Intravascular hemolysis in patients with new-generation prosthetic heart valves: A prospective study

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Objective: A prospective clinical study was designed to assess the frequency and severity of intravascular hemolysis in patients with new-generation, normally functioning prosthetic heart valves.

Methods: Hemolysis was evaluated in 172 patients with a mechanical prosthesis (53 CarboMedics and 119 Sorin Bicarbon) and in 106 patients with a bioprosthesis (15 St Jude Medical Toronto, 19 Baxter Perimount, and 72 Medtronic Mosaic) in the aortic position, mitral position, or both. Aortic valve replacement was performed in 206 patients, mitral valve replacement in 59 patients, and double valve replacement in 13 patients. The presence of hemolysis was assessed on the basis of the level of serum lactic dehydrogenase and serum haptoglobin and the presence and amount of reticulocytes and schistocytes in the peripheral blood. Severity of intravascular hemolysis was estimated on the basis of serum lactic dehydrogenase. Clinical, echocardiographic, and hematologic evaluations were performed 1, 6, and 12 months after discharge.

Results: None of the 278 patients experienced decompensated anemia, whereas at 12 months, mild subclinical hemolysis was identified in 49 patients, 44 (26%) with a mechanical prosthesis and 5 (5%) with a bioprosthesis ($P < .001$). At multivariate analysis, independent predictors of the presence of subclinical hemolysis were mitral valve replacement ($P < .001$), use of a mechanical prosthesis ($P = .002$), and double valve replacement ($P = .02$). Frequency of hemolysis in patients with stented aortic bioprostheses was 3%, whereas it was absent in those with stentless valves. Among mechanical valve recipients, double versus single valve replacement ($P = .04$) and mitral versus aortic valve replacement ($P = .05$) were correlated with the presence of hemolysis; double valve recipients also showed a more severe degree of hemolysis ($P = .03$). In patients with a Sorin Bicarbon prosthesis, hemolysis was less frequent (22% vs 34%, $P = .09$) and severe ($P < .001$) than in those with a CarboMedics prosthesis.

Conclusions: In normally functioning prosthetic heart valves, subclinical hemolysis is a frequent finding. A low incidence of hemolysis is found in stented biologic prostheses, and it is absent in stentless aortic valves. Modifications of valve design may contribute to minimize the occurrence of hemolysis in mechanical prostheses.

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Since the implantation of the first mechanical prosthesis by Hufnagel in 1956,[1] traumatic hemolysis has been recognized as a potentially serious problem after heart valve replacement. This complication, reported to occur in 5% to 15% of patients with a ball-caged valve, is rarely observed with current normally functioning prostheses but is still encountered in the setting of prosthetic valve dysfunction and regurgi-

tation.[2,3] However, it has been demonstrated that chronic subclinical hemolysis may be present in patients with mechanical or biologic valve prostheses.[4-6] Turbulence of flow with high shear-stress forces and abnormal flow jets through the prosthetic valve are thought to be causes of hemolysis.[7-9] Accordingly, modifications of valve design may contribute to the minimization of the occurrence of such complications by enhancing hemodynamic performance. The aim of this study was to evaluate prospectively the presence of hemolysis in patients with new-generation prosthetic valves and to correlate the frequency and severity of hemolysis to prosthesis number, type, size, and position.

Materials and Methods

Patient Population

From January 1997 to December 1998, a total of 434 patients who underwent mitral valve replacement (MVR), aortic valve replacement (AVR), or both were discharged with normally functioning prosthetic valves. Patients with renal, hepatic, or pulmonary disease were excluded from the study. Informed consent to be enrolled in this study was obtained from 300 patients. However, a complete set of clinical, hematologic, and echocardiographic assessments was available for only 280 of them. Two patients showing paraprosthetic leak at follow-up echocardiography were removed from the study, and the remaining 278 patients form the basis of the present report.

There were 157 men and 121 women, with a mean age of 67 ± 9 years (range, 27-86 years). The main preoperative characteristics are summarized in Table 1.

