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Hemolysis After Implantation of Prosthetic Heart Valves

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Hemolysis is still the most common side effect following implantation of prosthetic cardiac valves. Although it is usually mild and well compensated, anemia can be a problem in some patients. In addition, an increased incidence of cholelithiasis has been reported in prosthetic heart valve recipients probably due to excessive bilirubin production resulting from red cell destruction[6,11].

The present study was undertaken to clarify the factors leading to hemolysis after insertion of prosthetic valves.

Materials and method

Hemolysis was evaluated in a total of 70 patients. The follow-up period ranged from two months to 16 years (mean 5.2 ± 4.3 years). The ages at operation were seven to 63 years (mean 34 ± 13 years). There were 45 males and 25 females. Twenty-six had aortic valve replacement (AVR), 29 had mitral valve replacement (MVR) and eight had aortic and mitral valve replacement. Of the remaining seven patients, four had tricuspid valve replacement (TVR) and three had pulmonary valve replacement (PVR) or Rastelli's operation (right ventricular-pulmonary valved conduit). The valve substitutes implanted were Starr-Edwards (SE) prosthesis, Björk-Shiley (BS) prosthesis, Lillehei-Kaster (LK) prosthesis, Carpentier-Edwards (CE) bioprosthesis and others (Table 1).

The degree of hemolysis was predicted from; 1) serum hemoglobin by hydrosulfate method (normal range less than 10 mg per 100 ml), 2) serum haptoglobin by single radial immunodiffusion method (normal range 30 to 180 mg per 100 ml), 3) serum lactic dehydrogenase (LDH) by the Ultra-Violet reaction rate method (normal range 40 to 125 units) and 4) reticulocyte count by the standard method. Hemodynamic conditions were followed by radiocardiography, in which

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Table 1. Types of prostheses implanted in our cases.

Valve site	Valve type	Model	No.
Aortic Valve	Starr-Edwards	1000	1
		1200	1
		2300	1
		2310	1
		2320	7
	Björk-Shiley		10
	Lillehei-Kaster		13
Mitral Valve	Starr-Edwards	6120	8
		6300	1
		6320	5
		6350	1
	Björk-Shiely		4
	Lillehei-Kaster		16
	Carpentier-Edwards		2
Tricuspid Valve	Starr-Edwards	6350	1
	Björk-Shiley		1
	Lillehei-Kaster		1
	St. Jude		1
Pulmonary Valve	Björk-Shiley		2
	Hancock		1
Total			78

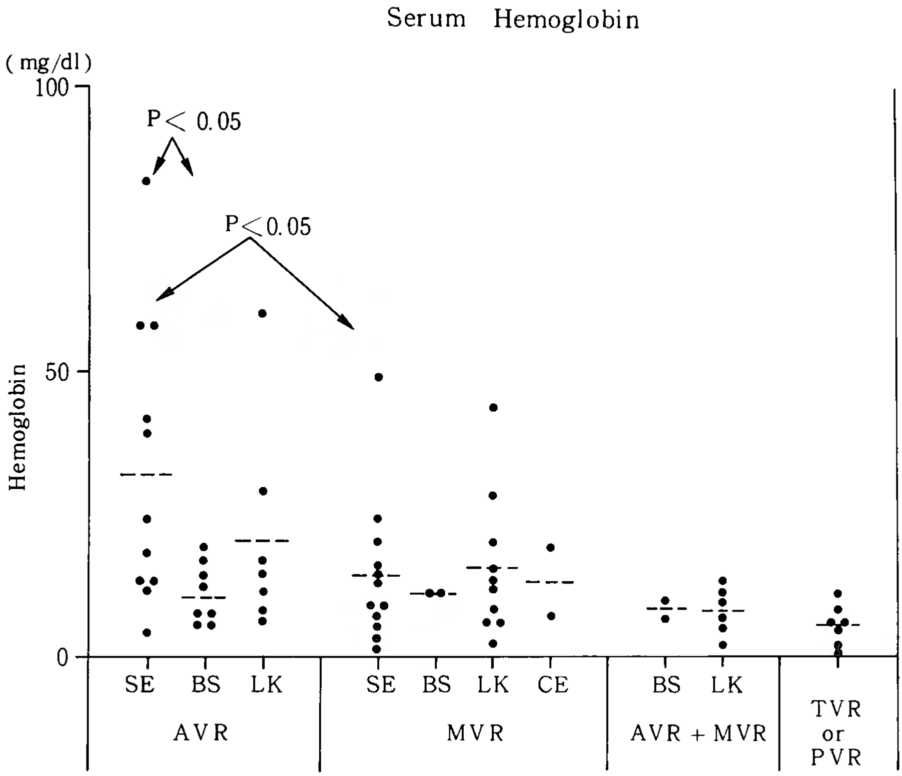
normal cardiac index and left heart volume were 3.63 ± 0.49 l/min/M^2 and 134 ± 24 ml/M^2, respectively[17].

