Right-sided infective endocarditis and pulmonary embolism: a multicenter study

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Abstract

The incidence of right-sided infective endocarditis (RSIE) is steadily increasing and it has been reported to be associated with high risk of embolic events (EE). The aim of our study was to identify the clinical characteristics of patients with RSIE complicated by PE. Indeed, the identification of patients at high risk of significant PE who will benefit from a more aggressive therapeutic strategy may improve the prognosis. From January 2015 to September 2020, 176 patients (pts) in 6 centers were found to have definite RSIE complicated by PE. Advanced imaging for PE including computed tomography pulmonary angiography (CTPA) was performed in 28 pts (16%) who represent our study group (24 male, mean age 50.6±18.29 years). They all underwent transesophageal echocardiography (TEE), in 12 cases (43%) also three-dimensional (3D) TEE, and 27 patients (99%) had both TEE and transthoracic echocardiography (TTE). A total of 53 vegetations (V) were detected. In 18 pts (64%) two or more vegetations were found. Native tricuspid valve was the most frequently involved valve (38 V, 71.7%), followed by catheter (5 V, 9.4%), tricuspid valve prosthesis (4 V, 7.5%), chordae and papillary muscle (2 V, 3.8%) and one vegetation (9%) in each of the following: pulmonic valve, inferior vena cava, eustachian valve, and right atrium. The most common location for vegetations was the anterior leaflet of the tricuspid valve (19 V, 35.8 %) followed by the posterior leaflet (11 V, 20.8%). The most common vegetations morphology was raceme-like shaped (35.8%). *Staphylococcus aureus* was the most common causative pathogen (14 pts, 50%). The incidence of PE was very high in patients with vegetation length above 1.5 cm (median 17.6±6.5 mm by TEE). Our results suggest that a routine CTPA should be advised in the presence of vegetations larger than 1.5 cm and with *S. aureus* infection. This behavior would identify patients at high risk of PE who will benefit from a more aggressive therapeutic strategy, leading to an improvement in the prognosis. Further prospective studies are required to better confirm our hypothesis.

Introduction

Embolic events (EE) are a frequent and life-threatening complication of infective endocarditis (IE) [1-6]. Compared with the extensive data on left-sided infective endocarditis (LSIE), there is lack of knowledge about the features and management of right-sided infective endocarditis (RSIE) [7]. This is due to the high compliance of the pulmonary vasculature to minor EE, the lower mortality and morbidity of pulmonary embolism (PE) and to the relatively low prevalence of the right-sided infective endocarditis. Recently, EUROENDO registry showed that EE were significantly associated with tricuspid or pulmonary IE [4]. Furthermore, the incidence of RSIE is steadily increasing and it has been reported to be associated with the highest risk of embolism [4]. However, the identification of patient's characteristics at high risk of pulmonary embolism (PE), who will benefit from a more aggressive therapeutic strategy and improve the prognosis [4,5,7], is not well established. Indeed, the current guidelines [1,2], gives no clear indications when performing advanced imaging to rule out PE in RSIE [1,2,3]. This is probably due to a lower prevalence of RSIE and a lower mortality and morbidity of PE when compared to systemic embolism [1,3,4,7,8]. In the clinical practice, the imaging for PE is currently done only in case of high clinical suspicion of PE, therefore in this clinical arena many challenging dilemmas exist. Aim of our study was to identify the clinical echocardiographic and microbiological features of patients with RSIE complicated by severe PE.

Methods

This is an observational and retrospective study. From January 2015 to September 2020, 176 patients (pts) in 6 centers were found to have definite RSIE complicated by significant PE. Advanced imaging for PE including computed tomography pulmonary angiography (CTPA) was performed in 28 pts (16%) who represent our study group (24 male, mean age 50.6±18.29 years) (Table 1). Of these, 27 patients (99%) underwent transthoracic echocardiography (TTE), 28 (100%) transesophageal (TEE), of which 12 (43%) had also three-dimensional (3D) TEE. Clinical, laboratory, echocardiography, and chest computed tomography (CT) scans were systematically reviewed in the final cohort.

The study was approved by the Institutional Research Committees (KFSH Research Ethics Committee approval number project RAC#2201215) and a waiver for informed consent was obtained.

