

# Cerebrovascular Complications in Patients with Left-Sided Infective Endocarditis Are Common: A Prospective Study Using Magnetic Resonance Imaging and Neurochemical Brain Damage Markers

Ulrika Snygg-Martin,<sup>1</sup> Lars Gustafsson,<sup>2</sup> Lars Rosengren,<sup>3</sup> Åsa Alsiö,<sup>4</sup> Per Ackerholm,<sup>5</sup> Rune Andersson,<sup>6</sup> and Lars Olaison<sup>1</sup>

Departments of <sup>1</sup>Infectious Diseases, <sup>2</sup>Radiology, and <sup>3</sup>Neurology, Sahlgrenska University Hospital, Göteborg, and Departments of <sup>4</sup>Infectious Diseases and <sup>5</sup>Radiology, and <sup>6</sup>Research and Development Center, Skaraborg Hospital, Skövde, Sweden

(See the editorial commentary by Baddour and Bayer on pages 31–2)

**Background.** Cerebrovascular complications (CVCs) have remained a major therapeutic and prognostic challenge associated with infective endocarditis, and definite risk factors have not been fully elucidated. This prospective study was designed to evaluate the total incidence of CVC associated with infective endocarditis and major risk factors.

**Methods.** During 2 study periods, from June 1998 through April 2001 and from September 2002 through January 2005, patients were prospectively enrolled in the study regardless of neurological symptoms. Study patients underwent neurological examinations and magnetic resonance imaging of the brain, and cerebrospinal fluid analyses of inflammatory and neurochemical markers of brain damage (neurofilament protein and glial fibrillary acidic protein) were performed.

**Results.** Sixty patients who experienced episodes of left-sided infective endocarditis were evaluated; 35% of these patients experienced a symptomatic CVC. Silent cerebral complications were detected in another 30% of the patients, and the total CVC rate was 65% (95% confidence interval, 58%–72%). Five percent of patients experienced their first neurological symptom after the initiation of antibiotic treatment without prior surgery. No new symptomatic CVCs were detected after 10 days of antibiotic treatment. No neurological deterioration was observed after surgery in patients who were established to have a symptomatic CVC preoperatively. A larger heart valvular vegetation size was a risk factor for both symptomatic and silent CVCs; *Staphylococcus aureus* etiology conferred a higher risk for symptomatic cerebral complication only.

**Conclusions.** The use of sensitive methods of detection indicates that the incidence of CVC associated with infective endocarditis is high, but the risk for neurological deterioration during cardiac surgery after a CVC is lower than previously assumed. The major mechanism behind cerebral complications associated with infective endocarditis is cerebral embolization, although the dominant neurological symptoms vary considerably.

A characteristic feature in patients with infective endocarditis is the propensity for heart valvular vegetation to embolize to different organs. Before penicillin was available, major cerebral embolization was one of the leading causes of death. Despite a marked reduction in

the mortality rate and in the rates of other complications in patients with infective endocarditis (a reduction attributable to modern antibiotic and surgical treatment regimens), the incidence of cerebrovascular complications (CVCs) has remained relatively stable at 12%–40% [1–5]. Numerous studies have attempted to establish and grade risk factors for cerebral embolization, including the size and morphology of vegetations, the valve infected, bacterial etiology, the presence of a prosthetic valve, delay of treatment, and patient age. One of the main obstacles in these studies has been the uncertainty of establishing a clinical diagnosis of cerebral embolization. Clinical symptoms may be vague

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Reprints or correspondence: Dr. Ulrika Snygg-Martin, Dept. of Infectious Diseases, Sahlgrenska University Hospital/Östra, S-41685 Göteborg, Sweden (ulrika.snygg-martin@infect.gu.se).

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or definite and depend on which cerebral area is affected and on different pathophysiological mechanisms involved; thus, the incidence and impact of silent CVC is unclear.

Calculating the risk of CVC is of major importance in making often-difficult decisions regarding acute heart surgery [6–10]. To establish major risk factors for and the incidence of cerebral embolism before and during episodes of infective endocarditis, we have performed a prospective study of treated, left-sided infective endocarditis cases, using the most up-to-date diagnostic methods, including MRI of the brain and detection of CSF markers for inflammation and brain damage.

