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Endocarditis-related stroke is not a contraindication for early cardiac surgery: an investigation among 440 patients with left-sided endocarditis

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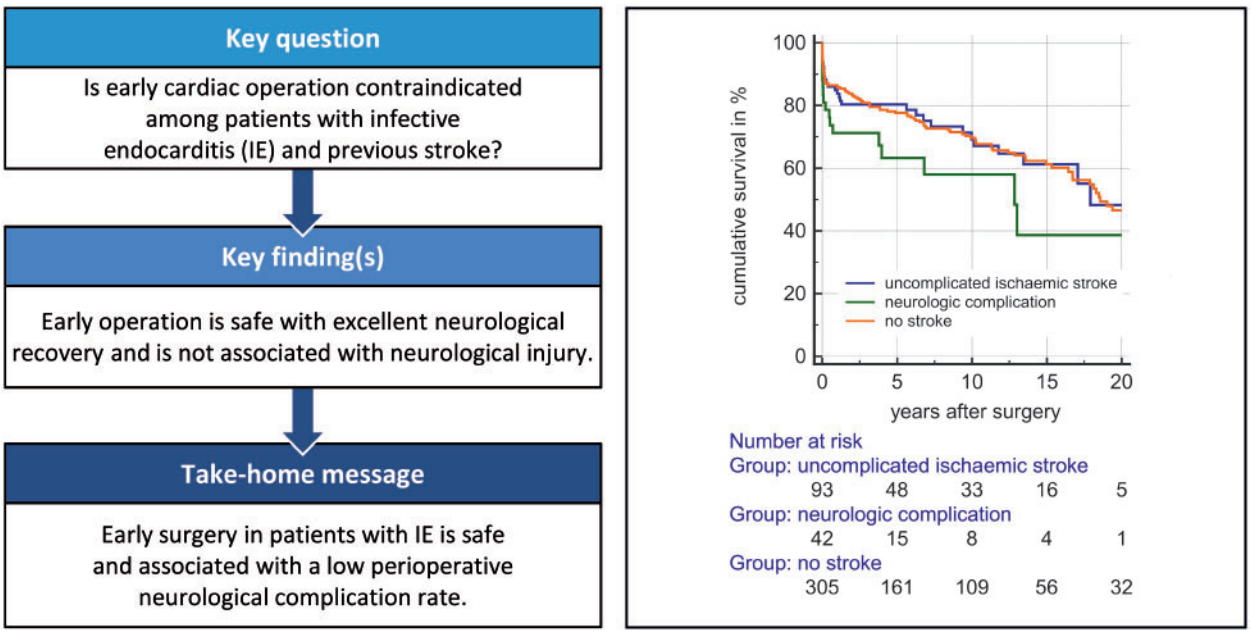

Abstract

OBJECTIVES: A treatment dilemma arises when surgery is indicated in patients with infective endocarditis (IE) complicated by stroke. Neurologists recommend surgery to be postponed for at least 1 month. This study aims to investigate the neurological complication rate and neurological recovery potential in patients with IE-related stroke.

Presented at the 33rd Annual Meeting of the European Association for Cardio-Thoracic Surgery, Lisbon, Portugal, 3–5 October 2019.

METHODS: A total of 440 consecutive patients with left-sided IE undergoing surgery were investigated. During follow-up, neurological recovery was assessed using the modified Rankin scale and the Barthel index. Mortality was assessed with regression models adjusting for age.

RESULTS: The median follow-up time was 9.0 years. Patients with previous strokes were more likely to suffer from mitral valve endocarditis (29.5% vs 47.4%, $P < 0.001$). Symptomatic stroke was found in 135 (30.7%) patients; of them, 42 patients presented with complicated stroke (additional meningitis, haemorrhagic stroke or intracranial abscess). Driven by symptomatic stroke, the age-adjusted hospital mortality risk was 1.4-fold [95% confidence interval (CI) 0.74–2.57; $P = 0.31$] higher and the long-term mortality risk was 1.4-fold higher (95% CI 1.003–2.001; $P = 0.048$). Hospital mortality was higher in patients with complicated stroke (21.4% vs 9.7%; $P = 0.06$) only; however, mortality rates were similar comparing uncomplicated stroke versus no stroke. Among patients with complicated ischaemic strokes, the observed risk for intraoperative cerebral haemorrhage was 2.3% only and the increased hospital mortality was not driven by cerebral complications. In the long-term follow-up, full neurological recovery was observed in 84 out of 118 survivors (71.2%), and partial recovery was observed in 32 (27.1%) patients. Neurological recovery was lower in patients with complete middle cerebral artery stroke compared to other localization (52.9% vs 77.6%; $P = 0.003$).

