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Infective endocarditis and neurologic events: indications and timing for surgical interventions

Nikolaos Bonaros[1]*, Martin Czerny[2], Bettina Pfausler[3], Silvana Müller[4], Thomas Bartel[5], Matthias Thielmann[6], Sharaf-Eldin Shehada[6], Thierry Folliguet[7], Jean-Francois Obadia[8], Johannes Holfeld[1], Roberto Lorusso[9], Alessandro Parolari[10], Ludwig Müller[1], Michael Grimm[1], and Elfriede Ruttmann-Ulmer[1]

[1]*Department of Cardiac Surgery, Medical University of Innsbruck, Anichstrasse 35, A-6020 Innsbruck, Austria;*
[2]*University Heart Center Freiburg-Bad Krozingen, Bad Krozingen, Germany;*
[3]*Department of Neurology, Medical University of Innsbruck, Innsbruck, Austria;*
[4]*Department of Internal Medicine III, Medical University of Innsbruck, Innsbruck, Austria;*
[5]*Department of Cardiology Mediclinic City, Hospital Dubai, Dubai, United Arab Emirates;*
[6]*Clinic for Thoracic and Cardiovascular Surgery, West German Heart and Vascular Centre Essen, Essen, Germany;*
[7]*Department of Cardiac Surgery and Transplantation, Henry Mondor Hospital, Paris, France;*
[8]*Department of Cardiac Surgery and Transplantation, Louis Pradel Hospital, Lyon, France;*
[9]*Department of Cardiothoracic Surgery, Maastricht University Medical Centre, Maaastricht, The Netherlands; and*
[10]*Department of Cardiac Surgery, San Donato Hospital, IRCCS, Milan, Italy*

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A therapeutic dilemma arises when infective endocarditis (IE) is complicated by a neurologic event. Postponement of surgery up to 4 weeks is recommended by the guidelines, however, this negatively impacts outcomes in many patients with an urgent indication for surgery due to uncontrolled infection, disease progression, or haemodynamic deterioration. The current literature is ambiguous regarding the safety of cardiopulmonary bypass in patients with recent neurologic injury. Nevertheless, most publications demonstrate a lower risk for secondary haemorrhagic conversion of uncomplicated ischaemic lesions than the risk for recurrent embolism under antibiotic treatment. Here, we discuss the current literature regarding neurologic stroke complicating IE with an indication for surgery.

Introducing the clinical scenario

Acute stroke is after congestive heart failure (CHF) the second most common complication of left-sided infective endocarditis (IE). Between 20% and 35% of those patients develop symptoms of ischaemic stroke, the incidence of which rises further up to 50% if the silent events are included.[1] The risk of IE-related embolic brain injury is substantially high (4.8/1000 patient-days) during the first week of antibiotic therapy and rapidly declines thereafter.[2] The current article comprises evidence and expert opinion on the diagnosis and management of patients with embolic stroke as the primary manifestation of left-sided IE. The main focus is given on the risk assessment for recurrent stroke as well as the timing and principles of surgical restoration of valve function.

Indications and timing of intervention

One in two patients affected by IE, must undergo surgical intervention, often salutary, but not devoid of risk.[3] Urgent

* Corresponding author. Tel: +43 512 504 80764, Fax: +43 512 504 22528, Email: nikolaos.bonaros@i-med.ac.at

Table 1 Indications for emergent or urgent cardiac surgical intervention

Haemodynamic instability due to valve insufficiency
Persistent fever despite appropriate antibiotic treatment
Spread of infection and development of peri-valvular abscesses of fistulas
Highly resistant microorganisms (*Staphylococcal strains, Coxielle burnetti*, Brucella, fungi, etc.)
Large size vegetations with high risk of embolism (>10 mm and highly mobile)
Vegetation size increase despite appropriate antibiotic treatment
Prosthetic valve endocarditis (particularly in the early post-operative phase)

valve surgery may be necessary depending on the haemodynamic state of the patient, the control of the septic condition, and the assessment of the risk of septic embolism (*Table 1*).

The risk of embolism

Septic embolism from valvular vegetations is a very frequent complication of IE.[4] This may often involve abdominal organs, such as the spleen, kidneys, liver, or the lower limb.[5] Embolic ischaemia in the corresponding organ may often transform to secondary abdominal organ abscess, an entity that is often found especially for the spleen.