AVR was performed in 206 (74%) patients, MVR was performed in 59 (21%) patients, and MVR plus AVR (double valve replacement [DVR]) was performed in 13 (5%) patients. For AVR, a mechanical prosthesis was used in 113 (41%) patients, and a bioprosthesis was used in 93 (33%) patients. MVR was performed with a mechanical prosthesis in 46 (17%) patients and with a bioprosthesis in 13 (5%) patients. All patients with DVR received mechanical prostheses. A total of 291 prostheses were implanted: 53 CarboMedics (CM; Sulzer Carbomedics, Inc, Austin, Tex), 119 Sorin Bicarbon (SB; Sorin Biomedica Spa, Saluggia, Italy), 15 St Jude Medical Toronto stentless (St Jude Medical, Inc, St Paul, Minn), 19 Baxter Perimount (Baxter Healthcare Corp, Edwards Division, Santa Ana, Calif), and 72 Medtronic Mosaic (Medtronic, Inc, Minneapolis, Minn) prostheses. All patients were receiving oral anticoagulant therapy with warfarin for 3 months after the operation. Thereafter, only patients with a mechanical prosthesis or those in chronic atrial fibrillation continued oral anticoagulation.

Study Protocol

Patients were evaluated preoperatively and postoperatively at 1, 6, and 12 months. Every follow-up examination consisted of (1) clinical evaluation with investigation for other possible causes of hemolytic anemia, (2) assessment of prosthetic valve function by means of transthoracic or transesophageal echocardiography, and (3) hematologic evaluation of hemolysis, as measured by total blood hemoglobin level, serum lactic dehydrogenase (LDH) level, serum haptoglobin level, reticulocyte count, and presence of schistocytes on a peripheral blood smear. All tests were performed in the same laboratory.

TABLE 1. Patient characteristics

No. of patients	278
Sex (M/F)	157/121
Age (y)	67 ± 9
NYHA class	2.5 ± 0.7
Sinus rhythm	232 (83%)
Atrial fibrillation	35 (13%)
Pacemaker	11 (4%)
Left ventricular ejection fraction (%)	51 ± 10
LDH (U/L)	357 ± 123
Haptoglobin (g/L)	1.8 ± 1.2
Hemoglobin (g/dL)	12.9 ± 1.6
Reticulocytes	1.6 ± 0.4
AVR	206 (74%)
Mechanical	113 (41%)
Biologic	93 (33%)
MVR	59 (21%)
Mechanical	46 (17%)
Biologic	13 (5%)
DVR	13 (5%)
Mechanical	13 (5%)

NYHA, New York Heart Association.

Criteria for Hemolysis

As suggested by Skoularigis and colleagues,[10] patients were considered to have intravascular hemolysis under the following conditions:

1. Serum LDH levels were greater than 460 U/L (normal, 230-460 U/L).
2. Any 2 of the following 4 criteria were present: (1) blood hemoglobin level of less than 13.8 g/dL for male patients (normal, 13.8-17.9 g/dL) and less than 12.4 g/dL for female patients (normal, 12.4-15.5 g/dL); (2) serum haptoglobin levels of less than 0.5 g/L (normal, 0.5-3.2 g/L); (3) reticulocyte count of greater than 2% (normal, <2%); or (4) presence of schistocytes in the peripheral blood smear (normally absent).

Frequency of hemolysis has been reported only at 12 months. Severity of intravascular hemolysis was estimated on the basis of serum LDH levels at 12 months.

Statistical Analysis

Data are presented as means ± SD and as simple percentages. A separate analysis was performed to identify the variables associated with the presence of subclinical hemolysis in the overall population, in aortic valve recipients, in mitral valve recipients, in mechanical valve recipients, and in bioprosthesis recipients. The variables analyzed were the following: sex; age; heart rhythm; use of mechanical or biologic prosthesis; prosthetic model, size, and site of implantation; single valve replacement or DVR; aortic and mitral peak and mean transprosthetic gradients; and left ventricular ejection fraction. Univariate analysis was performed with the χ^2 test or the Fisher test, as appropriate, for discrete variables and with the paired t test or the Mann-Wilcoxon test for continuous

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TABLE 2. Variables associated with hemolysis at univariate and multivariate analysis