## PATIENTS AND METHODS

**Patients.** From June 1998 through April 2001 and from September 2002 through January 2005, 63 patients with high clinical suspicion of infective endocarditis were enrolled in the study irrespective of neurological symptoms. All patients who were enrolled during the period 1998–2003 were treated at the Department of Infectious Diseases at Sahlgrenska University Hospital (Göteborg, Sweden); during the final year of the study (January 2004 through January 2005), patients from the Department of Infectious Diseases at Skaraborg Hospital (Skövde, Sweden) were also included. Informed consent was obtained from all patients according to local ethics committee guidelines.

**Study procedures.** Patients were examined according to a standardized protocol that involved repeated neurological examination and MRI or CT of the brain during the first 10 days of treatment and again after 2–3 months. If no contraindications were found and the patient consented, a lumbar puncture was performed during the first and fourth week of treatment. Serum samples were also obtained twice a week during the treatment period. The MRI protocol consisted of obtaining T1-, T2-, and PD-weighted images before and after the administration of a gadolinium contrast. Diffusion-weighted images were not obtained. In patients with contraindications for MRI (pacemakers, primarily), CT was performed with and without contrast. The examination findings were directly evaluated by the local supervising radiologist and were later reevaluated by 1 of 2 experienced neuroradiologists who were blinded to the neurological status of the patients. Identification of acute and subacute ischemic or hemorrhagic lesions and other differences between the 2 neurological investigations (at 10 days and at 2–3 months after the start of treatment) were considered in the diagnosis of a cerebral complication related to infective endocarditis [11, 12].

CSF samples were analyzed for bacterial culture growth, pleocytosis (mononuclear and polymorphonuclear leukocytes), glucose levels, albumin levels, and 2 neurochemical markers of brain damage (neurofilament protein [NFL] and glial fibrillary acidic protein [GFAP]). During the first study period (1998–2001), the S-100 protein level was also analyzed in CSF and serum samples, but no pathological results were obtained and

the analysis was not performed during the second study period or included in the final evaluation. Patients were considered to have an acute CVC related to infective endocarditis if they exhibited an increase in NFL or GFAP levels consistent with brain tissue damage. Patients were diagnosed as having meningitis if there were elevated polymorphonuclear leukocyte levels in CSF samples ( $>5 \times 10^6$  cells/mL), as described elsewhere [1, 3]. Isolated, minor increases in mononuclear leukocyte levels in CSF samples were not considered to be acute cerebral manifestations of infective endocarditis. NFL and GFAP are specific neuronal and astroglial proteins that are released from brain tissue at different stages of cell death, and measurement of these allows for the detection of brain infarctions with a volume  $<1$  mL. NFL and GFAP levels were measured using ELISAs, as described elsewhere [13, 14]. Laboratory reference levels were based on measurements of CSF samples from 141 neurologically healthy individuals (age, 18–83 years).

**Statistical analysis.** Comparisons of demographic data between our patients and the National Swedish Endocarditis Registry were performed using Fisher's exact test, and the *P* values are 2-tailed. Continuous variables were expressed as a mean ( $\pm$  SD) or median value. Univariable risk factor analysis was performed using Fisher's permutation test [15, 16]. Multivariable risk factor analysis was performed using a logistic regression model, and the discriminating ability was tested with receiver operating characteristic curves. The area under the receiver operating characteristic curve was calculated, and if values were in the interval of 0.8–0.9, the analysis was considered to have excellent discrimination. The area under the receiver operating characteristic curve equals the probability that a randomly chosen individual with a certain risk factor will have a higher value of the discriminating variable than will a randomly chosen individual without the risk factor [17, 18].

