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JACC STATE-OF-THE-ART REVIEW

Mechanical Hemolysis Complicating Transcatheter Interventions for Valvular Heart Disease

JACC State-of-the-Art Review

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ABSTRACT

Mechanical intravascular hemolysis is frequently observed following procedures on heart valves and uncommonly observed in native valvular disease. In most cases, its severity is mild. Nevertheless, it can be clinically significant and even life threatening, requiring multiple blood transfusions and renal replacement therapy. This paper reviews the current knowledge on mechanical intravascular hemolysis in valvular disease, before and after correction, focusing on pathophysiology, approach to diagnosis, and impact of other hematological conditions on the resultant anemia. The importance of a multidisciplinary management is underscored. Laboratory data are provided about subclinical hemolysis that is commonly observed following the implantation of surgical and transcatheter valve prostheses and devices. Finally, clinical scenarios are reviewed and current medical and surgical treatments are discussed, including alternative options for inoperable patients. (J Am Coll Cardiol 2021;77:2323–34) © 2021 by the American College of Cardiology Foundation.

Mechanical intravascular hemolysis (MIH) occurs when red blood cells (RBCs) are fragmented into blood vessels by mechanical injury. MIH can be observed in several noncardiac diseases (1) and conditions (2). It can be also produced by the transit of RBCs through native or prosthetic heart valves. The aim of this paper is to review the current knowledge about MIH in valvular disease and following valve procedures.

METHODS

Primary literature search for relevant articles was conducted using PubMed from the earliest date to October 2020. All the relevant articles were reviewed as a full text. A comprehensive analysis of the references of each report was performed to identify further articles of interest.

PATHOGENESIS OF MIH

The 2 main mechanisms leading to valve-related MIH are shear stress and the direct contact between RBCs and the internal surfaces of the heart (3–5). Their relative contribution to hemolysis has been widely debated in experimental studies. In response to shear stress, the erythrocyte changes its shape, and substantial stretching of its cell membrane may occur. When the deformation exceeds a critical value, hemolysis ensues. Healthy RBCs can withstand high shear stress only for a short time. Lethal shear stress for normal erythrocytes is approximately 50,000

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ABBREVIATIONS AND ACRONYMS

LDH = lactate dehydrogenase

LVOT = left ventricular outflow tract

MIH = mechanical intravascular hemolysis

RBC = red blood cell

RDW = red cells distribution width

TAVI = transcatheter aortic valve implantation

TMVI = transcatheter mitral valve implantation

dynes/cm^2, regardless of the duration of the stress (5). A shear stress between 4,000 and 8,000 dynes/cm^2 causes MIH when the exposure time is $\geq 10^{-4}$ s (3,6,7). Such an order of magnitude is well representative of RBC time of transit through a tight aortic valve stenosis within a high velocity jet (>4 m/s). In this high shear stress region, cell damage is mostly due to the shear stress itself, whereas cell–surface and cell–cell interactions play a minor role (3). At lower shear stress (<1,500 dynes/cm^2), MIH does not occur even after prolonged periods of exposure (order of magnitude: 10^2 s) (3). The interaction of RBCs with native or prosthetic surfaces becomes predominant, influenced by the features of the contact area and the stickiness of the surface (5). In vitro experiments showed that mechanical aortic valve prostheses generated shear stress in the low range (1,000 to 1,600 dynes/cm^2) at peak systole (8). These observations were in agreement with the mild degree of hemolysis commonly observed in patients with a mechanical prosthesis. Nevertheless, clinically significant MIH can occur even at low thresholds of shear stress if the membrane and the shape of the erythrocytes are abnormal, like hereditary elliptocytosis and spherocytosis (9,10).

Five hydrodynamic mechanisms leading to MIH in vivo have been recognized and associated with echocardiographic features of the mitral regurgitant jet (11): 1) fragmentation of a jet by an intervening solid structure (suture, chord, prosthetic ring); 2) collision of a jet against a solid structure; 3) acceleration of a jet of blood through a small (<2 mm) orifice; 4) a free jet originating from a >2 mm orifice, not constrained by solid structures until it reaches the posterosuperior wall of the left atrium; and 5) slow deceleration of a jet originating from a large orifice and deflected in a curved trajectory along the atrial wall.