	Hemolysis			Multivariate	
	Absent	Present	Univariate *P* value	*P* value	OR (95% CI)
Overall population					
Mean age (y)	67 ± 9	64 ± 10	.09	>.20	
Male/female (%)	85/79	15/21	.14		
MVR/AVR (%)	64/89	36/11	<.001	<.001	3.4 (1.7-7.0)
DVR/single valve replacement (%)	54/84	46/16	.006	.02	3.9 (1.2-13)
Mechanical/biologic prosthesis (%)	74/95	26/5	<.001	.002	4.9 (1.8-13)
Aortic valve recipients					
Mean age (y)	67 ± 9	63 ± 11	.07	>.20	
Aortic peak transprosthetic gradient	20 ± 8	25 ± 7	.01	>.20	
Aortic mean transprosthetic gradient	12 ± 5	15 ± 5	.03	>.20	
DVR/AVR (%)	54/89	46/11	.003	>.20	
Mechanical/biologic prosthesis (%)	79/98	21/2	<.001	.001	9.3 (1.6-53)
Mitral valve recipients					
Male/female (%)	75/58	25/42	.17		
Left ventricular ejection fraction	55 ± 5	52 ± 9	.17		
Aortic peak transprosthetic gradient	9 ± 3	7 ± 3	.16		
Mechanical valve recipients					
Male/female (%)	80/66	20/34	.05	>.20	
CM/SB prosthesis (%)	66/78	34/22	.09	.13	1.8 (0.8-3.8)
MVR/AVR (%)	63/79	37/21	.04	.05	2.3 (1.0-5.6)
DVR/AVR (%)	54/76	46/24	.08	.04	3.5 (1.0-12)
Bioprosthesis recipients					
MVR/AVR (%)	77/98	23/2	.01	.007	13.6 (2.0-92)

TABLE 3. Hematologic data

	1 mo	6 mo	1 y
Bioprostheses (n = 106)			
Hemoglobin (g/dL)	12.9 ± 1.3	13.6 ± 1.5	13.6 ± 1.8
Reticulocytes (%)	1.6 ± 0.6	1.5 ± 0.6	1.6 ± 0.6
Presence of schistocytes	–	–	–
LDH (U/L)	439 ± 122	424 ± 106	426 ± 113
Haptoglobin (g/L)	1.82 ± 0.99	1.53 ± 0.81	1.44 ± 0.76
Hemolysis (%)	6.3	4.7	4.7
Mechanical prostheses (n = 172)			
Hemoglobin (g/dL)	12.9 ± 1.4	13.9 ± 1.6	14.0 ± 1.6
Reticulocytes (%)	1.8 ± 0.6	1.6 ± 0.5	1.6 ± 0.5
Presence of schistocytes	3	1	1
LDH (U/L)	516 ± 134	525 ± 145	535 ± 140
Haptoglobin (g/L)	0.59 ± 0.82	0.32 ± 0.49	0.30 ± 0.44
Hemolysis (%)	29.3	25.6	25.6

variables. All parameters showing a *P* value of less than .10 at univariate analysis were introduced in a stepwise logistic regression for multivariate analysis. Only variables associated with hemolysis with *P* values of less than .20 at univariate or multivariate analysis were reported in Table 2.

Repeated-measures analysis of variance (ANOVA) with the Bonferroni multiple comparison test was used to assess the influence of time on serum LDH and haptoglobin levels. The α value for the Bonferroni test was set at .05. Statistical analysis was performed with NCSS 2000 software (Statistical Solutions Ltd, Cork, Ireland).

Results

Overall Population

All 278 patients underwent clinical, hematologic, and echocardiographic evaluation at 1, 6, and 12 months after the operation. All patients showed a significant clinical improvement during follow-up in terms of mean New York Heart Association functional class. Echocardiographic examination ruled out prosthetic dysfunction and the presence of periprosthetic leaks in all cases. Patients with a mechanical prosthesis showed mean LDH levels at 12-month follow-up that were significantly higher than those of patients with a bioprosthesis (535 ± 140 U/L vs 431 ± 138 U/L, $P < .001$). None of the 278 patients had decompensated anemia caused by intravascular hemolysis, whereas at 12 months, mild subclinical hemolysis was identified in 49 patients, 44 (26%) with a mechanical prosthesis and 5 (5%) with a bioprosthesis. At multivariate analysis, independent predictors of the presence of subclinical hemolysis at 12 months were MVR ($P < .001$; odds ratio [OR], 3.4; 95% confidence interval [CI], 1.7-7.0), use of a mechanical prosthesis ($P = .002$; OR, 4.9; 95% CI, 1.8-13), and DVR ($P = .02$; OR, 3.9; 95% CI, 1.2-13; Table 2).

