewhere in the potential course of the catheters). Large defects (ie, extending more than a quarter of the circumference of the prosthesis) may not be suitable for device deployment or may require more than 1 device, and leakages located close to the point of maximum leaflet excursion may interfere with leaflet movement by the closure device. Failure to accurately visualize the defect by echocardiography is also a predictor of failed percutaneous closure.

The procedure is technically demanding and time consuming, and its effects on hemolysis are inconsistent. In a series reported by our group, of 8 patients with hemolysis treated by Amplatzer occlusion, 3 showed a decrease in severity of hemolysis (though it recurred later in one of them), 3 showed an increase, and 2 had no change.[42] In another series, 2 patients with transfusion-dependent hemolysis remained transfusion-dependent after leak closure.[41] Some individual case reports noted a favorable effect of transcatheter treatment on hemolysis,[43,44] whereas others did not.[45,46] Because the current devices can hardly fit into the shape of the leaking area, there may be a certain degree of residual regurgitation, leading to postprocedural hemolysis that is even worse than the preprocedural one. Furthermore, the risk of certain procedure-specific complications should be borne in mind, including impingement on leaflet motion, worsening of leakage due to radial forces, device embolization, and damage to the valve. An example of perivalvular leak and its closure is shown in Figure 2A–D.

The newly developed live 3-dimensional TEE may represent a potential breakthrough in the imaging of leak characteristics and device deployment.[47,48] However, more data are needed to assess its exact role in this setting. The development of dedicated, preshaped, devices may help overcome these obstacles. Currently, percutaneous closure of paravalvular leaks is reserved for poor surgical candidates.

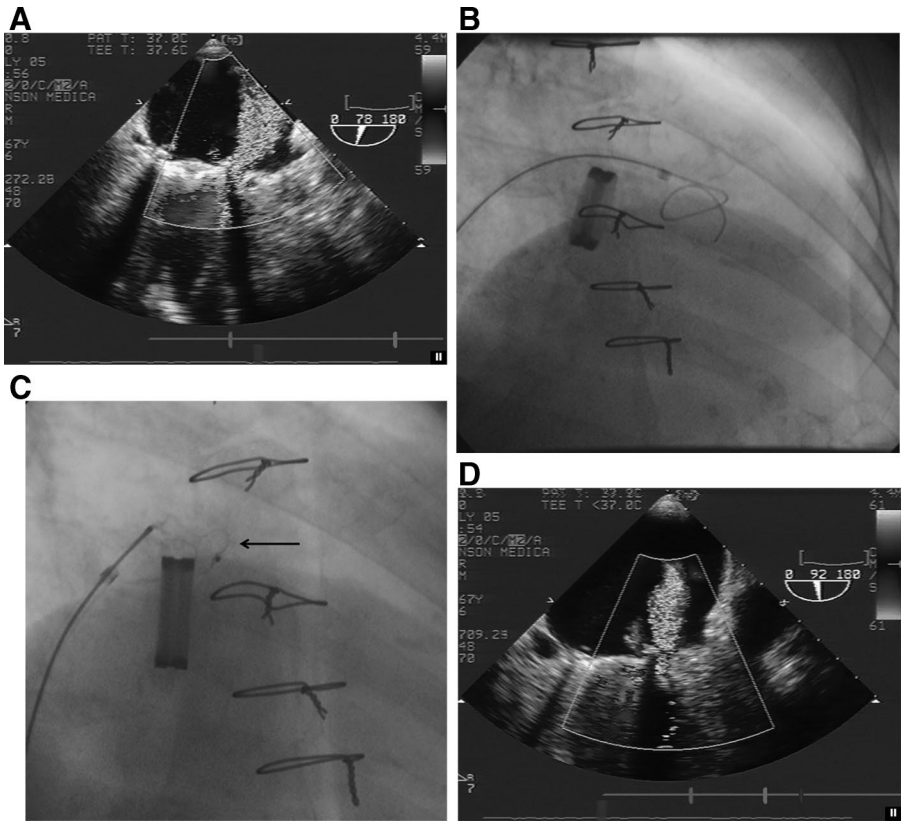

FIGURE 2. Percutaneous closure of a perivalvular leak: A, TEE showing moderately sized peri-mitral leak originating near the left atrial appendage. B, A catheter and wire across the leak. C, An Amplatzer PDA occluder placed at the leaking site, still connected to the wire. The arrow points to the device. D, Postprocedural TEE showing a lesser degree of perivalvular leak.

