ESC European Society of Cardiology

European Heart Journal - Case Reports (2022) **6**(2), 1–4
doi:10.1093/ehjcr/ytab348

EDITORIAL

Timing for diagnosis and treatment in initially uncomplicated endocarditis: still a thorny issue

Rita Pavasini [1]*, Timothy C. Tan [2], and Christoph Sinning [3]

[1]Cardiology Unit, Azienda Ospedaliero Universitaria di Ferrara, Via Aldo Moro 8, Cona, Ferrara 44124, Italy; [2]Department of Cardiology, Blacktown Hospital, Western Sydney University, 18 Blacktown Rd, Blacktown New South Wales 2148, Australia; and [3]Department of Cardiology, University Heart & Vascular Center Hamburg, Martinistraße 52, 20251 Hamburg, Germany

Received 26 July 2021; first decision 3 August 2021; accepted 25 August 2021; online publish-ahead-of-print 27 August 2021

This editorial refers to 'Acute posteromedial papillary muscle rupture secondary to aortic valve endocarditis: a case report', by A. Marumoto *et al.* doi:10.1093/ehjcr/ytab374 and 'Echocardiography fails to detect an extensive aortic root abscess in a patient with infective endocarditis: a case report' C.K. Zogg *et al.* doi:10.1093/ehjcr/ytac032.

Despite overall improvements in the general health condition of the global population and accessibility to health care in this modern era, infective endocarditis (IE) continues to remain a significant health issue. Global contemporary rates reflect a constant increase in the incidence and prevalence of IE.[1] Furthermore, patients with IE are now typically older, have multiple cardiovascular comorbidities, and are more likely to have a biological or mechanical prosthesis, implanted devices, congenital heart disease, or long-term intravenous access for cancer treatment posing a challenge in treatment.

Marumoto *et al.*[2] describe a case of group G streptococcal endocarditis in an 81-year-old patient with a perforated aortic valve resulting in moderate aortic regurgitation. The patient was initially asymptomatic on presentation with no evidence of embolic phenomenon or cardiac decompensation. The patient was conservatively managed with intravenous antibiotics based on current guideline recommendations.[3] After 7 days of treatment with penicillin G, the patient developed clinical signs of decompensated heart failure and was found to have acute significant mitral regurgitation secondary to a papillary muscle rupture. Interestingly, in this case there was no visual evidence of infection or vegetations on the mitral leaflets in the initial transoesophageal echocardiography (TOE).[2] This case highlights how the clinical indication and need for surgery can evolve within a short period of time from a relatively benign course to an urgent need for surgical intervention (Class I, Level of evidence B).[3] This case represents a common clinical scenario where the initial presentation relates to the presence of a leaflet perforation with no significant impact on the valve. Despite appropriate antibiotic therapy, ∼3% of stable patients with IE require unplanned surgery.[4] Management of IE patients is further complicated by the challenges associated with infection of valve prostheses or concurrent intracardiac devices infections.[5] These issues highlight a common conundrum associated with the management of valvular endocarditis, i.e. optimal timing for surgical intervention in IE. Unfortunately, there are presently no large randomized controlled trials available to answer this question, particularly in cases of seemingly uncomplicated IE. There are, however, four meta-analyses comparing early surgery with conventional medical treatment or late surgery, demonstrating an overall reduction in mortality in patients treated with early surgery (*Table 1*).[6–9] However, the studies included in these meta-analyses were largely observational trials or from propensity-matched studies, hence the heterogeneity of the data is high. Furthermore, the definition of early surgery varied considerably in the studies included and the subgroups of patients (e.g. with native valves vs. prosthetic valves, right-sided endocarditis, microbiological aetiology) are not often clearly differentiated.[6–9] Decision-making in a multidisciplinary endocarditis team may be the best course of action since this approach has been associated with a reduction of in-hospital and late mortality.[10,11] Another question arising from the case presented by Marumoto *et al.* pertains to the mechanism underlying the acute rupture of the papillary muscle. In the featured case, it appears that first-line imaging, i.e. echocardiography was not adequate in elucidating the extent of the underlying tissue affected as demonstrated in this case. This issue is also highlighted by the case of Zogg *et al.*[12] which shows how both transthoracic and TOE evaluation for IE in a severely calcified bicuspid valve was not sufficient to detect an extensive aortic root abscess. In this case report, the patient presented with streptococcus sanguinis bacteraemia and new-onset left bundle branch block that progressed to complete heart block.[12] Transoesophageal echocardiography showed the presence of

* Corresponding author. Tel: +39 (0)532 236450, Email: pvsrti@unife.it

Handling Editor: Amardeep Ghosh Dastidar

Table 1 Meta-analyses about early surgery vs. late surgery or medical treatment in endocarditis

