Evaluation with contrast ultrasound of the prevalence of splenic infarction in left-sided infective endocarditis

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Abstract

Purpose To prospectively evaluate the prevalence of the embolization of the spleen in patients with definite left-sided infective endocarditis (IE) using a contrast-enhanced ultrasound (CEUS).

Methods From March 2012 through September 2013, 18 consecutive patients (9 females and 9 males, aged 21–83 years) evaluated at our hospital and with definite left-sided IE according to the revised Duke criteria were enrolled. All of the patients gave informed written consent and the study was performed in conformity with the ethical guidelines of the Declaration of Helsinki. All of the patients were submitted to a CEUS of the spleen within 10 days after the definite diagnosis of IE. For the CEUS, a blood pool second-generation contrast agent and an

ultrasound machine with a contrast harmonic imaging technology were used.

Results The splenic CEUS showed infarctions in 11 patients (61 %) and resulted positive in the 2 patients with negative echocardiography.

Conclusions In this study, CEUS of the spleen, a repeatable and low-cost imaging technique, easily allowed the bedside detection of asymptomatic and even tiny infarctions and showed a high rate of embolization in patients with definite left-sided IE. Therefore, in the setting of IE (possible or definite), CEUS of the spleen has the potential to better define or accelerate the diagnosis itself.

Keywords Spleen · Endocarditis · Ultrasound · Contrast · Embolization

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Riassunto

Scopo valutare prospetticamente la prevalenza di embolizzazione splenica in pazienti con endocardite infettiva (EI) certa del cuore sinistro con l'utilizzo dell'ecografia con mezzo di contrasto (CEUS).

Metodi lo studio è stato effettuato presso il nostro Ospedale dal marzo 2012 al settembre 2013; sono stati arruolati 18 pazienti consecutivi (9 femmine e 9 maschi, con età compresa tra 21 e 83 anni) con diagnosi di EI certa del cuore sinistro secondo i criteri Duke rivisti. Tutti i pazienti hanno dato il loro consenso informato scritto e lo studio è stato condotto in conformità con le linee guida etiche della Dichiarazione di Helsinki. Tutti i pazienti sono stati sottoposti ad una CEUS della milza entro 10 giorni dalla diagnosi di EI certa del cuore sinistro. Per la CEUS è stato utilizzato un mezzo di contrasto di seconda generazione ed un ecografo dotato di imaging armonico.

Risultati la CEUS ha mostrato la presenza di infarto della milza in 11 pazienti (61%) ed è risultata positiva nei 2 pazienti con indagine ecocardiografica negativa.

Conclusioni in questo studio la CEUS della milza, una tecnica di imaging ripetibile e a basso costo, ha permesso facilmente la identificazione al letto del paziente di infarti asintomatici, anche di piccole dimensioni; ha dimostrato che nei pazienti con EI del cuore sinistro c'è una elevata frequenza di embolizzazione splenica. Pertanto, nel contesto di EI del cuore sinistro (possibile o certa), la CEUS della milza ha la potenzialità di accelerare o meglio definire la diagnosi stessa.

Introduction

Postmortem [1] and computed tomography [2–4] studies demonstrated a high asymptomatic splenic embolization rate (up to 40 %) in patients with infective endocarditis (IE). Indeed, vascular phenomena are considered in the revised Duke criteria for the diagnosis of IE [5, 6], and furthermore splenic infarctions should be persistently sought since they represent either a complication or an important diagnostic clue. Since splenic infarctions are often asymptomatic and gray-scale sonography of the spleen is not sensitive enough to detect them [7], clinicians must apply to heavy techniques such as computed tomography or magnetic resonance for the evaluation of splenic vascular defects. Contrast-enhanced ultrasound (CEUS) is considered as accurate as computed tomography for the detection of vascular defects of the spleen [8] and this technique is easily applicable to patients even at the bedside. Furthermore, the spleen is almost always visualized at

ultrasonography, making CEUS applicable to virtually all patients. In this study, we prospectively evaluated the prevalence of embolization of the spleen in 18 consecutive patients with definite left-sided IE using CEUS, six of which constituted a previously published series [7].

