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Neurological Outcome of Septic Cardioembolic Stroke After Infective Endocarditis

Elfriede Ruttmann, MD; Johann Willeit, MD; Hanno Ulmer, PhD; Orest Chevtchik, MD; Daniel Höfer, MD; Werner Poewe, MD; Günther Laufer, MD; Ludwig C. Müller, MD

Background and Purpose—The aim of this study was to evaluate mortality and neurological outcomes of cardioembolic cerebral stroke in infective endocarditis (IE) patients requiring cardiac surgery.

Methods—A consecutive series of 214 patients undergoing cardiac surgery for IE was followed up for 20 years. In 65 patients (mean age, 52 years), IE was complicated by computed tomography– or magnetic resonance imaging–verified stroke (n=61) or transient ischemic attack (n=4). Perioperative (30-day) and long-term mortality was assessed with regression models adjusting for age. Complete neurological recovery of IE survivors was defined by a modified Rankin score of ≤1 and a Barthel index of 20 points.

Results—Fifty of 61 stroke patients (81.9%) survived surgery. In comparison with nonstroke patients, the age-adjusted perioperative mortality risk was 1.70-fold (95% CI, 0.73 to 3.96, $P=0.22$) higher and long-term mortality risk was 1.23-fold (95% CI, 0.72 to 2.11, $P=0.45$) higher in stroke patients. Patients with complicated stroke (meningitis, hemorrhage, or brain abscess) showed a higher perioperative mortality rate (38.9% vs 8.5%, $P=0.007$) but no higher neurological complication rate than patients with uncomplicated ischemic stroke. Complete neurological recovery was achieved in 35 IE survivors (70%, 95% CI, 55% to 82%). However, in the case of middle cerebral artery stroke, recovery was only 50% and was significantly lower compared with non—middle cerebral artery stroke ($P=0.012$).

Conclusion—Uncomplicated IE-related stroke showed a favorable prognosis with regard to both long-term survival and neurological recovery. The formidable risk of secondary cerebral hemorrhage due to cardiac surgery seems to be much lower than previously thought. **(*Stroke*. 2006;37:000-000.)**

Key Word: infective endocarditis ■ neurologic rehabilitation ■ septic embolism ■ stroke

Stroke as a complication of infective endocarditis (IE) results from the embolization of endocardial vegetations with consecutive occlusion of an intracerebral artery. Dissemination of the emboli into cerebral or meningeal vessels can further lead to meningitis or intracerebral abscess formation.[1,2] The spectrum of neurological events includes ischemic infarction with or without hemorrhage, transient ischemic attack, meningitis, encephalopathy, brain abscess, peripheral neuropathy, seizure, and rarely mycotic aneurysm.

Septic cerebral embolism affects the clinical course of ≈40% of IE patients, and the incidence among IE patients has remained unchanged during the past few decades.[3–6] Embolic events caused by IE bear a ≥50% risk of recurrence; in addition, in patients with a short duration of clinical symptoms, the risk of recurrent cerebral infarction has been stated to be ≈80% and may tremendously aggravate the neurological outcome of the patient.[7]

Moreover, progression of IE can cause extensive destruction of cardiac valves, including paravalvular abscess formation, persistent sepsis, congestive heart failure, and recurrent septic embolism. When IE is complicated by neurological injury, early cardiac surgical treatment is favored in the absence of alternative treatment.[8,9] Early surgical treatment for IE seems to be superior for these patients, on 1 hand due to improved surgical techniques and results in general, and on the other hand due to the higher incidence of more aggressive forms of IE.[10–12] However, the safety of cardiopulmonary bypass (CPB) in patients with acute neurological injury has been controversially debated in the literature.[13–15] CPB is suspected to exacerbate neurological deficits due to heparinization and may increase the risk for secondary cerebral hemorrhage. Additionally, the hypotensive period during CPB may aggravate preexisting neurological ischemia and potentiate cerebral edema in areas of the disrupted blood-brain barrier.

