Archives of Cardiovascular Disease xxx (xxxx) xxx—xxx

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CLINICAL RESEARCH

Infective endocarditis with neurological complications: Delaying cardiac surgery is associated with worse outcome

Endocardite infectieuse avec complications neurologiques : le retard à la chirurgie est associée à un moins bon pronostic

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Received 15 November 2020; received in revised form 23 January 2021; accepted 28 January 2021

KEYWORDS
Valve disease;
Endocarditis;
Neurological complication;
Stroke

Summary
Background. — Infective endocarditis (IE) is associated with a high mortality rate, related in part to neurological complications. Studies suggest that valvular surgery should be performed early when indicated, but is often delayed by the presence of neurological complications.
Aim. — To assess the effect of delaying surgery in patients with IE and neurological complications and to identify factors predictive of death.

Abbreviations: CT, computed tomography; IE, infective endocarditis; MRI, magnetic resonance imaging; TOE, transoesophageal echocardiography; TTE, transthoracic echocardiography.

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https://doi.org/10.1016/j.acvd.2021.01.004

Please cite this article as: F. Arregle, H. Martel, M. Philip et al., Infective endocarditis with neurological complications: Delaying cardiac surgery is associated with worse outcome, Arch Cardiovasc Dis, https://doi.org/10.1016/j.acvd.2021.01.004

Methods. — In a prospective, single-centre study in a referral centre for IE, all patients with IE underwent systematic screening for neurological complications. The primary outcome was 6-month death. In patients presenting with neurological complications, the prognosis according to surgical status was analysed and a Cox regression model used to identify variables predictive of death.
Results. — Between April 2014 and January 2018, 351 patients with a definite diagnosis of left-sided IE were included. Ninety-four patients (26.8%) presented with at least one neurological complication. Fifty-nine patients (17.7%) died during 6-month follow-up. Six-month mortality rates did not differ significantly between patients with and without neurological complications ($P = 0.60$). Forty patients had a temporary surgical contraindication because of neurological complications. During the period of surgical contraindication, seven of these patients (17.5%) died, six (15.0%) presented a new embolic event, and 12 (30.0%) presented cardiac or septic deterioration. In multivariable analysis, predictive factors of death in patients presenting with neurological complications were temporary surgical contraindication (hazard ratio 7.36, 95% confidence interval 1.61—33.67; $P = 0.010$) and presence of a mechanical prosthetic valve (hazard ratio 16.40, 95% confidence interval 2.22—121.17; $P = 0.006$).
Conclusions. — Patients with a temporary surgical contraindication due to neurological complications had a higher risk of death and frequent major complications while waiting for surgery. When indicated, the decision to postpone surgery in the early phase should be weighed against the risk of infectious or cardiac deterioration.

MOTS CLÉS
Valvulopathie ;
Endocardite ;
Complication neurologique ;
Accident vasculaire cérébral

Résumé
Contexte. — L'endocardite infectieuse (EI) est associée à un taux de mortalité élevé, en partie lié aux complications neurologiques. Des études suggèrent que la chirurgie valvulaire, lorsqu'elle est indiquée, devrait être réalisée précocement, mais celle-ci est souvent différée en raison de complications neurologiques.
Objectif. — L'objectif de ce travail est d'apprécier l'impact du retard à la chirurgie cardiaque chez les patients atteints d'EI en raison d'une complication neurologique et de préciser chez ces patients quels sont les facteurs pronostiques.
Méthodes. — Dans une étude monocentrique, tous les patients atteints d'EI présentant une complication neurologique ont été comparés aux autres patients. Leur pronostic en fonction du statut chirurgical a été analysé pour détecter les facteurs prédictifs de mortalité.
Résultats. — Entre 2014 et 2018, 351 patients présentant une EI certaine ont été inclus. Parmi eux, 94 patients (26,8 %) ont présenté au moins une complication neurologique. Cinquante-neuf patients (16,8 %) sont décédés après 6 mois de suivi, sans différence significative entre les patients avec ou sans complication neurologique. Quarante patients présentaient une contre-indication chirurgicale temporaire en raison de leur état neurologique. Pendant cette période, 7 patients (17,5 %) sont décédés, 6 (15,0 %) ont présenté un évènement embolique, et 12 (30,0 %) ont présenté une détérioration clinique d'origine hémodynamique ou septique. Par analyse multivariée, les facteurs prédictifs de mortalité parmi les patients présentant une complication neurologique étaient la présence d'une contre-indication chirurgicale temporaire (HR 7,36, 95 % CI 1,61—33,67; $p = 0,010$) et la présence d'une prothèse valvulaire mécanique (HR 16,40, 95 % CI 2,22—121,17; $p = 0,006$).
Conclusions. — Les patients atteints d'EI avec contre-indication chirurgicale temporaire en raison d'une complication neurologique sont à haut risque de morbi-mortalité durant cette période. Le risque d'une intervention chirurgicale précoce chez ces patients doit être comparé au risque important de complications en l'absence de chirurgie.