CLINICAL AND LABORATORY FEATURES OF MIH

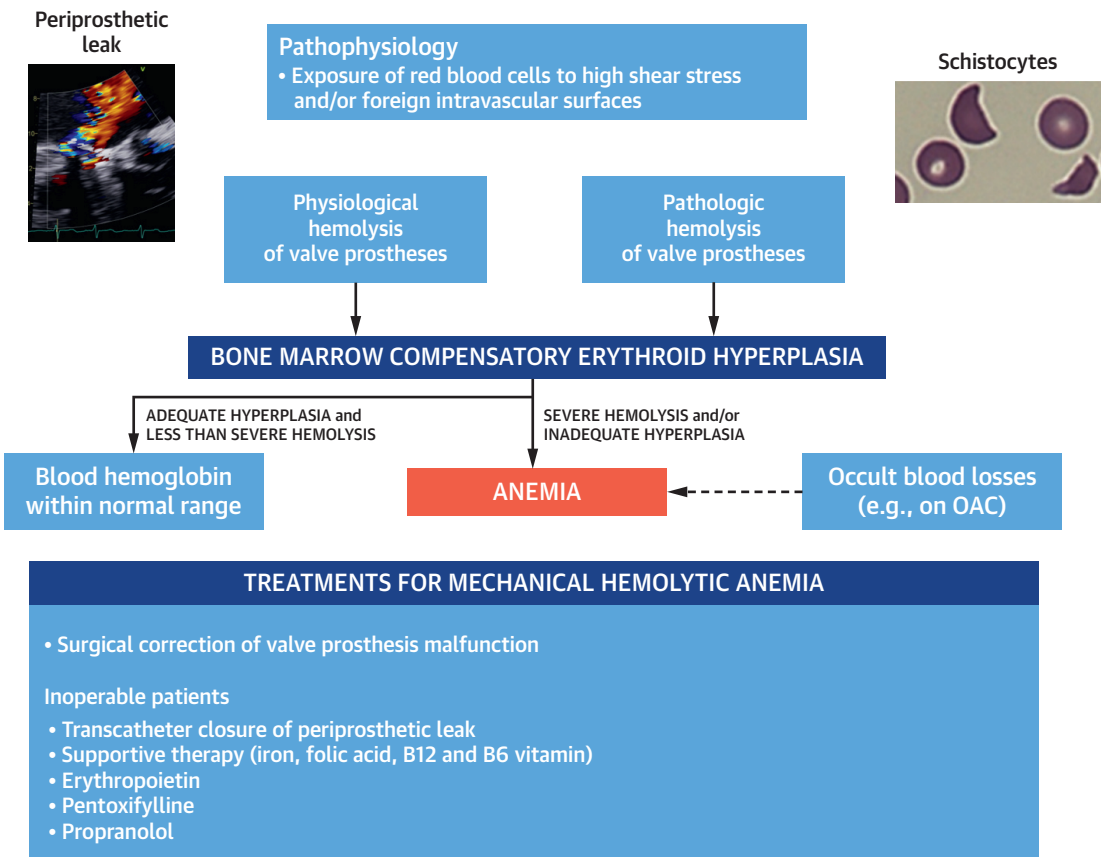
CLINICAL PICTURE. When the RBC destruction rate is not compensated by the production of new RBCs, hemoglobin values decrease below the normal range, and hemolytic anemia occurs (**Central Illustration**). Therefore, the clinical presentation of MIH may vary widely, ranging from asymptomatic laboratory features of chronic intravascular hemolysis to overt congestive heart failure secondary to prosthetic valve malfunction associated with severe anemia, jaundice, and dark-colored urine secondary to massive intravascular hemolysis. Fulminant onset of the hemolysis can rarely occur. Hemolytic anemia causes an increase in cardiac output, which, in turn, worsens the rate of hemolysis, thus creating a vicious circle. When laboratory tests suggest clinically significant MIH in a patient with a valve prosthesis, transesophageal echocardiography is indicated. On occasion, cinefluoroscopy may provide further information about a suspected dysfunction of a mechanical valve prosthesis. In contrast, the diagnosis of a peri-prosthetic leak should prompt laboratory investigations for hemolysis. Hematological consultation is strongly advised at all steps of the diagnostic process to rule out concomitant causes of anemia and to estimate the relative contribution of hemolysis to the underlying anemia. The pathophysiology of MIH is shown in **Figure 1**.

HIGHLIGHTS

- MIH occurs more frequently in patients undergoing catheter-based valve interventions than during the natural history of native valvular heart disease.
- The clinical manifestations of procedure-related hemolysis depend on the relative rates of hemolysis and bone marrow hematopoiesis.
- Even well-functioning valve prostheses cause mild hemolysis, but laboratory markers of hemolysis should be checked periodically, particularly in patients with mechanical valve prostheses or anemia.
- Although surgical correction is recommended when malfunctioning valves cause hemolysis, continued improvement in the outcomes of transcatheter procedures may reduce the frequency of hemolysis in the future.

LABORATORY TESTS. To date, a universal definition of MIH has not yet been established, and several laboratory criteria for the diagnosis of MIH have been proposed (**Table 1**). The guidelines of the European Society of Cardiology (12) recommend that blood tests for MIH be periodically performed during follow-up of heart valve prostheses. However, the timing of the evaluation should be tailored according to individual patient's characteristics. It seems reasonable to evaluate the serum lactate dehydrogenase (LDH) yearly and as soon as possible if new-onset anemia occurs. However, a closer follow-up is advisable for patients with a known, less than severe peri-prosthetic leak, and for those affected by

CENTRAL ILLUSTRATION **Mechanical Intravascular Hemolysis and Heart Valve Disease**