CONCLUSIONS: Contrary to current clinical practice and neurological recommendations, early surgery in IE is safe and neurological recovery is excellent among patients with IE-related stroke.

Clinical registration number local IRB: UN4232 382/3.1 (retrospective study).

Keywords: Infective endocarditis • Stroke • Timing of surgery • Neurological complications • Intracerebral haemorrhage

ABBREVIATIONS

CI	Confidence interval
CPB	Cardiopulmonary bypass
CT	Computed tomography
HR	Hazard ratio
IE	Infective endocarditis
MCAS	Middle cerebral artery stroke
MRI	Magnetic resonance imaging

INTRODUCTION

There has been a steady increase in the incidence of infective endocarditis (IE) over the past decade due to an increase in the population at risk of IE [1, 2].

IE is one of the most lethal infectious diseases, and cardioembolic events from valvular vegetations may involve other organ systems resulting in multi-organ failure. Furthermore, progression of IE can result in extensive destruction of cardiac valves, including paravalvular abscess formation, in addition to congestive heart failure and persistent sepsis [3]. A treatment dilemma, however, arises when IE is complicated by cerebral stroke and early cardiac surgery has to be performed given the lack of alternative treatment modalities [4]. Dissemination of emboli into cerebral and meningeal vessels can result in concomitant meningitis, intracerebral abscess formation or transformation to haemorrhagic stroke may occur. In patients with active IE, 40–50% of patients have evidence of acute septic emboli on preoperative brain computed tomography (CT) scans [5]. Embolic brain lesions can be found on magnetic resonance imaging (MRI) in as many as 60–80% of patients with left-sided IE [6]. Almost half of these patients have evidence of acute septic emboli on preoperative brain CT scans; up to 30% have been reported to suffer from asymptomatic brain lesions [5].

However, current guidelines recommend delaying cardiac surgery for at least 4 weeks to avoid full heparinization during cardiopulmonary bypass (CPB) [7]. This recommendation is based on experts' opinion, which predicts the risk of secondary cerebral bleeding to be greater than the benefit of stabilizing the infectious disease during CPB. In addition, continuous flow during CPB may aggravate cerebral ischaemia due to oedema formation in areas with a disrupted blood–brain barrier.

The aim of this study is, therefore, to investigate the perioperative neurological complication rate and the long-term neurological recovery potential in patients with IE-related stroke and indication for early surgery.

MATERIALS AND METHODS

Data were derived from a consecutive series of patients with left-sided IE undergoing cardiac surgery during the active phase of infection from 1995 to 2018 at the University Hospital Innsbruck.

In case of symptomatic cerebral embolism, a cerebral CT scan or MRI was performed to assess the topography and size of the infarct and to outline bleeding signs. After surgery, a second cerebral CT was performed among patient with previous strokes to investigate whether secondary cerebral bleeding had occurred during surgery.

Uncomplicated ischaemic strokes were defined as single or multiple ischaemic lesions; complicated ischaemic stroke was defined as the additional presence of meningitis, intracranial haemorrhage or abscess formation.

All patients had preoperative and intraoperative transoesophageal echocardiography to measure vegetation size, severity of valvular dysfunction or paravalvular abscess formation. Indications for early surgery were haemodynamic deterioration, high embolic risk (large vegetation size), paravalvular abscesses/fistulation or non-controllable sepsis despite appropriate antibiotic treatment.

All surgical procedures were performed with the use of CPB under mild hypothermia (32–35°C) and full anticoagulation. Heparinization was frequently monitored during extracorporeal circulation and was maintained by activated clotting times >480 s to avoid clotting. Haematocrit levels were kept between 26% and 30% by priming of the CPB or by adding erythrocytes to the CPB circuit.

All patients were evaluated by the endocarditis heart team of our hospital preoperatively to evaluate the indication and timing of surgery and operability of the patient. All survivors were followed up frequently by experienced cardiologists and neurologists and underwent clinical control and echocardiographic

examinations. Autopsies were performed among all non-survivors to evaluate the cause of death and neurological complications, such as secondary cerebral bleeding.