References	Year of publication	Number of studies included	Patients included	Comparison	Outcomes
Jia *et al.*[6]	2017	8 for in-hospital mortality 6 for follow-up mortality 4 for IE-related mortality	3940 patients for in-hospital mortality 840 patients for follow-up mortality 561 for IE-related mortality	Early surgery was defined as surgery performed in active phase; in case the duration between surgery and entrance to hospital was not more than 4 weeks; or surgery performed during initial hospitalization	Early surgery reduce in-hospital mortality, follow-up mortality, and IE-related mortality
Anantha Narayanan *et al.*[7]	2016	21 studies	11 048 patients	Early surgery was defined at 20 days or less and conservative management	Early surgical intervention is associated with significantly lower risk of mortality in patients with IE
Liang *et al.*[8]	2016	16 studies	8141 patients	Early surgery vs. non-early surgery. Early surgery was defined during initial hospitalization before the completion of a full therapeutic course of antibiotics	Early surgery was associated with lower in-hospital and long-term mortality compared with non-early surgical treatment for IE, especially in native valves. Optimal timing remain unclear
Chatterjee *et al.*[9]	2013	10 studies	3758 patients	Early surgery with conventional or conservative medical therapy in patients with IE. Early surgery was defined as surgical intervention with valve repair or replacement within 18 days of IE diagnosis, or during initial hospitalization	Early surgery in patients with IE may be beneficial for long-term survival

IE: infective endocarditis.

Table 2 Strengths and weaknesses of individual imaging modalities[3,13,14,16]

Imaging modality	Strength	Weakness
Transthoracic echocardiography	• Non-invasive • Assessment of valve severity • Visualization of size and mobility of vegetation, perforation • Follow-up of patients on antibiotic therapy and after surgery • No radiation exposure	• Difficult differential diagnosis with other masses (thrombi, cusp prolapse, cardiac tumours, myxomatous changes, Lambl's excrescences, strands, or non-infective vegetations) • Low sensitivity for abscess, pseudo-aneurism or fistulization • Low visualization of mechanical prosthesis, electrodes of devices, intravenous catheter
Transoesophageal echocardiography	• No radiation exposure • Better visualization of valve leaflets with lesions characterization and definition of valve severity • Better visualization of valve prosthesis, electrodes of devices, intravenous catheter • Good visualization of root abscess • Intra-operative monitoring of valve surgery	• Invasive • Low sensitivity for small abscess or in case of calcification • Acoustic shadowing in case of prosthesis and calcification
18F-fluorodesoxyglucose–positron emission tomography	• Detection of enhanced glucose metabolism within organs • Detection of abscess formation and perivalvular extension • Good assessment of prosthetic valves (no acoustic shadowing) and of device infection • Detection of peripheral embolic and metastatic infectious events	• Low sensitivity for small oscillating vegetations • Limitation in case of already started antibiotic treatment or in case of slowly evolving infection • Carefully evaluation in recent cardiac valve surgery (post-operative inflammatory response)
Computed tomography scan	• Perivalvular extent of abscess and pseudo-aneurism • Root abscess • Good assessment of prosthetic valves • Better evaluation in case of extensive calcification of the valve (no acoustic shadowing) • Assessment of coronary arteries • Detection of silent embolism and extracardiac manifestations/complications	• Radiation exposure • Low detection of small vegetation • Not applicable in case of severely impaired renal function • Not applicable in patients with unstable haemodynamics and with iodine allergy
SPECT/CT	• Provide exact anatomical localization of the enhanced isotope concentration • Good assessment of prosthetic valves (no acoustic shadowing) and of device infection • Better detection of infectious foci	• Radiation exposure • Time consuming • Low-dose contrast is necessary

CT, computed tomography; SPECT, single-photon emission computed tomography.

vegetations on the aortic valve but did not show any evidence of aortic root abscess.[12] A correct diagnosis was made only by using 18F-fluorodesoxyglucose–positron emission tomography (18FDG–PET) imaging, which revealed the presence of focal activity around the aortic root suggestive for active infection of the aortic valve and possible abscess, which was subsequently confirmed by visual inspection of the aortic root during surgery.

These two case reports also highlight the role of multi-modality imaging in patients with IE and raises the question of appropriate timing for follow-up in cases of uncomplicated IE. Both transthoracic and TOE are first-line diagnostic tools which are important in the diagnosis and monitoring regarding progression of IE, and provide information on the features of the lesion and allow characterization of the extent of damage to associated cardiac structures, i.e. simple vegetation vs. abscess or fistula.[13] In the case of aortic root abscesses, pseudo-aneurysms or fistulae, particular in the context of IE involving prosthetic valves where echo imaging may be suboptimal, computed tomography (CT), preferably electrocardiographic gated, has been shown to be non-inferior in terms of sensitivity compared to TOE[14] in achieving the diagnosis. There is also an emerging role for other more novel imaging modalities, i.e. 18FFDG–PET–CT and single-photon emission computed tomography fused with conventional CT.[15]