The risk of infective endocarditis-related stroke

Stroke is the main reason for death after CHF in IE. The major causes of stroke are embolism by migration of vegetation fragments into the cerebral circulation, and mycotic aneurysm rupture.[6,7] Although the rate of clinically manifest stroke is at least high, the existence of silent cerebral embolism is increasingly reported due to the improving access to advanced neuroimaging. Most of the cerebrovascular complications are symptomatic and dissemination of emboli into cerebral vessels can result in concomitant meningitis, intracerebral abscess formation, or haemorrhagic transformation (*Figure 1*). Moreover, mycotic aneurysms may develop with a high risk for intracranial bleeding[8] (*Figure 2*). At least 40–50% of the patients have evidence of acute septic emboli, but ~5% of all cases with IE are complicated by intracerebral haemorrhage, 60–90% of which affect the middle cerebral artery.[6]

Risk of recurrent embolism

Even though the risk of cerebral embolism in general is high, the risk of recurrence seems to be lower than initially suspected. In the vast majority, the first embolic episode occurs before the initiation of antibiotic treatment and it usually indicates the index clinical event leading to hospitalization.[9] The risk of recurrent embolism has been reported to be between 6% and 21% and decreases rapidly after the beginning of antibiotic treatment.[2]

Timing of intervention

The ideal timing for surgery in IE with preoperative neurological events remains controversial. The European Society of Cardiology 2015 guidelines advise urgent surgery for endocarditis complicated by 'silent' cerebral embolism or transient ischaemic events (Class IB).[1] Nevertheless, the timing of surgery remains contentious. Current recommendations are somewhat ambiguous, but generally favour deferral of surgical intervention for 2–4 weeks after a significant ischaemic cerebral infarct and at least 4 weeks after intracranial haemorrhage, unless a delay in surgery puts the patient at immediate risk of death.

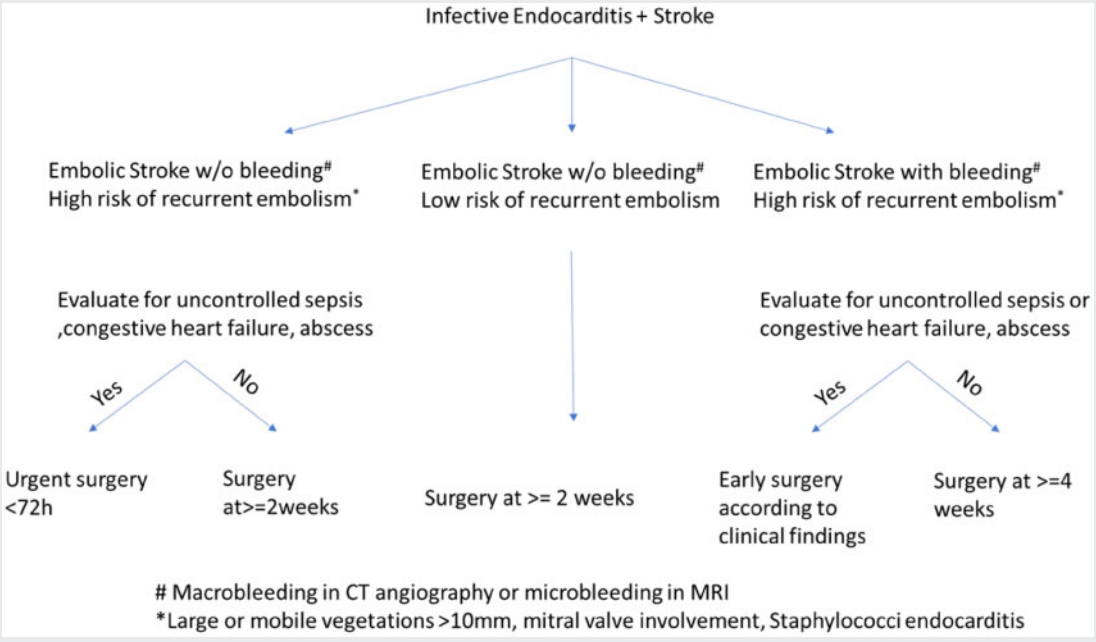
There have been no large, prospective studies to date that definitively guide decision making on the timing of surgery in IE following acute stroke. The International Collaboration on Endocarditis published 198 patients with IE-related stroke found that early surgery within the first week after stroke onset was not associated with a higher risk of 1-year mortality.[10] The results were confirmed by our group which demonstrated that patients with both uncomplicated or complicated (meningitis, haemorrhage, or brain abscess) ischaemic lesions showed no deterioration to haemorrhagic stroke after early surgery.[7] This may implicate that the risk of haemodynamic deterioration is higher during the first 1–2 weeks after initiation of antibiotic treatment than the risk of CPB.