The primary end point of this study was perioperative and long-term mortality. Secondary end points were the risk of new intracerebral haemorrhage and the long-term neurological recovery potential among all patients with pre-existing neurological deficits.

Neurological recovery from IE-related stroke was examined by the application to the modified Rankin scale and the Barthel index to assess the remaining disability. A Rankin score of 0 (no symptoms) or 1 (no impairment in daily living) and a Barthel index of 20 points (to assess everyday abilities regarding independence and maintenance need) were defined to indicate full neurological recovery.

Permission for this retrospective analysis was obtained from the local Institutional Review Board.

Statistical analysis

Data are presented as mean ± standard deviation for continuous variables and absolute numbers and percentages for categorical variables. The 2 patient groups (symptomatic stroke prior to surgery or not) were compared for differences in patient characteristics, surgical variables and perioperative outcomes, as well as long-term survival. Comparisons between the 2 groups were performed for categorical variables with the χ^2 or Fisher's exact test, as appropriate. Continuous variables were compared by Student's *t*-test or the Mann–Whitney *U*-test. Long-term survival between the 2 groups was assessed using Kaplan–Meier survival curves with log-rank testing. Age-adjusted odds ratios and hazard ratios (HRs) were calculated using logistic and Cox proportional-hazards regression analyses, respectively, to calculate the relative risks for perioperative and long-term mortality with $\alpha = 0.05$. Data documentation and statistical analysis were performed using SPSS 24.0 (IBM Corp., Chicago, IL, USA).

RESULTS

The median follow-up time of the entire cohort was 9.0 years (range 3 months to 24 years). A detailed patient description is displayed in Table 1.

In 135 (30.7%) patients, a symptomatic stroke occurred prior to surgery. Another 4 (0.9%) patients had transient ischaemic attacks without ischaemia found on cerebral CT or MRI scans and had recovered before cardiac surgery was performed. Among 106 (76.3%) patients, the neurological event was the reason for hospitalization; in 33 (23.7%) patients, stroke occurred whilst the patient was already receiving antibiotic treatment.

The mean age was 56.2 ± 16.8 in patients without previous stroke and 53.7 ± 15.9 years in patients with previous stroke ($P = 0.15$); two-third of patients were male. Impaired left ventricular function was present among 46.6% of patients without stroke and in 50.4% of patients with previous strokes ($P = 0.46$). Hospital acquired IE was prevalent among 35% of patients and prosthetic valve endocarditis was present among 22.3% of patients. Patients

Table 1: Demographic characteristics of patients undergoing cardiac surgery for left-sided endocarditis from 1995 to 2018

	No prior symptomatic stroke (*n* = 305 patients)	Symptomatic stroke (*n* = 135 patients)	*P*-value
Age (years), mean ± SD	56.2 ±16.8	53.7 ± 15.9	0.15
Male gender (%), *n* (%)	206 (67.5)	93 (68.9)	0.78
Impaired left ventricular function (LVEF < 48%), *n* (%)	142 (46.6)	68 (50.4)	0.46
LVEF (%), mean ± SD	50.4 ± 12.0	50.1 ± 11.5	0.80
Body mass index (kg/m^2), mean ± SD	24.8 ± 4.2	24.3 ± 4.5	0.65
Obesity, *n* (%)	32 (10.5)	13 (9.6)	0.78
Hospital acquired endocarditis, *n* (%)	105 (34.4)	49 (36.3)	0.70
Prosthetic valve endocarditis, *n* (%)	73 (23.9)	25 (18.5)	0.20
Affected heart valves, *n* (%)			
Aortic valve	173 (56.7)	51 (37.8)	
Mitral valve	90 (29.5)	64 (47.4)	
Aortic and mitral valve	41 (13.4)	20 (14.8)	
Mitral and tricuspid valve	1 (0.3)	0 (0)	<0.001
Paravalvular abscess formation	88 (28.9)	39 (28.8)	0.94
Causative microorganism, *n* (%)			
Staphylococcus	154 (50.5)	74 (54.8)	
Streptococcus	75 (24.6)	23 (17.0)	
Enterococcus	29 (9.5)	18 (13.3)	
Unknown	29 (9.5)	10 (7.4)	
Others	18 (5.9)	10 (7.4)	0.39
Additional fungal contamination	4 (1.3)	3 (2.2)	0.74
Peripheral embolism, *n* (%)	32 (10.5)	59 (43.7)	<0.001
Spleen	13 (4.3)	34 (25.2)	<0.001
Liver	0 (0)	7 (5.2)	<0.001
Kidney	7 (2.3)	24 (17.8)	<0.001
Lower limb	6 (2.0)	11 (8.1)	<0.001
Eye (A. retinae)	1 (0.3)	4 (3.0)	<0.001
Time from hospital admission or stroke to cardiac surgery (days), median (range)	8 (0–90)	4 (0–38)	0.001
Logistic EuroSCORE (%), mean ± SD	11.4 ± 4.2	12.6 ± 4.7	0.50