## RESULTS

**Baseline characteristics.** Of the 63 patients initially included in the study, 2 were later excluded according to the modified Duke criteria [19], and 1 withdrew from the study. The remaining 60 patients were evaluated, and 54 patients (90%) were classified as having a definite diagnosis of infective endocarditis. All episodes of infective endocarditis were left-sided. The mean age of patients ( $\pm$  SD) was  $63.5 \pm 16.1$  years (median age, 67.4 years), and 39 patients (65%) were men. Demographic and medical data on study patients, compared with data on patients included in the National Swedish Endocarditis Registry during the same period, are shown in table 1. The surgical rate was increased and hospital mortality was decreased in study patients, compared with patients in the National Swedish Endocarditis Registry. One-year mortality in the study group was 13%, and the median follow-up time was 4.3 years (range, 3 months to 9.1 years).

**Table 1. Demographic and clinical characteristics of patients included in the study and data from the National Swedish Endocarditis Registry, June 1998–December 2004.**

Variable	Study patients (n = 60)	National Swedish Endocarditis Registry (n = 1762)	P
Female sex	21 (35)	630 (36)	>.30
Age, mean years	63.5	62.7	>.30
Transesophageal echocardiogram performed	58 (97)	1418 (80)	<.001
Vegetation observed	42 (70)	1245 (71)	>.30
In-hospital mortality	1 (2)	182 (10)	.02
Mortality after 12 months	8 (13)	...	
Delay of treatment, median days (range)	8 (1–133)	8 (0–478)	
Injection drug user	3 (5)	211 (12)	.12
Surgery performed	20 (33)	354 (20)	.03
Involved valve <sup>a</sup>			
Aortic	35 (58)	826 (47)	.10
Mitral	23 (38)	729 (41)	>.30
Prosthetic	9 (15)	328 (19)	>.30
Involved organism			
<i>Staphylococcus aureus</i>	15 (25)	546 (31)	>.30
Viridans group streptococci	15 (25)	511 (29)	>.30
Enterococci	7 (12)	180 (10)	>.30
Other streptococci	6 (10)	120 (7)	>.30
Coagulase-negative staphylococci	4 (7)	98 (6)	>.30
Negative culture results	7 (12)	190 (11)	>.30
Miscellaneous <sup>b</sup>	6 (10)	107 (6)	>.30

**NOTE.** Data are no. (%) of patients, unless otherwise indicated.

<sup>a</sup> Two patients had infection involving both the aortic and mitral valves.

<sup>b</sup> Miscellaneous organisms included *Kingella kingae* (1 patient), *Granulicatella adiacens* (1), *Lactococcus garviae* (1), *Neisseria mucosa* (1), *Neisseria sicca* (1), and *Salmonella enteritidis* (1).

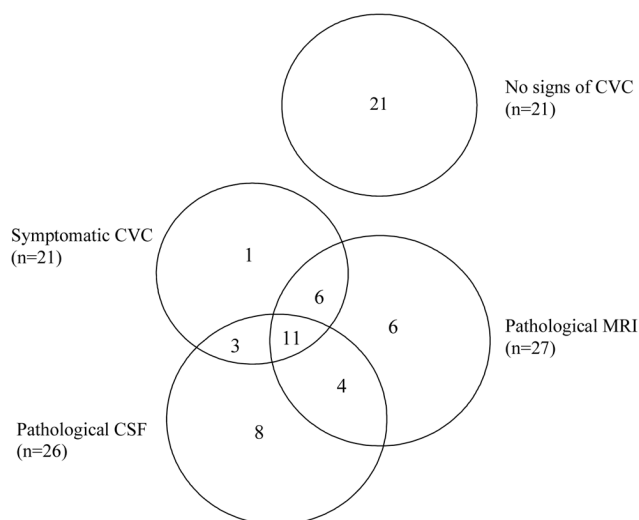
All patients underwent repeated neurological examinations. Thirty-nine patients had lumbar puncture performed at least once, 49 were examined using MRI, and 8 patients were examined with CT. Three patients refused radiological examination because of claustrophobia, but they underwent neurological examination and lumbar puncture.