Result

Although most of the patients had some hemolysis, it was mild and well compensated. There was no patient who showed significant hemolytic anemia.

Influence of valve type: There was a significant difference in the hemoglobin levels between patients with SE valves and BS valves in the aortic position ($p<0.05$) (Fig. 1). LK valves appeared to be less traumatic to red cells than SE valves, but more traumatic than BS valves. This was not significant in the numbers studied because of relatively wide range of variation in the data about the LK valves. The comparisons among various type of SE valves revealed that in the mitral position, cloth-covered valves (6300/6320) provoked significantly more hemolysis than non-cloth-covered valves (6120) (Table 2). The tendency towards hemolysis was also seen with aortic cloth-covered valves (2300/2310/2320).

Influence of valve site: Hemolysis appeared to be least when the prosthesis was in the right heart (TVR or PVR). Haptoglobin was significantly reduced in AVR and/or MVR, and hemoglobin was significantly increased in AVR (Fig. 2 & Table 3). However, the difference between AVR and MVR was found only with SE valves ($p<0.05$) (Fig. 1) probably because the AVR group included more cases with cloth-covered valves and the MVR more with non-cloth-



SE: Starr-Edwards, BS: Björk-Shiley, LK: Lillehei-Kaster, CE: Carpentier-Edwards.

Figure. 1. Serum hemoglobin values related to valve type and site. The mean values in each group are indicated by a broken line. Significant differences are observed between Starr-Edwards and Björk-Shiley valves in the aortic position and between aortic and mitral positions in Starr-Edwards valves.

Table 2. Comparison between cloth-covered and non-cloth-covered valves.

Type of Valve	No. of Case	Hemoglobin (mg/dl)	Haptoglobin (mg/dl)	LDH (unit)	Reticulocyte (‰)
Non-cloth-covered (6120)	8	6.3 ± 1.8	6.6 ± 5.4	136 ± 9	14.5 ± 1.7
Cloth-covered (6300/6320)	6	22.0 ± 7.3*	2.8 ± 2.9	291 ± 58*	20.8 ± 2.5

