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Radiolabeled white blood cells scan in the diagnostic workout of IE and CIED infection

Relatori
Chiar.Mo Prof. Giuliano Mariani
Chiar.Ma Dr.Ssa Paola Anna Erba

Controrelatore
Chiar.Mo Prof. Alberto Signore

Candidato
Dr.ssa Martina Sollini

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Chapter 1

Added value of ^{99m}Tc-HMPAO-labeled leukocytes SPECT/CT imaging in the characterization and management of patients with infectious endocarditis

ABSTRACT

Clinical performance of the Duke Endocarditis Service criteria to establish the diagnosis of infectious endocarditis (IE) can be improved through functional imaging procedures such as radiolabeled leukocytes (^{99m}Tc-HMPAO-WBC). Methods: We assessed the value of ^{99m}Tc-HMPAO-WBC scintigraphy including SPECT/CT acquisitions in a series of 131 consecutive patients with suspected IE. Patients with permanent cardiac devices were excluded. ^{99m}Tc-HMPAO-WBC scintigraphy results were correlated with transthoracic (TTE) or transesophageal (TEE) echocardiography, blood culture and the Duke criteria. Results: Scintigraphy was true positive in 46/51 and false negative in 5/51 cases (90% sensitivity, 94% NPV, 100% specificity and PPV). No false positive results were found. In 24/51 patients with IE we also found extracardiac uptake, indicating septic embolism in 21/24. Despite septic embolism was found in 11/18 cases of Duke “definite IE”, most of the added value from the ^{99m}Tc-HMPAO-WBC scan for decision-making was seen in patients in whom the Duke criteria yielded "possible" IE. The scan was particularly valuable in patients with negative and/or difficult-to-interpret echocardiographic findings since it correctly classified 11/88 of these patients as having IE. Furthermore, 3 patients were falsely positive at echocardiography but correctly negative at ^{99m}Tc-HMPAO-WBC scintigraphy. Conclusions: Our results demonstrate ^{99m}Tc-HMPAO-WBC scintigraphy ability to reduce the rate of misdiagnosed IE when combined to the standard diagnostic tests (a) in patients with high clinical suspicion but inconclusive echocardiographic findings; (b) for the differential diagnosis between septic and sterile vegetations detected at echocardiography; (c) when echocardiographic, laboratory and clinical data are contradictory, as also to exclude valve involvement (especially of a prosthetic valve) during febrile episodes, sepsis or post-surgical infections.

INTRODUCTION

The incidence of infectious endocarditis (IE), is approximately 2-4 cases per 100,000 persons/year (*1*). At present, 25-50% of the cases occur in patients older than 60 years (*2*).

The diagnosis of IE, first suspected on clinical ground, is further supported either by detecting a vegetation at transthoracic (TTE) or transesophageal (TEE) echocardiography, and/or by positive blood culture (*3*). In most institutions the final diagnosis is established using the Duke Endocarditis Service criteria (*4*), which also entail echocardiographic findings. Overall sensitivity is about 80% (*5*). However, in some instances blood culture or echocardiography are inconclusive, thus leading to a high proportion of unconfirmed cases of suspected IE. Indeed, up to 24% of the patients with pathologically proven endocarditis were misclassified as "possible" IE based on Duke criteria alone (*5*).

Attempts have been made at improving the diagnostic performance of the above criteria, and modifications that consider several additional clinical and microbiological parameters have been proposed (*6*). The so-called modified Duke criteria are now recommended for diagnostic classification (*7*). Traditional diagnostic criteria may also be integrated with information derived from radionuclide imaging, given the ability to localize functional hallmark of infection as represented by increased radiolabeled leukocytes recruitment. Using three-dimensional reconstruction of hybrid SPECT/CT or PET/CT images it’s possible to detect and precisely localized throughout the body all the sites of infections represented by areas of radiopharmaceutical uptake. In association with echocardiography, this imaging technique can be employed to confirm or rule out IE in equivocal and/or difficult-to-explore situations (i.e., marantic vegetations, artefacts caused by mechanical prosthesis). Furthermore, scintigraphy can also reveal the presence of extra-cardiac infection sites as the consequence of septic embolism originated from IE (*8*).

In this study we assessed the added value(s) of SPECT/CT with ^{99m}Tc-HMPAO-labeled autologous leukocyte (^{99m}T-HMPAO-WBC) in the characterization of patients with suspected or established IE, as defined according to Duke criteria.