Few studies, mainly focusing on secondary cerebral hemorrhage, have investigated the incidence of perioperative neurological complications in IE patients; however, the results were controversial. Piper and colleagues[15] concluded that cardiac surgery ought to be performed within 72 hours

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after an index neurological event when the risk of secondary cerebral hemorrhage seems to be low. Contrarily, Gillinov et al[14] demonstrated among 34 patients with preoperative neurological deficit that most patients do well if cardiac procedures can be delayed for 2 to 3 weeks. In addition, until now, no large consecutive study has ever investigated the neurological outcome in IE survivors who were affected by stroke.

The aims of the current study therefore were to (1) describe the incidence of septic cerebral embolism and its localization within the nervous system in IE patients requiring surgical treatment, (2) describe the incidence of perioperative neurological complications, (3) evaluate whether stroke affects perioperative and long-term mortality, and (4) investigate the neurological outcome and recovery of cardioembolic stroke in patients surviving IE.

Patients and Methods

Data were obtained from a consecutive series of 214 patients (from 1985 to 2004) undergoing cardiac operations for left-sided IE at the University Hospital Innsbruck. These patients have been followed-up for up to 20 years. When a stroke occurred, a brain computed tomography (CT) scan was performed to outline the topography and size of the infarct and hemorrhage and to assess brain edema. After cardiac surgery, before weaning from the respirator was attempted, a second brain CT scan was performed in patients with previous stroke to evaluate whether secondary cerebral hemorrhage had occurred during surgery.

All operative procedures were performed with the use of extracorporeal circulation (ECC) under mild hypothermia (28°C to 32°C) and full anticoagulation. Heparinization was frequently monitored while on-pump, and activated clotting time was maintained at >480 seconds to avoid clotting. Hematocrit levels were kept between 26% and 30% by priming of the ECC or adding erythrocytes to the ECC circuit.

All survivors were frequently followed up by experienced cardiologists, cardiac surgeons, and neurologists and underwent clinical examinations and echocardiographic controls. Autopsies were performed on all nonsurvivors to evaluate the cause of death and neurological complications, such as secondary hemorrhage.

In the follow-up, neurological recovery was assessed with the use of the modified Rankin scale and the Barthel index to assess remaining disability.[16,17] A Rankin score of 0 or 1 and a Barthel index of 20 points were defined to indicate full neurological recovery. In 22 IE stroke survivors, the National Institutes of Health (NIH) stroke index was assessed at the time of hospital admission.

Statistical Analysis

Data are shown as mean±SD for continuous variables and absolute numbers as well as percentages for categorical variables. In a first step, the 2 patient groups (previous stroke or not) were compared for differences in patient characteristics, surgical variables, and perioperative outcome, as well as long-term survival. Comparisons between the 2 patient groups were performed for categorical variables with the χ^2 or Fisher exact test, as appropriate. Continuous variables were compared by Student *t* test or the Mann-Whitney *U* test. Long-term survival was assessed by Kaplan-Meier analysis and log-rank testing. Relative risks for perioperative and long-term mortality were given as age-adjusted odds ratios and hazards ratios, estimated by logistic and Cox proportional-hazards regression analyses, respectively. To evaluate whether the NIH stroke index at admission was predictive for remaining neurological deficit, the Spearman correlation coefficient was calculated. A probability value <0.05 was considered significant. Data documentation and statistical analysis were performed with SPSS 11.0 (SPSS Inc).