Background

Despite improvements in its management, infective endocarditis (IE) is still associated with a high mortality rate [1,2]. This high rate is partly related to complications of the disease, including neurological complications in 20—40% of cases [3,4]. Several studies have shown that systematic cerebral imaging diagnoses silent cerebral embolism in 60—80% of patients [5,6]. These neurological events are largely due to embolization of vegetations or ruptured mycotic aneurysm. Symptomatic neurological events can be fatal [4,7], whereas silent cerebral embolism is associated with a better prognosis [7]. Studies suggest that valvular surgery, when indicated, should be performed early [8,9], but neurological complications often interfere with early surgical decision due to the risk of neurological deterioration. Current guidelines [10] support early surgery in cases of non-severe ischaemic cerebral events, but recommend delaying surgery for at least 1 month in case of intracranial haemorrhage or stroke with severe damage. These recommendations are, however, based on a low level of evidence, and patient clinical outcomes during this delay and the effect of a temporary surgical contraindication are not well understood. We therefore sought to assess the effect of delaying surgery in patients with IE and neurological complications and to identify factors predictive of death.

Methods

Between April 2014 and January 2018 all patients admitted to La Timone Hospital with a final diagnosis of IE based on the Duke modified criteria or the European Society of Cardiology criteria [10,11] were included. The only exclusion criteria were right-sided IE and missing data. Tests including blood cultures, serologies, transthoracic echocardiography (TTE) and transoesophageal echocardiography (TOE) were systematically performed within 48 hours of admission.

All patients hospitalized for suspected IE accepted on admission to participate in this research study. The study complies with the Declaration of Helsinki. Written consent was waived by La Timone Institutional Review Board, which gave its approval for this study.

Clinical, biological and echocardiographic data

The following data were collected prospectively: age, sex, history of cardiac surgery (mechanical prosthetic valve or bioprosthetic valve, homograft, valve repair), intravenous drug abuse, diabetes mellitus, hypertension, history of atrial fibrillation, coronary artery disease, history of stroke, human immunodeficiency virus infection, history of cancer, Charlson index score, treatments on admission (including oral anticoagulants and platelet inhibitors), non-cerebral embolism, congestive heart failure, septic or cardiogenic shock at time of admission or during hospitalization. The following biological data were also collected at the time of IE diagnosis: haemoglobin concentration, platelet count, leucocyte count, serum C-reactive protein serum concentration, and B-type natriuretic peptide concentration. Echocardiographic data were: presence of vegetation and its maximum length, presence of periannular lesion (defined as the presence of abscess and/or pseudoaneurysm and/or fistula), and presence of aortic or mitral regurgitation, quantified according to current recommendations [12,13].

Neurological complications

All patients included underwent systematic cerebral imaging including (at least) a cerebral computed tomography (CT) scan with Willis polygon CT-angiography. Four different types of neurological complications were studied: symptomatic ischaemic stroke, intracranial haemorrhage, silent cerebral embolism and cerebral abscess. Complications were classified as symptomatic when responsible for a focal neurological deficit or decreased level of consciousness. Ischaemic stroke was defined as the persistence for more than 24 hours of a focal neurological deficit caused by altered circulation of the cerebral hemispheres, brain stem or cerebellum. Silent cerebral embolism was diagnosed by cerebral imaging (cerebral CT scan and/or cerebral magnetic resonance imaging [MRI]). Intracranial haemorrhages included primary intracerebral haemorrhages, haemorrhagic infarctions and subarachnoid haemorrhages; they were diagnosed based on recent haemorrhagic lesions on CT scan or MRI. Diagnosis of mycotic aneurysm was always performed with cerebral angiography. Neurological complications were systematically confirmed by an experienced neurological specialist and their management was performed according to the guidelines [14—16].

Surgical indication

The indication for cardiac surgery during hospitalization was based on the guidelines [10] for the management of IE and was decided by the endocarditis team. Surgical temporary contraindication due to neurological complications was systematically decided in agreement with an experienced neurologist. At the end of the contraindication time, systematic brain imaging was performed before allowing surgery. Depending on the results, the temporary contraindication could be extended. The algorithm used for temporary surgical contraindication is shown in Fig. A. 1. Timing of surgery, when performed, was dichotomized into surgery during or after the active phase of antibiotic therapy.

Mortality and follow-up

Follow-up information was obtained during the hospitalization and after discharge, with scheduled visits at 1, 3 and 6 months.

Statistical analysis

For categorical variables, the relation between a variable and an event was studied using the χ^2 test or Fisher's exact test (2-tailed) if the expected count in any cell was < 5. Student's *t*-test or the Mann-Whitney U test was used for continuous variables. Survival curves were obtained by the Kaplan—Meier method. A Cox proportional hazards model was used to calculate adjusted hazards ratios (HRs) and their 95% confidence intervals (CIs). Six-month mortality among patients with neurological complications was analysed using