LVEF: left ventricular ejection fraction; SD: standard deviation.

with previous strokes were more likely to suffer from mitral valve endocarditis than those without (29.5% vs 47.4%, $P < 0.001$). Staphylococcal infection was the most predominant microorganism detected (50.5% vs 54.8%, $P = 0.39$).

Peripheral embolism was more prevalent in patients with previous strokes (10.5% vs 43.7%, $P < 0.001$) and most commonly affected the spleen (25.2% of all patients) followed by kidney infarctions (17.8%).

The median time from hospital admission or stroke to cardiac surgery was 8 days (range 0–90 days) among patients without previous stroke and 4 days (range 0–38 days) among patients with stroke.

The logistic EuroSCORE was 11.4 ± 4.2% among patients without stroke and 12.6 ± 4.7% in patients with IE-related stroke.

Short-term outcome of patients with symptomatic cardio-embolic strokes

Overall perioperative mortality (defined as 30-day mortality or death within the same hospital stay) was 12.6% in the stroke group (17 patients) and 13.1% (40 patients) in the non-stroke group ($P = 0.39$). Neither single-site embolism (13 patients, 12.3%) nor multiple-site embolism (7 patients, 11.1%) was associated with higher perioperative mortality. In the stroke group, however, there was a trend towards higher perioperative mortality in patients with complicated neurological injuries (9 patients, 21.4%) compared to patients with uncomplicated ischaemic lesions (6 patients, 6.5%; $P = 0.063$).

The perioperative mortality risk was 1.38-fold [95% confidence interval (CI) 0.74–2.57; $P = 0.31$], and the long-term mortality risk hazards ratio was 1.42-fold (95% CI 1.003–2.001; $P = 0.048$) in patients with symptomatic stroke. Advanced age showed a highly significant association with perioperative and long-term mortality (both $P < 0.001$) in the multivariable analyses.

Long-term outcome of patients with symptomatic cardio-embolic strokes

Actuarial 1-year survival was 85.7% in patients without stroke and 80.6% among patients with preoperative neurological events; the 5-year survival was 77.3% vs 75.1%; and the 10-year survival was 69.3% vs 65.6%, respectively (log-rank: $P = 0.25$). However, the age-adjusted long-term mortality risk was increased among patients with complicated ischaemic lesions (HR 2.1, 1.24–3.54; $P = 0.005$) but not in patients with uncomplicated ischaemic strokes (HR 1.18, 0.79–1.77; $P = 0.41$) (see Fig. 1).

Table 2 displays the types of stroke among the 135 patients with symptomatic stroke prior to surgery. Middle cerebral artery strokes (MCASs) were the most common cerebral lesions found among patients with stroke (39.3%). Of them, one-third had complete MCAS, and the other two-third of patients suffered from partial MCAS. Multiple-site cerebral lesions were diagnosed among 35 (25.9%) patients followed by frontoparietal involvement in 19 (14.1%) patients. Occipital strokes were diagnosed among 10 (7.4%) patients, and parietal strokes were diagnosed among 9 (6.7%) patients. More seldom, ischaemic lesions were found in the cerebellum, the brain stem and in the thalamus.

Approximately one-third of patients with stroke had additional neurological complications such as concomitant meningitis (16 patients, 11.9%) and intracranial abscess formation (10 patients, 7.4%), and 16 patients showed intracerebral bleeding signs (11.9%).