TABLE 1. Demographic Characteristics of Patients Undergoing Cardiac Surgery for IE From 1985 to 2004

	No Cerebral Embolism n=149 Patients	Septic Cerebral Embolism n=65 Patients	*P* Value
Age (mean, SD)	55.1±15.7	51.8±15.4	0.18
Male sex (%)	96 (64.4%)	46 (70.8%)	0.44
Impaired left ventricular function (LVEF<48%)	78 (52.3%)	37 (56.9%)	0.57
Left ventricular ejection fraction in % (mean, SD)	50±12	49±12	0.46
Hospital acquired endocarditis	46 (30.8%)	23 (35.4%)	0.52
Prosthetic valve endocarditis (n, %)	33 (22.1%)	12 (20%)	0.73
Affected heart valves			
Aortic valve	66 (44.3%)	23 (35.4%)	
Mitral valve	56 (37.6%)	32 (49.2%)	
Aortic and mitral valve	25 (16.8%)	9 (13.8%)	
Mitral and tricuspid valve	1 (0.7%)	1 (1.5%)	
Aortic and tricuspid valve	1 (0.7%)	0 (0%)	0.49
Causative microorganism			
Staphylococcus	64 (43%)	38 (58.5%)	
Streptococcus	53 (35.6%)	10 (15.4%)	
Enterococcus	15 (10.1%)	11 (16.9%)	
Unknown	13 (8.7%)	2 (3.1%)	
Others	4 (2.7%)	4 (6.2%)	0.008
Additional fungal contamination	2 (1.3%)	2 (3.1%)	
Median time from hospital admission or stroke to cardiac surgery	10 days (range 0 to 90)	4 days (range 0 to 38)	0.001
Main indication for surgery			
Refractory sepsis	57 (38.3%)	18 (27.7%)	
Cardiac-related (heart failure, progression of valve disease, AV-block)	58 (38.9%)	20 (30.8%)	
High embolic risk	34 (22.8%)	27 (41.5%)	0.02
Emergent surgical procedure (within 24 hours after diagnosis of IE)	19 (12.8%)	22 (33.8%)	0.001
EuroSCORE (perioperative riskscore, mean, SD)	11.1±3.9	12.2±4.3	0.72

Results

Preoperative Neurological Findings

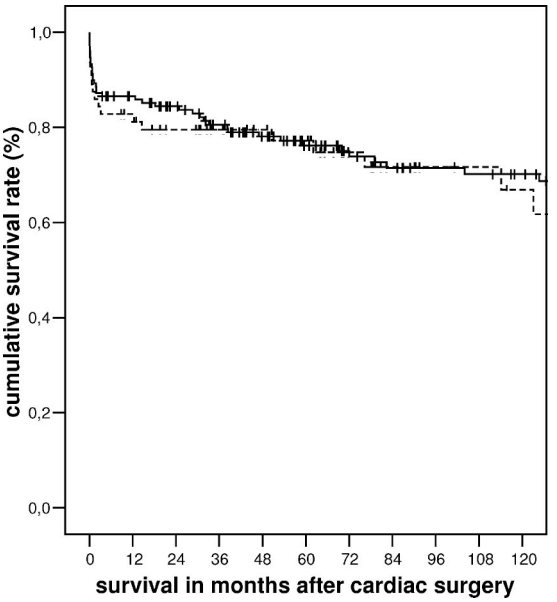
Detailed patient characteristics are summarized in Table 1. In 65 patients (30.4%), IE was complicated by an acute neurological event. Sixty-one of them (93.8%) were diagnosed with ischemic cardioembolic stroke, which was verified by CT scan or magnetic resonance imaging before cardiac surgery. Four patients (6.2%) experienced a transient ischemic attack and recovered before cardiac surgery was performed. In 55 patients (84.6%), the neurological event occurred before hospital admission; 10 patients had a cerebral

TABLE 2. Localization of IE-related Embolism Among 65 IE Patients With Acute Neurologic Deficits