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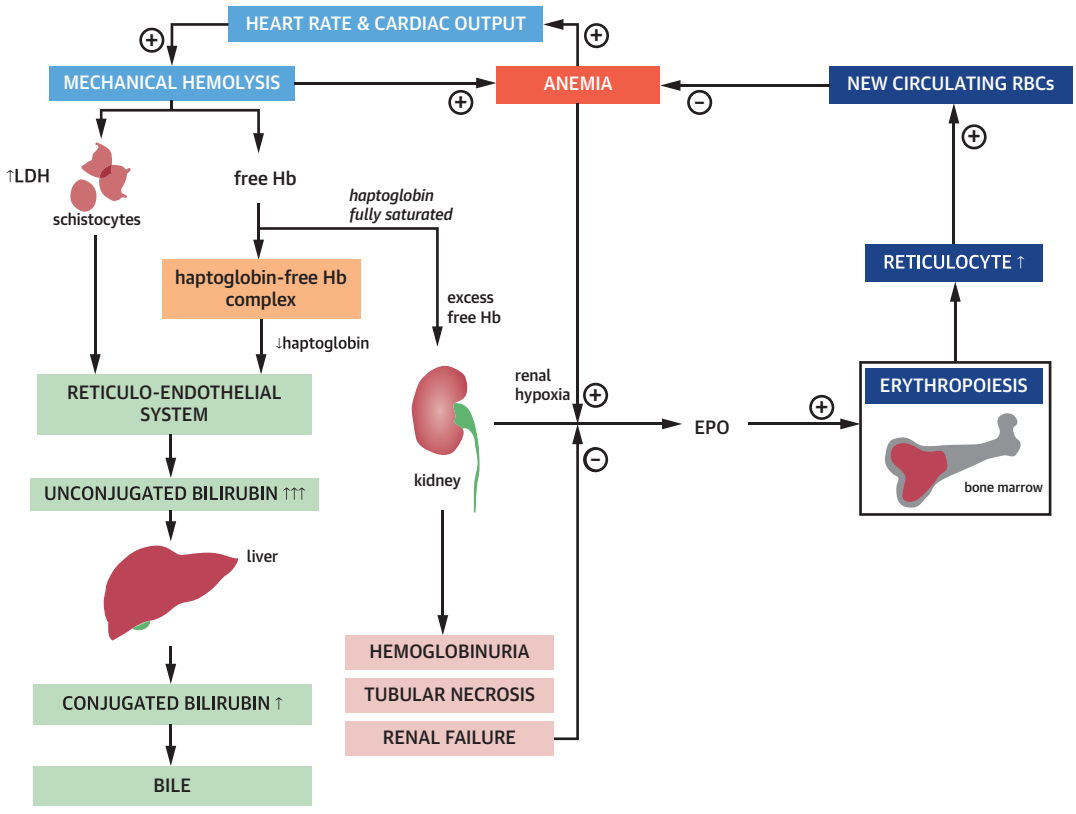
Mechanical intravascular hemolysis (MIH) occurs when circulating red blood cells are exposed to high shear stress and/or foreign surfaces. Examples are critical aortic valve stenosis, mechanical valve prostheses, and peri-prosthetic leaks. A mild degree of MIH is common among patients with a mechanical valve prosthesis, and it is usually well tolerated on the long term. However, moderate and severe MIH are associated with anemia, the degree of which depends on the balance between the destruction rate of the red blood cells and the adequacy of the bone marrow erythroid hyperplasia. Moreover, anemia could be worsened by other reasons (e.g., occult blood losses from the gastrointestinal tract in patients treated with oral anticoagulants). The correction of the cause of clinically significant MIH (prosthetic malfunction or native valve disease) is the only curative option, and surgery remains the gold standard therapy. Alternative treatments are reserved for inoperable patients.

concomitant nonhemolytic anemia or bone marrow disease. The interpretation of blood tests is eased by comparison to previous results obtained both at baseline and during the post-operative follow-up. This concept is especially relevant because none of the laboratory parameters used to evaluate hemolysis is per se diagnostic, and alterations of each parameter may be secondary to many other pre-existing, concomitant, or supervening clinical conditions. Finally, in interpreting laboratory testing, it should be kept in mind that blood parameters explore intravascular hemolysis whose markers behave slightly differently compared with extravascular hemolysis, such as that associated with autoimmune hemolytic conditions (13). Blood tests commonly adopted for the diagnosis of MIH are shown in Table 2.

Blood hemoglobin. Hemoglobin is the most direct indicator of the clinical severity in MIH. Severe anemia may complicate MIH, particularly in patients with depressed bone marrow function. Anemia may be independent of the degree of the hemolysis, and previous hemoglobin levels need to be considered when MIH is suspected.

Red cell distribution width. Red cells distribution width (RDW) is a quantitative measure of the variation of RBC volume (i.e., anisocytosis). RDW is

FIGURE 1 Pathophysiology of Hemolytic Anemia in Heart Valve Disease



Mechanical intravascular hemolysis (MIH) causes the fragmentation of red blood cells (RBCs) in schistocytes and the release of free hemoglobin (Hb). The schistocytes and the haptoglobin–hemoglobin complex are cleared by the reticuloendothelial system, generating unconjugated bilirubin, which is conjugated into the liver and excreted into the bile. When free Hb is >3 g, haptoglobin is fully saturated and the serum level of free hemoglobin starts to increase. If the amount of filtered free Hb exceeds the capacity of reabsorption of the tubule, hemoglobinuria occurs. The accumulation of derivatives of Hb into the proximal tubule can lead to renal failure. The compensatory response of bone marrow to anemia could be compromised by a decreased production of erythropoietin (EPO) secondary to renal failure. Anemia increases the heart rate and the cardiac output, which, in turn, increase the MIH, thus creating a vicious circle. LDH = lactate dehydrogenase.

usually higher than normal in MIH because of the increase in the number of the circulating reticulocytes.

Reticulocyte count. Reticulocytes are an index of bone marrow hemopoietic activity. The reticulocyte count does not significantly change in patients with a normally functioning valve prosthesis, because this condition usually implies subclinical hemolysis (14). An increased count supports a diagnosis of accelerated RBC destruction. However, counts within the normal range or even lower (i.e., ineffective erythropoiesis) do not rule out significant hemolysis. Rather, a thorough workup should be implemented to explore causes of impaired reticulocyte production, ranging from iron and/or vitamin deficiency, to decreased erythropoietin production or primary bone marrow disorders.

Schistocytes in peripheral blood smear. Schistocytes derive from mechanical fragmentation of RBCs and are occasionally detected on the peripheral blood smear from healthy subjects. Values >0.5% are needed to confirm the diagnosis of MIH. The count of schistocytes on a peripheral blood smear is performed by microscopy, which gives a reliable and direct estimate of ongoing hemolysis. It adds valuable information to hemolysis laboratory tests in evaluating the degree of MIH, especially when concomitant nonhemolytic anemia is present.