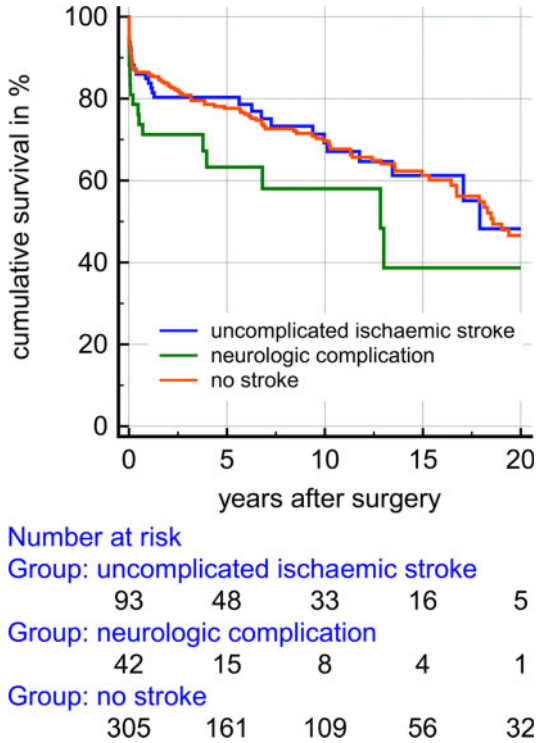

Figure 1: The Kaplan–Meier survival analysis of infective endocarditis patients without prior stroke (orange lines), patients with uncomplicated stroke (blue lines) and patients with complicated ischaemic stroke (green lines). The age-adjusted long-term mortality risk was increased among patients with complicated ischaemic lesions only [hazard ratio (HR) 2.1, 1.24–3.54; $P = 0.005$] but not in patients with uncomplicated ischaemic strokes (HR 1.18, 0.79–1.77; $P = 0.41$).

Table 2: Localization of septic embolism among 135 patients with IE-related strokes

	IE-related stroke ($n = 135$ patients), n (%)
Brain areas affected	
MCAS	53 (39.3)
Complete MCAS	19 (35.8)
Partial MCAS	34 (64.2)
Frontoparietal	19 (14.1)
Multiple site	35 (25.9)
Occipital	10 (7.4)
Parietal	9 (6.7)
Cerebellum	2 (1.5)
Brain stem	4 (3.0)
Thalamus	3 (2.2)
Additional neurological complications before surgery	42 (31.1)
Meningitis	16 (11.9)
Intracranial abscess	10 (7.4)
Haemorrhage	16 (11.9)

IE: infective endocarditis; MCAS: middle cerebral artery stroke.

Postoperative neurological outcome

In total, 118 patients with prior symptomatic strokes survived cardiac surgery (87.4%). Latency between stroke and cardiac surgery (within 4 days after stroke or later) was a non-significant factor for both the perioperative bleeding rate (0.7% vs 0%, $P = 0.96$) and full postoperative neurological recovery (78.7% vs 80.9%; $P = 0.78$). Moreover, there was no statistical significant difference in full neurological recovery in both uncomplicated (68 out of 84 survivors, 81.0%) and complicated neurological stroke survivors (24 out of 34 survivors, 70.6%, $P = 0.23$). Partial recovery of stroke symptoms occurred in 32 (27.1%) patients and no clinical recovery occurred in 1 (0.8%) patient. Aggravation of neurological injury after surgery was only found in 1 (0.8%) patient. The neurological recovery potential was lower in patients with complete MCAS compared to other localization of cerebral infarction (52.9% vs 77.6%; $P = 0.003$). However, there was no statistically significant difference in complete neurological recovery between partial and complete MCAS (58.8% vs 47.4%; $P = 0.42$).

DISCUSSION

The result of our current study clearly demonstrates that early surgery in patients with IE-related stroke seems to be safe and associated with a very low perioperative cerebral haemorrhage risk. Furthermore, the neurological recovery potential was high among survivors with both patients with uncomplicated ischaemic and complicated stroke. This implies the safety of CPB in the setting of IE with recent ischaemic stroke.

All of our patients with IE-related strokes were operated on within 38 days of stroke onset and this was, indeed, in contrast to current guideline recommendations [7]. However, from previous observations, we have become firmly convinced of the safety of CPB in the setting of ischaemic stroke [5]. Throughout our extensive experience, we have observed only 1 haemorrhage in a patient who already had massive bleeding prior to surgery. He was already comatose and craniotomized before cardiac surgery and ongoing heart failure was the indication for emergency surgery. He died on the fifth day postoperation due to ongoing cerebral bleeding.