	Septic Cerebral Embolism n=65 Patients
Brain areas affected	
MCAS (%)	28 (43.1%)
Complete MCAS	16 (24.6%)
Partial MCAS	12 (18.5%)
Frontoparietal	13 (20%)
Multilocular	7 (10.8%)
Cerebellum	1 (1.5%)
Brain stem	2 (3.1%)
Thalamus	3 (4.6%)
Transient ischemic attack (no infarct verifiable)	4 (6.2%)
Additional neurologic complications before surgery	18 (27.6%)
Meningitis	7 (10.7%)
Intracranial abscess	5 (7.7%)
Hemorrhage	6 (9.2%)
Additional peripheral embolism (%)	21 (32.3%)
Spleen	9 (13.8%)
Kidney	9 (13.8%)
Lower limb	6 (9.2%)
Eye (*A retinae*)	2 (3.1%)
Mesenteric infarction	1 (1.6%)
Right coronary artery	1 (1.6%)

event after being diagnosed with IE while under antibiotic treatment. Three patients received intravenous lysis therapy, as thrombotic occlusion was suspected before the diagnosis of IE. The median time from the cerebral event to cardiac surgery was 4 days (range, 0 to 38 days). The mean age of stroke patients was 51.8±15.4 years.

Table 2 summarizes the brain areas affected by stroke, the sites of multiorgan embolism, and additional neurological complications before surgery. Middle cerebral artery stroke (MCAS) occurred in a total of 28 patients (43.1%) and was the most predominant intracerebral lesion found in IE patients. Of these, 16 patients (57.1%) had complete MCAS, and 12 patients had partial MCAS (42.9%). Two of the 6 patients who had an intracerebral hemorrhage before surgery first had to undergo craniotomy. After surgery, 4 of the 6 hemorrhage patients died (66.5%). One of these patients (craniotomized before cardiac surgery) had a recurrence and lethal aggravation of cerebral hemorrhage and was diagnosed with brain death on the fifth postoperative day. Another patient died of myocardial infarction on the fourth postoperative day (autopsy report). The other 2 patients died of sepsis-related multiorgan failure (1 patient) and recurrent septic embolism to the lower limb (1 patient). The remaining 2 patients with preoperative cerebral hemorrhage (1 of them craniotomized before surgery) were stable without recurrence of bleeding after surgery and recovered without any neurological deficit. Two of 5 patients with intracerebral abscess formation died of persisting sepsis without any verifiable



Long-term survival after IE using Kaplan Meier analysis according to whether ischemic stroke had occurred before cardiac surgery. Patients with prior neurologic events are displayed by dashed line, patients without neurologic events by solid line (log rank: $P=0.74$).

perioperative neurological complication. All patients who experienced a transient ischemic attach before cardiac surgery (n=4) recovered well after surgery and developed no further neurological deficit.

Perioperative Mortality and Long-Term Outcome

The median follow up time was 5.9 years (range, 3.3 months to 20 years) in survivors without a previous cerebral embolism and 5.8 years (range, 3.6 months to 20.4 years) in patients with a previous neurological event ($P=0.24$). The Kaplan-Meier plot describing the cumulative survival of stroke versus nonstroke IE patients is displayed in the Figure. Table 3 displays the causes of death during the initial hospital stay and during long-term follow-up. Overall perioperative mortality (defined as death within 30 days or during the same hospital stay) was 14% (30 patients); 19 patients died without preoperative neurological events (12.8%) and 11 patients with a previous cerebral event (16.9%, $P=0.42$). In the stroke group, patients with additional neurological complications before surgery (meningitis, cerebral hemorrhage, or brain abscess) had a higher risk of dying perioperatively than did patients with uncomplicated ischemic stroke (38.9% versus 8.5%, $P=0.007$). Multiorgan embolism (cerebral and peripheral) was not significantly associated with higher perioperative mortality (15.9% versus 19.0%, $P=0.74$).

Actuarial 1-year survival was 85.9% in patients without previous stroke and 81.2% in patients with preoperative neurological events; 5-year survival was 76.2% versus 74.7%, and 10-year survival, 70.2% versus 66.9%, respectively (log-rank $P=0.74$). Age-adjusted perioperative mortality risk increased by 1.70 (95% CI, 0.72 to 2.11, $P=0.45$), and age-adjusted long-term mortality hazard ratio was increased by 1.23 (95% CI, 0.72 to 2.11, $P=0.45$) in patients with previous stroke. Young age showed a highly significant