Biochemical markers of hemolysis. Erythrocytes are rich in LDH. The serum level of LDH increases as a result of RBC fragmentation, usually to values proportionate to the degree of the ongoing hemolysis (12,15). LDH levels are usually significantly higher in MIH compared with conditions characterized by

TABLE 1 Proposed Criteria for Hemolysis in Patients With Prosthetic Heart Valves

Eyster Criteria for Severity of MIH (30,77)	Mild MIH	Moderate MIH	Severe MIH
Hemosiderinuria	Present	Present	Marked
Hemoglobinuria	Absent	Absent	Present
Schistocytosis, %	<1	>1	>>1
Reticulocyte count, %	<5	>5	>>5
Serum haptoglobin	Decreased	Absent	Absent
Serum LDH, IU/l	<500	>500	>>500

Skoularigis Criteria for MIH (28)	
Serum LDH	>460 IU/l and at least 2 of the following
Blood hemoglobin	<13.8 dl in males and <12.4 dl in females
Serum haptoglobin	<0.5 g/l
Reticulocyte count	>2%
Blood smear	Schistocytes present

Horskotte Criteria for Severity of MIH (78)	Serum LDH (IU/l)	Serum Haptoglobin (mg/dl)
No hemolysis	<220	>37
Mild hemolysis	220–400	10–37
Moderate hemolysis	400–800	1–9
Severe compensated hemolysis	>800	0
Severe decompensated hemolysis	>1,000	0

LDH = lactate dehydrogenase; MIH = mechanical intravascular hemolysis.

extravascular hemolysis (13). However, any other cause of cellular lysis or necrosis—ranging from acute myocardial infarction to high-proliferative index neoplasms—results in the release of this intracellular enzyme. Haptoglobin is an acute-phase glycoprotein whose major biological function is binding plasmatic free hemoglobin with high affinity to prevent both the loss of iron and hemoglobin-mediated renal injury. Therefore, it is decreased or absent in cases of hemolysis. However, haptoglobin is useless to measure the severity of intravascular hemolysis because of its limited capacity to bind free hemoglobin. It may become undetectable even for a mild to moderate amount of RBC destruction. Because it is an acute-phase glycoprotein, concomitant inflammatory states (e.g., endocarditis) may increase circulating haptoglobin levels. Its baseline levels may be significantly decreased due to liver disease. Therefore, such conditions should be taken into account for a correct interpretation of serum haptoglobin. Free hemoglobin is normally released into blood as a consequence of the intravascular destruction of senescent RBCs, which occurs at a rate of 2×10^6 erythrocytes/s. There is sufficient haptoglobin in circulation to bind and clear 3 g of hemoglobin, which would prevent free hemoglobin circulation in the body. In presence of MIH, plasmatic free hemoglobin increases to a degree that reflects haptoglobin-binding capacity. The hemoglobin–haptoglobin complex is internalized and degraded to release heme. Heme catabolism generates bilirubin, and unconjugated hyperbilirubinemia can result from accelerated RBC destruction. Bilirubin is more reliable as a marker for extravascular hemolysis. In most cases of MIH, unconjugated hyperbilirubinemia remains subclinical, at <3 mg/dl. However, jaundice can be observed in patients with severe MIH, particularly when liver disease prevents an adequate rate of conjugation and/or excretion of excess bilirubin. Hemoglobinuria occurs only in the setting of severe and rapid intravascular hemolysis and results from free plasma hemoglobin release in excess of haptoglobin-binding capacity. When the capacity of the proximal renal tubule to reabsorb the hemoglobin from the lumen is exceeded, the hemoglobin is freely excreted into the urine, and hemoglobinuria ensues (16). Serum ferritin is often increased in MIH. Normal or decreased ferritin may be caused by chronic occult blood loss in patients on oral anticoagulants. Ferritin is an acute-phase protein whose levels increase in inflammatory states, and high levels can be observed in patients with subacute prosthetic endocarditis complicated by MIH.

TABLE 2 Laboratory Tests on Blood for MIH

Test	Normal Range	Change in MIH
Hemoglobin, g/dl		= or ↓ – ↓↓↓
Male	13.5–17.5	
Female	12.0–15.5	
Serum free hemoglobin, mg/dl	<5	↑ – ↑↑↑
Red cell distribution width, %	11.5–14.5	= or ↑
Schistocytes on blood smear, %	<0.5	↑ – ↑↑↑
Serum LDH, IU/l	100–220	↑ – ↑↑↑
Serum haptoglobin, IU/l	16–199	↓ – undetectable
Serum unconjugated bilirubin, mg/dl	0.2–1.2	= or ↑ – ↑↑↑
Serum conjugated bilirubin, mg/dl	0–0.4	= or ↑
Serum ferritin, ng/ml		= or ↑ – ↑↑↑
Male	30–300	
Female	10–200	
Serum aspartate aminotransferase, IU/l	0–35	= or ↑

Abbreviations as in Table 1.

The Direct Coombs test detects antibodies in RBCs of patients, and it is used to diagnose autoimmune hemolytic anemia. It is negative in cases of mechanical hemolysis.

MIH-ASSOCIATED ANEMIA AND DISORDERS OF RBCs AND BONE MARROW. It has been suggested that anemia results if hemolysis decreases RBC life span from one-fifth to one-tenth of normal value

(5,17). However, the degree of the anemia depends on the balance between ongoing hemolysis and compensatory bone marrow erythroid hyperplasia. The balance may be tilted by either prosthetic valve malfunctioning or primary disorders of RBCs and/or bone marrow. Therefore, the clinician should try to correctly estimate the contribution of hemolysis to anemia relative to other coexisting conditions. This evaluation is fundamental to the institution of appropriate treatment.