Current recommendations indicate that surgery without any delay is indicated in patients after silent embolism or transient ischaemic attack (TIA) (IB, B). After a clinically manifest stroke, early surgery should be considered in the presence of uncontrolled sepsis, non-manageable CHF, progressing para-valvular destruction. However, secondary cerebral haemorrhage should be excluded. The so-called 'microbleeds' on magnetic resonance imaging (MRI), however, should not be classified to be active bleeding signs (IIa, B). After a cranial haemorrhage, surgery should be delayed for more than 1 month, however, the level of evidence is low (IIa, C). In patients with neurological symptoms, intracerebral mycotic aneurysms should be suspected. For very large, growing or ruptured aneurysms, immediate surgical therapy is recommended (I, C). Altogether, studies favouring early surgery for patients with IE-related stroke are predominating in the current literature and has led to a change in existing guidelines. A multidisciplinary 'heart team' approach involving cardiologists, cardiac surgeons, microbiologists, and neurologists, is recommended.

Multi-modality imaging for infective endocarditis

During the last decade, there has been a transition from simple to multi-modality imaging for the basic diagnosis and risk assessment of IE. Although vegetations represent the primary echocardiographic hallmark of the disease, other pathologies, such as abscess, fistula, pseudoaneurysm, prosthetic valve dehiscence, and valve perforation, are indicative of IE even in the absence of vegetations.[11] Transoesophageal echocardiography (TOE) is considered to be the diagnostic tool of choice in these cases due

Summary Table



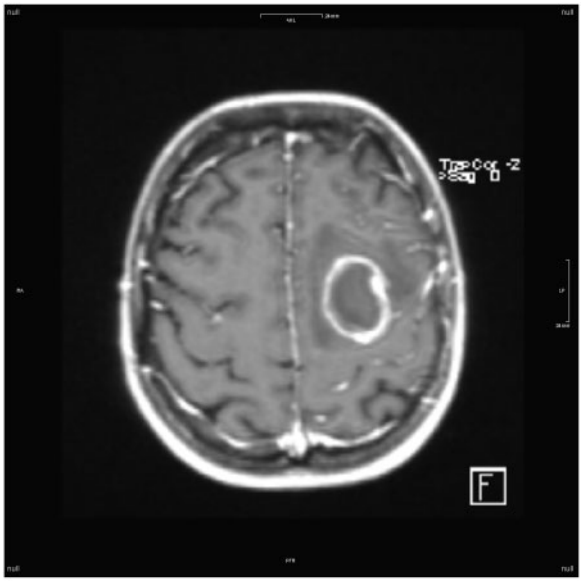


Figure 1 Magnetic resonance imaging: intracranial abscess at the left parietal side. The female patient received a mitral valve repair and underwent successful neuro-surgical intervention at the fourth post-operative day. She regained full neurologic recovery without sequelae.

to high sensitivity and specificity.[12] Transoesophageal echocardiography based tissue colour Doppler imaging was shown to identify specific motion patterns inherent to floating vegetations.[13] This is useful for distinction from other native valvular findings that may be taken for infective vegetations[11] (*Figure 3*). Real-time three-dimensional TOE has provided a 'surgical view' and shows the complete spectrum of pathologies even more precisely.[14] Cardiac computed tomography represents a complimentary diagnostic tool shown to be almost as sensitive as TOE for detection of vegetations, but not for leaflet destruction. Cardiac computed tomography (CT), on the other hand, is extremely helpful for the identification of a paravalvular abscess or pseudoaneurysm.[15]

Size, shape, location, echogenicity, and motion pattern are important echocardiographic features characterizing vegetations. Shaggy, amorphous, and lobulated shapes are considered most typical.[11] In particular, in staphylococcus endocarditis and in cases of mitral valve involvement, large vegetations with a length of >10 mm or those with increasing mass have a higher incidence of embolism compared to smaller ones and those being stable in size.[12] However, mobility, rather than vegetation size impacts risk of embolization in streptococcal endocarditis or aortic valve infection.[9,14]