**Clinical presentation.** Acute neurological symptoms were diagnosed in 21 patients (35%); 16 patients had symptoms that were diagnosed on presentation, and the remaining 5 patients had symptoms that were diagnosed within 10 days after the start of treatment. More than 1 neurological symptom was exhibited by 43% of patients, although 1 symptom dominated in each of the patient's initial presentations. Sixteen patients displayed focal neurological deficits, and 6 of these patients also had meningitis. All 9 patients with increased polymorphonuclear cell levels in CSF samples (range,  $11 \times 10^6$  cells/mL to  $277 \times 10^6$  cells/mL) had neurological symptoms, but none had positive results of liquor culture, and only 2 showed isolated meningeal symptoms with normal MRI and brain damage marker results. One patient had a transient ischemic attack with normal MRI and CSF analysis results.

Encephalopathy with confusion and acute mental status

changes was observed in 6 patients; all 6 demonstrated multiple ischemic lesions in MRI and had increased NFL and GFAP levels in CSF samples. Silent CVC was detected in 18 patients (30%) by MRI and/or by increased levels of NFL and GFAP markers, and a total of 39 patients (65%) were determined to have CVCs (figure 1).

Overall, 10 (17%) of 60 patients had a symptomatic CVC diagnosed after the start of antibiotic treatment, but only 3 patients (5%) experienced their first cerebral event after antibiotic treatment was initiated (with no association with surgery). Additionally, 2 patients receiving antibiotic treatment developed focal neurological deficits after surgery, and neither was symptomatic prior to surgery (figure 2). One of the surgically treated patients had increased NFL and GFAP levels but no neurological symptoms before surgery, indicating that a silent CVC had existed preoperatively. In this patient, postoperative MRI showed multiple old lacunar infarctions and a new ischemic area in the cerebellum, and the patient had a temporary hemiparesis. No new CVCs were detected in any study patient after 10 days of antibiotic treatment, with the exception of 1 patient with late subarachnoidal bleeding. Neurological sequelae were observed in 10 patients (17%) at the



**Figure 1.** Neurological symptoms and results of all examinations. Circles represent the patients with cerebrovascular complications (CVCs) detected by each method.

time of discharge from the hospital. Four of these neurological sequelae were characterized as major.

**Hemorrhagic complications.** Hemorrhage during treatment was detected in 6 patients by MRI, but in 2 it was only visible as minimal traces of hemosiderin in earlier ischemic lesions on a second MRI. One patient with recurrent CVCs had a small amount of blood detected by her first MRI after receiving 2 days of intravenous treatment, and she underwent surgery 5 days later with no further cerebral complications. Two patients with acute infective endocarditis underwent surgery before their first MRI and displayed traces of blood in small ischemic areas postoperatively. One of these patients was asymptomatic; the second had minor preoperative symptoms without exacerbation postoperatively. Subarachnoid bleeding from a ruptured mycotic aneurysm occurred on presentation in 1 patient who had a 3-month delay of treatment. An additional case of subarachnoid bleeding occurred 4 months after the completion of medical therapy in a patient with infective endocarditis due to *Salmonella enteritidis*. Angiographic examination of this patient showed a saccular aneurysm in the posterior communicating artery that was embolized. The aneurysm was probably congenital but might have been secondarily infected during the patient's infective endocarditis episode and predisposed to rupture. This complication was not included in the final analysis because of the absence of cerebral events during the period of infective endocarditis treatment, but it underscores the insidious nature of cerebral complications associated with infective endocarditis. No hemorrhagic complications were detected in patients receiving anticoagulant therapy or aspirin.

**Surgery and cerebrovascular complications.** Cardiac surgery was performed during the period of intravenous treatment

in 20 patients (33%). Eight patients with a symptomatic CVC on presentation underwent surgery after a median of 8 days of treatment (range, 4–71 days), and no neurological deterioration was observed in this group. Twelve patients without previous neurological symptoms underwent surgery after a median of 12 days (range, 1–39 days), and 2 developed neurological symptoms postoperatively. The main indications for surgery were severe valve regurgitation with or without congestive heart failure (in 9 patients), persistent vegetation >10 mm in length after cerebral embolization (5), abscess formation in native-valve or prosthetic-valve endocarditis (4), and uncontrolled infection (2).

