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Authors: Gonzalo Cabezón Villalba, Javier López, Pablo Elpidio Garcia-Granja, Teresa Sevilla, Ana Revilla, Maria de Miguel, Paloma Pulido, Itziar Gómez, J. Alberto San Román

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Measurement of vegetations in infective endocarditis: An inaccurate method to decide the therapeutical approach

Gonzalo Cabezón Villalba et al., Interobserver variability of vegetation size

Gonzalo Cabezón Villalba, Javier López, Pablo Elpidio Garcia-Granja, Teresa Sevilla, Ana Revilla, María de Miguel, Paloma Pulido, Itziar Gómez, J. Alberto San Román

Instituto de Ciencias del Corazón (ICICOR), Hospital Clínico Universitario de Valladolid, Ciber de Enfermedades Cardiovasculares (CIBERCV), Valladolid, Spain

Address for correspondence: Gonzalo Cabezón Villalba, MD, Instituto de Ciencias del Corazón (ICICOR), Hospital Clínico Universitario Valladolid, Valladolid, Spain, tel: 34 983 420000, fax: 34 983 255305, e-mail: gonzavilla10@hotmail.com

ABSTRACT

Background: The European Society of Cardiology and American Heart Association guidelines give a central role to the maximal vegetation diameter in the indication for surgery to prevent embolism in left sided infective endocarditis (LSIE). Vegetation measuring is likely to be inaccurate. The hypothesis herein, is that the vegetation diameter is not an appropriate surgical criterion given the variability of its measurement.

Methods: Two trained echocardiographers independently measured the maximal vegetation diameter by transesophageal echocardiogram of 76 vegetations in 67 consecutive patients with definite infective endocarditis in an off-line workstation. The interobserver variability was calculated by the interclass correlation coefficient. The relationship between the strength of agreement for the cut-off points of 10 and 15 mm was also calculated. Finally, the number of patients whose surgical indication would have changed depending on which operator measured the vegetation was evaluated.

Results: Interobserver interclass correlation coefficient in the measurement of the maximal longitudinal diameter of the vegetations was 0.757 (0.642–0.839). The strength of agreement of the interobserver analysis for the cut-off point of 10 mm was 0.533 (0.327–0.759). For the cut-off point of 15 mm it was 0.475 (0.270–0.679). If heart failure or uncontrolled infections had been absent, the surgical indication would have changed in a total of 33 patients (33/76; 43%) depending on which operator measured the vegetation.

Conclusions: The variability in the measurements of the maximal longitudinal diameter by transesophageal echocardiogram is high. Surgical indications based on the cut-off points recommended by the international guidelines should be revised.

Key words: endocarditis, vegetation size, interobserver variability, surgery, embolism prevention

INTRODUCTION

The European and American guidelines of infective endocarditis indicate surgery in left-sided infective endocarditis (LSIE) in three clinical scenarios: heart failure, uncontrolled infection and prevention of embolic events [1, 2]. While there is wide consensus in operating on patients presenting heart failure or uncontrolled infection, the evidence supporting surgery to prevent embolic events is weaker. Vegetation maximal diameter is considered a key parameter to indicate surgery. However, restricting the prediction of embolic risk in LSIE to maximal vegetation diameter and previous embolism is controversial as many other parameters are related to embolic events. Time of initiation for antibiotic therapy [3], mitral or aortic localization, atrial fibrillation, diabetes mellitus, vegetation-related characteristics as area, morphology or mobility are variables described to be associated with an embolic event [4, 5]. Importantly, *S. aureus* as causative microorganism is closely related to systemic embolism, ranging between 12 to 35% depending on the series studied [6]. Moreover, methodological caveats may be encountered when measuring a vegetation, due to its high mobility, absence of good acoustic window and operator experience. As the vegetation size has a central role in the indication of surgery in LSIE it should be a reproducible parameter. The aim of the present study is to evaluate the interobserver variability in the measurement of longitudinal diameter of vegetations in LSIE and to analyze its impact on the indication of surgery if the diameter thresholds of the guidelines are considered.