Challenges in risk assessment

Risk stratification for post-stroke cerebral bleeding

Ischaemic strokes are the most frequent embolic cerebral events in IE and haemorrhagic transformation is a dreaded complication in all stroke patients. There is a wide range of bleeding complications after stroke, such as subtle petechial up to large symptomatic bleedings beyond the border of the infarction.[16,17] Haemorrhagic transformation of acute ischaemic stroke is a complex mechanism, triggered

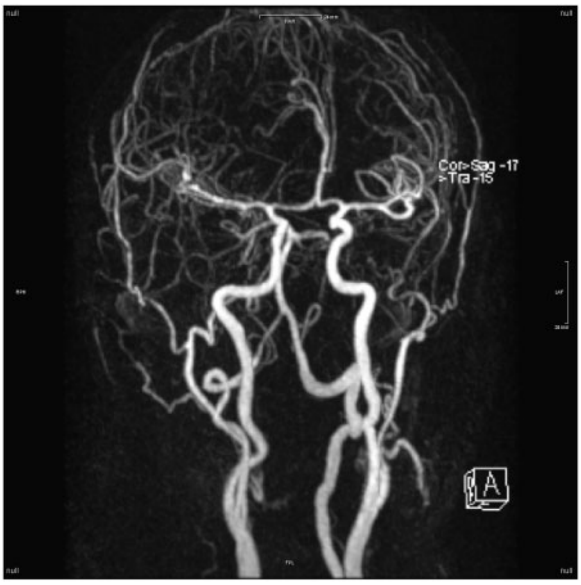


Figure 2 Contrast agent magnetic resonance angiography: 3 mm × 2.5 mm large mycotic aneurysm of a M2-branch of the middle cerebral artery at the right side. The male patient suffered from severe aortic valve endocarditis with paravalvular abscess formation (*Staphylococcus aureus*). Neurosurgical intervention was performed 3 days before aortic root replacement therapy. He died due to septic multi-organ failure but without intracerebral haemorrhage.

by cellular and metabolic derangements, disruption of the blood–brain barrier, and the cerebral autoregulation.[18] Because of the need of systemic heparinization during extracorporeal circulation there are concerns regarding the risk of haemorrhagic transformation and enlargement of petechial bleedings. In the general stroke population, spontaneous bleeding complications are below 1.5%. In patients with intravascular thrombolysis with recombinant tissue plasminogen activator (r-tPA) bleeding complications grow up to 40%, but symptomatic haemorrhagic transformation is rare (<9%).[19] Risk factors for intracranial haemorrhage in r-tPA-treated patients are older age, severe stroke, hypertension, renal impairment, diabetes mellitus, ischaemic heart disease, atrial fibrillation, baseline antiplatelet use, and visible acute infarction.[20] It is unclear if these factors can be transferred to patients undergoing surgery for IE. Reports of neurological worsening during early surgery are from older case studies in which modern imaging techniques were not available. Small lesions detected by modern MRI sequences have a lower haemorrhagic transformation risk compared to larger strokes. Earlier surgery must therefore be considered in stable small haemorrhagic lesions, especially if high embolic risk from existing vegetations is expected. In those selected cases, surgery can be considered even at 14 days after intracranial haemorrhage.

Risk stratification for recurrent embolism

Although the individual risk cannot be determined, there are well established risk factors for recurrent embolism in untreated patients. A vegetation larger than 10 mm in size and with floating mobility is the most independent risk factor for further cerebral emboli.[21] Location at the anterior mitral valve leaflet, less the aortic valve, and an infection with staphylococci or fungi, age, diabetes, atrial fibrillation, and previous embolic events are additional risk factors. Risk of embolism is highest within the first week of initiation of antibiotic therapy and clearly decreases after the second week.[2,22] Because of potentially ongoing silent embolism imaging reassessment is always necessary. In case of acute large territorial ischaemic strokes intravenous thrombolysis and thrombectomy must be considered on an individual basis. Compared to thrombolysis, haemorrhagic complications seem to be less frequent in patients who undergo interventional thrombectomy.[23]

