SURGICAL MANAGEMENT OF INFECTIVE ENDOCARDITIS ASSOCIATED WITH CEREBRAL COMPLICATIONS

Multi-center retrospective study in Japan

To establish guidelines for the surgical treatment of patients with infective endocarditis who have cerebrovascular complications, we conducted a detailed retrospective study of 181 of 244 patients with cerebral complications among 2523 surgical cases of infective endocarditis of the Japanese Association of Thoracic Surgery. The results showed that 9.7% of all patients with infective endocarditis had associated cerebral complications: 108 (44.3%) had active native valve endocarditis, 96 (39.3%) had healed native valve endocarditis, and 40 (16.4%) had prosthetic valve endocarditis. The hospital mortality of the patients with cerebral complications was 11.0% in the group as a whole: 13.9% in active native valve endocarditis, 3.1% in healed native valve endocarditis, and 37.5% in prosthetic valve endocarditis. Diseased valves included the following: aortic valve in 55.5%, mitral valve in 49.8%, tricuspid valve in 1.3%, and pulmonary valve in 1.3%. In 181 patients with cerebral complications, organisms were detected as follows: gram-positive cocci in 133 (73.5% [*Streptococcus* in 85, *Staphylococcus* in 32]), gram-negative in 18 (9.9%), fungus in 11 (6.1%), and unknown in 19 (10.5%). Types of cerebral complications included cerebral infarction in 64.6%, cerebral bleeding in 31.5%, cerebral abscess in 2.8%, and meningitis in 1.1%. Hospital mortality rate and an exacerbation rate of cerebral complications, including related death, according to the interval from onset of cerebral infarction to cardiac surgery, were as follows: 66.3% and 45.5% within 24 hours, 31.3% and 43.8% between 2 and 7 days, 16.7% and 16.7% between 8 and 14 days, 10.0% and 10.0% between 15 and 21 days, 26.3% and 10.5% between 22 and 28 days, and 7.0% and 2.3% over 4 weeks later, respectively. A significant correlation existed between the interval and the exacerbation of cerebral complications (tied $p = 0.008$). Preoperative risk factors affecting exacerbation of cerebral complications were as follows: (1) severity of cerebral complication ($p = 0.006$), (2) intervals ($p = 0.012$), and (3) uncontrolled congestive heart failure as indications for cardiac surgery ($p = 0.014$). One patient underwent a cardiac operation within 24 hours of the onset of cerebral hemorrhage and died of cerebral damage. No exacerbations occurred in 10 patients who underwent their operation between 2 and 28 days. Nevertheless, exacerbations occurred in 19.0% of patients whose operation was done more than 4 weeks later. These data suggest that cardiac operations can be done safely 4 weeks after cerebral infarction, and if the delay is more than 2 weeks, the

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exacerbation rate will be around 10%. The risk of progression of cerebral damage is still significant 15 days and even 4 weeks after cerebral hemorrhage. (J Thorac Cardiovasc Surg 1995;110:1745-55)

The best means of treating patients with infective endocarditis who have various complications such as severe congestive heart failure, intramyocardial abscesses, sepsis, major embolization, or cerebral aneurysm is the subject of controversy. In the past decade, early surgical treatment has been recommended even during the active stage before progression of the lesions.[1-3] In patients with cerebrovascular complications, however, a surgical approach to the cardiac lesion still involves several unsolved problems.[4-11] A major concern is the timing of cardiac surgery in these patients, because cardiopulmonary bypass with unusual hypotension and total heparinization would amplify the cerebral ischemic damage and hemorrhage.[8] Several groups, ours included, have tried to clarify the safety period between the cerebrovascular event and the cardiac operation, instead of limiting the number of patients with cerebral complications in each group.[5, 8-10] To establish the surgical treatment of patients with infective endocarditis associated with cerebrovascular complications, we conducted a detailed, retrospective analysis of 181 of 244 patients with cerebral complications among 2523 surgical cases of infective endocarditis of the Japanese Association of Thoracic Surgery (JATS).

Patients and methods

We sent a questionnaire to 600 centers belonging to the JATS and received replies from 261 centers, including 174 departments with 2523 patients having cardiac operations for infective endocarditis. A total of 244 patients had associated cerebral complications, and 181 of them were analyzed in detail. The questionnaire consisted of two parts: (1) Each center was asked for a summary of the number and outcome of patients with infective endocarditis according to the types of infective endocarditis[1] (active/healed and native valve/prosthetic valve) and the presence of cerebral complications; (2) the other portion inquired about each patient with cerebral complications, asking for details such as age, gender, atrial fibrillation, anticoagulant therapy, diseased valve, organism, effectiveness of antimicrobial therapy, reason for early cardiac operation, interval between the onset of symptoms and the cardiac operation, type of cerebral complication, cerebral aneurysm, prior cerebral surgery, severity, influence of operation on cerebral damage, and outcome.