Erythropoietin

Another therapeutic option for cases of severe hemolysis and high reoperative risk is erythropoietin. This method was initially reported by Kornowski et al[49] and has since been applied in several small series. Although the overstimulation of and already over-reactive red-cell line may not make a lot of sense, erythropoietin administration has been effective in reducing blood transfusion rate, especially in patients with some degree of renal impairment.[50,51]

Tailoring Therapy

Mild, compensated, hemolysis can probably be managed by observation, whereas severe hemolysis requiring frequent blood transfusions warrants reoperation in patients who are not at very high surgical risk, or treatment with beta adrenergic blockers, folate, erythropoietin, or pentoxifylline in poor surgical candidates. Percutaneous closure of paravalvular leaks with coils or devices is emerging as an alternative to reoperation, although alleviation of hemolysis cannot be guaranteed.

Prevention

Significant early paravalvular leakage following elective valve replacement necessitates a second pump-run in nearly 2% of cases.[52,53] It might be prevented by the routine use of intraoperative TEE. In patients with active infectious endocarditis, meticulous eradication of any infected tissue during surgery is mandatory to avoid late paravalvular leak. Extensive mitral annular calcification can be approached with special techniques, such as resection of the calcium bar and creation of a new annulus with pericardium.[54]

CONCLUSIONS

In conclusion, mild, compensated hemolysis associated with mechanical heart valves is not uncommon even in the current era. Severe hemolysis is rare and is usually related to paravalvular leak. There is a gamut of available therapeutic approaches—medical, transcatheter, and surgical—to this complication. Ideally, therapy should be tailored to the individual patient.

REFERENCES

1. Edmunds LH Jr, Clark RE, Cohn LH, et al. Guidelines for reporting morbidity and mortality after cardiac valvular operations. *J Thorac Cardiovasc Surg*. 1996;112:708–711.
2. Rose JC, Hufnagel CA, Fries ED, et al. The hemodynamic alterations produced by plastic valvular prosthesis for severe aortic insufficiency in man. *J Clin Invest*. 1954;33:891–900.
3. Marsh GW, Lewis SM. Cardiac haemolytic anaemia. *Semin Hematol*. 1969; 6:133–149.
4. Kloster FE. Diagnosis and management of complications of prosthetic heart valves. *Am J Cardiol*. 1975;35:872–885.
5. Iguro Y, Moriyama Y, Yamaoka A, et al. Clinical experience of 473 patients with the omnicarbon prosthetic heart valve. *J Heart Valve Dis*. 1999;8:674–679.
6. Skoularigis J, Essop MR, Skudicky D, et al. 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.
7. Mecozzi G, Milano AD, De Carlo M, et al. Intravascular hemolysis in patients with new-generation prosthetic heart valves: a prospective study. *J Thorac Cardiovasc Surg*. 2002;123:550–556.
8. Mitlyng BL, Chandrashekhar Y, Furne JK, et al. Use of breath carbon monoxide to measure the influence of prosthetic heart valves on erythrocyte survival. *Am J Cardiol*. 2006;97:1374–1376.
9. Conti VR, Nishimura A, Coughlin TR, et al. Indications for replacement of

the Beall 103 and 104 disc valves. *Ann Thorac Surg*. 1986;42:315–320.