Echocardiography

A comprehensive two-dimensional (2D) transthoracic and transesophageal echocardiography with a main focus in the tricuspid (TV) and pulmonic (PV) valves and the right ventricle was performed [9,10] using commercially available ultrasound system (iE33, EPIC 7 and CVX Philips, Andover, MA, USA, and Vivid E90 and E95, General Electrics, USA). The severity of tricuspid regurgitation was assessed as mild, moderate or severe according to ASE recommendations [11]. The right ventricle (RV) was also imaged from multiple views, including the RV-focused and RV-modified apical four-chamber views. 2D RV size and function were measured according to the American Society of Echocardiography recommendations (Figure 1).

Vegetations

Vegetation was defined as a fixed or oscillating mass adherent to a leaflet or other cardiac structure with a distinct echogenic structure and independent motion. The lesion had to be visible in multiple views and detectable during the complete cycle. Vegetation assessment was performed by selecting the frame in which the vegetation was optimally visible. The measurements of vegetations were obtained in various planes, and the maximal length was used. In the presence of multiple vegetations, the largest value was used for analysis [5]. The 2D TTE and TEE measurement of maximal length of vegetation (MLV) was obtained from standard planes and their modified views to select the largest value for each patient as previously described [12]. The sizing of the vegetation by 3D was obtained by cropping the volume of the vegetation with the best 2D plane to obtain the largest measurement. In the presence of multiple vegetations, the vegetation with the largest size was selected [13].

The vegetations with a minor diameter/major diameter ratio ≤0.5 were considered to be filiform or tubular. Among those with a wide implantation base (ratio >0.5), were distinguish between sessile and raceme-like shaped vegetation. This last subtype includes usually larger and more heterogeneous vegetation with multiple evaginations over its surface (Figure 1) [5,13,14].

The mobility of vegetation was be categorized in 4 grades, according to Sanfilippo's scale [5,14] as follows: Grade 1 (absent): fixed with no detectable independent motion; Grade 2 (low): fixed base with mobile free edge; Grade 3 (moderate): pedunculated vegetation that remains within the same chamber throughout the cardiac cycle; Grade 4 (severe): prolapsing vegetations that cross the leaflet coaptation plane.

Table 1. Utilization of imaging for PE RSIE.

Center (n=6)	Total (n=176)	Imaging PE (n=28) (16 %)
1	61	11 (18%)
2	35	5 (14%)
3	60	8 (13%)
4	14	3 (21%)
5	5	1 (2%)
6	3	0 (0%)

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Numbers, location and attachment of vegetations and the presence of left side vegetations were also reported.

Pulmonary embolism diagnosis

Specific diagnosis of PE was based on computed tomographic pulmonary angiography. When available, data from planar ventilation/perfusion V/Q (lung scintigraphy) were retrieved.

Definition of significant PE by cardiac CT includes the following:

i) Arterial occlusion with failure to enhance the entire lumen due to a large filling defect.
ii) The artery may be enlarged compared with adjacent patent vessels.
iii) A partial filling defect surrounded by contrast material.
iv) Peripheral wedge-shaped areas of hyper attenuation that may represent infarcts.

Statistical analysis

Categorical variables will be represented as frequency and percentage, and continuous variables as mean value and standard deviation (SD). Discrete variables were be compared with a chi-square test. All tests were two-sided, and differences will be considered statistically significant at p-values <0.05. Statistical analysis was performed with SPSS package.

Results

General characteristics of the final cohort examined in the study are presented in Table 2.

Echocardiographic features

All patients with PE had vegetation size more than 1 cm. The echocardiographic features of the population are reported in Table 3. Fifty-three vegetations were detected, they were multiple in the 64% of the cases, located mainly on the anterior TV leaflet, more frequently with filiform or raceme shaped and mobile. In a low percentage they were complicated with perforation and abscess and associated with left sided vegetations (Table 3). Severe tricuspid regurgitation was found in 7 patients (25%). The echocardio-

Table 2. General data.

	Total pts (n=28)
Mean age	50.60 SD 18.29 range 16-90 yrs
Male-female	24 (85.7%) / 4 (14.3%)
IDA	6 (21.4%)
Catheter-PM wire	5 (17.9%)
Surgery	9 (32.1%)
Pulmonary embolism	27 (96%)
Vegetation size ≥1.5 cm	27 (96%)

IDA, intravenous drug abusers; PM, papillary muscle.