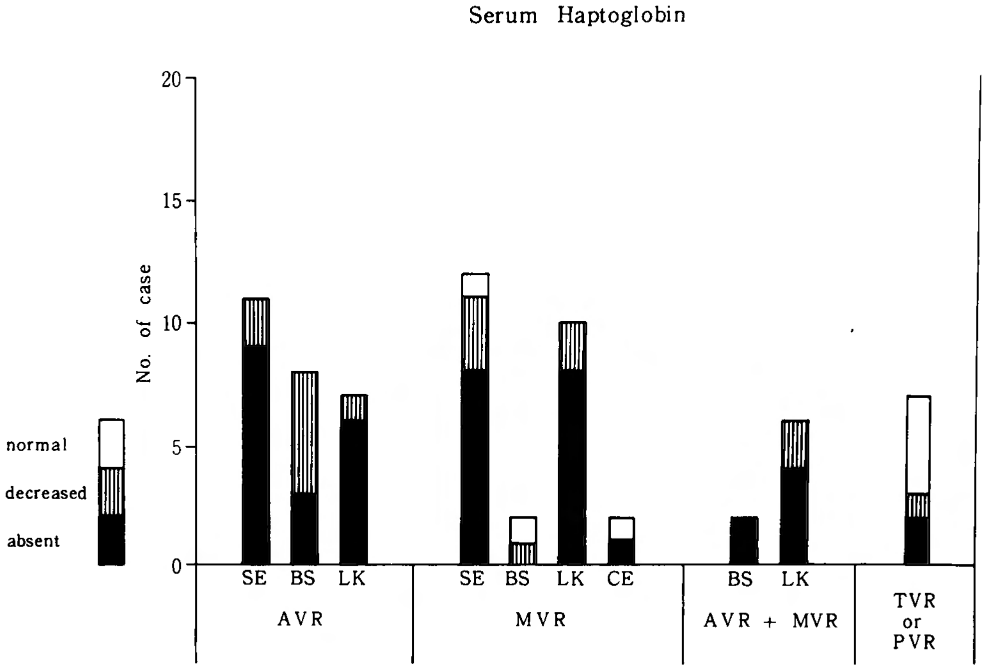
*$p<0.05$ mean±SE

Type of Valve	No. of Case	Hemoglobin (mg/dl)	Haptoglobin (mg/dl)	LDH (unit)	Reticulocyte (‰)
Non-cloth-covered (1000/1200)	2	15.7 ± 2.6	1.7 ± 1.6	(not examined)	
Cloth-covered (2300/2310/2320)	9	36.7 ± 8.8	0.8 ± 0.8	326 ± 34	17.3 ± 3.2

mean±SE

covered valves.

Influence of valve size: The degree of hemolysis was compared in patients with smaller and



SE: Starr-Edwards, BS: Björk-Shiley, LK: Lillehei-Kaster, CE: Carpentier-Edwards.

Figure. 2. Serum haptoglobin levels related to valve type and site.

Table 3. Serum hemoglobin, haptoglobin, lactic dehydrogenase and reticulocyte count related to valve site.

Valve site	No. of case	Hemoglobin (mg/dl)	Haptoglobin (mg/dl)	LDH (unit)	Reticulocyte (‰)
AVR	26	22.7±4.1*	1.4±0.5**	251±32	21.9±5.9
MVR	29	14.3±2.3	13.7±7.5*	187±27	18.6±1.8
AVR+MVR	8	8.0±1.3	3.2±2.8*	306±99	(not examined)
TVR or PVR	7	5.5±1.3	53.7±21.5	169±19	

mean±SE

*p<0.05, **p<0.01, when compared with right heart valves. (TVR or PVR)

larger valves (Table 4). The "smaller" aortic valves were size 10A or less SE valves, 19 mm or less BS valves and 16 mm or less LK valves. The smaller mitral valves were 2M or less SE valves, 29 mm or less BS valves and 20 mm or less LK valves. The orifices of the smaller valves calculated by Gorlin's formula were 1.5 cm² or less for aortic valves and 2.5 cm² or less for mitral valves.[15,20] With both aortic and mitral valves, no significant differences in the degree of hemolysis were noted between the smaller and larger groups, regardless of valve type.

Influence of postoperative period: Hemoglobin levels did not change significantly with time after surgery (Fig. 3). High values occurred with certain types of SE valves, but not with the length of the postoperative period.

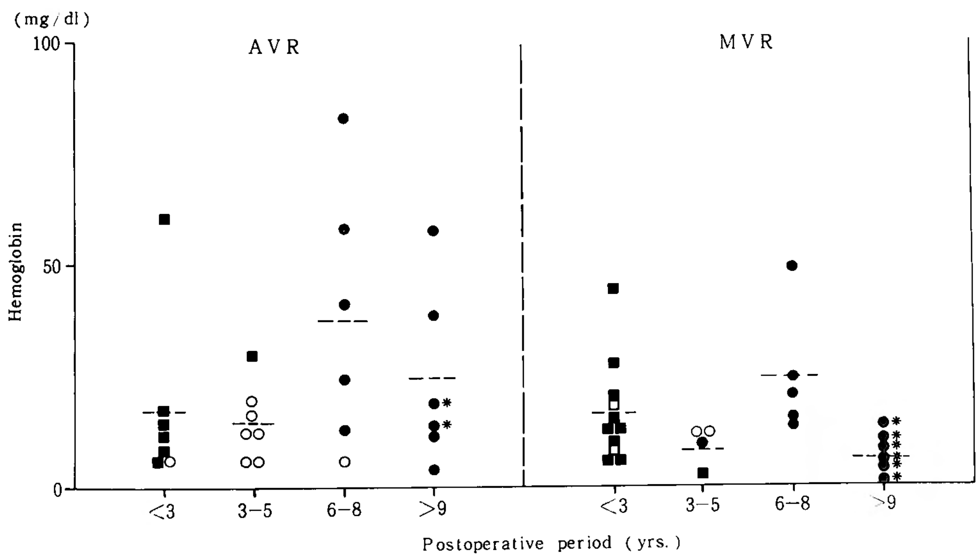
Table 4. Comparison between smaller and larger valves.