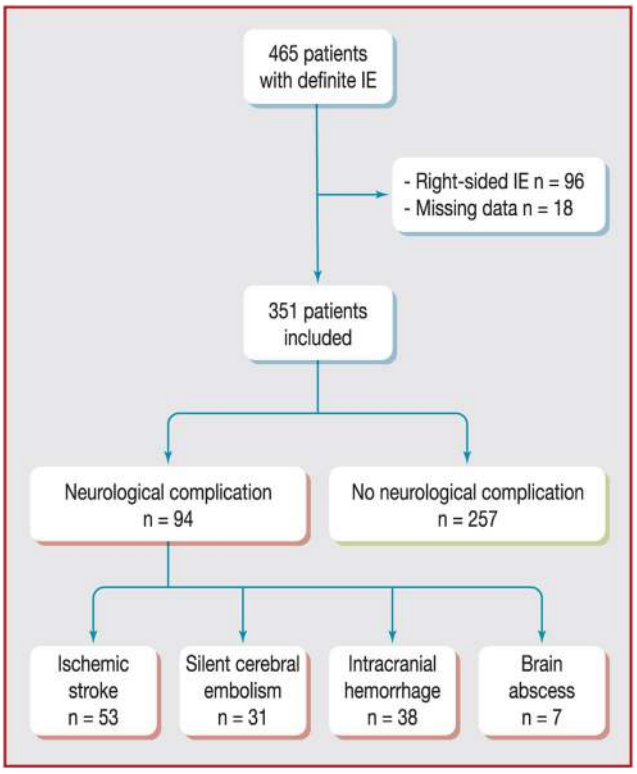

Figure 1. Patient flow chart.

a logistic regression model. Clinically relevant variables associated with the outcome in univariate analysis ($P < 0.20$) were introduced into the multivariable model. Final models were selected using a forward stepwise procedure. Significance was defined as $P < 0.05$. Statistical analyses were performed using R 3.5.1 (www.R-project.org).

Results

Among the 465 patients with a final diagnosis of IE, 96 who presented with right-sided IE and 18 with missing data were excluded (Fig. 1). The study population therefore comprised 351 patients, 94 (26.8%) of whom had at least one neurological complication. Ischaemic complications were the most frequent, including ischaemic stroke in 53 patients (15.1%) and silent cerebral embolism in 31 patients (8.8%). Symptomatic stroke occurred in 71.7% of patients before starting antibiotic therapy and in 11.3% during the first week of treatment. In the 17.0% of other cases, embolism occurred between the second and fourth week of therapy.

Thirty-eight patients (10.8%) presented with intracranial haemorrhage, related to ruptured mycotic aneurysm in six patients (1.7%) and haemorrhage after an acute ischaemic stroke in 20 patients (5.7%). The cause of haemorrhage was unknown for 12 patients. Diagnosis of intracranial haemorrhage was performed before starting antibiotic therapy in 26.3% of patients. In patients with ruptured mycotic aneurysms, three occurred before starting antibiotic therapy, two during the first week of treatment and one 18 days after starting treatment. Four of the six ruptured mycotic aneurysms complicated streptococci IE, and two complicated *Enterococcus faecalis* IE. Three of these patients had endovascular therapy with occlusion of the ruptured mycotic aneurysm and three had neurosurgery. Seven patients (2.0%) had a brain abscess.

Characteristics of patients with neurological complications

The clinical, biological, microbiological and echocardiographic characteristics of patients, overall and according to neurological complications, are presented in Table 1. Overall, median age was 68.0 years. Patients with neurological complications less frequently had a history of cardiac surgery ($P = 0.01$) and were less likely to be on oral anticoagulant therapy ($P = 0.02$), particularly vitamin K antagonists ($P = 0.005$). Patients with neurological complications had a higher prevalence of non-cerebral embolism ($P = 0.005$) and vegetations ($P < 0.001$), and vegetations were longer ($P < 0.001$).

Mortality according to presence of neurological complications

Eighteen of the 351 patients were lost to follow-up at 6 months. Among the 333 patients with 6-month follow-up data, 6-month mortality was 17.7% (59 deaths) (Table 2). Fourteen of the patients with neurological complications were dead at 6 months (15.4%). Six-month mortality was similar among patients with and without neurological complications (15.4% vs 18.6%; $P = 0.60$) (Table 2). By complication type, 6-month mortality was not significantly different among patients with silent cerebral embolism than among those with ischaemic stroke, despite a trend in lower mortality among those with silent embolism (10.0% vs 18.0%; $P = 0.33$) (Table 2).

At 1 year, 32 patients were lost to follow-up. One-year mortality did not differ between patients with and without neurological complications (14/86 [16.3%] vs 54/233 [23.2%]; $P = 0.19$).

Impact of surgery on outcome of patients presenting neurological complications

Among the 94 patients with neurological complications, valvular surgery was theoretically indicated in 79 (84.0%) of them (Fig. 2), but was performed in only 59 (62.8%) of them, including 46 (48.9%) during the active phase of antibiotic therapy and 13 (13.8%) after the active phase. Table 3 shows characteristics of patients presenting with neurological complications according to their surgical status. Postoperative neurological deterioration occurred in only one patient (cerebral haematoma). At 6-month follow-up, seven operated patients had died (Fig. 2). In case of medical treatment, seven patients out of 34 with follow-up data were dead at 6 months. Central illustration shows survival probability in patients with neurological complications depending on their valvular surgery status. Patients in whom surgery was indicated but not performed had the worse survival probability at 6 months. Twenty-six patients of 91 patients with follow-up data (28.6%) had a persistent neurological deficit at 6 months.

Table 1 Characteristics of 351 patients with IE with and without neurological complications.