Analyses and statistics. The difference in mortality between the group without cerebral complications and the group with cerebral complications was tested for significance by χ^2 analysis. A diseased valve and an organism were summarized as characteristics of the patients having associated cerebral complications. The type and timing of cerebral disease were documented. To study the influence of cardiac surgery on preoperative cerebral complications, we analyzed the interval between the onset of cerebral complications and performance of the cardiac operation, as well as other preoperative variables. The effectiveness of antimicrobial therapy was ranked in three grades (1 = ineffective, 2 = effective, and 3 = well controlled). Also, the severity of cerebral complications was ranked (1 = mild, 2 = moderate, and 3 = severe). Indications for early cardiac surgery included ineffectiveness of antimicrobial therapy, vegetations, and uncontrolled congestive heart failure. Cerebral angiographic examination was done in 58.8% of the patients with cerebral hemorrhage. A correlation between the interval and the exacerbation of cerebral complications was evaluated by means of the Spearman rank correlation coefficient. The intervals were then classified in several groups, and a variability between the groups for the exacerbation was estimated by Scheffe's F procedure for post-hoc comparisons, according to the Kruskal-Wallis test. To analyze the risk factors affecting exacerbation of cerebral complications, we expressed preoperative variables as mean ± standard error. The difference between the groups with and without exacerbation was tested for significance by the unpaired t test, and incidence was expressed as percentage of patients having the variable compared with the entire group of patients and then compared by χ^2 analysis. Moreover, all variables and incidence (transformed to continuous variables) were estimated by stepwise regression analysis. Statistical significance was accepted at a p level of <0.05. These analyses were done with the Stat View system (Abacus Concepts, Inc., Berkeley, Calif.).

Results

Summary of all patients with infective endocarditis. In total, 2523 patients having infective endocarditis were treated surgically in 174 centers of JATS. Of all the patients, 893 (35.4%) had active native valve endocarditis, 1317 (52.2%) had healed native valve endocarditis, and 315 (12.5%) had prosthetic valve endocarditis. Operative mortality rate was 13.5% in those with active endocarditis, 4.0% in those with healed endocarditis, and 33.3% in those with prosthetic valve endocarditis. On the other hand, 244 patients, 9.7% of all patients with infective endocarditis, had associated cerebral complications. A total of 1080 (44.3%) had active endocarditis, 96 (39.3%) had healed endocarditis, and 40

Table I. *Summary of 2523 patients with infective endocarditis*

	Without cerebral complications		*With cerebral complications*		*Total*	
	No. of patients	*% HD*	*No. of patients*	*% HD*	*No. of patients*	*% HD*
ANVE	784	13.4	108	13.9	893	13.5
HNVE	1220	4.1	96	3.1	1317	4.0
PVE	275	32.7	40	37.5	315	33.3
Total	2279	10.8	244	13.5	2523	11.0

HD, Hospital death; *ANVE,* active native valve endocarditis; *HNVE,* healed native valve endocarditis; *PVE,* prosthetic valve endocarditis.

Table II. *Diseased valve in 244 patients*

	No.	*%*
Aortic	126	55.5
Mitral	113	49.8
Tricuspid	3	1.3
Pulmonary	3	1.3

Table III. *Organism in 181 patients*

	No.	*%*
Gram positive	133	73.5
Streptococcus	85	63.9
Staphylococcus	32	24.1
Others	16	12.0
Gram negative	18	9.9
Enterococcus	5	27.8
Escherichia coli	3	16.7
Others	10	55.6
Fungus	11	6.1
Candida	8	72.7
Others	3	27.3
Unknown	19	10.5

(16.4%) had prosthetic valve endocarditis. The mortality rates of the patients with cerebral complications were 13.9% (active endocarditis), 3.1% (healed endocarditis), and 37.5% (prosthetic valve endocarditis). No differences in mortality were detected between the group without cerebral complications and the group with cerebral complications (Table I).

Characteristics of patients having cerebral complications. Diseased valves in 244 patients having cerebral complications included the following: aortic valve, 126 (55.5%); mitral valve, 113 (49.8%); tricuspid valve, 3 (1.3%), and pulmonary valve, 3 (1.3%) (Table II). In 181 patients of 244 having infective endocarditis with cerebral complications, organisms were detected as follows: gram-positive cocci in 133 (73.5% [*Streptococcus* in 85, *Staphylococcus* in 32]), gram-negative in 18 (9.9%) [*Enterococcus* in 5, *Escherichia coli* in 3], fungus in 11 (6.1%) [*Candida* in 8], and unknown in 19 (10.5%) (Table III).

Cerebrovascular disease as the complication in patients with infective endocarditis. Details of cerebrovascular disease were analyzed in 181 patients of 244 who had infective endocarditis with cerebral complications. The types of cerebral complication were as follows: cerebral infarction in 117 (64.6%), cerebral bleeding in 57 (31.5%), cerebral abscess in 5 (2.8%), and meningitis in 2 (1.1%). Cerebral infarction occurred before the operation in 112, during the operation in 2, and after the operation in 3. Hospital mortality rates were 21.4% in patients with preoperative onset, 100% in those with onset during the operation, and 33.3% in those with postoperative onset. Cerebral bleeding occurred before the operation in 34, during the operation in 8, and after the operation in 15. Hospital mortality rates were 17.6% in patients with preoperative onset, 50.0% in those with perioperative onset, and 73.3% in those with postoperative onset.

