Hemolysis After Mitral Valve Replacement With Mechanical Valve Prostheses

Objective: **We evaluated effects of type, size, and orientation of mechanical mitral valve prostheses on hemolysis.** ***Methods:*** **Subjects were 84 patients who had undergone mitral valve replacement. Lactate dehydrogenase was mainly used as a marker of hemolysis and was measured before surgery, 1 month after surgery, and in the late postoperative period.** ***Results:*** **Valves used included 16 Medtronic-Hall, 32 St. Jude Medical, and 36 CarboMedics valves. Medtronic-Hall valves caused less hemolysis than St. Jude Medical or CarboMedics valves in the late postoperative period. This resulted because hemolysis due to Medtronic-Hall valves was more severe 1 month after surgery than in the late postoperative period and because hemolysis due to St. Jude Medical or CarboMedics valves was more severe in the late postoperative period than 1 month after surgery. One reason for this finding is that cardiac output was greater in the late postoperative period than 1 month after surgery, making regurgitation through the pivots of bileaflet valves more severe. The orifice area and the orientation of prostheses did not affect hemolysis.** ***Conclusion:*** **St. Jude Medical or CarboMedics valves caused more severe hemolysis than Medtronic-Hall valves in the late postoperative period. (JJTCVS 2001; 49: 230–235)**

Key words: mitral valve replacement, hemolysis, mechanical heart valve prosthesis

Mikio Ninomiya, MD, Kuniyoshi Yagyu, MD,* Yukihiro Kaneko, MD, Yutaka Kotsuka, MD, and Shinichi Takamoto, MD.

Since implantation of the first mechanical prosthesis by Hufnagel in 1956, hemolysis has been recognized as a potentially serious complication. Despite many studies on hemolysis after valve replacement, few reports have described changes in postoperative hemolysis.[1,2] In this study, we evaluated the effects of type, size, and orientation of mechanical mitral valve prostheses on hemolysis, and changes in the severity of hemolysis over time.

Subjects and Methods

From 1981 to 1998, 350 adult patients underwent single mitral valve replacement at our institution. Of these, patients who had undergone valve replacement with Medtronic-Hall (MH), St. Jude Medical (SJM), or CarboMedics (CM) valves, and those who have been followed up at our outpatient clinic through September 1999 were included in this study. Patients with liver dysfunction (glutamic pyruvic transaminase > 40 IU/l), paravalvular leakage, tricuspid regurgitation of degree 2 or more, or a history of tricuspid annuloplasty with a ring prosthesis were excluded. Blood test results of hemolysis markers measured before surgery, about 1 month after surgery, and at the most recent outpatient clinic visit (7.2 ± 4.1 years after surgery) were recorded. Lactate dehydrogenase (LDH), glutamic oxaloacetic transaminase (GOT), total bilirubin (TB), and LDH isozyme-1 and 2 (LDH-1,2) were used as hemolysis markers. LDH isozymes were measured only at the outpatient clinic. Normal ranges for each marker are LDH: 125–237 IU/l; GOT: 9–38 IU/l; TB: 0.3–1.3 mg/dl; LDH-1: 17.8–32.6%; and LDH-2: 29.0–39.0%. Units are omitted hereafter. Blood pressure and heart rate were recorded about 1 month after surgery and at the most recent outpatient clinic visit.

From the Department of Cardiothoracic Surgery, Faculty of Medicine, University of Tokyo, Tokyo, Japan, and *Department of Cardiovascular Surgery, Japanese Red Cross Medical Center, Tokyo, Japan.

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Address for reprints: Mikio Ninomiya, MD, 6–15–13–902 Hon-Komagome, Bunkyo-ku, Tokyo 113–0021, Japan.

Table I. *Patient profiles*

	MH group (n = 16)	*SJM group (n = 25)*	*CM group (n = 29)*	*AR group (n = 14)*
age (year)	57.9 ± 10.5	57.5 ± 10.7	56.8 ± 10.9	55.5 ± 7.4
male/female	7/9	9/16	13/16	4/10
time from operation (year)	12.5 ± 3.0*	7.6 ± 5.2	3.9 ± 2.0	7.3 ± 5.2
mitral stenosis/regurgitation	8/8	15/10	16/13	7/7
atrial fibrillation/sinus rhythm	14/2	20/5	20/9	12/2
NYHA functional class I/II	3/13	3/22	7/22	3/11

NYHA, New York Heart Association. *, p < 0.01 vs CM group.