Characteristic	Total ($n = 351$)	Neurological complication		P
		No ($n = 257$)	Yes ($n = 94$)	
Male sex	239 (68.1)	173 (67.3)	66 (70.2)	0.60
Age (years)	68.0 (57.5—76.0)	68.0 (58.0—77.0)	67.0 (55.8—74.8)	0.28
Medical history				
Intravenous drug abuse	18 (5.1)	12 (4.7)	6 (6.4)	0.59
Cardiac surgery	165 (47.0)	132 (51.4)	33 (35.1)	0.01
Renal failure	33 (9.4)	26 (10.1)	7 (7.4)	0.58
HIV infection	4 (1.1)	4 (1.6)	0 (0.0)	0.58
Diabetes mellitus	78 (22.2)	57 (22.2)	21 (22.3)	1.00
Hypertension	166 (47.3)	116 (45.1)	50 (53.2)	0.22
Atrial fibrillation	106 (30.2)	83 (32.3)	23 (24.5)	0.20
Charlson index	3.0 (2.0—5.0)	3.0 (2.0—5.0)	3.00 (2.0—4.0)	0.77
Treatment before episode				
Oral anticoagulant	129 (36.8)	104 (40.5)	25 (26.6)	0.02
Vitamin K antagonist	113/350 (32.3)	94/256 (36.7)	19/94 (20.2)	0.005
Aspirin	100/349 (28.7)	70/255 (27.5)	30/94 (31.9)	0.49
ACE inhibitor	73/349 (20.9)	57/255 (22.4)	16/94 (17.0)	0.35
Diuretic	117/349 (33.5)	95/255 (37.3)	22/94 (23.4)	0.02
Beta-blocker	100/349 (28.7)	80/255 (31.5)	20/94 (21.3)	0.08
Statin	80/349 (22.9)	55/255 (21.6)	25/94 (26.6)	0.39
Healthcare-associated source of IE	49 (14.0)	42 (16.3)	7 (7.4)	0.03
Clinical data				
Congestive heart failure	121 (34.5)	89 (34.6)	32 (34)	0.92
Cardiogenic shock	18 (5.1)	14 (5.4)	4 (4.3)	0.79
Septic shock	21 (6.0)	16 (6.2)	5 (5.3)	0.76
Non-cerebral embolism	111/349 (31.8)	70/256 (27.3)	41/93 (44.1)	0.005
Atrial fibrillation during IE	88/345 (25.5)	66/251 (26.3)	22/94 (23.4)	0.68
Biology				
Haemoglobin (g/L)	106.0 (95.0—119.8)	105.0 (96.8—118.0)	108.0 (93.0—123.8)	0.53
Leucocytes ($\times 10^9$/L)	9.8 (7.6—13.2)	9.7 (7.4—13.0)	10.0 (8.2—15.0)	0.07
Platelets ($\times 10^9$/L)	232.0 (169.2—315.0)	244.0 (168.8—317.2)	214.5 (170.0—305.8)	0.23
C-reactive protein (mg/L)	65.0 (28.7—120.8)	63.0 (27.0—111.8)	72.3 (33.5—166.5)	0.09
Serum creatinine (μmol/L)	95.0 (74.0—124.5)	96.0 (74.8—125.0)	91.5 (72.0—118.8)	0.31
BNP (ng/L)	304.5 (130.8—606.8)	304.5 (142.2—630.0)	305.0 (113.5—549.5)	0.43
Microbiology				
Positive blood cultures	281 (80.1)	201 (78.2)	80 (85.1)	0.20
Staphylococcus aureus	71 (20.2)	45 (17.5)	26 (27.7)	0.04
Coagulase-negative staphylococci	25 (7.1)	22 (8.6)	3 (3.2)	0.13
Oral streptococci	57 (16.2)	35 (13.6)	22 (23.4)	0.03
Enterococcus faecalis	57 (16.2)	43 (16.7)	14 (14.9)	0.68
Streptococcus gallolyticus	33 (9.4)	29 (11.3)	4 (4.3)	0.06
Gram-negative bacilli	14 (4)	10 (3.9)	4 (4.3)	1.00
Other	26 (7.4)	18 (7.0)	8 (8.5)	0.63
Echocardiographic data				
IE location				
Aortic	150 (42.7)	104 (40.5)	46 (48.9)	0.51
Mitral	162 (46.2)	119 (46.3)	43 (45.7)	0.93
Aortic + mitral	39 (11.1)	33 (12.8)	6 (6.4)	0.09
Prosthesis	123/349 (35.2)	96/255 (37.6)	27 (28.7)	0.13
Vegetation(s)	234 (66.7)	155 (60.3)	79 (84.0)	< 0.001
Maximum length of vegetation (mm)	10.0 (0.2—15.0)	7.5 (0.2—14.0)	12.0 (8.0—16.5)	< 0.001
Periannular lesion	107/348 (30.7)	78/256 (30.5)	29/92 (31.5)	0.96
Surgery				
Valvular surgery	177 (50.4)	118 (45.9)	59 (62.8)	0.006
Surgery during active phase	135 (38.5)	89 (34.6)	46 (48.9)	0.01
Surgery after active phase	42 (12.0)	29 (11.3)	13 (13.8)	0.52

Data are expressed as number (%) or median (interquartile range). ACE, angiotensin-converting enzyme; BNP, B-type natriuretic peptide; HIV, human immunodeficiency virus; IE, infective endocarditis.