Influence of cardiac surgery on preoperative cerebral infarction. In 11 patients, the cardiac operation was performed within 24 hours after the onset of cerebral infarction (mortality rate 66.3%) (Figs. 1 and 2). The operation was performed between 2 and 7 days later in 16 patients (mortality rate 31.3%), between 8 and 14 days later in 12 patients (mortality rate 16.7%), between 15 and 21 days later in 10 patients (mortality rate 10.0%), between 22 and 28 days later in 19 patients (mortality rate 26.3%), and more than 4 weeks later in 43 patients (mortality rate 7.0%). The rates of exacerbation of cerebral complications, including related death, were as follows: 45.5% in patients who were operated on within 24 hours, 43.8% in those operated on within 2 to 7

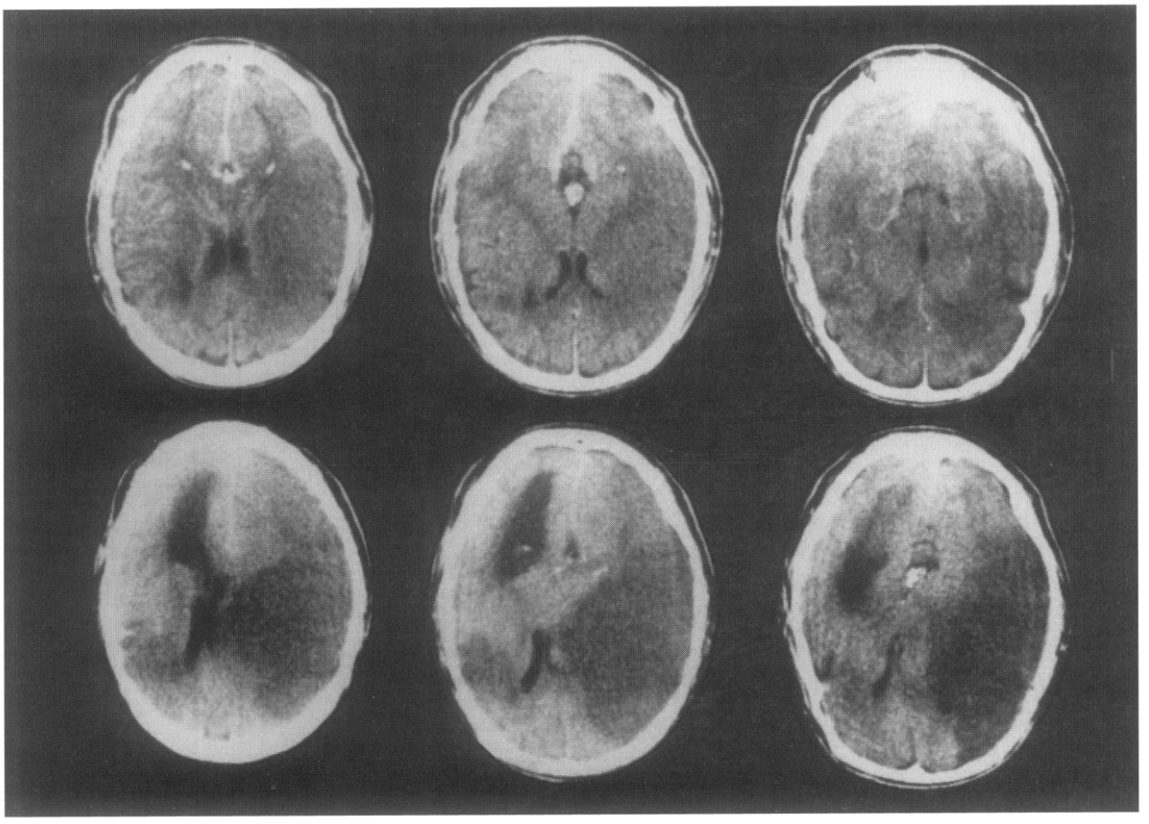

Fig. 1. Computed tomographic scans of a patient with right middle cerebral artery infarction resulting from infective endocarditis. This patient underwent a Bentall–type operation for graft infection on the same day, resulting in massive brain swelling, and died 3 days later. *Top row,* Preoperative computed tomographic scans; *bottom row,* postoperative scans.

days, 16.7% for those operated on within 8 to 14 days, 10.0% for those operated on within 15 to 21 days, 10.5% for those operated on within 22 to 28 days, and 2.3% for those operated on more than 4 weeks later (Fig. 3). A significant correlation existed between the interval and the exacerbation of cerebral complications by the Spearman rank correlation coefficient (tied $p = 0.008$). When the intervals were classified in three groups (within 7 days, 8 to 14 days, and 15 to 28 days), a significant difference for the exacerbation was confirmed by post-hoc comparisons ($p = 0.022$) between the group within 7 days and the group treated at 15 to 28 days (Fig. 4).