The additional information obtained from this hybrid imaging approaches which integrate the metabolic and anatomic findings allows for more accurate identification of foci of tissue inflammation not available with echo or CT imaging on its own (*Table 2*).[14–16]

With regards to appropriate follow-up for cases of uncomplicated IE, the best approach is still unclear. Current clinical practice would typically repeat imaging at least 7 days post-initiation of antibiotic therapy to assess for changes in a patient with IE (both to confirm a possible IE in case of positive blood cultures with initially absence of vegetations or to check for progress and development of complications in IE).[13] However, what makes IE truly insidious is its unpredictability in terms of timing for the development of complications, as demonstrated by both highlighted cases.[2,12] New trials are still clearly needed to identify potential risk factors which may predict likely progression of IE which could be useful in risk stratification of patients. This in turn would enable us to identify patients most likely to benefit from further investigation or early intervention and thus can help further improve our current management of patients with IE.

Lead author biography

Rita Pavasini is assistant professor and consultant cardiologist at the Cardiology Unit of the University Hospital of Ferrara, Italy. She is responsible for the echocardiographic laboratory, author of more than 80 papers published in high impact factor journals. She participated as investigator in several randomized, multicentre, international clinical trials. Her main field of research are ischemic heart disease and comorbidities (chronic obstructive pulmonary disease), valvular heart disease, cardiac amyloidosis, ischemia reperfusion injury, antiplatelet therapy, percutaneous coronary intervention, frailty in cardiovascular disease.

Conflict of interest: None declared.

Funding: None declared.

References

1. Cahill TJ, Prendergast BD. Infective endocarditis. *Lancet* 2016;**387**:882–893.
2. Marumoto A, Shijo T, Okada M, Hasegawa S. Acute posteromedial papillary muscle rupture secondary to aortic valve endocarditis: a case report. *Eur Heart J Case Rep* 2021;ytab374. Doi:10.1093/ehjcr/ytab374.
3. Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F et al.; ESC Scientific Document Group. 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**:3075–3128.
4. Iversen K, Ihlemann N, Gill SU, Madsen T, Elming H, Jensen KT et al. Partial oral versus intravenous antibiotic treatment of endocarditis. *N Engl J Med* 2019;**380**:415–424.
5. Blomström-Lundqvist C, Traykov V, Erba PA, Burri H, Nielsen JC, Bongiorni MG et al.; ESC Scientific Document Group. European Heart Rhythm Association (EHRA) international consensus document on how to prevent, diagnose, and treat cardiac implantable electronic device infections-endorsed by the Heart Rhythm Society (HRS), the Asia Pacific Heart Rhythm Society (APHRS), the Latin American Heart Rhythm Society (LAHRS), International Society for Cardiovascular Infectious Diseases (ISCVID) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Europace* 2020;**22**:515–549.
6. Jia L, Wang Z, Fu Q, Bu H, Wei M. Could early surgery get beneficial in adult patients with active native infective endocarditis? A meta-analysis. *Biomed Res Int* 2017;**2017**:3459468.
7. 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**:950–957.
8. Liang F, Song B, Liu R, Yang L, Tang H, Li Y. Optimal timing for early surgery in infective endocarditis: a meta-analysis. *Interact Cardiovasc Thorac Surg* 2016;**22**:336–345.
9. Chatterjee S, Sardar P. Early surgery reduces mortality in patients with infective endocarditis: insight from a meta-analysis. *Int J Cardiol* 2013;**168**:3094–3097.
10. Nappi F, Spadaccio C, Moon MR. A management framework for left sided endocarditis: a narrative review. *Ann Transl Med* 2020;**8**:1627.
11. 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**:2466–2473.
12. Zogg CK, Avesta A, Bonde PN, Mani A. Echocardiography fails to detect an extensive aortic root abscess in a patient with infective endocarditis: a case report. *Eur Heart J Case Rep* 2021;ytac032. https://doi.org/10.1093/ehjcr/ytac032.
13. Bruun NE, Habib G, Thuny F, Sogaard P. Cardiac imaging in infectious endocarditis. *Eur Heart J* 2014;**35**:624–632.
14. Ye W, Ren G, Zhong X, Jian X, Chen O, Ma Q et al. ECG-gated CT in Aortic perivalvular abscess: comparison with transesophageal echocardiography and intraoperative findings. *Radiology* 2020;**297**:334–341.
15. Chen W, Sajadi MM, Dilsizian V. Merits of FDG PET/CT and functional molecular imaging over anatomic imaging with echocardiography and CT angiography for the diagnosis of cardiac device infections. *JACC Cardiovasc Imaging* 2018;**11**:1679–1691.
16. Cahill TJ, Baddour LM, Habib G, Hoen B, Salaun E, Pettersson GB et al. Challenges in infective endocarditis. *J Am Coll Cardiol* 2017;**69**:325–344.