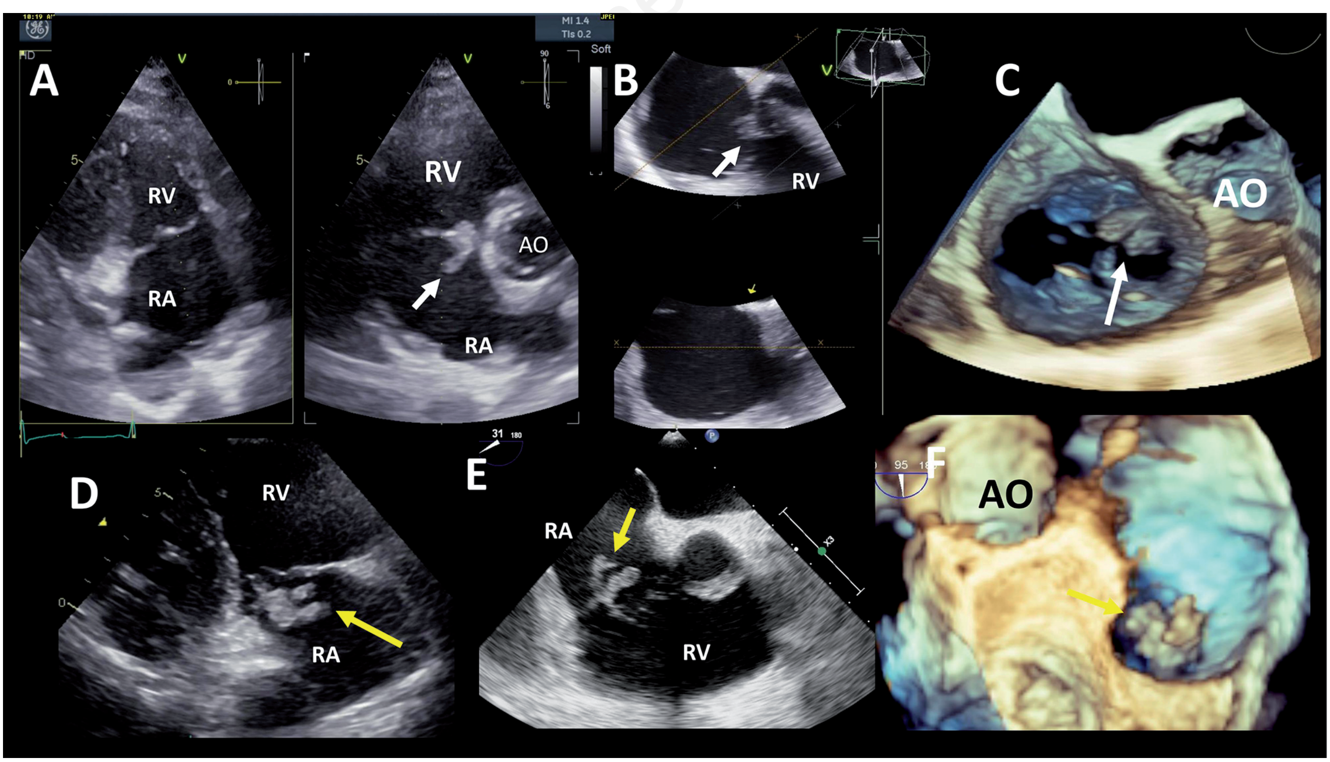

Figure 1. A-C) Tubular vegetation septal TV leaflet (white arrow); A) TTE RV long axis; B) 2DTEE cross sectional planes; C) 3D TEE RA view from above. D-F) Raceme vegetation of posterior TV leaflet; D) TTE RV long axis; B) 2DTEE; C) 3D TEE RA view from above. RV, right ventricle; RA, right atrium valve; TV, tricuspid valve; AO, aorta.

Table 3. Echocardiographic features.