Preoperative risk factors affecting exacerbation of cerebral complications were analyzed statistically. The significant variables were severity of cerebral complication ($p = 0.006$), intervals ($p = 0.012$), and uncontrolled congestive heart failure as an indication for cardiac surgery ($p = 0.014$) (Table IV). The rate of ineffectiveness of antimicrobial therapy was two times greater in the group with exacerbation than in the group without exacerbation, although the difference was not verified statistically.

Influence of cardiac surgery on preoperative cerebral hemorrhage. One patient underwent a cardiac operation within 24 hours after the onset of cerebral hemorrhage and died of cerebral damage. In another patient the cardiac operation was performed successfully 5 days later, with prior surgical treatment for cerebral aneurysm. In five patients the cardiac operation was performed between 15 and 21 days later (mortality rate 20.0%) (Fig. 5). The operation was done between 22 and 28 days later in six patients with no mortality and more than 4 weeks later in 21 patients (mortality rate 19.0%). No exacerbation of cerebral complications occurred in patients who underwent their cardiac operation between 2 and 28 days. Nevertheless, exacerbations did occur, at a rate of 19.0%, in patients who were operated on more than 4 weeks later (Figs. 6 and 7). The group having exacerbations of symptoms contained only five patients, and there was no correla-

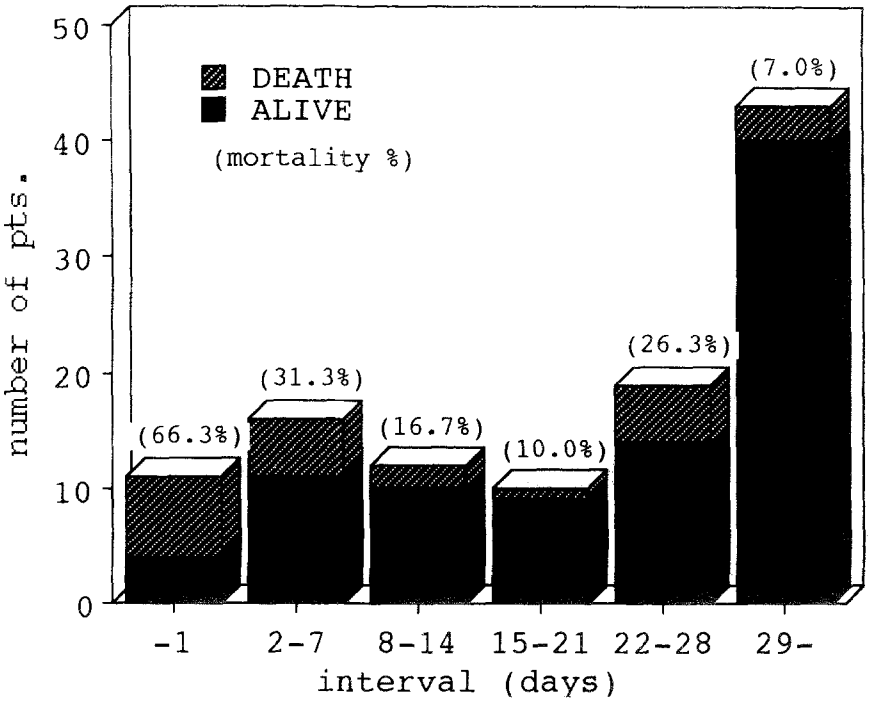

Fig. 2. Distribution of the patients and hospital mortality according to intervals from the onset of cerebral infarction until the cardiac operation.