METHODS

67 transesophageal echocardiogram studies were recorded in patients consecutively diagnosed of definite LSIE in a single tertiary center according to the modified Duke criteria [7]. Two experimented echocardiographers (T.S. and A.R.), who

own the certification in echocardiography of Spanish National Society of Cardiology and had been working for more than 15 years in a tertiary hospital with at least 30 episodes of infective endocarditis per year, measured the longitudinal diameter of 76 vegetations in the workstation of the documented central image-processing unit using the Echo Pac 3.1.0 software package. Vegetation was defined as anomalous oscillating or not oscillating intracardiac mass on valve or other endocardial structure or on implanted intracardiac material [1]. Standard transesophageal echocardiogram (TEE) images (4-chamber, bi-commissural, 2-chamber, long axis and short axis at aortic level) and atypical views in which the vegetation was best visualized and expanded were obtained at the discretion of the operator recording the images. The two operators measured the vegetations using the same views. Vegetation size was measured using its maximal length diameter, as recommended by the guidelines of clinical practice. Two-dimensional TEE was performed in all cases to visualize vegetations. Different frames at the points of the cardiac cycle in which the vegetation was clearly defined were selected. The measure of maximal diameter was made in, at least, two orthogonal views. Maximal diameter was defined as the maximum length obtained in any of the views. As the vegetation measurement in the presence of a prosthesis can be challenging, we excluded patients with mechanical or biological prosthesis from the population study.

To assess the impact of the interobserver variability of vegetation measurement on the indication of surgery, two categorical classifications of vegetations according the American and European guidelines were considered, respectively: ≤ 10 mm and > 10 mm; ≤ 15 mm and > 15 mm.

Written informed consent was obtained from all participating patients before the echocardiograms were performed under an approved protocol, as required by the committee of our institution. Only those patients fulfilling the modified Duke criteria for definite IE were included in the analysis. Right-sided IE, prosthetic IE, device-related IE and free-vegetation episodes were exclusion criteria.

Ethical approval

Informed consent was obtained from all individual participants included in the study. Local ethics committee approved the data collection of the study and have therefore been performed in accordance with the ethical standards of Helsinki Declaration.

Statistical analysis

Categorical variables are reported as frequency (n) and percentages and continuous variables as mean value and standard deviation. To evaluate interobserver variability, absolute and relative differences from the mean of the measurements were calculated. Then, the intraclass correlation coefficient and its 95% confidence interval to determine the variability of the measurements were calculated. Bland-Altman analysis was also used for evaluating interobserver variability.

To analyze the interobserver concordance in the surgical indications, the longitudinal diameter considering the cut-off points of the guidelines were categorized (10 and 15 mm) and the Kappa index and its 95% confidence interval in each of the situations were calculated. Data were analyzed using the IBM SPSS Statistics for Windows, Version 25 (IBM, Armonk, New York) and R software, version 3.6.1 (R Project for Statistical Computing).

RESULTS

Baseline characteristics of the 67 patients with definite LSIE included in the study are presented in Table 1. It represents a typical population of a tertiary center, predominantly male with frequent comorbidities and *Staphycolococci* spp. as the most frequent microorganisms. Despite the wide use of cardiac surgery (58%), complications during hospitalization and in-hospital mortality were high.

The absolute and relative differences (3.3 ± 2.9 mm and 23.2 ± 20%) and the interclass correlation coefficient found in the measurements of the maximal diameter of the vegetations are summarized in Table 2. The Bland-Altman plot evaluating the interobserver variability is shown in Figure 1.

Disagreement between operators (Table 3) were estimated by the Kappa coefficient and the observed concordance. When the cut-off point of 10 mm was considered, disagreement between the experts was found in 18% of cases (14/76). With a cut-off of 15 mm, disagreement was found in 25% of cases (19/76).

DISCUSSION

In LSIE patients, the benefit of surgery is well established when heart failure or uncontrolled infection are present. In the absence of these complications, surgery indication is a matter of debate [8, 9], but is recommended if the vegetation is larger than 15 mm or 10 mm by the current European and American guidelines, respectively

[1, 2]. The current study shows that the interobserver variability of the length of a vegetation is high enough to affect the surgical indication in an unacceptable proportion of patients and should be taken with caution in establishing a surgical indication.

Since the seminal paper published by Mugge [10] supporting the concept that the larger the vegetation the higher the probability of developing embolism, guidelines recommend surgery to prevent embolisms if the size of a vegetation exceeds specific cut-off points.