Risk stratification for uncontrolled infection

Uncontrolled infection is another main indicator for urgent surgery in IE, defined as enlarging vegetations, abscess-forming cavity, or fistula due to infective myocardial tissue destruction or persisting positive blood cultures refractory to appropriate antibiotic treatment for 7–10 days and control of septic foci (Class I, B).[1] It is even aggravated by resistant or malignant pathogens; fungi or multi-drug resistant organisms (Class I, C) or staphylococci or non-HACEK Gram-negative bacteria affecting prosthetic valve endocarditis (PVE; Class IIa, C). Moreover, the current guidelines indicate that surgery should be considered (Class IIa, B), if blood cultures remain positive despite antibiotic-adapted regime for three consecutive days and after exclusion of other causes. Uncontrolled infection is an independent risk factor for early mortality in patients with IE.[24] It is most frequently related to peri-valvular abscess extended infection to adjacent tissues. Thus, the presence of local or systemic signs of uncontrolled infection is an indicator for urgent surgery, unless major comorbidities exist, the presence of which should be taken into account for risk stratification.

Risk stratification for heart failure

Congestive heart failure is one of the major determinants for adverse outcome and poor prognosis in the setting of acute IE and therefore, most important for the decision on timing of surgery.[25] In acute IE, CHF is usually the result of evolving valve regurgitation due to infective destruction of the native or prosthetic valve. Most common causes are severe aortic or mitral valve regurgitation which can only be poorly tolerated. Rarely causes are tricuspid or pulmonary valve regurgitation, as well as protruding or bulky infective vegetations causing acute valve obstruction rapidly leading to progressive CHF with refractory pulmonary oedema up to cardiogenic shock. Even more rarely but not less dangerous are any intra-cardiac shunting or fistula due to infective myocardial tissue destruction or abscess-forming cavity. For decision-making of further therapeutic measures, a continuous clinical assessment including laboratory investigations, cerebral CT scan or MRI, and repeated cardiac examinations by transthoracic echocardiography (TTE) and/or TOE is of crucial importance.[1]

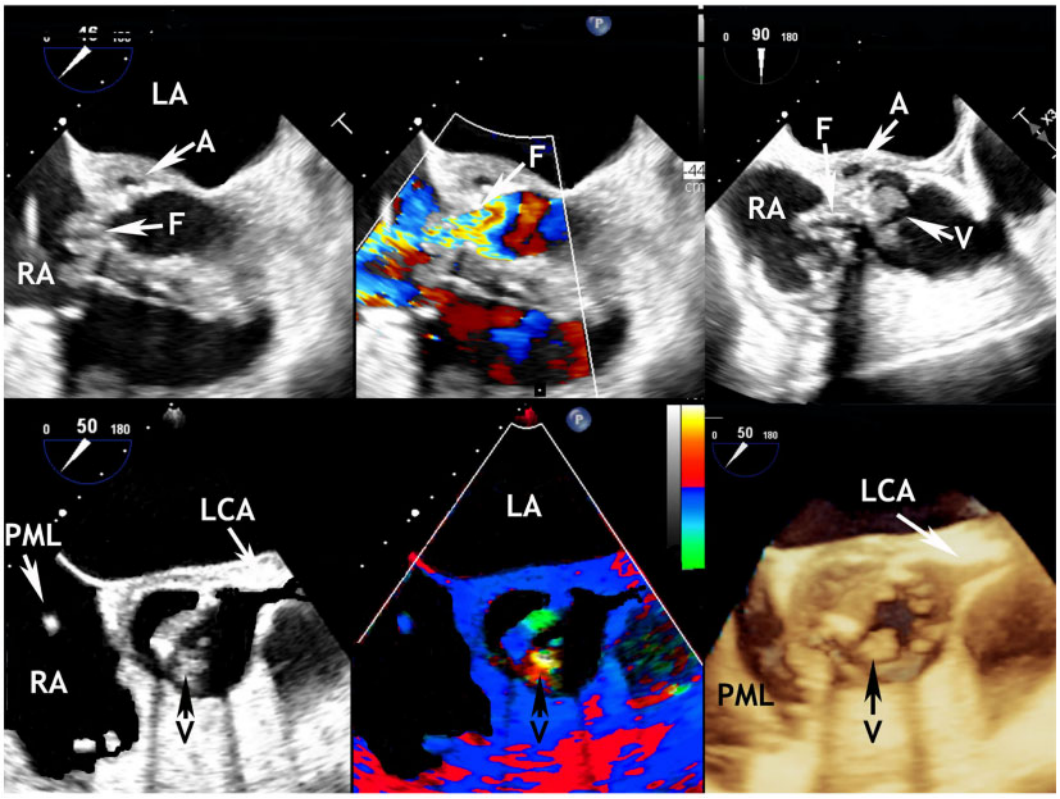


Figure 3 The upper panel shows paravalvular abscess, fistula to the right atrium complicating severe aortic valve endocarditis with vegetations are larger than 1 cm. Lower panel shows the aortic valve to be bicuspid with two- and three-dimensional display of a vegetation characterized by distinctive tissue Doppler motion pattern. A, abscess; F, fistula; LA, left atrium; LCA, left coronary artery; PML, pacemaker lead; RA, right atrium; V, vegetation.