Table II. *Changes in hemolysis markers*

measurements	*groups*	*before operation*	*early postoperative period*		*late postoperative period*	
LDH (IU/l)	MH	253 ± 94	363 ± 136	**	260 ± 42	* (MH vs SJM); # (MH vs CM)
	SJM	167 ± 68	218 ± 55	##	337 ± 78	
	CM	217 ± 124	302 ± 129	*	378 ± 127	
GOT (IU/l)	MH	28.3 ± 6.8	33.7 ± 12.3		30.9 ± 7.9	
	SJM	21.4 ± 4.9	25.5 ± 6.2		34.2 ± 15.3	
	CM	23.5 ± 7.6	26.3 ± 9.3		31.2 ± 10.7	
TB (mg/dl)	MH	1.2 ± 1.1	0.8 ± 0.4		0.6 ± 0.3	
	SJM	0.9 ± 0.5	0.5 ± 0.3		0.6 ± 0.2	
	CM	0.7 ± 0.4	0.5 ± 0.2		0.6 ± 0.4	
LDH-1 (%)	MH	—	—		29.0 ± 3.0	** (MH vs SJM); ## (MH vs CM)
	SJM	—	—		32.5 ± 3.7	
	CM	—	—		34.8 ± 4.5	
LDH-2 (%)	MH	—	—		33.9 ± 1.3	* (MH vs CM)
	SJM	—	—		34.9 ± 1.5	
	CM	—	—		35.3 ± 1.8	

*, **, #, ##, p < 0.05, 0.01, 0.001, 0.0001, respectively.

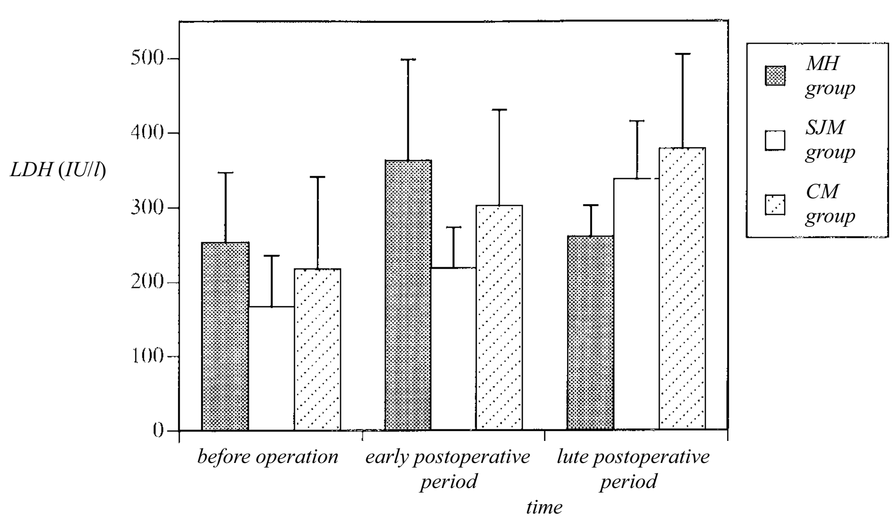

Fig. 1. Changes in LDH.

Subjects were divided into 4 groups. Patients with grade 2 or more aortic regurgitation (AR) were included in the AR group. For the remaining patients, those with MH valves were included in the MH group,

Table III. *Correlation between valve area index and hemolysis*

groups		*MH* (*n = 16*)	*SJM* (*n = 25*)	*CM* (*n = 29*)
VAI (*mm*^{2}/*m*^{2})		*247 ± 20*	*248 ± 43*	*258 ± 34*
correlation between VAI and				
early postoperative	LDH (IU/l)	n.s.	n.s.	n.s.
	GOT (IU/l)	n.s.	n.s.	n.s.
	TB (mg/dl)	n.s.	n.s.	n.s.
late postoperative	LDH (IU/l)	n.s.	n.s.	n.s.
	GOT (IU/l)	n.s.	n.s.	n.s.
	TB (mg/dl)	n.s.	n.s.	n.s.
	LDH-1 (%)	n.s.	n.s.	n.s.
	LDH-2 (%)	n.s.	n.s.	n.s.

VAI, Valve area index; *n.s.*, not significant.

Table IVa. *Effects of bileaflet valve orientation on hemolysis in SJM and CM groups*

measurements		*anatomical position* (*n = 39*)	*anti-anatomical position* (*n = 15*)	*p-value*
early postoperative	LDH (IU/l)	261 ± 119	298 ± 90	n.s.
	GOT (IU/l)	25.7 ± 8.4	27.0 ± 7.8	n.s.
	TB (mg/dl)	0.5 ± 0.2	0.5 ± 0.3	n.s.
late postoperative	LDH (IU/l)	351 ± 113	382 ± 100	n.s.
	GOT (IU/l)	30.5 ± 11.4	37.2 ± 15.8	n.s.
	TB (mg/dl)	0.6 ± 0.4	0.6 ± 0.2	n.s.
	LDH-1 (%)	33.9 ± 4.6	32.4 ± 2.9	n.s.
	LDH-2 (%)	35.1 ± 1.7	35.4 ± 1.8	n.s.