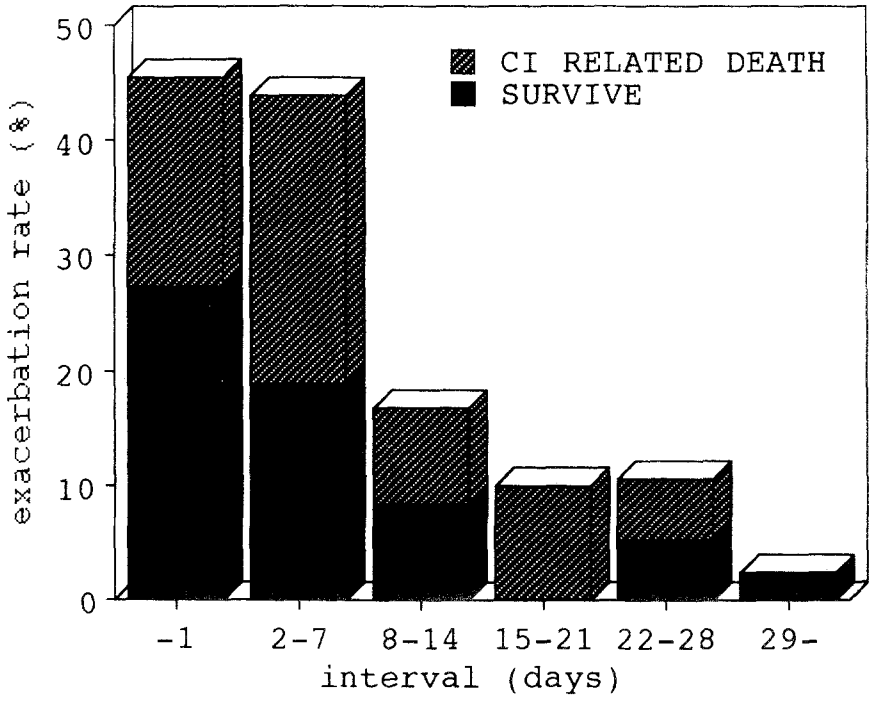

Fig. 3. Exacerbation rate of cerebral damage including death related to cerebral injury according to the intervals from the onset of cerebral infarction *(CI)* until the cardiac operation.

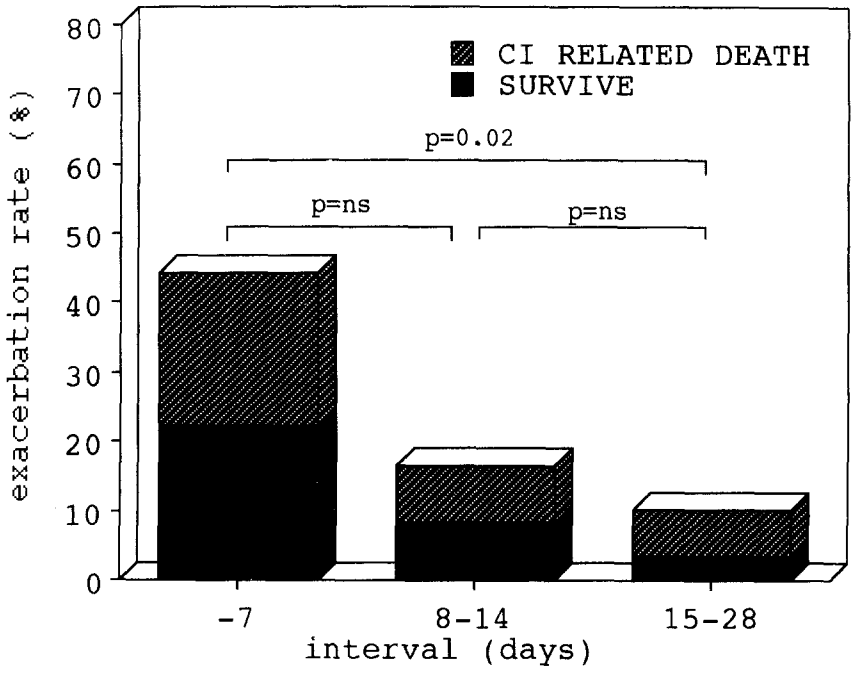

Fig. 4. Correlation between the interval from the onset of cerebral infarction *(CI)* until the cardiac operation and the exacerbation of cerebral complications. When the intervals were classified into three groups, a significant difference in exacerbations was confirmed by post-hoc comparisons between the group operated on within 7 days and the group operated on within 15 to 28 days. *ns,* Not significant.

tion between the interval and the exacerbation of cerebral complications.

All of the patients with exacerbation and 76.5% without exacerbation had cerebral arterial aneurysm before the operation, although a cerebral angiographic examination was done in 58.8% of the patients with cerebral hemorrhage. No one with exacerbation had received surgical treatment for cerebral aneurysm before the cardiac operation, whereas 27.6% without exacerbation had undergone an operation for cerebral disease. The variable influencing exacerbation, according to stepwise regression analysis ($p = 0.013$), was atrial fibrillation (Table V).

Discussion

This study consisted of a questionnaire to the centers belonging to the JATS. The 181 patients gleaned from 244 patients with cerebral complications undergoing surgical treatment for infective endocarditis were able to be analyzed in detail. Several groups have tried to assess the effect of the timing of surgical therapy on patients with recent neurologic injuries.[5, 8-10] However, because of the limited number of cases, the appropriate timing of surgical intervention has not been addressed adequately. This study was based on a sufficient number for discussion of the effect of cardiac operations on patients with cerebral complications.

Characteristics of patients with cerebral complications. It has been reported that 20% to 30% of patients with infective endocarditis may have cerebrovascular complications.[6, 8, 12-17] In this review of 2523 surgical cases of infective endocarditis, 9.7% of the total (12.1% of patients having active native valve endocarditis, 7.3% of those having healed native valve endocarditis, and 12.7% of those having prosthetic valve endocarditis) had associated cerebral complications. Cerebral ischemia was present in 64.6% and hemorrhage in 31.5%.[6, 18] *Staphylococcus aureus* was the most virulent organism involved in the central nervous system.[1, 6, 7, 18-20] However, in this study of cerebral complications, *Streptococcus* was the most common organism followed by *Staphylococcus*. This trend mirrors findings in the whole population of patients with infective endocarditis.[1] In 42% of the patients with cerebral complications, antibiotics were ineffective.