Assessment of interobserver variability is an integral part of any research aiming at finding links between parameters measured by different methods and clinical events. However, only one of the studies referenced in the European Society of Cardiology guidelines in the recommendations for surgery to prevent embolic events [4, 11–14] reported interobserver variability. Thuni et al. [13] obtained a k value of 0.8. However, they neither specify their cut-off points used for calculating this k value nor provide the confidence interval needed to determine the accuracy of this calculation. Moreover, one of the studies did not even perform TEE in the first 11 years of the study and only in some cases thereafter [14]. When subtle differences in the measuring of a vegetation affect the therapeutic strategy, it is mandatory to be aware of the variability of this measurement.

The variability of the vegetation maximal diameter obtained in the present study is explained by the fact that it is a hard task to decide what the maximal diameter of a very mobile irregular mass is, and which frame should be used. Moreover, the low echodensity showed by some vegetations make it difficult to put the pointer exactly at the distal edge of the vegetation. Likewise, the boundary separating the vegetation from the endocardial surface of the affected valve cannot be accurately identified in many cases. Furthermore, some patients have more than one vegetation, and some of these vegetations are quite similar in length. Which should be considered the largest is subject to error. At this point, it is worth underscoring that the current study investigated the variability obtained in an off-line analysis. Probably, if we have not compared an off-line analysis but an on-line analysis, which is much closer to the routine practice, interobserver variability would have been much higher.

As it is shown in the results section (Table 3), the interobserver variability of vegetation size is high enough to have an impact in the decision of performing surgery. To overcome this fact, it was believed that the vegetation size cannot be regarded as the sole parameter to estimate the embolic risk in LSIE. In this regard, the present study considered that predicting embolic events in LSIE is an issue that requires a multiparametric approach, including clinical, echocardiographic and microbiological variables. It has been clearly stated that the best strategy to prevent embolisms is to initiate adequate antibiotic treatment as soon as possible [3]. Besides, not only the maximal diameter but also other morphologic characteristics of the vegetation impact on the incidence of embolism. The attachment width to the endocardial surface (pedunculated, sessile), the mobility [15], the shape (thin, thick, cauliflower-like octopus-like, regular shape) and consistency defined by echodensity are parameters that may affect the embolic risk. Moreover, it is known that the location of the vegetation plays a role in the probability of embolism, being mitral localization more prone to embolism than aortic [4]. Furthermore, particular organisms [5, 6], especially *S. aureus* with incidence of embolisms ranging between 12 and 35% depending on the series, biological markers [16] and previous embolisms [13] have been found to be associated to embolisms. Some authors reported on a calculator to evaluate the embolic risk in LSIE [11], which brings to light the need of a multiparametric assessment.

Surgical indications aimed to prevent embolisms are somewhat different between the American and the European guidelines, reflecting the lack of agreement in this issue [1, 2]. It is believed herein, that a single variable, vegetation maximal diameter, cannot determine whether a patient should go to surgery due to an inaccurate prediction of embolic events and the interobserver variability of its measure.

Limitations of the study

There are some limitations of this study. This is a single centre study. To really determine the variability of a continuous variable as the maximal diameter of a vegetation, a multicentre study with a central core-lab would be needed. However, in real life, images are not sent to a central core-lab. In fact, this method was not used to decide the cut-off thresholds of vegetation size accepted by the guidelines. As aforementioned, the variability was calculated by using off-line images in the same frame. This is not a routine scenario, in which the operators may choose different frames of different views. Taking this into account, the real variability would be even higher than that reported. We have not used 3-dimensional TEE, which theoretically might decrease variability. Whether 3-dimensional imaging improves accuracy and decreases variability should be assessed and, in that case, new recommendations would help in the decision-making process. Finally, the present message can be deemed as useless given that it is uncommon in clinical practice to send a patient to surgery based only on the vegetation size (6% in the Euro Heart Survey) [17]. suggesting that clinicians cast doubt on this indication. The current results add new evidence that support that behaviour.

CONCLUSIONS

Variability in the echocardiographic measurements of the vegetation leads to a change in the surgical indication in a high proportion of patients when the indication of surgery is based only on the vegetation size. The indication of surgery based only on the size of a vegetation should be called into question.