Factors increasing the rate of hemolysis. Prolonged states of high cardiac output can further increase the rate of MIH. In hereditary spherocytosis and elliptocytosis, RBCs are more prone to mechanical damage from high shear stress because of reduced deformability and increased fragility (9,10,18). A spherical shape seems to be more susceptible to fragmentation compared with an elliptical shape (10). Caprari et al. (9) described cases of asymptomatic carriers of hereditary elliptocytosis and spherocytosis who developed decompensated MIH following valve replacement with a mechanical valve.

Ineffective erythropoiesis. Deficient bone marrow erythropoiesis-secondary to vitamin and iron deficit, or primary bone marrow disorders-can prevent the achievement of a rate of RBC production adequate for replacement of damaged erythrocytes. In this setting, decompensated anemia could occur even when the fragmentation rate is less than severe.

Occult blood loss. Patients with prosthetic valves and rings are often on oral anticoagulants and/or antiplatelet medications. Therefore, anemia secondary to hemolysis could be worsened by chronic occult blood losses.

RENAL FAILURE IN SEVERE MIH. Renal failure may complicate severe intravascular hemolysis (19,20). It significantly increases the risk of valvular reoperations performed for MIH. Plasma free hemoglobin is filtered by the glomerulus and completely reabsorbed by the cells of the proximal tubule. Serum haptoglobin acts as a circulating buffer protecting the kidney when, and for whatever reason, free hemoglobin level starts to increase. The molecular size of the haptoglobin–hemoglobin complex is too large to be filtered by the kidney. When the binding capacity of serum haptoglobin is fully saturated, the increase of circulating free hemoglobin becomes unconstrained. When the capacity of the tubule to reabsorb hemoglobin from the lumen is exceeded, hemoglobin is freely excreted into the urine, and hemoglobinuria ensues (16). The accumulation of large amounts of hemoglobin derivatives (heme, heme proteins, and hemosiderin) in the cells of the proximal tubule leads to acute tubular necrosis because of direct cytotoxicity, endothelial dysfunction, and renal vasoconstriction (19,20). Moreover, the formation of methemoglobin casts into the distal tubule may cause intrarenal obstruction, eventually worsening the injury to the proximal part of the tubule. Renal hemosiderosis has been proposed as a cause of inadequate erythropoietin production in patients affected by severe MIH (21), promoting the decompensation of anemia.

MIH AND HEART VALVES: CLINICAL SCENARIOS

NATIVE HEART VALVE DISEASE. There are few reports about MIH associated with native valve disease, probably because of its rarity as a clinical entity. Hemolysis seems to be significantly greater in stenotic aortic valves compared with stenotic mitral valves (5). The reason of this difference is likely related to the much higher blood flow velocity through an aortic stenosis. Jacobson et al. (22) reported cases of subclinical hemolytic anemia in patients affected by aortic valve or subaortic stenosis with systolic pressure gradients of ≥50 mm Hg at cardiac catheterization. Such gradients were associated with a calculated shear stress of 4,000 dynes/cm^2 on RBCs, in good agreement with previous experimental data (3,6,7). These observations were confirmed later (23,24). Kawase et al. (23) described the case of a severe calcific aortic valve stenosis associated with hematuria and anemia. The transaortic peak pressure gradient was 125 mm Hg (aortic valve area: 0.46 cm^2), hemoglobin 7.9 g/dl, and serum LDH 2,295 IU/l. Following aortic valve replacement, the hemoglobin level returned to normal, and LDH values approached the normal range. Acquired von Willebrand deficiency may worsen anemia secondary to MIH in patients affected by critical aortic valve stenosis or left ventricular outflow tract (LVOT) obstruction (25). It is a disorder of hemostasis caused by high shear stress conditions into the blood flow. These promote the cleavage of the multimeric von Willebrand factor in smaller molecules that are hemostatically less effective. In patients affected by critical aortic valve stenosis, the acquired deficiency of von Willebrand factor may produce Heyde syndrome, which is characterized by intestinal bleeding. It is intriguing that both hemolysis and Heyde syndrome share the cause, that is, the high shear stress generated by the blood flowing at high velocity through a critical narrowing, and a clinical manifestation (i.e., the anemia).

Subclinical MIH has been reported in cases of mitral regurgitation on a native valve (26). Increased serum levels of LDH have been observed in patients with an eccentric regurgitant jet directed toward the left atrial wall compared with patients with a central jet.

LVOT OBSTRUCTION. There is evidence that subclinical hemolysis is associated with LVOT obstruction in hypertrophic cardiomyopathy. A significant correlation between markers of hemolysis and LVOT pressure gradient has been reported (27).

NORMALLY FUNCTIONING SURGICAL VALVE PROSTHESES. Subclinical MIH is frequently observed in patients with contemporary mechanical prostheses. Its incidence ranges from 26% to 95% according to the adopted diagnostic criteria (14,28,29). Nevertheless, hemolytic anemia is an infrequent finding in absence of prosthesis malfunction. Unfortunately, detailed evidence is available only for mechanical valves (**Table 3**), whereas model-specific data on bioprostheses are still lacking.