Mortality of cardiac surgery in patients having infective endocarditis with cerebral complications compared with that of patients without cerebral complications. The operative outcome would be influenced by the organism, the intensity of cardiac

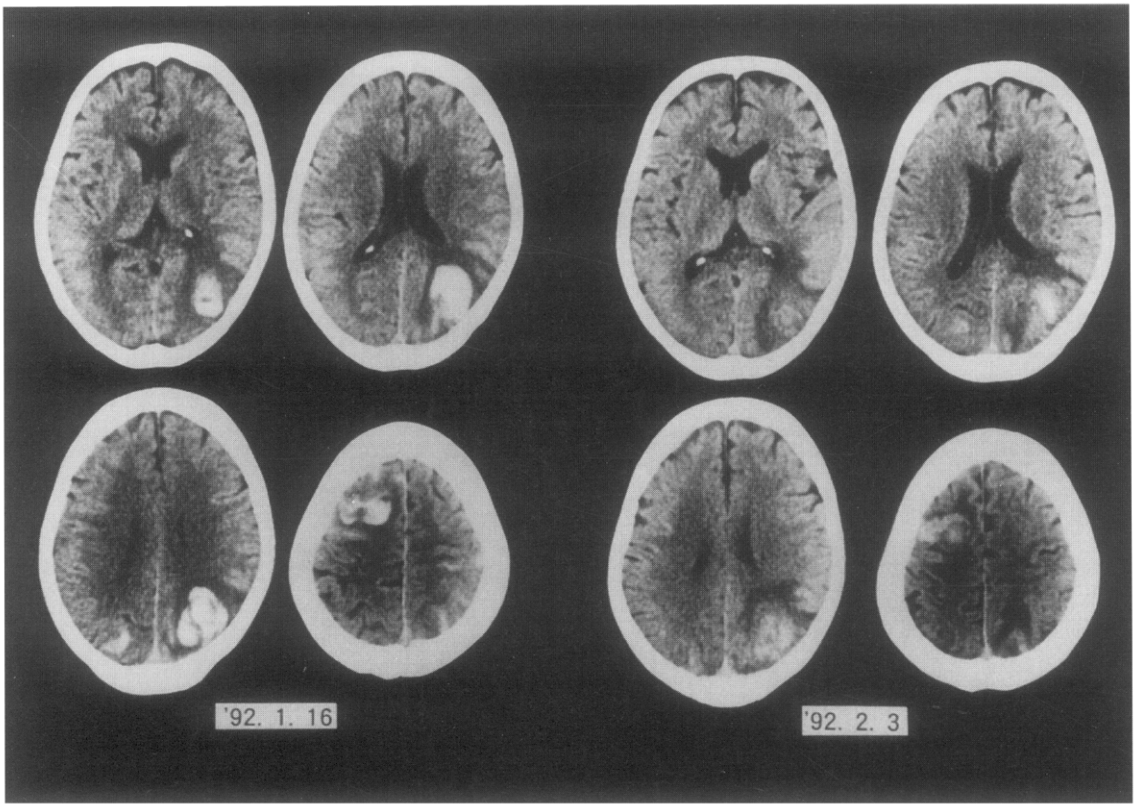

Fig. 5. Computed tomographic scans of a patient with cerebral hemorrhage resulting from infective endocarditis. This patient underwent mitral valve rereplacement 15 days after cerebral hemorrhage without any complications. *Left,* Preoperative computed tomographic scan; *right,* postoperative scan.

Table IV. *Analysis of risk factors affecting exacerbation of cerebral complications in 68 patients who had cerebral infarction within 4 weeks*

	Exacerbation		
	With (n = 17)	*Without (n = 51)*	*Significance*
Continuous variables (mean ± SE)			
Age (yr)	45.5 ± 3.7	40.4 ± 2.1	$p = 0.237$
Effect of AM (1/2/3)	1.6 ± 0.2	2.0 ± 0.1	$p = 0.126$
Severity of CC (1/2/3)	2.2 ± 0.2	1.7 ± 0.1	$p = 0.006$†
Interval (days)	7.9 ± 2.2	15.1 ± 1.4	$p = 0.012$
Nominal variables (%)‡			
Gender (male)	47.1	52.9	$p = 0.674$
Atrial fibrillation	17.6	25.5	$p = 0.509$
Anticoagulant therapy	35.3	23.5	$p = 0.341$
Aortic lesion	70.6	51.0	$p = 0.159$
Mitral lesion	41.1	62.7	$p = 0.119$
Ineffectiveness of AM	41.2	20.0	$p = 0.083$
Vegetation	70.6	84.0	$p = 0.227$
Congestive heart failure	76.5	42.0	$p = 0.014$

SE, standard error; *AM,* antimicrobial therapy; CC, cerebral complication. *Underlining* showed the significant factor by t or χ^2 test.