**Risk factors for cerebrovascular complications.** Vegetations with a median maximal length of 10 mm (range, 2–32 mm) were present in 71% of patients. By use of Fisher's permutation test, the correlation between risk factors for embolization with the occurrence of symptomatic CVCs and total CVCs, respectively, was studied. The presence of vegetation and the size of vegetation had a positive correlation with both symptomatic and silent CVCs, while *Staphylococcus aureus* etiology only correlated to symptomatic emboli. Patients with preexisting valvular lesions experienced fewer symptomatic cerebral events. The surgical rate was higher in the total CVC group but not among patients with a symptomatic cerebral complication (table 2). Using multivariable logistic regression analysis, the only variable that correlated with an increased risk for both symptomatic and total CVC was the size of vegetation, whereas *S. aureus* etiology only conferred a higher risk of symptomatic cerebral emboli (table 3). At the time of presentation, symptomatic CVC was not a significant risk factor for a new symptomatic event; however, of 16 patients with neurological symptoms on presentation, 5 (31%) had a recurrent emboli, and of 44 patients without cerebral symptoms on presentation, 5 (11%) developed a CVC after antibiotics were administered. There was no correlation between the incidence of CVC and age, sex, or affected valve, and the numbers of patients experiencing atrial flutter or receiving anticoagulant or aspirin therapy were too small for further statistical analysis. Silent embolization to other organs was not investigated, but symptomatic peripheral embolism was observed in 23 patients (38%) with no correlation with cerebral complications.

Sensitivity for the diagnostic methods used was calculated; the total CVC rate was significantly higher than the symptomatic CVC rate (65% [95% CI, 53%–77%] and 35% [95% CI, 23%–47%], respectively;  $P = .002$ ). Among the 35 patients who underwent both MRI and lumbar puncture, the total CVC rate remained higher than the symptomatic CVC rate. The diagnostic sensitivity for CSF analysis of NFL and GFAP was also significantly higher than the diagnostic sensitivity for symptomatic neurological complications (figure 3).

## DISCUSSION

Compared with patients described in the National Swedish Endocarditis Registry during the same period of time, the patients in this prospective radiological and neurochemical study are well matched and reflect an elderly cohort with a high rate of cardiovascular comorbidity, similar to patients in other modern infective endocarditis studies [5, 20]. The relatively high proportion of patients with definite infective endocarditis in the present study can be explained by the inclusion of only patients with a high clinical suspicion of infective endocarditis. The higher rate of surgery observed for patients in our study, compared with that for patients in the National Swedish Endocarditis Registry, is not surprising, because similar rates of surgery have often been documented in studies from referral centers [20–22]. There is also a higher incidence of symptomatic CVC in this prospective study, which was focused on neurological presentation, than in most similar retrospective studies. This is partly explained by the fact that only left-sided infective endocarditis cases were included, but it might also reflect the variable presentation of CVC associated with infective endocarditis, which may be misjudged in the clinical situation and not properly documented in a retrospective study design. Mortality rate during this study's treatment period was low, but the 1-year mortality was 13%, which is in better agreement with other studies [23].

In the present study, 2 CSF markers for brain damage were used. Both markers are organ specific, but they are unspecific in the sense that any brain-damaging syndrome can influence marker levels in the CSF. NFL is an important constituent of large myelinated axons in the brain. Concentrations of NFL increase in the CSF of patients with disorders involving neuronal and axonal damage, and the increase is known to correlate with the size of the brain lesion and the clinical severity of the damage [24, 25]. The other marker, GFAP, is a protein of astroglial cells. Levels of GFAP are known to increase in CSF in response to a variety of neurological disorders associated with

**Table 2. Correlation of patient-related risk factors with symptomatic and total cerebrovascular complications (CVCs) in 60 prospectively studied patients.**