Materials and methods

From March 2012 through September 2013, 18 consecutive patients (9 females and 9 males, aged 21–83 years) admitted to our hospital and diagnosed with left-sided IE were recruited for the study. All of the patients gave informed written consent and the study was performed in conformity with the ethical guidelines of the Declaration of Helsinki. The definite diagnosis of IE was established on the basis of the revised Duke criteria [5, 6] and was the lonely inclusion criterion. Exclusion criteria included age below 18, previous splenectomy, previous or ongoing pancreatic diseases (specifically acute or chronic pancreatitis and tumors), previous or ongoing portal vein thrombosis, sickle cell disease, and pregnancy. In all patients, blood cultures were obtained prior to antibiotic therapy. At least three blood cultures were obtained in all patients, each set from separate venipuncture sites. The blood cultures were submitted for aerobic and anaerobic organisms. All of the patients were submitted to a transthoracic echocardiography (TTE); 15 patients subsequently underwent a transesophageal echocardiography (ETE). Echocardiograms were performed by our hospital cardiologists who were aware of the clinical data and of the setting of suspect IE. Echocardiography was considered positive when evidence of left-sided endocardial involvement consistent with IE, as defined in the Duke criteria, was identified. All

Fig. 1 Longitudinal view of the spleen. The images are displayed on a split screen: on the *left-hand side* the CEUS in the venous phase showing, in the *middle portion* of the spleen, a single wedge-shaped hypovascular area based on the capsule. On the *right side* of the screen are shown the gray-scale images

Table 1 Positive Duke criteria, CEUS and gray-scale sonography results for patients with definite left-sided infective endocarditis

Patients	Duke major criteria	Duke minor criteria	CEUS of the spleen: number and diameter of the infarcted area (s)	Focal lesion (s) at gray-scale ultrasound of the spleen
1	<i>Streptococcus mitis</i>	Fever Mitral valve prolapse Osler's nodes	1 area: 9 mm	Negative
2	MSSA Vegetations on the native mitral valve	Fever Multiple brain abscesses	2 areas: 30 mm and 40 mm	1 oval hypoechoic area with a longitudinal diameter of 37 mm
3	<i>Pseudomonas aeruginosa</i> Vegetations on the biological mitral valve prosthesis	Fever Biological mitral valve prosthesis	2 areas: 9 and 6 mm	Negative
4	<i>Streptococcus gallolyticus</i> Vegetation on the native aortic valve	Fever	2 areas: 13 and 7 mm	Negative
5	<i>Staphylococcus epidermidis</i> Vegetation on the native mitral valve	Fever Mitral valve regurgitation	1 area: 7 mm	Negative
6	<i>Streptococcus anginosus</i> Vegetations on the native aortic valve	Fever Aortic valve stenosis	Negative	Negative
7	EF Vegetation on the native mitral valve	Fever Biological aortic valve prosthesis	Negative	Negative
8	MSSA Vegetation on the native mitral valve	Fever Janeway lesions	4 areas: 13, 16, 18 and 20 mm	1 oval hypoechoic area with a longitudinal diameter of 8 mm
9	EF Vegetation on the native aortic valve	Fever	Negative	Negative
10	EF Vegetation on the native mitral valve	Fever	1 area: 13 mm	Negative
11	<i>Streptococcus mitis</i> Vegetation on the native aortic valve	Fever Aortic valve stenosis	Negative	Negative
12	<i>Micrococcus luteus</i>	Fever Mechanical mitral valve prosthesis glomerulonephritis	3 areas, each of 15 mm	Negative
13	<i>Staphylococcus epidermidis</i> Vegetation on the native mitral valve	Fever Biological aortic valve prosthesis	Negative	Negative
14	<i>Streptococcus salivarius</i> vegetations on the native mitral and aortic valve	No	2 areas: 35 and 17 mm	Negative
15	EF Vegetation on the native aortic valve	No	1 area: 43 mm	1 oval hypoechoic area with a longitudinal diameter of 43 mm
16	<i>Staphylococcus epidermidis</i> Vegetation on the native mitral valve	Fever	2 area: 30 and 13 mm	Negative