Older generation surgical valve prostheses. Available evidence showed that caged-ball prostheses were associated with the highest degree of MIH, particularly those in the aortic position. Eyster et al. (30) reported that laboratory signs of hemolysis were present in 72% of patients with an aortic caged-ball prosthesis. MIH was observed by Slater et al. (31) in 91.8% of patients with Starr-Edwards prostheses compared with 22.8% of patients with the Björk-Shiley tilting disk prostheses. Moreover, hemolysis was significantly more pronounced in caged-ball prostheses compared with tilting disk mitral prostheses (mean serum LDH: 1,023 ± 429 IU/l vs. 499 ± 181 IU/l). Hemolysis associated with the Starr-Edwards caged-ball model was higher in the aortic position than in the mitral position (5,31,32).

Contemporary surgical valve prostheses. The St. Jude (St. Jude Medical, Inc., St. Paul, Minnesota) and ATS-Medtronic Open Pivot (ATS Medical, Minneapolis, Minnesota, Medtronic, Minneapolis, Minnesota) mechanical bileaflet valve prostheses were associated with an intermediate degree of hemolysis (28,29,33,34). Bicarbon (Sorin Biomedica, Saluggia, Italy-Livanova, London, United Kingdom) and On-X (On-X Life Technologies Inc., Austin, Texas) bileaflet prostheses showed the lowest values of LDH (35,36). In contrast to caged-ball prostheses, bileaflet prostheses were associated with a higher degree of hemolysis when implanted in the mitral position (14,28,33,35,36). As expected, mean serum LDH was significantly higher after combined mitral and aortic valves implantation than after single valve implantation (29,36,37). Subclinical MIH was reported in only 5% of patients with bioprostheses (14), but it should be noted that the available evidence is scant.

TABLE 3 Serum LDH in Normally Functioning Contemporary Mechanical Valve Prostheses

Prothesis Model	Mean LDH (IU/l)	First Author (Ref. #)
Isolated aortic valve protheses		
St. Jude standard	594 ± 142 (271–864)	Lund (29)
St. Jude standard	582	Skoularigis (28)
St. Jude standard 19 mm	610 ± 62	Ismeno (34)
St. Jude HP	287 (163–374)	Suedkamp (37)
St. Jude HP 19 mm	580 ± 58	Ismeno (34)
St. Jude Regent	274 (151–386)	Suedkamp (37)
Sorin Bicarbon	226	Josa (35)
On-X	225 ± 41	Palatianos (36)
ATS	551 ± 182	Matskche (33)
Isolated mitral prothesis		
St. Jude	654	Skoularigis (28)
Sorin Bicarbon	258	Josa (35)
On-X	253 ± 65	Palatianos (36)
ATS	622 ± 133	Matskche (33)
Combined mitro-aortic protheses		
St. Jude	775	Skoularigis (28)
Sorin Bicarbon	334	Josa (35)
ATS	650 ± 82	Matskche (33)

Values are mean ± SD (range), mean, mean ± SD, or mean (range).
Abbreviation as in **Table 1**.

TRANSCATHETER AORTIC VALVE PROSTHESES. During the last decade, transcatheter aortic valve implantation (TAVI) has gained widespread use. Interest about hemolysis has been greater for transcatheter than surgical bioprostheses, probably because of the higher incidence of peri-prosthetic leaks in the former group. However, only a limited amount of published evidence is available on MIH following TAVI. MIH was detected in 15% of cases in the series from Laflamme et al. (38), which consisted of balloon- (95%) and self-expandable (5%) prostheses. Among patients with MIH, mean serum LDH was 287 ± 53 IU/l, and no patients experienced decompensated hemolytic anemia. The prevalence of MIH was also significantly dependent on the degree of patient–prosthesis mismatch. It was 6% in the absence of mismatch, but 18% and 31% when mismatch was moderate and severe, respectively. Finally, laboratory evidence of hemolysis was more frequently observed in patients with moderate to severe prosthetic valve regurgitation. Recently, Ko et al. (39) investigated the frequency of hemolysis at 6 months from TAVI implantation. In 81% of cases, a self-expandable prosthesis was implanted. Interestingly, subclinical MIH was present in 22% of patients before treatment and increased to 38% following

TAVI. However, the investigators did not observe any case of decompensated MIH. Mean serum level of haptoglobin decreased significantly after TAVI (from 126.7 ± 75.1 to 86.3 ± 57.1 mg/dl; p = 0.003). A bicuspid aortic valve and the severity of paravalvular leak were predictors of MIH. These findings are not surprising, because a bicuspid aortic valve is a well-known risk factor for the development of paravalvular leak following TAVI. Recently, Širáková et al. (40) reported a study on a series of 102 TAVIs with a CoreValve prosthesis (Medtronic). At 1 year from the procedure, the incidence of MIH varied from 9% to 28% according to the adopted definition of hemolysis. However, it was mild in all cases and significantly associated with moderate and/or severe peri-prosthetic regurgitation. The mean serum LDH was 238.8 ± 49.2 IU/l. The investigators did not observe a significant association with patient–prosthesis mismatch. The survival at 6 years was not influenced by the presence of hemolysis.

CLINICALLY SIGNIFICANT MIH OCCURRING AFTER SURGICAL VALVE PROCEDURES.