Number of vegetations (n=53)	
Location of infection	
TV native	38 (71.7%)
TV and catheter-PM wire	5 (9.4%)
TV and chordae-PM	2 (3.8)
TV and RA	1 (1.9%)
TV and PV	1 (1.9%)
TV and IVC	1 (1.9%)
TV prosthesis	4 (7.5%)
TV and eustachian	1 (1.9%)
TV bioprosthesis	2 (3.8%)
Single vegetation	10 (35.7%)
Multiple vegetations	18 (64.3)
Leaflet	
Anterior	19 (35.8%)
Posterior	11 (20.8%)
Septal	13 (24.5%)
Morphology	
Filiform or tubular	16 (30.2%)
Sessile	18 (34%)
Raceme	19(35.8%)
Mobility	
Grade 1	11 (20.8%)
Grade 2	37 (69.8%)
Grade 4	5 (9.4%)
Complications	
Perforation	3 (10.7%)
Abscess	1 (3.6%)
Left sided vegetations	4 (14.3%)
Regurgitation	
Mild	11 (39.2%)
Moderate	10 (35.7%)
Severe	7 (25%)

TV, tricuspid valve; PM, papillary muscle; RA, right atrium; PV, pulmonic valve; IVC, inferior vena cava.

graphic measurement of the vegetations size by the different echocardiographic techniques are reported in Table 4. The TEE 3D was the technique able to achieve the maximal vegetation length.

Microbiological profile

The microbiological profile of the study group is described in Table 5. The *S. aureus* was the most frequent bacterium (50%), while the others were detected in a lower percentage. In addition, it was the most frequent causative bacterium in patients who underwent surgery

Discussion

In the EURO-ENDO registry [4], embolic events were the most frequent complications, being observed in 20.6% of patients, and they were significantly associated with tricuspid or pulmonary IE, presence of a vegetation and *S. aureus* IE.

It was also reported that multislice CT was performed in 53.1% of the patients associated with cardiac CT in 9.6% of the patients. In our study group the utilization of CT in order to detect PE was 16% so far less when compared to EURO-ENDO registry results even when we exclude the patient that have performed this technique for cardiac reason.

In our study, 96% of patients with PE had a vegetation size higher than 1.5 cm demonstrating a strong association with incidence of PE. Fifty percent of patients with *S. aureus* infection also had PE. Similar incidence of leaflets involvement (even though the higher on the anterior) and V morphology was also detected. Our results emphasize the need of utilization of CTPA in relation to vegetation size and causative pathogen, likewise left sided vegetations.

Table 4. Echocardiographic measurements.

	TTE max	TTE min	TEE max	TEE min	TEE 3D max	TEE 3D min
Number of patients	27	21	20	17	12	11
Mean	15.08	10.09	17.61	9.94	23.83	14.27
SD	9.47	7.03	6.46	5.04	8.84	7.93

TTE, transthoracic echocardiography.

Table 5. Microbiological profile of the study population.

	Total (n=28)	Pulmonary embolism (n=28)	No pulmonary embolism (n=1)	p-value
Staphylococcus aureus	14 (50%)	14 (50%)	0 (0%)	<0.001
Staphylococcus epidermis	2 (7.1%)	2 (7.4%)	0 (0%)	ns
Pseudomonas aeruginosa	2 (7.1%)	2 (7.4%)	0 (0%)	ns
Campylobacter	1 (3.6%)	1 (3.7%)	0 (0%)	ns
Lactobacillus species	1 (3.6%)	1 (3.7%)	0 (0%)	ns
Candida parapsilosis	1 (3.6%)	1 (3.7%)	0 (0%)	ns
Candida albicans	1 (3.6%)	1 (3.7%)	0 (0%)	ns
Streptococcus	1 (3.6%)	1 (3.7%)	0 (0%)	ns
Klebsiella pneumoniae	1 (3.6%)	1 (3.7%)	0 (0%)	ns
Negative	4 (14.3%)	4 (14.8%)	0 (0%)	ns

ns, not significant.

Previous studies dealing with vegetations sizing and embolism suggested that 3DTEE may help in better sizing the right sided vegetations and therefore to predict embolic events [6,15,16]. This study reported on data collected by previously commercially available machines that had a significantly lower frame rate and spatial resolution than the most recent ones [16-18]. The most recent commercially available releases have significantly increased temporal and spatial resolution compared to previous releases, closing the gap with two-dimensional imaging [9,16]. Indeed, in the current imaging scenario, the 3DTEE has a higher potential for sizing the V than previous studies.

The study had two limitations: i) it was a retrospective study; and ii) we only included patients who underwent CTPA.

Conclusions

Our findings suggest that routine CTPA should be recommended in the presence of vegetations larger than 1.5 cm in diameter and *S. aureus* infection. This behavior would identify patients who are at high risk of PE and would benefit from a more aggressive therapeutic strategy, resulting in a better prognosis. More prospective studies are needed to confirm our hypothesis.

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