Conflict of interest: None declared

References

1. Habib G, Lancellotti P, Antunes MJ, 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; 21: 3075–3128, doi: 10.1093/eurheartj/ehv319, indexed in Pubmed: 26320109.

2. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2021; 143(5): e35–e71, doi: 10.1161/CIR.0000000000000932, indexed in Pubmed: 33332149.

3. Dickerman SA, Abrutyn E, Barsic B, et al. ICE Investigators. 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(6): 1086–1094, doi: 10.1016/j.ahj.2007.07.023, indexed in Pubmed: 18035080.

4. Vilacosta I, Graupner C, San Román JA, et al. Risk of embolization after institution of antibiotic therapy for infective endocarditis. J Am Coll Cardiol. 2002; 39(9): 1489–1495, doi: 10.1016/s0735-1097(02)01790-4, indexed in Pubmed: 11985912.

5. Yang A, Tan C, Daneman N, et al. Clinical and echocardiographic predictors of embolism in infective endocarditis: systematic review and meta-analysis. Clin Microbiol Infect. 2019; 25(2): 178–187, doi: 10.1016/j.cmi.2018.08.010, indexed in Pubmed: 30145401.

6. Asgeirsson H, Thalme A, Weiland O. Staphylococcus aureus bacteraemia and endocarditis — epidemiology and outcome: a review. Infect Dis (Lond). 2018; 50(3): 175–192, doi: 10.1080/23744235.2017.1392039, indexed in Pubmed: 29105519.

7. Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis. 2000; 30(4): 633–638, doi: 10.1086/313753, indexed in Pubmed: 10770721.

8. Fosbøl EL, Park LP, Chu VH, et al. The association between vegetation size and surgical treatment on 6-month mortality in left-sided infective endocarditis. Eur Heart J. 2019; 40(27): 2243–2251, doi: 10.1093/eurheartj/ehz204, indexed in Pubmed: 30977784.

9. Cabezón G, López J, Vilacosta I, et al. Reassessment of vegetation size as a sole indication for surgery in left-sided infective endocarditis. J Am Soc Echocardiogr. 2022; 35(6): 570–575, doi: 10.1016/j.echo.2021.12.013, indexed in Pubmed: 34971762.

10. Mügge A, Daniel WG. Echocardiographic assessment of vegetations in patients with infective endocarditis: prognostic implications. Echocardiography. 1995; 12(6): 651–661, doi: 10.1111/j.1540-8175.1995.tb00858.x, indexed in Pubmed: 10158102.

11. Hubert S, Thuny F, Resseguier N, et al. Prediction of symptomatic embolism in infective endocarditis. J Am Coll Cardiol. 2013; 62(15): 1384–1392, doi: 10.1016/j.jacc.2013.07.029.

12. Kang DH, Kim YJ, Kim SH, et al. Early surgery versus conventional treatment for infective endocarditis. N Engl J Med. 2012; 366(26): 2466–2473, doi: 10.1056/nejmoa1112843.

13. Thuny F, Di Salvo G, Belliard O, et al. Risk of embolism and death in infective endocarditis: prognostic value of echocardiography: a prospective multicenter study. Circulation. 2005; 112(1): 69–75, doi: 10.1161/CIRCULATIONAHA.104.493155, indexed in Pubmed: 15983252.

14. García-Cabrera E, Fernández-Hidalgo N, Almirante B, et al. Neurological complications of infective endocarditis: risk factors, outcome, and impact of cardiac surgery: a multicenter observational study. Circulation. 2013; 127(23): 2272–2284, doi: 10.1161/CIRCULATIONAHA.112.000813, indexed in Pubmed: 23648777.

15. Rohmann S, Erbel R, Görge G, et al. Clinical relevance of vegetation localization by transoesophageal echocardiography in infective endocarditis. Eur Heart J. 1992; 13(4): 446–452, doi: 10.1093/oxfordjournals.eurheartj.a060195, indexed in Pubmed: 1600980.

16. Durante Mangoni E, Adinolfi LE, Tripodi MF, et al. Risk factors for "major" embolic events in hospitalized patients with infective endocarditis. Am Heart J.

2003; 146(2): 311–316, doi: 10.1016/S0002-8703(02)94802-7, indexed in Pubmed: 12891201.