Table IVb. *Effects of bileaflet valve orientation on hemolysis in AR group*

measurements		*anatomical position* (*n = 9*)	*anti-anatomical position* (*n = 5*)	*p-value*
early postoperative	LDH (IU/l)	303 ± 144	207 ± 55	n.s.
	GOT (IU/l)	29.0 ± 8.0	17.3 ± 4.9	< 0.05
	TB (mg/dl)	0.6 ± 0.2	0.4 ± 0.1	n.s.
late postoperative	LDH (IU/l)	327 ± 82	392 ± 133	n.s.
	GOT (IU/l)	28.4 ± 10.4	29.8 ± 5.9	n.s.
	TB (mg/dl)	0.6 ± 0.2	0.4 ± 0.1	n.s.
	LDH-1 (%)	33.0 ± 2.8	33.1 ± 3.2	n.s.
	LDH-2 (%)	36.4 ± 2.0	35.3 ± 0.8	n.s.

those with SJM valves in the SJM group, and those with CM valves in the CM group. For the MH, SJM, and CM groups, the following studies ①–⑤ were conducted, and for the AR group, only study ③ was conducted:

Study ①: Effects of the type of prostheses on changes in hemolysis over time were evaluated.

Study ②: From patient body surface area (BSA, m^2) and prosthesis orifice area (mm^2), valve area index (= orifice area of prosthesis/BSA) was calculated, and the relationship of the index to early and late postoperative hemolysis was evaluated.

Study ③: Effects of the orientation of bileaflet valves on early and late postoperative hemolysis were evaluated.

Study ④: The relationship of blood pressure and heart rate to early and late postoperative hemolysis was evaluated.

Study ⑤: Echocardiography was conducted in both early and late postoperative periods, and stroke volume was calculated using the formula of Teichholz.[3] The cardiac output index (CI) was calculated using the formula CI (l/min/m^2) = stroke volume × heart rate/BSA. CI was compared between early and late post-

Table V. *Blood pressure and heart rate*

groups	*blood pressure (mmHg)* early postoperative period	late postoperative period	*heart rate (/min)* early postoperative period	late postoperative period
MH (n = 16)	135 ± 13	138 ± 13	68 ± 14	64 ± 15
SJM (n = 25)	142 ± 10	139 ± 19	71 ± 11	71 ± 14
CM (n = 29)	131 ± 19	135 ± 20	76 ± 8	71 ± 12*

*, $p < 0.05$ vs early postoperative period.

Table VI. *Changes in CI*

groups	*early postoperative period*	*late postoperative period*
MH (n = 16)	3.18 ± 0.82	4.01 ± 0.85*
SJM (n = 25)	3.41 ± 0.82	3.97 ± 0.93**
CM (n = 29)	3.38 ± 0.88	3.74 ± 0.93***

CI, Cardiac output index (l/min/m^2).
*, $p < 0.05$; **, $p < 0.001$; ***, $p < 0.01$ vs early postoperative period.

operative periods.

For statistical analysis, Student's t-test, the χ square test, ANOVA, repeated measured ANOVA, and Spearman rank correlation were used. Findings of $p < 0.05$ were considered statistically significant.

Results

Subjects numbered 84 — 16 in the MH group, 25 in the SJM group, 29 in the CM group, and 14 in the AR group. All subjects in the AR group had bileaflet valves — 7 SJM and 7 CM valves. Concomitant surgical procedures included 16 tricuspid annuloplasties with the Kay procedure, 5 left atrial thrombectomies, and 1 suture closure of an atrial septal defect. Table I presents patient profiles.

Table II summarizes changes in LDH, GOT and TB over time. Fig. 1 shows changes in LDH. The type of prosthesis interacted significantly only with LDH ($p < 0.0001$ by repeated measure ANOVA). Only the MH group had a different pattern of LDH changes (Fig. 1). LDH in the SJM and CM groups was higher in the late postoperative period than in the early postoperative period, while that in the MH group was lower in the late postoperative period than in the early postoperative period. In the late postoperative period, LDH and LDH-1 were lower in the MH group than in the SJM and CM groups, and LDH-2 was lower in the MH group than in the CM group.

Table III summarizes Study ② results. The valve area index showed no correlation to hemolysis.