MATERIALS AND METHODS

Patient Population

Between October 2005 and December 2010, a total of 185 consecutive patients were referred for scintigraphy with ^{99m}T-HMPAO-WBC for suspected IE. Fifty-four of these patients were excluded from the present analysis because they were bearing permanent cardiac devices, a condition that might introduce confounding factors linked to the different mechanism of infection (*9*). Therefore, the population for the present work included the remaining 131 patients (45 women and 86 men, mean age 62.8±16.6 years), in whom IE was suspected, or established as definite according to the Duke criteria; in the latter case, scintigraphy was performed to exclude septic embolism. All patients had undergone clinical examination, blood tests including WBC counts, CRP, ESR, acute phase proteins, electrophoresis, urinalysis and echocardiography (either TTE, TEE or both). Three sets of blood cultures including at least one aerobic and one anaerobic from a peripheral vein were performed for all patients (*10*). The main clinical features and risk factors of the patients are summarized in Table 1.

Table 1. Main features of the 131 patients included in the study.

Age (years)	Mean ± SD	Median	Range
	62.8 ± 16.6	66	19-89
Sex	Women	Men	
	45/131 (34%)	86/131 (66%)	
Risk factors	Diabetes	Renal failure	Cutaneous lesions
	20/131 (15%)	24/131 (18%)	10/131 (8%)
Blood tests	ESR	CR	Leukocytosis
	110/131 (84%)	78/131 (60%)	55/131 (42%)
Blood culture	Positive	Negative	
	67/131 (51%)	64/131 (49%)	
Duke criteria	Definite	Possible	Rejected
	28/131	55/131	48/131

Final diagnosis of IE, or exclusion of this condition and identification of an alternative cause of disease was defined based on the final microbiological (n=20) or clinical diagnosis (n=31), with clinical follow-up of 12 months for all patients. Based on these combined parameters, IE was confirmed in 51 out of the 131 patients, that is, in 24/28, 25/55 and 2/48 of the cases in which IE had been classified as definite, possible, or rejected, respectively, according to Duke criteria.

In the 51 patients who were eventually diagnosed as having IE, infection involved more frequently the aortic valve and affected almost equally native valves either biological or mechanical prosthetic implants (Table 2). In patients with prosthetic valves early IE (< 2 months from valve replacement) was present in 9/35 patients, semi-late IE (between 2 and 12 months) in 11/35 and late-onset IE in 15/35 (Table 2).

Table 2. Site of IE, type of valve and time of infection onset.

Type of valve	Native	Biological prosthesis	Mechanical prosthesis	
	16/51 (31%)	19/51 (38%)	16/51 (31%)	
Site of IE	Aortic	Mitral	Tricuspid	Aortic + mitral
Native	9/30 (30%)	6/19 (32%)	1/1 (100%)	-
Biological prosthesis	10/30 (33%)	8/19 (42%)	-	1/1 (100%)
Mechanical prosthesis	11/30 (37%)	5/19 (26%)*	-	-
Type of infection	Early IE	Semi-late IE	Late IE	
	9/35 (26%)	11 (31%)	15 (43%)	
Time from valve replacement (months)	mean 1.39 range 0.5-2	mean 6 range 3-10	mean 51.4 range 6-204	

(*) including 2 patients with anuloplasty.

Staphylococcus spp. was the microorganism more frequently responsible for the infection (24/51), followed by *Enterococcus* spp. (11/51), *Streptococcus* spp. (10/51), and *P. aeruginosa* (4/51). *Haemophilus* and *Candida* were found in 2/51 patients each.

Radiolabelling of Autologous Leukocytes and Image Acquisition Protocol

Autologous radiolabeled WBCs were prepared according to the EANM Guidelines for the labeling of leukocytes with ^{99m}Tc-HMPAO (*11,12*). Radiolabelling efficiency was always between 70-85%, and viability of the radiolabeled leukocytes was always tested by the Tripan blue exclusion test before reinfusion.

Whole body and spot planar images were obtained after 30 minutes (early), then 4-6 and 20-24 hours (delayed images) after reinfusion of 370-555 MBq of ^{99m}Tc-HMPAO-WBC. SPECT/CT of the chest was performed in all patients at 6 hours and repeated at 24 hours in case of negative or doubtful imaging at 6 hours. Images were acquired using a dual-head, variable-angle SPECT/CT gamma camera (Hawkeye, GE Healthcare). The low-dose CT

transmission scan was acquired for 16 seconds over 220° for each transaxial slice. The full FOV consisting of 40 slices was completed in 10 minutes. The transmission data were reconstructed using filtered back-projection to produce cross-sectional images. Resolution of the CT scan was 2.2 mm and localization images were produced with a 4.5-mm pixel size, similar to the nuclear medicine emission images. The CT scans were reconstructed into a 256×256 matrix. The SPECT component of the same FOV was acquired using a 128×128 matrix, 360° rotation, 6° angle step, and 40/60-sec-per-frame acquisition time at 6 and at 24 hours, respectively. Both CT-attenuation corrected and non-corrected SPECT images were evaluated in the coronal, transaxial, and sagittal planes, as well as in tridimensional maximum intensity projection (MIP) cine mode. Matching pairs of x-ray transmission and radionuclide emission images were fused using the Xeleris software, and hybrid images of overlying transmission and emission data were generated.