Table 2 Six-month mortality according to the presence of neurological complications and for each type of complication among patients not lost to follow-up at 6 months.

	Six-month mortality
All patients with 6-month follow-up data ($n = 333$)	59 (17.7)
No neurological complication ($n = 242$)	45 (18.6)
Any neurological complication(s) ($n = 91$)	14 (15.4)
Ischaemic stroke ($n = 50$)	9 (18.0)
Silent cerebral embolism ($n = 30$)	3 (10.0)
Intracranial haemorrhage ($n = 36$)	8 (22.2)

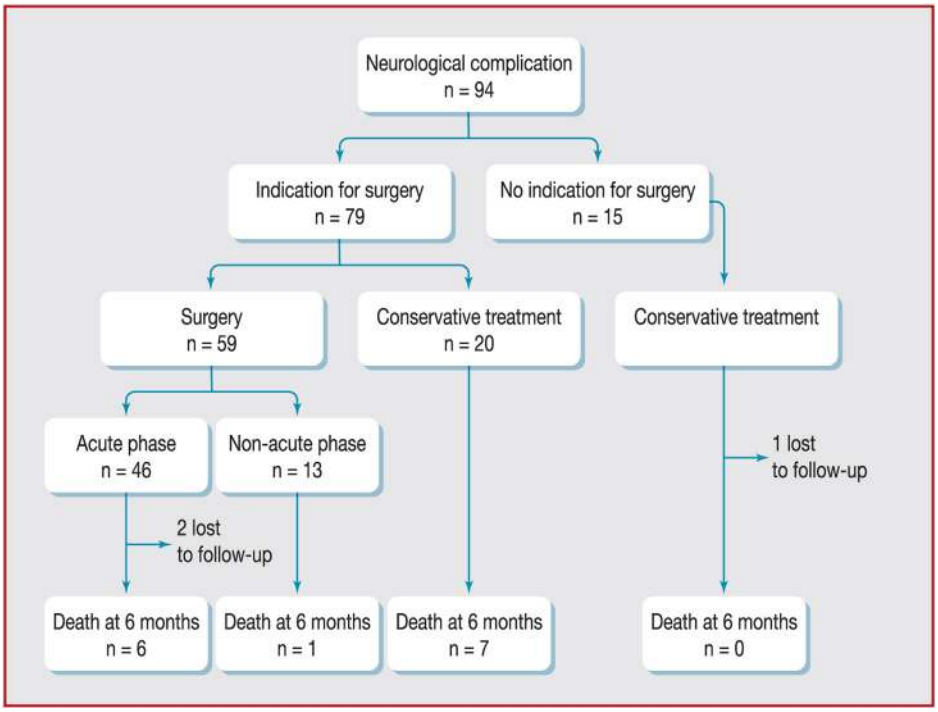

Figure 2. Outcome of patients presenting with a neurological complication.

Outcome of patients with contraindication to surgery due to neurological complications

Three patients presented definitive surgical contraindication due to neurological complications (impaired consciousness or coma) and had conservative treatment. Forty other patients with theoretical indication for surgery during the active phase (11 haemodynamic indication, nine embolic, four infectious and 16 multiple indications) had temporary surgical contraindication related to neurological complications. The mean duration of temporary contraindications was 4 weeks (range 2—12 weeks). This contraindication was caused by intracranial haemorrhage in 32 patients and by a large ischaemic stroke in eight patients. We observed a high rate of death or complications during the contraindication period. Seven patients (17.5% of those with temporary contraindication) died during surgical contraindication time (Fig. 3): four deaths were the consequence of the neurological complications (ischaemic strokes for two patients and intracranial haemorrhage of undetermined aetiology for two patients), one death was related to acute respiratory failure, one was the consequence of septic shock and there was one sudden cardiac death. During the temporary surgical contraindication period, five non-cerebral systemic embolisms and eight new cerebral complications occurred. Twelve patients (30.0%) presented a worsening of their cardiac or septic state (Fig. 3). Among the 40 patients with temporary surgical contraindication, 25 (62.5%) finally benefited from valvular surgery.

As a comparison, 36 patients who presented with neurological complications with a theoretical indication for surgery did not have surgical contraindication. While waiting for surgery, no patients died. Four patients presented new embolic events, one presented a worsening of his cardiac status (cardiogenic shock), one presented a worsening of his septic state (new periannular abscess) and two presented a new cerebral complication (one embolic event and one intracranial haemorrhage). Thirty-five of these patients (97.2%) finally benefited from surgery.

Table 3 Characteristics of patients presenting with neurological complications according to their surgical status.