10. Murakami M, Tanaka H, Watanabe M, et al. Severe hemolysis due to cloth wear 23 years after aortic valve replacement on a Starr-Edwards ball valve model 2320. *Cardiovasc Surg*. 2002;10:284–286.
11. Rallidis LS, Moyssakis IE, Ikonomidis I, et al. Natural history of early aortic paraprosthetic regurgitation: a five-year follow-up. *Am Heart J*. 1999;138: 351–357.
12. Miller DL, Morris JJ, Schaff HV, et al. Reoperation for aortic valve periprosthetic leakage: identification of patients at risk and results of operation. *J Heart Valve Dis*. 1995;4:160–165.
13. Jindani A, Neville EM, Venn G, et al. Paraprosthetic leak: a complication of cardiac valve replacement. *J Cardiovasc Surg (Torino)*. 1991;32:503–508.
14. Schoen FJ. The first step to understanding valve failure: an overview of pathology. *Eur J Cardiothorac Surg*. 1992;6(suppl 1):S50–S53.
15. Koch A, Cesnjevar R, Buheitel G, et al. Aortic root abscess complicated by fistulization and intracerebral hemorrhagic infarction. *Pediatr Cardiol*. 2003; 24:576–580.
16. Alonso-Lej F. Straight suture plane to avoid periprosthetic leak in aortic valve replacement. *Ann Thorac Surg*. 1975;19:571–573.
17. Bortolotti U, Mazzucco A, Milano A, et al. Technical considerations in reoperation for porcine bioprosthetic valve failure. *J Card Surg*. 1988;3:459–466.
18. Laks H, Pearl JM, Barthel SW, et al. Aortic valve replacement using a continuous suture technique. *J Card Surg*. 1993;8:459–465.
19. Dhasmana JP, Blackstone EH, Kirklin JW, et al. Factors associated with periprosthetic leakage following primary mitral valve replacement: with special consideration of suture technique. *Ann Thorac Surg*. 1983;35:170–178.
20. Garcia MJ, Vandervoort P, Stewart WJ, et al. Mechanisms of hemolysis with mitral prosthetic regurgitation. Study using transesophageal echocardiography and fluid dynamic simulation. *J Am Coll Cardiol*. 1996;27:399–406.
21. Schwalm SA, Sugeng L, Ward RP, et al. Combination of acceleration and collision involving the left atrial appendage limbus as a mechanism of hemolytic anemia in the setting of periprosthetic mitral valve regurgitation. *J Am Soc Echocardiogr*. 2004;17:913–915.
22. 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.
23. Weesner KM, Rocchini AP, Rosenthal A, et al. Intravascular hemolysis associated with porcine mitral valve calcification in children. *Am J Cardiol*. 1981;47:1286–1288.
24. Horstkotte D. *Heart Valve Consultant*. 1st ed. London: ICR Publishers; 1991.
25. Maraj R, Jacobs LE, Ioli A, et al. Evaluation of hemolysis in patients with prosthetic heart valves. *Clin Cardiol*. 1998;21:387–392.
26. Okita Y, Miki S, Kusuhara K, et al. Propranolol for intractable hemolysis after open heart operation. *Ann Thorac Surg*. 1991;52:1158–1160.
27. Santinga JT, Flora JD, Rush JB, et al. The effect of propranolol on hemolysis in patients with an aortic prosthetic valve. *Am Heart J*. 1977;93:197–201.
28. Aoyagi S, Fukunaga S, Tayama E, et al. Benefits of a β-blocker for intractable hemolysis due to paraprosthetic leakage. *Asian Cardiovasc Thorac Ann*. 2007;15:441–443.
29. Golbasi I, Turkay C, Timuragaoglu A, et al. The effect of pentoxifylline on haemolysis in patients with double cardiac prosthetic valves. *Acta Cardiol*. 2003;58:379–383.
30. Vahanian A, Baumgartner H, Bax J, et al. Guidelines on the management of valvular heart disease: the Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology. *Eur Heart J*. 2007;28:230–268.
31. Pansini S, Ottino G, Forsennati PG, et al. Reoperations on heart valve prostheses: an analysis of operative risks and late results. *Ann Thorac Surg*. 1990;50:590–596.
32. Cohn LH, Aranki SF, Rizzo RJ, et al. Decrease in operative risk of reoperative valve surgery. *Ann Thorac Surg*. 1993;56:15–20.