Principles of intervention

Infective endocarditis surgery displays several similarities with cancer surgery: after a first step of complete excision of infected tissues, the surgical procedure focuses on the repair/replacement of the infected valve(s), and the neighbouring structures.[26] The choice of the surgical technique is anticipated by the preoperative diagnostic imaging and confirmed by the perioperative findings. Minimal manipulation before cardiac arrest, radical debridement with orthotopic reconstruction are the key components of the surgical approach. Planning can be achieved with comprehensive imaging. As CTA should be performed in every case to get the entire picture of the thoracic vascular system, alternative cannulation sites, such as the right subclavian artery might be very useful to avoid manipulation of a diseased ascending aorta or to gain safe arterial access in patients after previous heart surgery before redo sternotomy. Radical debridement of the infected tissue and drainage of intra and paracardial abscesses remains key. The range is from mere excision of a native single valve to complete resection of the aorto-mitral continuity needing the most extensive form of orthotopic reconstruction, being the so-called Commando operation where the aorto-mitral continuity has to be rebuilt and an aortic root replacement needs to be performed.

In native aortic valve IE without extensive annular involvement, isolated aortic valve replacement is the technique of choice. In-hospital mortality and long-term survival are independent of the type of prosthesis used.[27] The Society of Thoracic Surgeons clinical practice guidelines reported an evolving trend of aortic valve replacement in the setting of IE towards biological prostheses.[28] The aortic valve localization is more often complicated by annular abscess than other native valve IE.[29] Extensive debridement could lead to patch repair of the involved portion of the aortic annulus. This technique offers a solid structure for the implantation of the prosthesis while creating a localized infected cavity with the subsequent risk of patch leakage and paravalvular regurgitation. Finally, in patients with annular defects not amenable to patch repair, aorto-ventricular discontinuity, or parietal destruction, a homograft or a pericardium-based total root replacement offers several advantages.

In native mitral valve IE, mitral valve repair should be encouraged owing to its apparent better results as compared to replacement, in term of survival, reoperation, and valve-related complications.[30] The possibility of mitral valve repair depends on the anatomic lesions, active or healed presentation of IE and surgical experience. Repair rates are extremely variable in published series.[31] However, the overall incidence of mitral valve repair has increased significantly.[28] Conversely, in case of valvular destruction leading to extensive tissue debridement/resection, mitral valve replacement seems the only reasonable option. As for native aortic valve IE, the results after mitral

valve replacement are similar regardless of the type of prosthesis.

Extracorporeal circulation and hypothermia in recent cerebral ischaemia

Generally speaking, brain injury during extracorporeal circulation can be attributed to inadequate cerebral flow which is related to either hypoperfusion or micro- and macro-embolism. In patients with pre-existing neurological injury the possible effects of cardiopulmonary bypass maybe detrimental. This is has been linked to the risk of haemorrhagic bleeding at the penumbral zone of the area of recent embolism which is related to the increased permeability and vulnerability of brain cells in case of repeat hypoperfusion or microembolism.[18] Especially in patients with recent cerebral embolism due to IE, there is an increased risk of recurrent stroke due to hypoperfusion during extracorporeal circulation on the grounds of absence of an adequate collateral network. This risk is associated with the 'letzte Wiese' hypothesis which assumes that at the event of hypoperfusion the most distal field of a supply territory is prone to temporary or permanent injury.[32]

Although the 'letzte Wiese' hypothesis is rarely associated with relevant clinical manifestations, there are three factors which may aggravate neurologic symptoms in a patient with recent stroke after surgery for IE:

(1) The decrease or absence of collateralization due to the previous embolic event.
(2) The non-pulsatile flow of extracorporeal circulation together with haemodynamic alterations in the perioperative period.
(3) Temperature management and the extent of hypercapnia which may affect cerebral blood flow.