Table IV summarizes Study ③ results. The orientation of bileaflet valves was classified into two groups: an "anatomical" position group with the axis between hinges parallel to the axis between mitral commissures and an "antianatomical" position group with the axis perpendicular to that of the "anatomical" position. For the SJM and CM groups (Table IVa), no difference was observed in hemolysis severity related to orientation. For the AR group (Table IVb), GOT in the early postoperative period was higher in the anatomical position subgroup than in the antianatomical position subgroup.

Table V summarizes Study ④ results. Blood pressure and heart rate showed no correlation to hemolysis.

Table VI summarizes Study ⑤ results. CI was higher in the late postoperative period than in the early postoperative period in all groups.

Discussion

Hemolysis presents both old and new problems in valve replacement. Since the 1960s, many reports on hemolytic anemia, cholelithiasis, or hemosiderosis associated with valve replacement have been published.[2,4–12] Moreover, Gencbay et al.[13] recently found a correlation between hemolysis and the amount of prosthesis-induced microbubbles, first reported in 1975[14] and suspected of causing neurologic thromboembolism.[15–17]

Ellis et al.[18] classified the causes of prosthesis-induced hemolysis into 3 factors — (1) blood impact with valve suprastructures, (2) turbulent shear stress in disturbed forward flow, and (3) shear stress due to transvalvular leakage — reporting that the effects of leakage were greater than those of the other causes. Leakage jets arise mainly from small gaps between leaflet edges and housings in MH valves, but from hinges in SJM and CM valves. High-pressure regurgitant flow through complicated hinge structures is considered the main cause of bileaflet valves having a greater degree of hemolysis than tilting disc valves, as reported by several studies,[11,12] even though bileaflet valves were superior to tilting disc valves in shear stress in forward flow.[19,20]

We found that late postoperative hemolysis was higher in the SJM and CM groups than in the MH group because hemolysis in the SJM and CM groups was more severe in the late postoperative period than in the early postoperative period (Table II, Fig. 1). Since the MH valve uses a Teflon sewing ring, which is fine-textured and minimally covered by the endocardium, the decrease in late postoperative hemolysis is thought to have occurred because artificial material such as pledgets and stitches was covered by endocardium. Although the SJM valve is thought to result in less late than early postoperative hemolysis because its Dacron sewing ring is loose-textured and covered by endocardium, our findings were not consistent with this. The CM valve has a carbon-coated Dacron sewing ring to prevent excessive endocardial proliferation, but increased hemolysis in the late postoperative period was still not consistent with general belief. Concerning these late postoperative increases in hemolysis in the SJM and CM groups, we surmised that shear stress against blood through pivot recesses may be higher in the late postoperative period than in the early postoperative period because the transvalvular regurgitant flow increases in the late postoperative period as cardiac function improves. Nevaril et al.[21] reported that, above a certain level, a small increase in shear stress resulted in hemolysis of many cells. Rambod et al.[22] reported that patients with an ejection fraction > 0.45 had a higher frequency of microbubbles, which was reported to be related to hemolysis.[13] This hypothesis is supported by Study ⑤, which showed that the late postoperative CI was higher than the early postoperative CI. Although blood pressure and heart rate theoretically affect transvalvular regurgitant flow, no significant correlation was seen between these parameters and hemolysis.

Nevaril et al.[21] reported that the pressure gradient through valve prostheses affected hemolysis. The pressure gradient is principally related to both the prosthetic orifice area and cardiac output. Many studies have reported no correlation between hemolysis and the size of valve prostheses.[2,10,11,23] We used valve area index as a parameter of shear stress in forward flow, but no significant correlation was observed between this parameter and hemolysis (Table III). As far as hemolysis is concerned, it is not necessary to use larger valve prostheses if it is technically difficult.

Several studies found no relationship between hemolysis and the orientation of bileaflet prostheses unless there was significant AR.[9] We observed no statistically significant difference in hemolysis between anatomical and antianatomical position subgroups in SJM and CM groups (Table IVa). If AR exists, anatomically positioned bileaflet prosthesis is thought to cause hemolysis, since AR jets will hit a leaflet of the prosthesis.[9] In our study, although early postoperative GOT was higher in the anatomical than in the antianatomical position subgroup in the AR group, no significant difference was observed in LDH between the two subgroups (Table IVb).

Conclusion

Although SJM and CM valves are now widely used, patients with these valves exhibited greater hemolysis in the late postoperative period than in the early postoperative period, having more severe hemolysis than patients with MH valves in the late postoperative period. The status of hemolysis should therefore be followed up long-term even in patients with normal-functioning valve prostheses.

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