Risk factor	<i>P</i> by Fisher's permutation test for correlation with risk factors	
	Patients with symptomatic CVCs	Total patients with CVCs
Female sex	.29	.51
Age	.26	.75
Definite infective endocarditis	.13	.22
Surgical treatment received	.16	.04 <sup>a</sup>
Delay of treatment	.96	.95
Preexisting valvular lesion	.01 <sup>b</sup>	.15
Native-valve endocarditis	.64	.65
Prosthetic-valve endocarditis	.64	.77
Vegetation presence	.02 <sup>a</sup>	.01 <sup>a</sup>
Vegetation size	.001 <sup>a</sup>	<.001 <sup>a</sup>
Abscess	.13	.13
CVC on presentation	.16	...
Involved valve		
Aortic	.68	.68
Mitral	.42	.39
Involved organism		
<i>Staphylococcus aureus</i>	.009 <sup>a</sup>	.27
Viridans streptococci	.65	.86
Enterococci	.43	.94
Other streptococci	.61	.70
Coagulase negative staphylococci	.33	.24
Negative culture results	.43	.94
Miscellaneous <sup>c</sup>	.61	.70

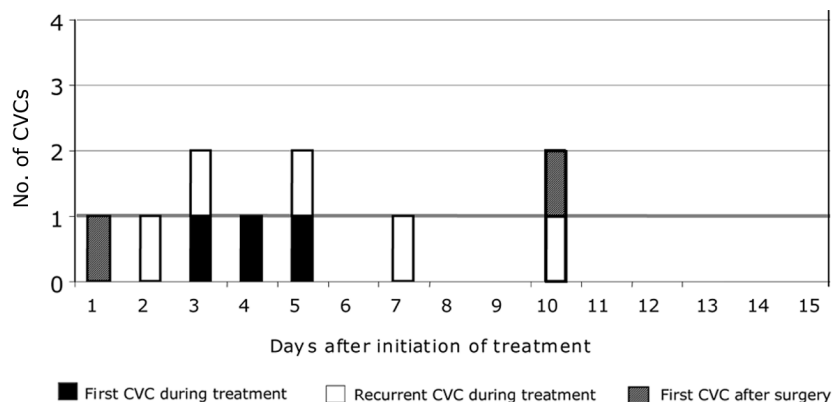
<sup>a</sup> Positive correlation.

<sup>b</sup> Negative correlation.

<sup>c</sup> Miscellaneous organisms included *Kingella kingae*, *Granulicatella adiacens*, *Lactococcus garviae*, *Neisseria mucosa*, *Neisseria sicca*, and *Salmonella enteritidis*.

cerebral damage, including stroke, and levels correlate with the severity of the injury [26, 27].

Focal cerebral lesions were documented clinically using MRI or by measuring the release of specific neurochemical markers of brain damage into the CSF in 19 of 21 patients with symp-



**Figure 2.** Timing of symptomatic cerebrovascular complications (CVCs) during treatment

**Table 3. Correlation of risk factors with symptomatic and total cerebrovascular complications (CVCs), by multivariable logistic regression analysis.**

Risk factor	Patients with symptomatic CVCs		Total patients with CVCs	
	P	OR (95% CI)	P	OR (95% CI)
Vegetation size	.005	1.17 (1.05–1.30)	.001	1.23 (1.08–1.39)
<i>Staphylococcus aureus</i>	.01	6.12 (1.54–24.34)	NS	...

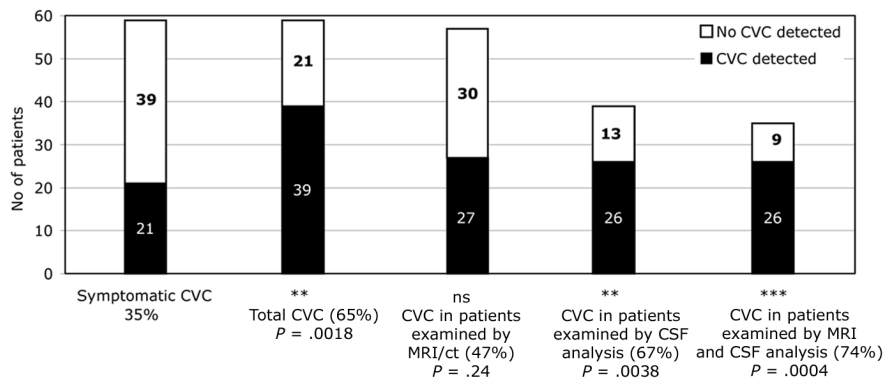
**NOTE.** NS, not significant.