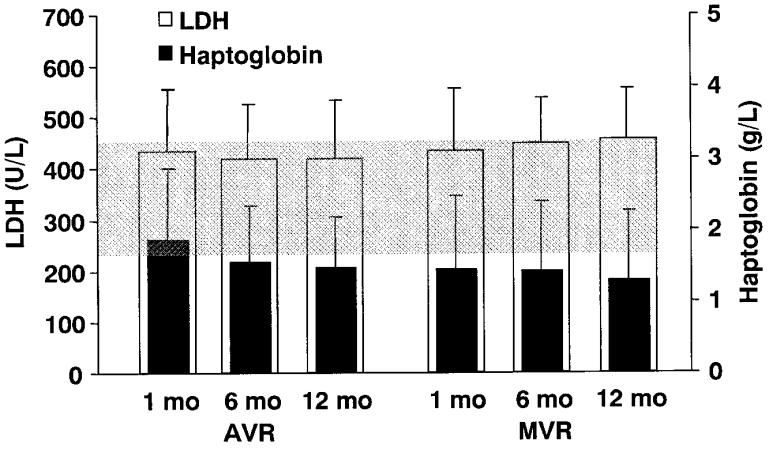

Figure 1. Serum LDH (in units per liter) and haptoglobin (in grams per liter) distribution at 1, 6, and 12 months after AVR and MVR with a bioprosthesis. The *horizontal gray band* represents the range of normality for LDH levels.

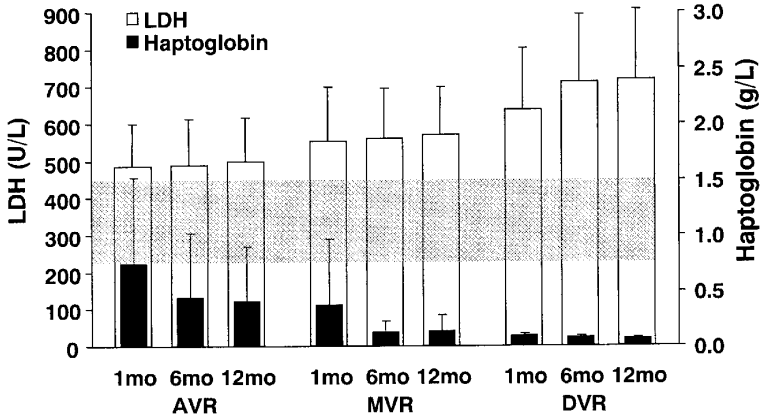

Figure 2. Serum LDH (in units per liter) and haptoglobin (in grams per liter) distribution at 1, 6, and 12 months after AVR, MVR, and DVR with a mechanical prosthesis. The *horizontal gray band* represents the range of normality for LDH levels.

Considering only patients with subclinical hemolysis at 1 year, mean levels of LDH were 593 ± 104 U/L for patients undergoing AVR versus 654 ± 134 U/L for patients undergoing MVR ($P = .05$), 641 ± 134 U/L for mechanical valve recipients versus 535 ± 75 U/L for bioprosthesis recipients ($P = .04$), and 809 ± 195 U/L for patients undergoing DVR versus 621 ± 122 U/L for patients undergoing single valve replacement ($P = .002$).

In the subgroup of patients with AVR, multivariate analysis indicated the use of a mechanical prosthesis as the only independent predictor of subclinical hemolysis at 12 months ($P = .001$; OR, 9.3; 95% CI, 1.6-53; Table 2). In the subgroup of patients with MVR, multivariate analysis was not performed because no variables were associated with subclinical hemolysis at 12 months with a P value of .10 or less at univariate analysis (Table 2).