Characteristic	Surgery ($n = 59$)	No surgery ($n = 35$)	*P*
Male sex	46 (78.0)	20 (57.1)	0.03
Age (years)	65 (54—73)	69 (65—78)	0.02
Charlson index	3 (2—4)	4 (2—5)	0.08
Clinical data			
Congestive heart failure	27 (45.8)	5 (14.3)	0.002
Cardiogenic shock	3 (5.1)	1 (2.9)	0.60
Septic shock	2 (3.4)	3 (8.6)	0.88
Systemic embolism	55 (93.2)	29 (82.9)	0.12
Cerebral embolism	51 (86.4)	28 (80.0)	0.41
Symptomatic	31 (52.5)	22 (62.9)	0.33
Silent	24 (40.7)	7 (20.0)	0.04
Intracranial haemorrhage	26 (44.1)	12 (34.3)	0.35
Brain abscess	6 (10.2)	1 (2.9)	0.19
Microbiology			
Positive blood cultures	54 (91.5)	26 (74.3)	0.02
Staphylococcus aureus	20 (33.9)	6 (17.1)	0.08
Echocardiographic data			
IE location			
Aortic	31 (52.5)	15 (42.9)	0.37
Mitral	25 (42.4)	18 (51.4)	0.39
Prosthesis	14 (23.7)	13 (37.1)	0.16
Vegetation(s)	49 (83.1)	30 (85.7)	0.73
Periannular lesion	23 (39.0)	6 (17.1)	0.03
Temporary surgical contraindication due to neurological complications	25 (42.4)	15 (42.9)	0.96
Morbimortality			
Six-month mortality	7 (11.9)	7 (20.0)	0.28
Neurological sequelae at 6 months	12 (20.3)	14 (40.0)	0.04

Data are expressed as number (%) or median (interquartile range).

Predictive factors of mortality among patients with neurological complications

Predictive factors of 6-month mortality in patients with IE with neurological complications were studied by multivariable analysis (Table A.1). Two factors were significantly associated with risk of death: mechanical prosthetic valve (HR 16.40, 95% CI 2.22—121.17; $P = 0.006$) and temporary surgical contraindication (HR 7.36, 95% CI 1.61—33.67; $P = 0.010$).

Discussion

In this study of patients with IE, 6-month mortality rates were similar among patients with and without neurological complications. However, patients who were not operated on when surgery was indicated had a significantly worse outcome. Further, delaying surgery because of neurological complications was associated with worse outcome.

Neurological complications of IE

In the current study, neurological complications occurred in 26.7% of IE cases, which is comparable to rates reported in other studies [3,4,7]. In agreement with another previous study [17], neurological events were mainly ischaemic (23.9% of patients) and intracranial haemorrhages were less frequent (10.8%). As has been previously reported [18,19], we found a predominance of haemorrhagic transformations of cerebral infarction, with a high frequency of streptococcal infections. The majority of symptomatic ischaemic complications (71.7%) occurred before the introduction of antibiotic therapy. This observation is in line with the reported reduction of embolic risk after early initiation of antibiotic treatment [3,7,20]. In contrast, only 26.3% of cases of haemorrhagic complications occurred before the introduction of antibiotic therapy. This could be explained by the fact that most of them were linked to haemorrhagic transformations complicating cerebral infarction.

Prognosis of patients with neurological complications

In our study, 6-month mortality was similar in patients with and without neurological complications, even when considering each subgroup separately. Previous studies concerning the impact of neurological complications on mortality gave conflicting results, with one study showing no effect on short-term mortality [21], while others classified them as a risk factor for death [3,4]. Recent studies have shown that

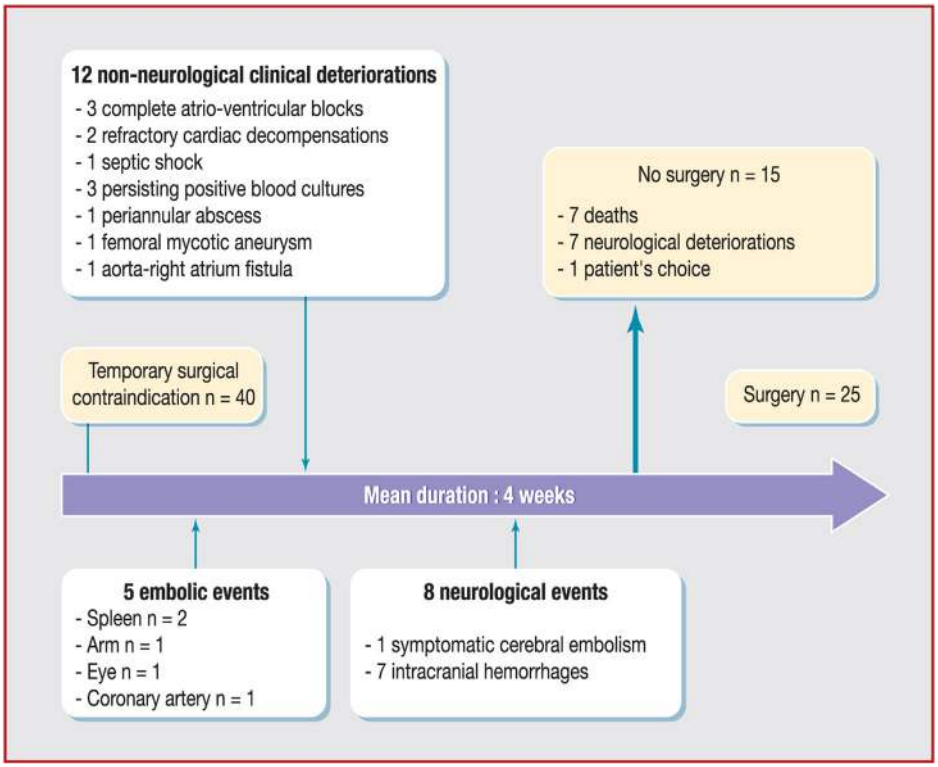

Figure 3. Outcome of the 40 patients with a temporary surgical contraindication.

the risk of death depends on the type of neurological complication: patients with silent embolism had a better prognosis, while symptomatic strokes remained a risk factor for death [7,22].