33. Jones JM, O'Kane H, Gladstone DJ, et al. Repeat heart valve surgery: risk factors for operative mortality. *J Thorac Cardiovasc Surg*. 2001;122:913–918.
34. Lytle BW, Cosgrove DM, Taylor PC, et al. Reoperations for valve surgery: perioperative mortality and determinants of risk for 1,000 patients, 1958–1984. *Ann Thorac Surg*. 1986;42:632–643.
35. Akins CW, Buckley MJ, Daggett WM, et al. Risk of reoperative valve replacement for failed mitral and aortic bioprostheses. *Ann Thorac Surg*. 1998;65:1545–1551.
36. Tyers GF, Jamieson WR, Munro AI, et al. Reoperation in biological and mechanical valve populations: fate of the reoperative patient. *Ann Thorac Surg*. 1995;60:S464–S468.
37. Blackstone EH, Kirklin JW. Death and other time-related events after valve replacement. *Circulation*. 1985;72:753–767.
38. Hourihan M, Perry SB, Mandell VS, et al. Transcatheter umbrella closure of valvular and paravalvular leaks. *J Am Coll Cardiol*. 1992;20:1371–1377.
39. Hein R, Lang K, Wunderlich N, et al. Percutaneous closure of paravalvular leaks. *J Interven Cardiol*. 2006;19:S73–S77.
40. Pate GE, Thompson CR, Munt BI, et al. Techniques for percutaneous closure of prosthetic paravalvular leaks. *Catheter Cardiovasc Interv*. 2006;67:158–166.
41. Pate GE, Al Zubaidi A, Chandavimol M, et al. Percutaneous closure of prosthetic paravalvular leaks: case series and review. *Catheter Cardiovasc Interv*. 2006;68:528–533.
42. Shapira Y, Hirsch R, Kornowski R, et al. Percutaneous closure of perivalvular leaks with Amplatzer occluders: feasibility, safety, and short-term results. *J Heart Valve Dis*. 2007;16:305–313.
43. Moore JD, Lashus AG, Prieto LR, et al. Transcatheter coil occlusion of perivalvular mitral leaks associated with severe hemolysis. *Catheter Cardiovasc Interv*. 2000;49:64–67.
44. Moscucci M, Deeb GM, Bach D, et al. Coil embolization of a periprosthetic mitral valve leak associated with severe hemolytic anemia. *Circulation*. 2001;104:E85–E86.
45. Eisenhauer AC, Piemonte TC, Watson PS. Closure of prosthetic paravalvular mitral regurgitation with the Gianturco-Grifka vascular occlusion device. *Catheter Cardiovasc Interv*. 2001;54:234–238.
46. Hussain ST, Devagourou V, Sampath Kumar A. Management of mitral paravalvular leak: therapy or misadventure? *J Thorac Cardiovasc Surg*. 2003;126:879–880.
47. Biner S, Rafique AM, Kar S, et al. Live three-dimensional transesophageal echocardiography-guided transcatheter closure of a mitral paraprosthetic leak by Amplatzer occluder. *J Am Soc Echocardiogr*. 2008;21:1282.e7–e9.
48. Fischer GW, Adams DA. Real-time three-dimensional TEE-guided repair of a paravalvular leak after mitral valve replacement. *Eur J Echocardiogr*. 2008;9:868–869.
49. Kornowski R, Schwartz D, Jaffe A, et al. Erythropoietin therapy obviates the need for recurrent transfusions in a patient with severe hemolysis due to prosthetic valves. *Chest*. 1992;102:315–316.
50. Shapira Y, Bairey O, Vatury M, et al. Erythropoietin can obviate the need for repeated heart valve replacement in high-risk patients with severe mechanical hemolytic anemia. Report of 3 cases and review of the literature. *J Heart Valve Dis*. 2001;10:431–435.
51. Hirawat S, Lichtman SM, Allen SL Recombinant human erythropoietin use in hemolytic anemia due to prosthetic heart valves: a promising treatment. *Am J Hematol.* 2001;66:224–226.
52. Click RL, Abel MD, Schaff HV. Intraoperative transesophageal echocardiography: 5-year prospective review of impact on surgical management. *Mayo Clin Proc*. 2000;75:241–247.
53. Shapira Y, Mordehay M, Weisenberg DE, et al. Impact of intraoperative transesophageal echocardiography in patients undergoing valve replacement. *Ann Thorac Surg*. 2004;78:579–583.
54. Feindel CM, Tufail Z, David TE, et al. Mitral valve surgery in patients with extensive calcification of the mitral annulus. *J Thorac Cardiovasc Surg*. 2003;126:777–782.