Bioprostheses

At all follow-up intervals, the majority of patients with a bioprosthesis had hemoglobin, LDH, and haptoglobin levels and reticulocyte counts within the range of normality (Table 3). Serum LDH levels showed a small but significant decrease during follow-up (ANOVA F = 3.1, $P = .05$) and were slightly lower in patients with an aortic than in those with a mitral bioprosthesis (421 ± 115 U/L vs 458 ± 97 U/L at 12-month follow-up, $P = .07$; Figure 1). Only 5 (5%) patients with a bioprosthesis fulfilled the criteria for intravascular hemolysis, 2 (3%) patients with an aortic

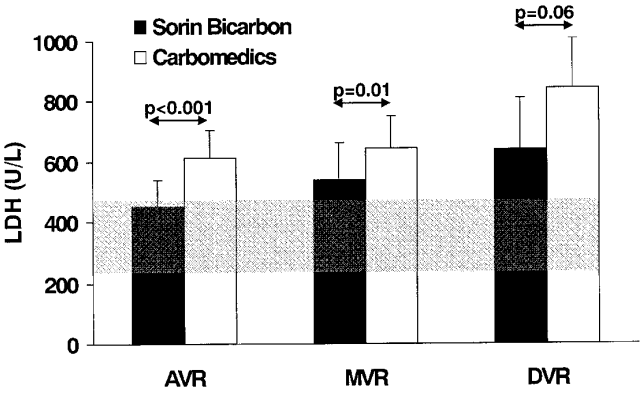

Figure 3. Serum LDH (in units per liter) levels at 12 months after AVR, MVR, and DVR with an SB or CM prosthesis. The *horizontal gray band* represents the range of normality for LDH levels.

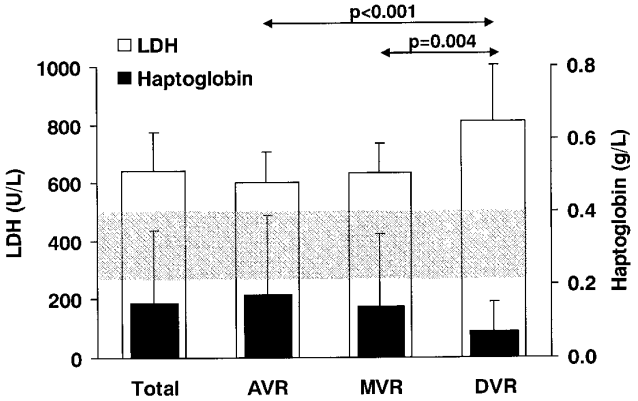

Figure 4. Serum LDH (in units per liter) and haptoglobin (in grams per liter) levels at 12 months in patients with subclinical hemolysis after AVR, MVR, and DVR with a mechanical prosthesis. The *horizontal gray band* represents the range of normality for LDH levels.

stented valve and 3 (23%) with a porcine valve in the mitral position. None of the 15 patients with a stentless aortic bioprosthesis showed signs of intravascular hemolysis. At multivariate analysis, the only independent predictor of subclinical hemolysis at 12 months was MVR (P = .007; OR, 13.6; 95% CI, 2.0-92; Table 2).

Mechanical Prostheses

Serum LDH levels significantly increased during follow-up (ANOVA F = 6.2, P = .002), with levels at 12-month follow-up being significantly higher than those at 1-month follow-up (P = .04, Bonferroni test; Table 3 and Figure 2). At 12-month follow-up, mean levels of LDH were 718 ± 192 U/L for patients undergoing DVR versus 520 ± 123 U/L for patients undergoing single valve replacement (P < .001) and 500 ± 116 U/L for patients undergoing AVR versus 569 ± 129 U/L for patients undergoing MVR (P = .001). Serum levels of LDH in patients with an SB were lower than those found in patients with a CM prosthesis after AVR (450 ± 88 U/L vs 609 ± 93 U/L, P < .001), MVR (539 ± 126 U/L vs 644 ± 109 U/L, P = .01), and DVR (639 ± 170 U/L vs 844 ± 167 U/L, P = .06; Figure 3). Serum haptoglobin levels significantly decreased during follow-up (ANOVA F = 30.7, P < .001, Figure 2); the Bonferroni test showed a significant difference between 1-month follow-up and both 6- and 12-month follow-up (P < .001). At 12-month follow-up, haptoglobin levels were abnormally reduced in 60% of patients undergoing AVR, 79% of patients undergoing MVR, and 100% of patients undergoing DVR. However, hemoglobin levels and reticulocyte counts were approximately within the normal range, indicating that decompensated anemia was not occurring in these patients.