*p Values for continuous variables were determined by the unpaired t test.

†Significant ($p = 0.017$) by stepwise regression analysis.

‡p Values for nominal variables were determined by the χ^2 test.

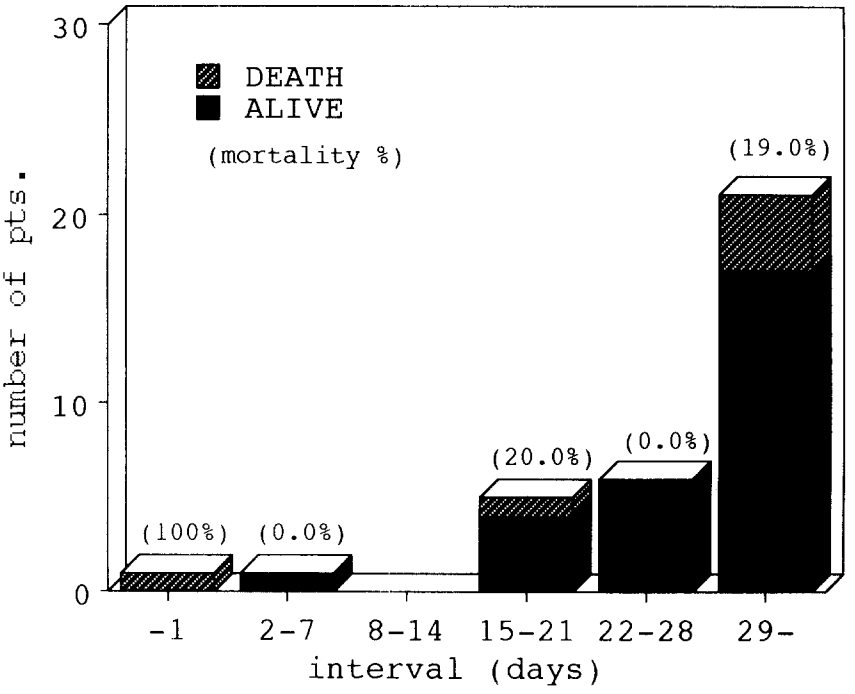

Fig. 6. Distribution of the patients and hospital mortality according to the intervals from the onset of cerebral hemorrhage until the cardiac operation.

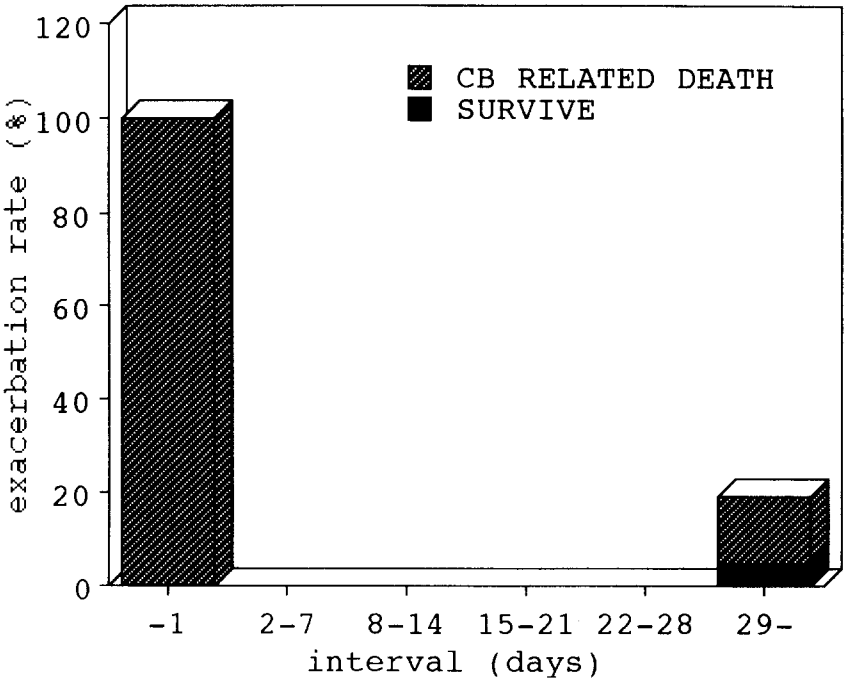

Fig. 7. Exacerbation rate of cerebral damage including death related to cerebral injury *(CB)* according to the intervals from the onset of cerebral hemorrhage until the cardiac operation.