TABLE 3. Causes of Death During Hospital Stay and During Long-Term Follow-Up

	No Cerebral Embolism n=149 Patients	Septic Cerebral Embolism n=65 Patients
Perioperative deaths	19 (12.8%)	11 (16.9%)
Sepsis (% of perioperative deaths)	14 (73.7%)	7 (63.6%)
Myocardial infarction	1 (5.3%)	1 (9.1%)
Mesenteric infarction	2 (10.6%)	2 (18.2%)
Aortic dissection	1 (5.2%)	0 (0%)
Left venticular rupture (myocardial abscesses)	1 (5.2%)	0 (0%)
Cerebral bleeding	0 (0%)	1 (9.1%)
Causes of death during long-term follow-up	31 (20.8%)	11 (16.9%)
Heart failure (% of long-term mortality)	16 (51.6%)	5 (45.4%)
Myocardial infarction	2 (6.5%)	0 (0%)
Sepsis	3 (9.6%)	0 (0%)
Recurrent endocarditis	5 (16.1%)	3 (27.3%)
Trauma	2 (6.5%)	0 (0%)
Malignoma	2 (6.5%)	1 (9.1%)
Cerebral bleeding (anticoagulation related)	1 (3.2%)	1 (9.1%)
Ischemic stroke	0 (0%)	1 (9.1%)

protective effect against both perioperative and long-term mortality (both $P<0.001$) in the multivariate analyses.

Postoperative Neurological Recovery

Fifty of 61 patients with CT-verified preoperative stroke survived cardiac surgery (81.9%). Latency between the neurological event and cardiac surgery (within 4 days after stroke or later) was a nonrelevant factor with respect to both the perioperative neurological complication rate (3.2% versus 0%, $P=0.32$) and the postoperative neurological recovery (75% versus 70%, $P=0.68$). Full neurological recovery was achieved in 35 of 50 stroke patients (70%; 95% CI, 55% to 82%). However, when MCAS occurred before surgery, full neurological recovery was achieved in only 50% and was significantly lower when compared with patients with ischemic events affecting other parts of the brain (83.3%, $P=0.012$). Patients who had a complete MCAS did not show significantly higher rates of remaining neurological deficit than did patients with partial MCAS (6 of 10 versus 4 of 10, $P=0.66$).

Table 4 summarizes the neurological outcome of IE survivors with regard to the NIH stroke index assessed at hospital admission (available in 22 patients). There was a significant correlation between NIH stroke index at admission and later neurological outcome ($r=-0.5$, $P=0.02$); however, in MCAS patients, the NIH stroke index was less predictive for later neurological outcome ($r=-0.38$, $P=0.3$). Table 5 summarizes the neurological outcome of IE survivors according to the modified Rankin scale and the Barthel index.

TABLE 4. Neurologic Outcome of IE Survivors According to the NIH Stroke Index at Admission (Available in 22 Patients)

NIH Stroke Scale at Admission	n=22 Patients	Full Neurologic Recovery
4 to 9	9	7 (77.8%)
10 to 15	7	4 (57.1%)
>15	6	2 (33.3%)

TABLE 5. Postoperatve Neurologic Outcome of 50 IE Patients With Septic Cardioembolic Stroke According to the Modified Rankin Scale and the Barthel Index Assessed During Follow-Up

Rankin Scale in IE Survivors	n=50
0	35 (70%)
1	0 (0%)
2	5 (10%)
3	7 (14%)
4	3 (6%)
Barthel Index in IE Survivors	n=50
20	35 (70%)
18	4 (8%)
17	4 (8%)
16	1 (2%)
15	3 (6%)
14	1 (2%)
12	1 (2%)
11	1 (2%)

Discussion

The present study demonstrates that 70% of IE survivors who experienced a cardioembolic stroke achieve full neurological recovery after cardiac surgery. Patients who had additional neurological complications before surgery had a significantly higher mortality rate than did patients with uncomplicated ischemic stroke. However, when an MCAS occurred, the recovery rate was significantly lower when compared with patients with stroke affecting other parts of the brain. Because we observed only 1 recurrent postoperative cerebral hemorrhage after craniotomy and cardiac surgery, the risk of postoperative cerebral hemorrhage seems to be much lower than previously thought.