Forty-four (26%) patients with mechanical valves fulfilled the criteria for hemolysis: 21 after AVR, 17 after MVR, and 6 after DVR. A difference in the frequency of hemolysis between AVR and MVR (21% vs 37%, P = .04) and between DVR and single valve replacement (46% vs 24%, P = .08) was found. Hemolysis was also more frequent in patients with a CM (34%) than in patients with an SB (22%, P = .09). At multivariate analysis, independent predictors of the presence of subclinical hemolysis at 1 year were DVR (P = .04; OR, 3.5; 95% CI, 1.0-12) and MVR (P = .05; OR, 2.3; 95% CI, 1.0-5.6; Table 2).

Considering only patients with subclinical hemolysis at 1 year, mean levels of LDH were 809 ± 195 U/L after DVR, 599 ± 106 U/L after AVR (P < .001 vs DVR), and 633 ± 99 U/L after MVR (P = .004 vs DVR, Figure 4). Serum levels of LDH in patients with an SB were lower than those found in patients with a CM, irrespective of valve position (728 ± 123 U/L vs 580 ± 107 U/L, P < .001).

Discussion

Mild degrees of intravascular hemolysis are common among patients with normally functioning prostheses.[6,10-13] Absence of severe hemolysis in the present series may be related to the use of newer-generation valves and better methods of evaluating prosthetic valve function. Transesophageal echocardiography is increasingly used in the evaluation of prosthetic dysfunction and is particularly useful in determining the site and mechanism of prosthetic regurgitation.[14] Detection of subclinical periprosthetic leaks is important because they contribute to the degree of intravascular hemolysis.[2] Intravascular hemolysis has been reported also in patients with dysfunctional biologic prostheses in the aortic, as well as the mitral, position.[15,16] Experimental works with stented porcine or pericardial prostheses have shown that turbulent shear stresses might cause endothelial damage and sublethal or lethal damage to

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blood corpuscles.[17,18] This can explain the few cases of subclinical hemolysis found in our series of patients with biologic prostheses. Moreover, none of the patients with a stentless porcine aortic valve showed subclinical hemolysis, most likely indicating a better hemodynamic performance and flow characteristics of such devices.[19,20] Intravascular hemolysis may be found in 40% to 85% of patients with normally functioning mechanical prostheses.[1,6,10,11] Early reports showed higher LDH levels for aortic ball valves,[21] but this trend was reversed for some tilting disc valves[22] and for bileaflet valves.[5,11] In the present series of patients with a new generation of bileaflet prosthetic valves, subclinical hemolysis was found in 26% of patients. We also observed a greater frequency and severity of hemolysis in patients undergoing DVR, as reported by others.[10,23] Significant LDH elevation occurs after single AVR or MVR, but it is higher in patients undergoing MVR.

Recently, fluid-dynamic simulation models have identified distinct patterns of regurgitant flow disturbances in patients with mitral mechanical prostheses that were associated with high shear stress and may therefore produce hemolysis.[14] This observation would indicate that low levels of hemolysis generated by bileaflet valves are probably caused by backflow and closing phenomena rather then forward flow.[24] The SB and CM prostheses are widely used, and many reports have confirmed their excellent hemodynamics and durability, but there are no reported studies comparing the incidence of hemolysis with these 2 prostheses. The results of our study show that in the present series SB prostheses were associated with a lower severity of hemolysis than CM prostheses. Several factors may account for this, but we believe that the peculiar design of the SB prosthesis with the curved profile of the 2 leaflets may play an important role. Indeed, in vitro studies have demonstrated a shorter spatial extension of the turbulent zone in the forward flow phase in this prosthesis when compared with prostheses with 2 flat-surface leaflets.[25] Moreover, experimental studies comparing leakage flow and shear stress within the gap flow of different mechanical bileaflet valves have shown that the SB prosthesis has a lower blood-damage index and hemolysis than the CM prosthesis.[24] Finally, we were not able to identify any possible correlation between the frequency and severity of intravascular hemolysis and cardiac rhythm, left ventricular ejection fraction, prosthetic size, and transprosthetic peak and mean pressure gradients. Furthermore, the low levels of hemolysis observed, particularly in mechanical valve recipients, in the present study were of no clinical relevance at 1-year follow-up, and in our opinion they should not represent a problem in the long term.

In conclusion, in normally functioning prosthetic heart valves subclinical hemolysis is a frequent finding that remains stable during follow-up. A low incidence of hemolysis is found in stented biologic prostheses, whereas it is absent in stentless valves after AVR. Modifications of valve design may contribute to a further minimization of the occurrence of hemolysis in mechanical prostheses.

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