Table V. *Analysis of risk factors affecting exacerbation of cerebral complications in 34 patients who had cerebral hemorrhage preoperatively*

	Exacerbation		
	With (n = 5)	*Without (n = 29)*	*Significance*
Continuous variables (mean ± SE)*			
Age (yr)	37.6 ± 3.4	38.1 ± 3.2	$p = 0.953$
Effect of AM (1/2/3)	2.0 ± 0.4	2.1 ± 0.1	$p = 0.827$
Severity of CC (1/2/3)	2.4 ± 0.2	2.0 ± 0.1	$p = 0.296$
Interval (days)	178 ± 111	80.5 ± 25	$p = 0.196$
Nominal variables (%)†			
Gender (male)	60.0	65.5	$p = 0.812$
Atrial fibrillation	40.0	13.8	p = 0.156‡
Anticoagulant therapy	20.0	27.6	$p = 0.723$
Aortic lesion	80.0	58.6	$p = 0.364$
Mitral lesion	20.0	48.3	$p = 0.110$
Ineffectiveness of AM	40.0	20.7	$p = 0.347$
Vegetation	40.0	58.6	$p = 0.440$
Congestive heart failure	60.0	65.6	$p = 0.812$
Cerebral aneurysm	100	76.5	$p = 0.348$
Cerebral operation	0.0	27.6	$p = 0.179$

SE, Standard error; AM, antibiotics; CC, cerebral complication.
*p Values for continuous variables were determined by the unpaired t test.
†p Values for nominal variables were determined by the χ^2 test.
‡Significant ($p = 0.013$) by stepwise regression analysis.

dysfunction, the presence of annular abscess, and so forth. Irrespective of these factors, the mortality rate in patients with cerebral complications was no higher than that in patients without cerebral complications in this study (13.5% versus 11.0%). Also, the mortality rate in the patients with cerebral hemorrhage was no higher than that in patients with cerebral infarction (20.0% versus 20.7%). Pruitt and associates[21] reported that the mortality rate for 84 patients with neurologic complications was 58%, in contrast to the 20% mortality rate among the 134 patients without neurologic involvement. Operative mortality for early valve replacement ranges from 10% to 37%.[2, 7, 20, 22-26] The preoperative condition of the patients with cerebral complications, especially of those requiring early operation, would be more severe. Our results showed that preoperative cerebral complications caused a substantial number of deaths. It is clear that the timing of the cardiac operation affects the outcome in patients with cerebral infarction.

Influence of cardiac surgery on preoperative cerebral infarction. The major purpose of this study is to clarify how long to wait before performing a cardiac operation after the onset of cerebral complications in patients in whom early cardiac repair would be advisable. In 43.8% of the patients requiring a cardiac operation within 7 days after cerebral infarction, cerebral damage was exacerbated. The exacerbation rate decreased gradually with the timing of the operation and, in the group operated on after 28 days, it was 2.3%.

According to these data, a cardiac operation can be done safely after 4 weeks; after a delay of more than 2 weeks, the exacerbation rate will be around 10%. If the natural history of the patient receiving medication is expected to be very bad, surgical repair might be appropriate even in a week. Moreover, if the patient requires an early operation because of uncontrolled heart failure or if the preoperative cerebral infarction is severe, the risk of surgical treatment would be higher than expected according to timing of the operation. Ineffectiveness of antimicrobial therapy may affect cerebral damage, although such an effect was not verified statistically.

Influence of cardiac surgery on preoperative cerebral hemorrhage. The number of patients who underwent a cardiac operation within 4 weeks after cerebral infarction was large, whereas the number having the operation within 4 weeks after hemorrhage might be too small (13 patients) to allow us to evaluate the influence of the passage of time before heart surgery. However, heart surgery within 24 hours after cerebral hemorrhage has a high risk of causing fatal cerebral damage. Although no one of

the 11 patients who underwent cardiac surgery between 15 days and 28 days after cerebral hemorrhage had exacerbation of cerebral damage during the operation, 19.0% of 21 patients operated on more than 4 weeks later had an exacerbation. These data suggest that there is some risk of progression of cerebral damage 15 days and even 4 weeks after the hemorrhage, regardless of the timing of the operation. The severity of cerebral complications and the ineffectiveness of antimicrobial therapy may affect cerebral damage, although this effect was not verified statistically. The incidence of clinically apparent mycotic aneurysm in patients with bacterial endocarditis was reported as 2% to 10%.[13-16, 19, 27, 28] In our study, a cerebral aneurysm was noticed in about 80% of the patients with cerebral hemorrhage who received cerebral angiograms, and surgical treatment for cerebral aneurysm or hemorrhage would be expected to reduce the risk of cerebral damage during cardiac operations. To decrease the tendency toward hemorrhage, reduced heparinization in conjunction with a heparin-coated pump system would be useful during cardiac operations.

Conclusion

From a multi-center retrospective study, 181 patients with infective endocarditis and cerebral complications were analyzed in detail. The rate of exacerbation of cerebral complications decreased to 10% in patients who underwent surgical treatment more than 15 days after cerebral infarction and to 2.3% in those operated on more than 4 weeks later. Preoperative risk factors were severity of cerebral complications, interval from onset of symptoms to operation, and uncontrolled heart failure as the indication for cardiac surgery. More than 15 days after cerebral hemorrhage, the risk of the progression of cerebral damage is still significant, and this risk persists even 4 weeks later.

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