Symptomatic stroke occurred among 30.7% of all patients with IE undergoing cardiac surgery. Patients suffering from mitral valve endocarditis were more likely to be affected from symptomatic strokes (47.4%) and patients with prosthetic valve endocarditis were less likely to be affected by septic cerebral lesions (26.8%).

Primary mitral valve endocarditis mainly occurs as a result of underlying degenerative valve disease [8, 9]. We have found 90% of patients to have underlying degenerative mitral valve disease on the basis mitral valve endocarditis occurs; this rate was 50% only among non-immunocompetent patients with previous solid organ transplantation or chemotherapy [9].

Thus, mitral repair is possible for a large proportion of patients with secondary mitral endocarditis. In our experience, we have performed 98 mitral valve repairs among 178 patients with native mitral valve endocarditis (55.1%). Moreover, in a previous publication, we were able to demonstrate excellent mid-term results among these patients undergoing mitral valve repair [8]. Postoperative oral anticoagulation is not mandatory in patients undergoing mitral repair for IE and might be a further possible advantage.

These findings are supported by a publication by Klein *et al.* [10] that investigated the long-term risk of haemorrhagic stroke in patients with IE. In this Danish national cohort study, follow-up of 5735 patients with left-sided IE showed that IE does not directly increase the long-term risk of haemorrhagic stroke. Applying mediation analysis, the apparent excess risk of haemorrhagic stroke in patients with previous IE was explained by mediating factors, including mechanical heart valve insertion, atrial fibrillation and anticoagulation medication rather than conversion of ischaemic stroke to haemorrhagic.

In mitral valve endocarditis, the experience of mitral repair for IE, however, is sparse. Cuerpo *et al.* [11] showed that mitral valve repair was not inferior to valve replacement in IE. However, the repair rate among this cohort of patients was 18.4% only. As with Cuerpo *et al.*, El Gabry *et al.* also demonstrated excellent short-term results among 35 patients with mitral valve repair for IE [12]. In addition, a study on leaflet reconstruction with fresh autologous pericardium for mitral valve repair in IE demonstrated good long-term outcomes with 10 years freedom from reoperation was 82% with a survival rate of 84% [13].

In our study, we have demonstrated that early operation was safe in the setting of symptomatic stroke. Ghoreishi [13,14] has found similar results among 69 patients with mitral valve endocarditis and stroke with only 1 haemorrhagic conversion of an acute infarct; although one-third of patients were clinically asymptomatic in their study.

In our study, clinical outcomes were worse in patients with complicated strokes only. In a prospective multicentre study, Thuny *et al.* [15] showed that among 109 patients with cerebrovascular complications, mortality after IE was dependent on the type of cardiovascular complication. In their study, manifest stroke was a strong predictor of mortality, and silent stroke or transient ischaemic attacks were not associated with excess mortality. However, the rate of patients not undergoing cardiac surgery procedures was extremely high. In addition, they found that, among IE-related stroke patients, survival was better in patients undergoing surgery compared to patients treated conservatively despite theoretical indication for surgery.

Early cardiac surgery in patients with IE-related stroke is resisted as it has been hypothesized that hypotension and heparinization during CPB may worsen neurological outcome.

In our study, however, 71.2% of patients undergoing surgery achieved full neurological rehabilitation and, in 27.1%, a partial recovery of stroke occurred. This excellent neurological outcome supports our conviction that early surgery should be performed such patients. Piper *et al.* [16] showed that the risk of exacerbation to haemorrhagic stroke was low when cardiac surgery was performed within 72 h after stroke onset. Another investigation by Okita *et al.* [17] reported delayed surgery (2 weeks after stroke onset) to be associated with a higher incidence of hospital deaths. In patients with intracerebral haemorrhage, however, mortality was higher among patients undergoing surgery within 7 days after the index neurological event.

In our hospital, the rate of patients with stroke receiving conservative treatment despite indication for surgery is extremely low. The vast majority of patients with IE-related complications such as stroke or peripheral embolism undergoes surgery within several days. The report of Eishi *et al.* [18], however, published an exacerbation rate of 43.8% in patients requiring cardiac operation within 7 days after IE-related stroke; this rate was significantly lower in patients operated on after 28 days. However,

no information was given about patients being treated conservatively.