There are arguments explaining the favorable neurological outcome in IE patients. First, stroke had not occurred in association with atherosclerotic vessel disease. Second, the much younger age of IE patients compared with patients with stroke due to other causes is an additional reason for the improved neurological recovery.[18]

Gillinov et al[14] recommended that the cardiac procedure is safe when it can be delayed for 2 to 3 weeks. However, this treatment strategy might not be appropriate for most IE patients, owing to sepsis, progression of cardiac disease, or the risk of recurrent embolism. Our results are in line with the recommendations by Piper et al,[15] who reported that the risk of secondary cerebral hemorrhage seems to be low if cardiac surgery is performed early after the neurological event.

Cerebral stroke is the leading cause of disability in industrialized countries. It affects 400 of 100|000 inhabitants per year, leaves 40% of stroke patients with moderate functional impairment, and leaves up to 30% with severe disability.[16,17] Septic cardioembolic stroke, however, is a rare cause of stroke but forces surgeons to perform highly invasive procedures to eliminate the infective cardiac source.

Several epidemiological studies have shown a high disability rate after all-cause stroke, but until now, no large consecutive study has ever investigated the neurological outcome of IE-related stroke patients. Because IE is a rare disease, occurring predominantly in young patients, studies on neurological recovery in IE stroke patients are necessary. Until now, only a small study by Zisbrod et al[12] in 1987 described a 57% complete neurological recovery rate among 13 IE survivors. Because it has been the conventional wisdom that cardiac surgery should not be performed during loss of autoregulation in the penumbra zone (ie, up to 4 weeks), no clinical data to support this strategy are available. IE patients have a high mortality risk because of their cardiac conditions, although the neurological recovery rate in survivors is higher when compared with other stroke patients. Additionally, either the neurological complication rate or the neurological outcome was similar in patients who underwent surgery early or late after a neurological event. However, in contrast to previous studies, perioperative mortality and long-term survival in stroke patients were not significantly different from those of IE patients without neurological injury in our study.[1,19]

The inflammatory response to ECC has been investigated by many research groups.[20,21] Additionally, ECC-related anticoagulation might be associated with a higher risk for bleeding in stroke patients. In the past decade, several neurological studies have investigated isovolemic or hypervolemic hemodilution as a treatment option for stroke patients to lower viscosity and increase cerebral blood flow in the penumbra zone.[22,23] However, experimental studies have stated a target hematocrit of 30% to be highly effective to reduce cerebral infarct size and improve cerebral microcirculation.[24,25] Regarding these findings, most studies were not able to show the efficacy of hemodilution in stroke patients because of too high hematocrit target levels.[26,27] Yanaka et al[28] demonstrated in an experimental hemodilution trial in dogs (hematocrit target levels of 30%) that hemodilution within 3 hours after MCA occlusion was highly effective in reducing infarct size; later treatment, however, was associated with a higher risk of cerebral hemorrhage.

Considering that ECC causes isovolemic hemodilution with hematocrit target levels between 26% and 30%, a partial beneficial effect (if no hemorrhage occurs) in stroke patients could be emphasized. Systemic hypothermia during cardiac surgery may further add to potential cerebrovascular protection. Furthermore, if anticoagulation during ECC does not provoke secondary hemorrhage, possible fragmentation and a more peripheral dislocation of the cerebral embolus in the cerebrovascular circulation could additionally explain the relatively good postoperative neurological outcome.

Finally, our data suggest that cardioembolic stroke has a favorable prognosis compared with stroke of other causes, and stroke rehabilitation has a high success rate among these predominantly young patients. Additionally, because the suspected risk for secondary hemorrhage in uncomplicated ischemic stroke seems to be very low, we recommend early surgical procedure after stroke.

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