When comparing the mortality rate in this study to one published in 2007 in the same centre [7], we observed that overall 6-month mortality of patients with neurological complications reduced between the studies (22% in 2007 vs 15.4%). This might be related to the fact that the ''endocarditis team'' now make a multidisciplinary decision for each patient, allowing a better management of neurological complications.

Influence of delayed surgical therapy

In our study, there was a high rate of valvular surgery in patients with neurological complications (62.8%), significantly higher than in patients without neurological complications (45.9%). This high rate of surgery contrasts with another major study [4] that involved 340 patients with neurological complications, in which only 39% of patients underwent cardiac surgery. Some studies have indeed highlighted the protective role of surgery in patients with neurological complications [7,18,23]. The worse prognosis of non-operated patients despite a surgical indication in our study is also in favour of this trend.

When surgical management is indicated, the delay from the onset of neurological complications is not formally established. The decision must consider the risk of clinical worsening, mainly of cardiac status, and the potential risk of neurological worsening secondary to intracerebral bleeding and hypotension during heart surgery. Regarding ischaemic complications, most recent studies have not shown an excess of mortality or clinical worsening following early surgery [24,25]. The persistence of an embolic risk also tends to favour surgery in the acute phase of the disease. The optimal surgical timing is, however, not clear regarding large cerebral infarctions (with a significant risk of bleeding during surgery) and intracranial haemorrhages.

To our knowledge, this is the first study to analyse the consequences of temporary contraindication to surgery in patients who had neurological complications. Forty patients with a theoretical indication for early surgery who developed neurological complications had a temporary surgical contraindication. The average duration of contraindication (4 weeks) was in agreement with current recommendations [10]. During this period of contraindication, the rate of embolic recurrence was high (15.0%) and worsening of heart symptoms or non-optimal infectious control was observed in one third of the patients. In addition, three deaths unrelated to the neurological complication occurred. Only 62.5% of the contraindicated patients finally underwent surgery. New embolic events and cardiac or septic deterioration could have been avoided by early surgical treatment, highlighting the potential harmful consequences of surgery contraindication decision, which must be weighed against operative neurological risk. This was supported by multivariable analysis of predictors of 6-month mortality in patients with neurological complications, which showed that a temporary surgical contraindication was an independent risk factor for mortality. This study highlights the need to weigh the decision to contraindicate a patient to surgery and to discuss—in some cases—reducing the duration of contraindication when the patient is at high cardiac risk or

at significant risk of embolic recurrence. A recent study reported a low postoperative neurological worsening rate in patients undergoing surgery 2 weeks after intracranial haemorrhage [26]. Another study by Salaun et al. [18], which focussed on IE complicated by intracranial haemorrhage also highlighted a higher mortality of patients with conservative treatment compared to operated patients. Among the latter, none presented with postoperative neurological deterioration, even those operated within 1 month. Other studies are warranted to better assess the optimal timing of surgery in these patients.

Limitations

This was a single-centre study of patients hospitalized in a referral centre for the management of IE. The rate of neurological complications, their type, severity and the proportion of valvular surgery may not reflect the reality of other hospitals. Although brain CT was performed in all patients, the rate of asymptomatic embolism may have been underestimated as brain MRI was not systematically performed. In addition, the low numbers of events and low mortality make it difficult to interpret the results. Finally, this observational study cannot allow us to conclude a cause-and-effect relationship between the absence of surgery and prognosis.

Conclusions

Neurological complications of IE are frequent in patients with IE and often affect patients presenting a major embolic risk. Patients with a temporary contraindication to surgery due to their neurological complications have an increased risk of death. When indicated, the decision to postpone surgery in the early phase should be weighed against the risk of infectious or cardiac worsening, which is common in these patients. Future studies should focus on selecting the optimal timing of cardiac surgery in these patients. A multidisciplinary approach within an endocarditis team which favours early surgery in these patients could be one way to reduce mortality.

Sources of funding

None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://doi.dx.org/10.1016/j.acvd.2021.01.004.

Disclosure of interest

The authors declare that they have no competing interest.

References

[1] Murdoch DR, Corey GR, Hoen B, Miro JM, Fowler Jr VG, Bayer AS, et al. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the International Collaboration on Endocarditis-Prospective Cohort Study. Arch Intern Med 2009;169:463—73.

[2] Galvez-Acebal J, Rodriguez-Bano J, Martinez-Marcos FJ, Reguera JM, Plata A, Ruiz J, et al. Prognostic factors in left-sided endocarditis: results from the Andalusian multicenter cohort. BMC Infect Dis 2010;10:17.

[3] Heiro M, Nikoskelainen J, Engblom E, Kotilainen E, Marttila R, Kotilainen P. Neurologic manifestations of infective endocarditis: a 17-year experience in a teaching hospital in Finland. Arch Intern Med 2000;160:2781—7.

[4] Garcia-Cabrera E, Fernandez-Hidalgo N, Almirante B, Ivanova-Georgieva R, Noureddine M, Plata A, et al. Neurological complications of infective endocarditis: risk factors, outcome, and impact of cardiac surgery: a multicenter observational study. Circulation 2013;127:2272—84.