Mitral valve repair. MIH is an infrequent complication of mitral valve repair. Observed mechanisms of RBC destruction were collision of a moderate jet of residual mitral regurgitation on the prosthetic ring (41–43), moderate to severe mitral regurgitation secondary to prosthetic ring dehiscence (44), and rapid acceleration of blood flow through a small perforation of a leaflet (41) or through a small orifice (45). MIH was reported as secondary to systolic anterior motion of the mitral valve following a repair (46,47). It is likely that foreign surfaces of prosthetic rings and suture material serve as pathophysiological substrate for MIH in most cases. Yeo et al. (42) reported that most patients presented with signs of hemolysis within 3 months from the operation, and mitral regurgitation was severe in 62% of cases. The culprit regurgitant jet was usually absent at intraoperative post-repair transesophageal echocardiography. At re-operation, the initial repair was found intact in 67%. The largest series of MIH following mitral valve repair was published by Lam et al. (48); it consisted of 32 patients over a 21-year period. Median time from the initial operation to the presentation with hemolytic anemia was 3 months. Residual or recurrent mitral regurgitation was present in all the patients with MIH, and it was 3+ or 4+ in 77% of them. At re-operation, the initial repair was physically intact in most cases (81%). In the remaining cases, surgical inspection showed leaflet perforation or tear, dehiscence of the mitral ring. or rupture of expanded polytetrafluoroethylene neo-chords. Similar findings were also reported by Cerfolio et al. (49).

Aortic root replacement. Stanger et al. (50) reported a case of severe hemolytic anemia following aortic root replacement. The cause of RBC fragmentation was the high shear stress generated by a kink of the tube graft. MIH resolved completely following replacement of the tube graft.

Malfunction of surgical valve prostheses. Clinically relevant MIH may complicate a paravalvular regurgitation secondary to prosthesis dehiscence, which can occur either early or late after surgery. Unfortunately, a large series describing patients with MIH secondary to valve prosthetic malfunction has not been published. The incidence of clinically significant peri-prosthetic leak without obvious infection is low, being 6% and 19.7% at 20 years following first and re-do mitral valve replacement, respectively (51). MIH has been reported in 34% of 259 patients with peri-prosthetic leaks (52). Therefore, most leaks are not complicated by clinically significant hemolysis. Lund et al. (29) observed that serum LDH were sensibly higher in patients with moderate peri-prosthetic regurgitation (range: 1,117 to 1,874 IU/l) compared with patients without it (mean: 594 IU/l). An elevated LDH mean value (mean: 707 IU/l; range: 620 to 805 IU/l) was also detected in trivial peri-prosthetic regurgitation. Even if larger leaks are usually associated with a higher degree of MIH, hemodynamically significant leaks can be present without substantially elevated LDH (37). Hemolysis rarely occurs because of the structural degeneration of a bioprosthesis, particularly when the device becomes severely stenotic (53,54). Brown et al. (55) reported an unusual case of dissection of a leaflet of a Carpentier-Edwards porcine mitral bioprosthesis (Edwards Lifesciences, Irvine, California) associated with the occurrence of severe MIH. The likely mechanism of MIH was the acceleration of RBCs through the dissecting tract. Hemolytic anemia resolved following the replacement of the malfunctioning bioprosthesis with another porcine valve.

CLINICALLY SIGNIFICANT MIH FOLLOWING TRANSCATHETER MITRAL VALVE PROCEDURES.

Acute hemolysis has been observed rarely following transcatheter edge-to-edge mitral valve repair using MitraClip (Abbott Vascular, Abbott Park, Illinois), and it was associated with the persistence of mitral regurgitation after the procedure (56,57). Recent evidence (58) showed that the incidence of MIH was significantly higher after transcatheter mitral valve implantation (TMVI) into a severely calcified mitral annulus (38.5%) compared with valve-in-valve (1.5%) and valve-in-ring (7.1%) procedures. Frequently, the cause of hemolysis was a mild or greater

peri-prosthetic leak. In other cases, MIH was secondary to LVOT obstruction from a protruding mitral prosthesis or the impact of a regurgitant jet from the aortic valve on the mitral prosthesis. Interestingly, 2 cases of early fulminant hemolysis were also reported following TMVI (59,60).

TREATMENT OF MIH COMPLICATING SURGICAL VALVE PROCEDURES

PROGNOSIS OF MIH-ASSOCIATED ANEMIA. Unfortunately, few studies specifically addressed the impact on the prognosis of the hemolytic anemia secondary to valvular and prosthetic dysfunction. Mild MIH is common among patients with a prosthetic heart valve, and it is likely that it does not worsen the long-term prognosis. Moderate forms could be tolerated for years, especially if periodic blood transfusions are not required. A spontaneous and consistent improvement of relevant MIH can be observed infrequently in clinical practice, and it has been anecdotally reported in the literature (55). Poor survival is expected when frequent blood transfusions are needed, and severe congestive heart failure and chronic renal failure are concomitant. Among patients with mild to moderate peri-prosthetic mitral regurgitation, hemolytic anemia at diagnosis was the only predictor of event-free survival at 3 years (61). Therefore, correction of the valvular condition that causes clinically significant MIH is recommended, whenever feasible. Fulminant hemolysis can be life-threatening, and it may require urgent correction. Supportive care is not curative, and it is aimed at decreasing the frequency of blood transfusions and increasing the quality of life.

SURGICAL TREATMENT. Replacement of a malfunctioning prosthesis (11) or the suture of the prosthetic dehiscence are effective treatments of clinically relevant MIH in most patients. Hematological evaluation is of paramount importance to ascertain the relative contribution of MIH to anemia and to evaluate the risk/benefit ratio of re-operation. The European Society of Cardiology Guidelines (12) recommend re-operation if a peri-prosthetic leak causes hemolysis that requires multiple blood transfusions or severe anemia-related symptoms. Therefore, clinically significant MIH could indicate the need of re-operation even if the peri-prosthetic leak is less than severe. Similarly, the American Heart Association/American College of Cardiology Guidelines recommend re-operation in operable patients with a mechanical prosthesis, severe prosthetic or peri-prosthetic regurgitation, and intractable hemolysis (62). The replacement of a normally functioning mechanical prosthesis with a bioprosthesis could be considered in cases of new-onset decompensated anemia secondary to MIH in patients affected by previously unknown genetic disease of the erythrocyte membrane and who require periodic blood transfusions (9,18). Obviously, the potential benefit should be weighed against the surgical risk of the re-operation on a case-by-case basis. MIH complicating mitral valve repair can be effectively treated by valve replacement (41,42,46,48) or even re-repair in select cases (42,44,48,49). In-hospital mortality of the re-operation for MIH after mitral valve repair ranges from 0% to 6% (48,49).