Except for delaying surgery, several strategies have been proposed to avoid cerebral injury. Maintaining an adequate arterial pressure during extracorporeal circulation is indispensable to avoid cerebral O_2 demand/delivery mismatch. Most importantly, the relationship of blood pressure and cerebral perfusion is depending on brain autoregulation which may be suppressed during extracorporeal circulation. There are ways to preserve cerebral autoregulation mechanisms by avoiding low perfusion temperatures and hypocapnia. In our department, we keep all patients in normothermia or mild hypothermia (35°C) and continuously monitor and adjust CO_2 levels at the pump to avoid an intracerebral steal phenomenon.[33] Moreover, avoiding oxygen carrier deficiency by maintaining a haematocrit level above 24% and monitoring blood glucose levels to early detect hyperglycaemia are important steps to reduce the risk of cerebral oedema.[34]

Antithrombotic management as bridging to intervention

Vegetations of IE are blood clots consisting of fibrin and platelets populated by bacteria. The blood clot itself protects the pathogens from immune defence leading to higher bacterial densities than in skin abscesses.[35] Therefore, it is obvious that IE initiates an interplay between haemostatic coagulation and the immune system, especially the innate immunity. It remains a matter of debate whether thrombosis or endocarditis are effect or consequence of vegetations. This fact makes clinical decision-making for a successful antithrombotic management so difficult and at the same time individual.

Antiplatelet drugs, anticoagulants, and fibrinolytic drugs have been investigated for the management of IE. However, due to the acute setting of such patients lack large-scale prospective, randomized-controlled clinical trials are missing. Therefore, recommendations remain at a low level of evidence.

A meta-analysis of patients with infected mechanical valve prosthesis showed that discontinued anticoagulation leads to a significantly higher risk of thromboembolism.[36] In a prospective cohort-study patients with native valve endocarditis showed smaller vegetations when they were under warfarin therapy.[37] In a large US nationwide registry of stroke patients undergoing thrombolysis 222 patients suffering from IE where included. Those had a significantly higher rate of cerebral haemorrhage (20%). Thus, the use of fibrinolytic drugs in IE cannot be recommended.[38]

European and American guidelines recommend to continue anticoagulation therapy with great caution in IE patients if needed for other indications. But there is no recommendation to start an anticoagulation regimen. Bridging of Vitamin K antagonists with low molecular weight (LMW) heparin may be done in patients at risk. No evidence exists for the use of antiplatelet drugs. Therefore, both European and American guidelines do not recommend their use in patients with IE.[1,39]

Management of specific indications

Prosthetic and transcatheter valve endocarditis

Prosthetic valve endocarditis represents 20% of all cases of IE, and its incidence is increasing over time[40]; stroke is a frequent presentation occurring in ~30% of the patients with a valve prosthesis previously implanted.[41] Notably, PVE is by itself associated to substantial mortality rates, around 20–33%, which are exacerbated by preoperative stroke as presentation, being a well-known risk factor for mortality.[42] This condition may also affect transcatheter valves with incidence rates from 0% to 14.3%. The most common organisms involved in post-transcatheter aortic valve implantation (TAVI) IE were *Enterococci*, *Staphylococci*, and *Streptococci*.[43] Although surgery is a valuable option in PVE cases with stroke, at the moment there are no clear indications on how to manage these patients, and case by case discussion of multidisciplinary endocarditis teams is very important for the final decision. Usually, surgery is reserved for the cases (<50% of the total) presenting with the more severe complications of PVE, which are very similar to the ones of native endocarditis: severe prosthetic valve dysfunction, abscess/fistula, persistent fever, or HF, whereas early and emergency surgery

are reserved only to cases showing refractory congestive HF leading to pulmonary oedema or shock.[1]

Areas of uncertainties and future perspectives

Taken together, the timing of surgery, remains a grey zone in patients who have already sustained any kind of neurological injury before surgery, in particular, in patients with haemorrhagic lesions or in patients with ischaemic lesions being at high risk for haemorrhagic transformation. The current article suggests an algorithm favouring an early surgical strategy based on the risk of recurrent embolism, the presence of cerebral bleeding as well as signs of uncontrolled infection and CHF. Sophisticated imaging will help to further characterize 'risky' vegetations and abscess formation, differentiate, and predict. Finally, the debate persists, how to handle antibiotic prophylaxis during dental and other surgical procedures where the pendulum seems to swing back to a more liberal application of antibiotic prophylaxis in these scenarios.

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