[5] Cooper HA, Thompson EC, Laureno R, Fuisz A, Mark AS, Lin M, et al. Subclinical brain embolization in left-sided infective endocarditis: results from the evaluation by MRI of the brains of patients with left-sided intracardiac solid masses (EMBOLISM) pilot study. Circulation 2009;120:585—91.

[6] Hess A, Klein I, Iung B, Lavallee P, Ilic-Habensus E, Dornic Q, et al. Brain MRI findings in neurologically asymptomatic patients with infective endocarditis. AJNR Am J Neuroradiol 2013;34:1579—84.

[7] Thuny F, Avierinos JF, Tribouilloy C, Giorgi R, Casalta JP, Milandre L, et al. Impact of cerebrovascular complications on mortality and neurologic outcome during infective endocarditis: a prospective multicentre study. Eur Heart J 2007;28:1155—61.

[8] Kang DH, Kim YJ, Kim SH, Sun BJ, Kim DH, Yun SC, et al. Early surgery versus conventional treatment for infective endocarditis. N Engl J Med 2012;366:2466—73.

[9] Anantha Narayanan M, Mahfood Haddad T, Kalil AC, Kanmanthareddy A, Suri RM, Mansour G, et al. Early versus late surgical intervention or medical management for infective endocarditis: a systematic review and meta-analysis. Heart 2016;102:950—7.

[10] Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, et al. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC), endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J 2015;36:3075—128.

[11] Li JS, Sexton DJ, Mick N, Nettles R, Fowler Jr VG, Ryan T, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis 2000;30:633—8.

[12] Lancellotti P, Pibarot P, Chambers J, Edvardsen T, Delgado V, Dulgheru R, et al. Recommendations for the imaging assessment of prosthetic heart valves: a report from the European Association of Cardiovascular Imaging endorsed by the Chinese Society of Echocardiography, the Inter-American Society of Echocardiography, and the Brazilian Department of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2016;17:589—90.

[13] Lancellotti P, Tribouilloy C, Hagendorff A, Popescu BA, Edvardsen T, Pierard LA, et al. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2013;14:611—44.

[14] Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. 2018 Guidelines for the early management

of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2018;49:e46—110.

[15] Hemphill JC, 3rd, Greenberg SM, Anderson CS, Becker K, Bendok BR, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2015;46:2032—60.

[16] Steiner T, Al-Shahi Salman R, Beer R, Christensen H, Cordonnier C, Csiba L, et al. European Stroke Organisation (ESO) guidelines for the management of spontaneous intracerebral hemorrhage. Int J Stroke 2014;9:840—55.

[17] Yanagawa B, Pettersson GB, Habib G, Ruel M, Saposnik G, Latter DA, et al. Surgical Management of Infective Endocarditis Complicated by Embolic Stroke: Practical Recommendations for Clinicians. Circulation 2016;134:1280—92.

[18] Salaun E, Touil A, Hubert S, Casalta JP, Gouriet F, Robinet-Borgomano E, et al. Intracranial haemorrhage in infective endocarditis. Arch Cardiovasc Dis 2018;111:712—21.

[19] Monteleone PP, Shrestha NK, Jacob J, Gordon SM, Fraser TG, Rehm SJ, et al. Clinical utility of cerebral angiography in the preoperative assessment of endocarditis. Vasc Med 2014;19:500—6.

[20] Dickerman SA, Abrutyn E, Barsic B, Bouza E, Cecchi E, Moreno A, et al. The relationship between the initiation of antimicrobial therapy and the incidence of stroke in infective endocarditis: an analysis from the ICE Prospective Cohort Study (ICE-PCS). Am Heart J 2007;154:1086—94.

[21] Cabell CH, Pond KK, Peterson GE, Durack DT, Corey GR, Anderson DJ, et al. The risk of stroke and death in patients with aortic and mitral valve endocarditis. Am Heart J 2001;142:75—80.

[22] Selton-Suty C, Delahaye F, Tattevin P, Federspiel C, Le Moing V, Chirouze C, et al. Symptomatic and asymptomatic neurological complications of infective endocarditis: impact on surgical management and prognosis. PLoS One 2016;11:e0158522.

[23] Sonneville R, Mirabel M, Hajage D, Tubach F, Vignon P, Perez P, et al. Neurologic complications and outcomes of infective endocarditis in critically ill patients: the ENDOcardite en REAnimation prospective multicenter study. Crit Care Med 2011;39:1474—81.

[24] Okita Y, Minakata K, Yasuno S, Uozumi R, Sato T, Ueshima K, et al. Optimal timing of surgery for active infective endocarditis with cerebral complications: a Japanese multicentre study. Eur J Cardiothorac Surg 2016;50:374—82.

[25] Barsic B, Dickerman S, Krajinovic V, Pappas P, Altclas J, Carosi G, et al. Influence of the timing of cardiac surgery on the outcome of patients with infective endocarditis and stroke. Clin Infect Dis 2013;56:209—17.

[26] Wilbring M, Irmscher L, Alexiou K, Matschke K, Tugtekin SM. The impact of preoperative neurological events in patients suffering from native infective valve endocarditis. Interact Cardiovasc Thorac Surg 2014;18:740—7.