Table 1 continued

Patients	Duke major criteria	Duke minor criteria	CEUS of the spleen: number and diameter of the infarcted area (s)	Focal lesion (s) at gray-scale ultrasound of the spleen
17	EF + <i>Streptococcus viridans</i> Vegetation on the native aortic valve	No	Negative	Negative
18	<i>Streptococcus mutans</i> Vegetation on the native mitral valve	Fever Mitral valve prolapse	Negative	Negative

Duke major criteria: 1) blood cultures results, 2) Echocardiography results

MSSA Methicillin-sensitive *Staphylococcus aureus*

EF *Enterococcus faecalis*

Fever is a body temperature ≥ 38 °C (100.4 °F)

of the patients were submitted to a CEUS of the spleen within 10 days after the definite diagnosis of IE. One of the authors, with more than ten years experience in abdominal CEUS, performed all CEUS examinations and was aware of the diagnosis of definite left-sided IE, the laboratory results, and the therapy the patients were receiving. A gray-scale sonography of the spleen was performed immediately before the CEUS. For the CEUS, a blood pool second-generation contrast agent (2.4 mL of SonoVue®, Bracco, Milan, Italy) was used. During the CEUS examination, the patients were laying slightly on the right side. For all examinations, a Philips iU22 ultrasound machine (Philips Healthcare, Best, The Netherlands) with a contrast harmonic imaging technology was used. All of the examinations were performed with a 2–5 MHz convex probe. The real-time images were displayed on a split screen: the left-hand side displayed the contrast harmonic imaging allowing the visualization of the microvascularization without the fundamental gray-scale echoes; the right side of the screen displayed the gray-scale images. Every single CEUS examination lasted less than five minutes. A second bolus of SonoVue® was not necessary for any of the patients. The examinations were performed without any special preparation. Image interpretation: evaluations were performed during the venous phase (1 min after the intravenous injection and for about 4–5 min); wedge-shaped or oval hypovascular areas based on the spleen capsule and pointing towards the hilum were considered findings consistent with splenic infarctions (Fig. 1). No side effects after the CEUS were observed. None of the patients were excluded because of exclusion criteria.

Results

The diagnosis of definite IE was established with both major criteria in 16 patients and with one major criterion plus three minor criteria in 2 patients (Table 1: patient 1

and 12) who had negative echocardiography (both TTE and ETE). The echocardiography demonstrated an involvement of the mitral valve in 9 patients (the biological valve prosthesis in 1 patient; the native valve in 8 patients), of the aortic native valve in 6 patients, of both the native mitral and aortic valve in one patient, and resulted negative in 2 patients who were considered to have left-sided IE since one had a mitral valve prolapse and the other had a mechanical mitral valve prosthesis (Table 1: patient 1 and 12). The results of the blood cultures are shown in Table 1. The gray-scale ultrasound of the spleen tested negative in 15 patients and showed oval hypoechoic parenchymal areas in 3 patients (Table 1). The splenic CEUS showed findings consistent with infarction areas in 11 patients; four patients had a single infarction and seven patients had multiple infarctions. Splenic CEUS detected embolization in both the patients with negative echocardiography. None of the patients with splenic infarctions presented symptoms related to splenic embolization. Results are shown in Table 1. None of the patients were excluded because of inappropriate visualization of the spleen with ultrasound due to meteorism or obesity.