	Smaller valves		Larger valves	
	AVR	MVR	AVR	MVR
No. of Case	13	12	13	17
Hemoglobin (mg/dl)	25.0±6.3	13.6±4.9	20.4±5.5	14.7±2.5
	20.3±4.3		17.2±2.7	
Haptoglobin (mg/dl)	0.6±0.3	4.5±3.6	2.2±1.1	18.6±11.4
	2.2±1.5		11.5±6.5	
LDH (unit)	269±47	214±79	240±71	221±38
	222±31		211±27	
Reticulocyte (‰)	28.5±17.3	13.7±2.1	12.6±1.7	21.2±3.0
	23.6±5.7		16.8±2.0	

mean±SE

Influence of atrial fibrillation: There was no relation between hemolysis and atrial fibrillation (Table 5).

Influence of paraprosthetic leaks: No significant differences in hemolytic parameters, except for the reticulocyte count, were noted between cases with and without perivalvular leakage of aortic and mitral prosthesis (Table 6). The severity of leakage was less than grade II of Seller's



● Starr-Edwards, ○ Björk-Shiley, ■ Lillehe-Kaster, □ Carpentier-Edwards
(*Starr-Edwards non-cloth-covered valve)

Figure. 3. Serum hemoglobin values related to postoperative period. The broken lines indicate the mean values in each group.

Table 5. Comparison between sinus rhythm and atrial fibrillation.

	Sinus Rhythm	Atrial Fibrillation
No. of Case	38	31
Hemoglobin (mg/dl)	17.2±3.0	14.2±2.2
Haptoglobin (mg/dl)	11.1±5.0	15.6±6.7
LDH (unit)	230±28	213±25
Reticulocyte (‰)	22.5±6.3	17.6±2.0

mean±SE

Table 6. Comparison between patients with and without perivalvular leakage.

	Perivalvular leakage	No leakage
No. of Case	5(AVR4, MVR 1)	47
Hemoglobin (mg/dl)	22.6±9.0	18.0±2.5
Haptoglobin (mg/dl)	3.3±3.0	8.0±4.2
LDH (unit)	260±54	212±22
Reticulocyte (‰)	44.3±18.6*	16.8±1.6

*$p<0.01$ mean±SE

classification.

Influence of hemodynamic conditions: The grade of hemolysis was divided into two groups according to hemoglobin level. More than 20 mg/dl of hemoglobin with reduced or no haptoglobin was defined as higher degree of hemolysis. Hemolysis, regardless of its severity, had no significant relation to the New York Heart Association classification, cardiothoracic ratio, cardiac index or left heart volume (Table 7). Valve malfunction was not demonstrated in any of the patients.

Influence of thromboembolism: Embolic episodes occurred in six patients, two with AVR and four with MVR. All of these patients had SE valves. Four of them had non-cloth-covered valves. The mean hemoglobin and haptoglobin levels of these six patients were 13.7±3.8 mg/dl and 6.6±5.3 mg/dl, respectively, These values mean only mild hemolysis in this study.

Table 7. Comparison between higher and lower degree of hemolysis.

	Higher degree hemolysis	Lower degree hemolysis
No. of Case	14	49
NYHA Class	1.5±0.1	1.6±0.1
Cardiothoracic ratio	0.57±0.03	0.61±0.01
Cardiac Index (l/min/M²)	2.98±0.03	3.23±0.14
Left heart volume (ml/M²)	254±39	206±15

mean±SE

Discussion

It is generally considered that all cardiac valves must produce some intravascular hemolysis. This was true in our cases, but fortunately the hemolysis was not severe enough to cause clinical anemia. However, four of our patients who had a relatively high grade of hemolysis were found to have gallstones, and one of them had had a cholecystectomy[8].