This was in line with the systematic review and meta-analysis of observational data published by Tam *et al.* [19]. Available observational data supported delaying surgery by 7–14 days if possible in IE complicated by ischaemic stroke and >21 days in haemorrhagic stroke to decrease perioperative mortality and neurological exacerbation rates. However, there was no difference in long-term mortality but reporting was sparse. Early surgery, however, was often performed for clinical deterioration, negatively biasing outcomes and has to be taken into account. From our point of view, we have not experienced excess mortality in patients being operated within 4 days or later.

Thuny *et al.* [20], however, found that operation within the first week after antibiotic treatment initiation was associated with a trend of decrease in 6-month mortality. Patients in this subgroup were younger and were more likely to have *Staphylococcus aureus* infections, congestive heart failure and larger vegetations. In contrast, surgery within the first week was associated with an increased number of relapses or postoperative valvular dysfunctions. They recommended performing surgery very early to improve survival in patients with the most severe complicated IE taking into account the higher risk for recurrence of IE.

Staphylococcus aureus was the most predominant microorganism in both patients with stroke and non-stroke in our study. In a large prospective study of 116 consecutive patients with IE with staphylococcal endocarditis, to evaluate the effect of early surgery on mortality, and the predictors of outcome following surgery, the authors found that early surgery was associated with reduced overall mortality and should thus be considered in selected cases [21].

To our knowledge, this is the first study investigating the neurological rehabilitation potential of patients with IE with prior stroke. Our study shows, convincingly, excellent neurological recovery potential in patients without complete MCAS. These results are in line with a previous publication of our study group that showed a high rehabilitation potential in a smaller subset of patients with a very low risk for perioperative cerebral haemorrhage [5]. Our studies and experience have increased our confidence in early surgery for patients with prior strokes. Moreover, long-term outcome was similar among patients with or without prior uncomplicated stroke.

Furthermore, our study classifies the type of stroke in terms of affected brain areas and complicated forms of cerebral embolic events. MCAS and multiple-site cerebral lesions were most commonly found in preoperative cerebral CT scans or magnetic resonacnae tomography (MRT). A trend towards a higher perioperative mortality and long-term mortality was only found among patients with complicated cerebral lesions only.

Transoesophageal echocardiography is a mainstay in the diagnosis of IE and has relevant impact on the timing of surgery in IE. An echocardiographic study by Di Salvo *et al.* [22] demonstrated that the presence of vegetations on transoesophageal echocardiography was predictive of embolism and that the morphological characteristics of vegetations were helpful in predicting embolic events in both mitral and aortic valve IE. They also suggested that early operation was recommended in patients with vegetations larger than 15 mm and high mobility, irrespective of the degree of valvular destruction, heart failure and response to antibiotic therapy.

A vegetation size of >10 mm has often been suggested as an optimal cut-off to estimate the risk of embolism, but the evidence is largely based on small observational studies. A systematic review and meta-analysis by Mohananey *et al.* [23] has investigated this issue and found that vegetation size >10 mm had significantly increased odds of embolism and mortality. This may help clinicians to adequately risk stratify patients and will also help facilitate discussions regarding early surgery in patients with previous stroke and vegetation size >10 mm.

Limitations

There are several limitations associated with the retrospective nature of this study. Furthermore, the number of patients with preexisting haemorrhagic stroke was limited.

The results of our study strongly suggest that early surgery is safe with respect to intracerebral conversion to haemorrhagic stroke and is associated with excellent neurological recovery potential for both uncomplicated and complicated cerebral lesions. Optimal timing means that vasoplegia before surgery should be under control. Operating in patients with high catecholamine support before surgery due to sepsis should be avoided.

Conflict of interest: none declared.

Author contributions

Elfriede Ruttmann: Conceptualization; Data curation; Formal analysis; Methodology; Supervision; Writing—original draft; Writing—review & editing. **Hannes Abfalterer:** Data curation; Investigation; Methodology; Project administration; Writing—review & editing. **Julian Wagner:** Conceptualization; Data curation; Investigation; Methodology; Writing—review & editing. **Michael Grimm:** Conceptualization; Methodology; Writing—review & editing. **Ludwig Müller:** Conceptualization; Methodology; Project administration; Writing—review & editing. **Katie Bates:** Data curation; Formal analysis; Methodology; Writing—review & editing. **Hanno Ulmer:** Conceptualization; Formal analysis; Methodology; Project administration; Validation; Writing—review & editing. **Nikolaos Bonaros:** Conceptualization; Data curation; Investigation; Methodology; Supervision; Validation; Writing—review & editing.

Reviewer information

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