Discussion

In this study, two-third of the patients had splenic embolization; in previous pathologic [1] and radiologic [2–4] studies, the percentage of patients with splenic embolization was up to 40 % of the cases. The higher percentage of splenic embolization, in this study, may derive from the high sensitivity that CEUS has for even tiny hypovascular splenic defects. Indeed, many of these patients had infarcted areas, all with capsular localization, of less than 15 mm; moreover, CEUS was able to detect an infarcted area of only 7 mm. On the other hand, gray-scale sonography demonstrated, in this study, to have a low sensitivity for the detection of splenic infarctions. None of these

patients complained symptoms related to splenic infarctions and all the lesions would have gone underdiagnosed simply on a clinical basis. The Duke criteria themselves have some limitations so that the diagnosis of IE may not result simple. Nevertheless, IE is a disease for which a definite and prompt diagnosis is advisable, and in the suspect of IE the presence of peripheral embolization should be persistently sought to obtain a certain diagnosis; this is not easily achievable at the splanchnic level. The possibility of identifying peripheral embolization at the splanchnic level even at the bedside, and moreover with a simple and repeatable technique, may help clinicians in outstripping the aforementioned limitations and may have a positive impact on the diagnostic accuracy. In this study, CEUS demonstrated to be able to detect even tiny vascular defects; this fact together with the confirmation that the spleen is a frequent target of embolization may suggest a role for the splenic CEUS in the workup of patients with possible IE. Furthermore, both the 2 patients (Table 1, patient 1 and 12), in this study, with negative echocardiography (both TTE and ETE) had positive splenic CEUS. There are several limitations in this study: at first, this is a single-center study and all the CEUS examinations were performed by a single operator who was aware of the diagnosis of IE, and therefore some concerns may arise about the objectivity of the results. Secondly, the number of patients is low. Then a gold standard technique such as computed tomography is lacking. The spleen was visualized in all of the patients of this study but this technique may suffer of the well-known ultrasound limitations in some patients. Furthermore, one patient was affected by an hematological disease (Table 1, patient 16) and 2 patients had a history of intravenous drug injection (Table 1, patient 3 and 8); therefore, they have a higher probability of splenic infarctions not related to the left-sided IE. Nevertheless, since the percentage of splenic embolization revealed by CEUS in this group of patients resulted high, it would be worthwhile to test splenic CEUS as a diagnostic clue in patient with possible IE in wider series.

Acknowledgments All procedures followed were in accordance with the ethical standards of the responsible committee on human

experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent All patients provided written informed consent to enrollment in the study and to the inclusion in this article of information that could potentially lead to their identification.

Ethical standards All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.

Human and animal studies The study described in this article does not contain studies with animal subjects performed by any of the authors.

References

1. Fernández Guerrero ML, Álvarez B, Manzarbeitia F, Renedo G (2012) Infective endocarditis at autopsy: a review of pathologic manifestations and clinical correlates. *Medicine (Baltimore)* 91:152–164
2. Trouillet JL, Hoen B, Battik R et al (1999) Splenic involvement in infectious endocarditis. *Association for the Study and Prevention of Infectious Endocarditis. Rev Med Interne* 20:258–263
3. Ting W, Silverman NA, Arzouman DA, Levitsky S (1990) Splenic septic emboli in endocarditis. *Circulation* 82(IV):105–109
4. Haft JJ, Altieri J, Smith LG, Herskowitz M (1988) Computed tomography of the abdomen in the diagnosis of splenic emboli. *Arch Intern Med* 148:193–197
5. Durack DT, Lukes AS, Bright DK (1994) New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. *Duke Endocarditis Service. Am J Med* 96:200–209
6. Li JS, Sexton DJ, Mick N et al (2000) Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis* 30:633–638
7. Menozzi G, Maccabrini V, Gabbi E, Leone N, Calzolari M (2013) Contrast-Enhanced Ultrasound evaluation of splenic embolization in patients with definite left-sided infective endocarditis. *Ultrasound Med Biol* 39:2205–2210
8. Piscaglia F, Nolsøe C, Dietrich CF et al (2012) The EFSUMB Guidelines and Recommendations on the Clinical Practice of Contrast Enhanced Ultrasound (CEUS): update 2011 on non-hepatic applications. *Ultraschall Med* 33:33–59