Factors influencing hemolysis have been discussed by a number of authors. The almost constant finding in the literature is that hemolysis is more severe with SE aortic cloth-covered valves than with other types, including SE non-cloth-covered valves[1,4,5,13,19]. Our data were very similar, although the most significant difference was between SE cloth-covered and non-cloth-covered valves in the mitral position. A comparison between BS and LK valves showed no significant difference in the severity of hemolysis. However, NITTER-HANGE[14], DALE[4], LEVANG[10] and their associates found more hemolysis in patients with LK than with BS valves. Valve size might appear to be another factor in producing hemolysis. However, it has been significant only in SE aortic cloth-covered valves[4,13], and not in other valves[2]. In the present study valve size was not a factor in increased hemolysis by any type or at any site. The position of the valves, mitral or aortic, appears to be of only minor importance in hemolysis[14,19], although a significant difference was observed between prostheses in the left heart (AVR or MVR) and those in the right heart (TVR or PVR) in this study.

Red cell destruction may be caused by either one of two different mechanisms, direct trauma by crushing or shear stress by turbulence. The difference in the degree of hemolysis between SE cloth-covered (metal ball) and non-cloth-covered (silastic rubber ball) valves suggests that red cells may be damaged by Teflon covering or by metal ball. This probably occurs by trapping the red cells within the cloth and preventing their escape when the metal ball collides against the valve ring or by forced contact of the cells with bare Teflon fibers[13,19]. Furthermore, the slightly greater hemolysis caused by LK than by BS valves, which was not demonstrated in this study, is considered to be due to mechanical crushing because of the overlapping mechanism in the former type[2,7,10,14] Therefore, turbulence appears to have little effect on hemolysis. On the other hand, shear stress[16] is considered to be related to valve size or the pressure gradient across the valve, paravalvular leak[7], valve malfunction and cloth wear[3,18]. None of these factors were significant in the present study, although we previously reported severe hemolytic anemia following mitral valvuloplasty due probably to valvular turbulence[12].

Summary

Intravascular hemolysis following implantation of prosthetic heart valves was studied in 70 patients by determinations of serum hemoglobin, serum haptoglobin, serum lactic dehydrogenase and reticulocyte count.

1) Valve replacement in the left heart (aortic and/or mitral valves) was associated with more hemolysis than that in the right heart (tricuspid or pulmonary valve).

2) Starr-Edwards mitral cloth-covered valves provoked significantly more hemolysis than

did non-cloth-covered valves of the same type.

3) Valve site, such as mitral or aortic, valve size, length of the postoperative period, atrial fibrillation, paravalvular leakage, hemodynamic conditions and thromboembolism were not significantly related to hemolysis.

The present study suggests that mechanical crushing causes more hemolysis than does turbulence.

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和文抄録

人工弁置換后の溶血

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白石　義定，山里　有男，千葉　幸夫，村口　和彦
村田　真司，青田　正樹，北野　満
日笠　頼則

人工弁置換術后の溶血は，貧血を生じるほどの強度なものは稀であるが，相変らず術后合併症の一つとして注目されている．今回は自験例をもとに，血清ヘモグロビン，血清ハプトグロビン，LDH および網状球の検査より溶血の原因となる因子を探らんと試みた．その結果①三尖弁あるいは肺動脈弁置換など右心の弁置換は左心の大動脈弁あるいは僧帽弁置換に比較して有意に溶血は少なかった．②Starr-Edwards cloth-covered 弁は他弁に比して溶血が多かった．③その他の因子のうち，左心における弁の位置（大動脈弁 vs 僧帽弁），弁の大きさ，術后期間の長さ，心房細動，人工弁の leak，循環動態，血栓症などは有意に溶血には関係しなかった．

これらの結果より，人工弁に伴う溶血は機械的な直接作用による因子が，乱流などの因子より強く影響しているように考えられた．