omatic CVCs; the remaining 2 patients presented with meningism and isolated pleocytosis in CSF. All 18 patients who experienced silent CVCs were characterized as having focal lesions using MRI or by assaying for increased levels of brain damage markers in CSF. This supports the theory that the major pathogenic mechanism that causes cerebral complications associated with infective endocarditis is embolization from vegetations [11, 12, 28]. A clinical syndrome involving embolic encephalopathy and multiple lesions observed by MRI has also been documented by Singhal et al. [29]; this syndrome was confirmed here by the release of neurochemical brain damage markers into CSF. The presentation and initial neurological symptoms of CVC associated with infective endocarditis, however, are often more complex than in other types of stroke, and septic, cardiac, or general symptoms may dominate the clinical situation. Hemorrhagic complications were rare and only influenced the clinical course during infective endocarditis treatment for 1 patient.

In 76% of patients with a symptomatic CVC, neurological symptoms were already present at presentation, similar to the findings of DiSalvo et al. [30]. However, a new symptomatic event (a first-time or a recurrent event) was observed during treatment for almost one-half of the 21 symptomatic patients. Because of the limited number of patients studied, this finding should be interpreted cautiously; however, it underscores the importance of aggressive diagnostic efforts when neurological

symptoms occur in patients with infective endocarditis to evaluate whether emergency surgery should be performed, anticoagulants should be withheld, or other therapeutic adjustments should be implemented.

There were no new postoperative symptomatic CVCs in the patients with preoperative neurological symptoms who underwent surgery; however, 2 patients without previous neurological symptoms developed postoperative neurological deficits, indicating a perioperative CVC. Cardiac surgery in patients who have infective endocarditis is a high-risk procedure, but this study, in agreement with other recent reports [10, 20], suggests that the risk of neurological deterioration after early cardiac surgery in patients with infective endocarditis and an established CVC is lower than previously proposed [7, 8, 31]. Residual neurological symptoms at hospital discharge were observed in almost one-half of the patients with a symptomatic CVC before or during infective endocarditis, and major neurological impairment was observed in 19%. This underscores the severe long-term impact of CVCs in patients with successfully cured infective endocarditis, although a favorable neurological prognosis is observed in patients with cardioembolic stroke attributable to infective endocarditis who undergo acute cardiac surgery, compared with other stroke patients [10]. A beneficial influence of surgery on the overall survival of patients with infective endocarditis has also been shown [32–36]. There was no correlation between age or valve involved and the in-



**Figure 3.** Number of cerebrovascular complications (CVCs) in each diagnostic setting, compared with the symptomatic CVC rate. \*\*, Statistically significant; ns, not statistically significant.

idence of CVC in this study, and the number of patients was too low to evaluate mortality rate, which is known to be increased in patients with neurological complications [23, 37–39]. Vegetation size and *S. aureus* as the causative agent of infective endocarditis have been documented as risk factors for cerebral emboli in several recent studies [20, 30, 39, 40]; these risk factors were also observed in our study, but having a previous CVC was not a statistically significant risk factor.

In a large, prospective study of cerebrovascular complications in patients with infective endocarditis by Thuny et al. [20], the total incidence of CVC was 22% for cases documented clinically or by CT of the brain and was 4% for emboli characterized as silent. In our study, silent CVCs were detected in 30% of patients using MRI and/or CSF analysis of NFL and GFAP. This is a remarkably high figure, probably a reflection of the superior sensitivity of the diagnostic methods used and attributable to the fact that the examinations were repeated to document new CVCs during treatment. It is not clear whether more sensitive methods would reveal a higher incidence of silent CVC, and the clinical importance of silent CVC associated with infective endocarditis also needs to be clarified. Our results do not support a need for MRI of the brain or CSF analysis for patients with infective endocarditis without neurological symptoms, but these procedures could be considered in a subset of symptomatic patients. Although it has been better addressed in larger studies [10, 20], our data suggests that the risk of neurological deterioration during cardiac surgery after established cerebral embolism is low, and if indicated, surgery should not be withheld, except in cases involving neurological symptoms and documented intracerebral bleeding.

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