17. Tornos P, Iung B, Permanyer-Miralda G, et al. Infective endocarditis in Europe: lessons from the Euro heart survey. Heart. 2005; 91(5): 571–575, doi: 10.1136/hrt.2003.032128, indexed in Pubmed: 15831635.

Table 1. Main characteristics of the patients included in the study (n = 67).

Age, mean ± standard deviation	66 ± 11
Male	52 (78%)
Diabetes mellitus	16 (24%)
Cancer	9 (13%)
Nosocomial	16 (24%)
Staphylococcus aureus	14 (21%)
Coagulase negative *Staphylococci*	4 (6%)
Viridans streptococci	11 (16%)
Enterococci	13 (19%)
Negative cultures	5 (7%)
Mitral	30 (45%)
Aortic	22 (33%)
Multivalvular	8 (12%)
Heart failure	46 (69%)
Renal failure	28 (42%)
Septic shock	16 (24%)
Stroke	14 (21%)
Peripheral embolism	17 (25%)
Surgery	39 (58%)
In-hospital mortality	26 (39%)

Table 2. Interobserver absolute and relative differences.

	Absolute	**Relative**
Longitudinal diameter	3.3 ± 2.9 mm	23.2 ± 20%
Interclass correlation coefficient	0.757 (0.642–0.839)	

Table 3. Strength of agreement of the interobserver analysis for the cut-off points of 10 and 15 mm.

Vegetation threshold	**Inter-observer Kappa**	**Patients whose surgical indication changed**
> 10 mm	0.533 (0.327–0.759)	14/76 (18%)
> 15 mm	0.475 (0.270–0.679)	19/76 (25%)

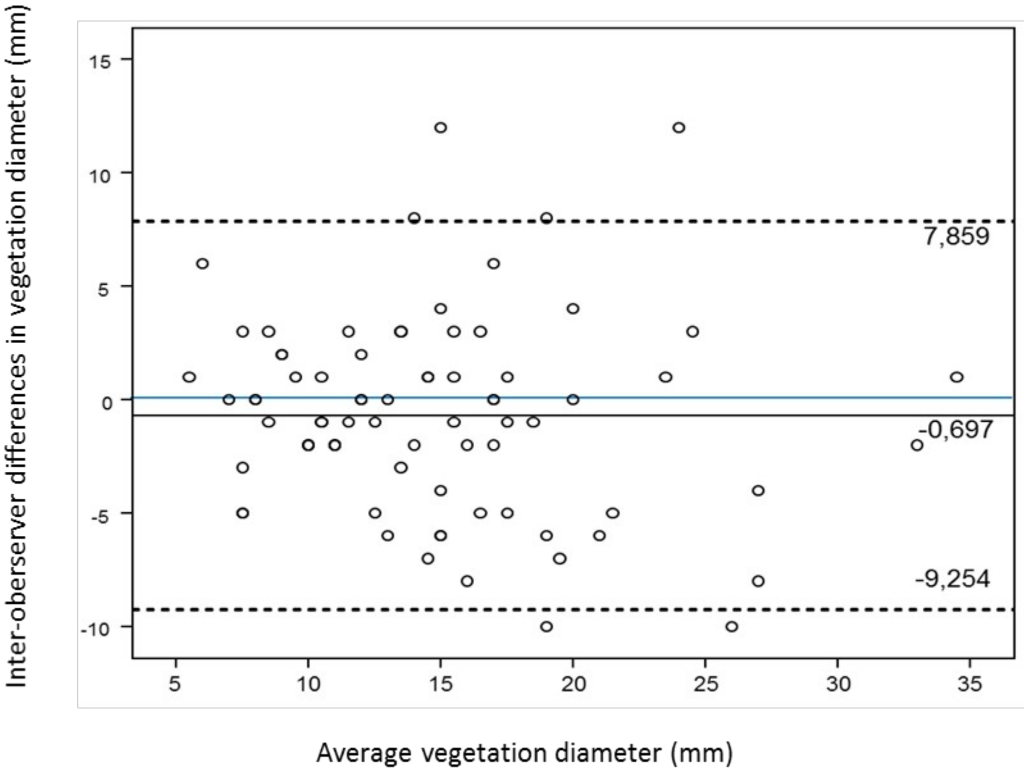

Figure 1. Blant-Almant plots evaluating inter-observer variability.