ALTERNATIVE TREATMENTS OF MIH FOR HIGH-RISK AND INOPERABLE PATIENTS. Transcatheter treatment. Transcatheter closure of peri-prosthetic leaks is gaining increasing diffusion and may be indicated to treat clinical MIH in patients at high or prohibitive surgical risk (12,62). However, clinical outcomes are still suboptimal because of the technical difficulty of the procedure. Particularly, the procedure seems to be less effective for hemolysis compared with symptoms of congestive heart failure (62–64). Interestingly, MIH may worsen following attempted transcatheter closure in one-third of cases and new-onset MIH may develop in 10% of patients (65,66). It has been suggested that the outcome following closure may depend more on elimination (or the generation) of the paravalvular microjets that produce high shear stress than on the reduction of the regurgitant volume (64,67). It could be hypothesized that a favorable modification of these microjets-secondary to endothelization, thrombosis, or inflammation-could be involved in cases of spontaneous resolution of MIH. Kliger et al. (68) reviewed the published experiences on transcatheter closure of leaks in 252 patients. Technical success (defined as the correct deployment of the device, without significant residual regurgitation or new prosthetic valve malfunction) was achieved in 78.9% of cases, but clinical success (improvement in dyspnea and/or mechanical hemolysis) occurred only in 63%. By considering only the outcomes from the 2 largest studies, technical and clinical success increased up to 86% and 76,7%, respectively. Recently improved results were reported in a series of 28 patients with MIH secondary to a peri-prosthetic leak (69). The success rate in eliminating the need for blood transfusions was 84% and 100% among the patients who underwent transcatheter closure of mitral and aortic peri-prosthetic leaks, respectively.

Supportive medical treatment. Increased RBC turnover secondary to ongoing MIH may deplete body stores of vitamins needed for hemopoiesis. Iron stores and hemoactive vitamin (i.e., folic acid, vitamins B12 and B6) levels should be periodically checked in all patients after valve surgery and supplementation started to correct any deficiency (70). This policy may prevent worsening of anemia and need for RBC transfusions.

Erythropoietin. Therapy with recombinant erythropoietin has proved to be anecdotally effective in severe hemolytic anemia secondary to valve prosthesis malfunction in inoperable patients. It allowed amelioration of both blood hemoglobin level and symptoms from congestive heart failure and significantly decreases the need of frequent transfusions (21,71). Renal hemosiderosis has been proposed as a cause of inadequate erythropoietin production in patients affected by severe MIH (21), promoting the decompensation of anemia. Moreover, erythropoietin may decrease the iron overload secondary to chronic hemolysis by enhancing iron mobilization from the reticulo-endothelial and parenchymal sites to be used for hematopoiesis. Therapy with erythropoietin is indicated if the circulating level of native erythropoietin is inadequate to the degree of anemia and is particularly beneficial in the presence of chronic renal failure, which is highly prevalent in severe MIH.

Pentoxifylline. Pentoxifylline is a xanthine derivative that increases erythrocyte deformability and decreases blood viscosity and platelet aggregation. It may have a potential therapeutic role for MIH through the improvement of the ability of RBCs to withstand conditions of high shear stress (72). In a randomized controlled trial, pentoxifylline (400 mg orally 3 times/day) was associated with a significant improvement in signs of MIH in 60% of patients with aortic and mitral mechanical prostheses (73). However, the lack of benefit from pentoxifylline has been reported by other investigators (74).

Propranolol. The nonselective beta-blocker propranolol may decrease the shear stress acting on circulating RBCs through its negative chronotropic and inotropic effects. Two case reports (75,76) have been published showing some improvement of valve prosthesis–related MIH following treatment with propranolol.

CONCLUSIONS AND CLINICAL PERSPECTIVES

MIH occurs frequently following heart valve replacement with surgical prostheses, but in most cases, it is mild without negatively affecting long-term prognosis. Emerging evidence shows that TAVI seems to be associated with a minimal degree of hemolysis, even if a significant peri-prosthetic leak is present. The method of implantation and the absence of a bulky sewing ring with a fabric covering could explain the superiority of TAVI on the surgical prostheses in terms of MIH. The malfunction of a valve prosthesis increases the risk of developing clinically significant hemolysis. Therefore, the diagnosis of malfunction should prompt a workup for hemolysis and vice versa. The interpretation of laboratory tests is greatly facilitated by the knowledge of hemolysis values in the past. Therefore, the importance of evaluating them periodically during post-operative follow-up cannot be overstated. The consultation of the hematologist is especially advised in patients with chronic anemia in whom the relative contribution of the hemolysis is difficult to ascertain. The prognosis of the patients affected by MIH and congestive heart failure secondary to a prosthetic malfunction is poor, particularly if frequent blood transfusions are needed. Supportive care should be managed in cooperation with the hematologist. The correction of the malfunction is the only curative option, and surgery remains the gold standard of therapy, but with an increased in-hospital mortality. Transcatheter closure of a peri-prosthetic leak is currently a good alternative for patients judged inoperable because of their health status or anatomical difficulties. Such techniques are showing a continuous improvement in terms of clinical success, and, in perspective, their benefits in terms of low biological invasiveness could be extended to most patients.

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