Interpretation Criteria

Two experienced nuclear physicians aware of the patients' clinical history and of the results of prior conventional imaging tests reviewed independently the planar scans and the SPECT/CT images, with regard to the presence and location of any focus of abnormal radioactivity accumulation indicating infection. Preliminary analysis of the SPECT/CT images included visual inspection to exclude misregistration between the SPECT and the CT components.

The scintigraphic studies were classified as negative when no sites of abnormal uptake were observed at SPECT/CT images, or positive for infection when at least one focus of abnormal uptake characterized by time-dependent increase in radioactivity from early planar to delayed images was observed (*13*). This time-dependent pattern of uptake is especially relevant for the cardiac region, considering that physiologic accumulation of radiolabeled leukocytes in the bone marrow (as in the sternum, overlying the heart) early after reinfusion

can interfere with interpretation of the planar images. When present, focal uptake indicating infection was further classified as pertaining to the heart and/or to extracardiac sites.

The contribution of SPECT/CT was considered with special attention to the possibility of anatomically localizing the exact site of infection, particularly for the heart region. In fact, neither the planar nor the stand-alone SPECT images allow to localize areas of focal uptake of the radiolabeled leukocytes in the cardiac region as pertaining or not to endocardium.

Data Analysis

Results of ^{99m}Tc-HMPAO-WBC scintigraphy were correlated with those of TTE, TEE, blood culture and the Duke criteria. The ability to detect or to exclude the presence of IE was defined based on the final microbiological or clinical diagnosis. Furthermore, in patients with known IE the ability to identify septic emboli and metastatic sites of infection was considered, in order to assess the ability of ^{99m}Tc-HMPAO-WBC scintigraphy to define disease burden.

No comparative analysis was performed between the stand-alone SPECT and the SPECT/CT findings concerning intracardiac location of infection, because in case of focal uptake in the cardiac region no further topographic localization is possible with the former sets of images, considering that the mitral valve and, i.e., the aortic valve (the most frequent site of IE) are <1 cm apart one from each other.

Statistical Analysis

All values are expressed as median and range, as customary for nonparametric data.

RESULTS

By adopting the interpretation criteria described above for scintigraphic detection of infection, it was possible to classify all the scans as either frankly positive or frankly negative, therefore without any equivocal result at scintigraphy. With these criteria, ^{99m}Tc-HMPAO-WBC scintigraphy was totally negative in 34/131 patients for either cardiac and/or extracardiac sites of focal uptake indicating infection, without any discordant results between planar and

SPECT/CT acquisitions. At least one abnormal area with focal uptake of the radiolabeled leukocytes was detected in 97 out of the 131 patients included in this study. When considering the 51 patients with final diagnosis of IE, the uptake was either limited to the heart only (n=23; Figures 1, 2 and 3), both at the heart and at extracardiac sites (n=23), or at extracardiac sites only (1 case with septic embolism in the spleen, which was therefore considered as a false negative scan for IE).

Figure 1. ^{99m}Tc-HMPAO-WBC scintigraphic images in a patient with aortic endocarditis. The MIP image (A) demonstrates focal increase of radiolabeled WBCs in the heart region. Transiaxial SPECT/CT images (panel B) show that such focal uptake is localized at the mechanical prosthesis of the aortic valve (CT section in left panel, fused SPECT/CT section in center panel, SPECT right panel).

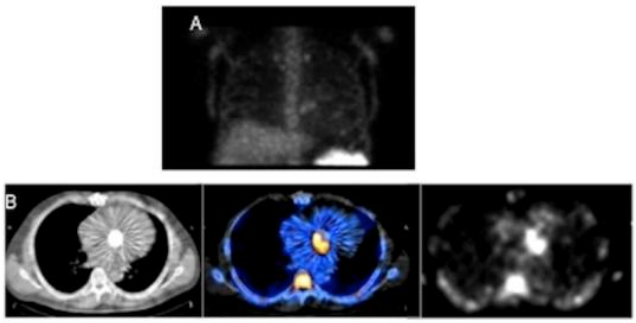


Figure 2. ^{99m}Tc-HMPAO-WBC SPECT/CT images obtained in a patient with positive blood culture and fever arose few months after substitution of the mitral valve with a mechanical prosthesis (coronal sections in upper panel, transaxial sections in lower panel; CT images in left panels, SPECT/CT images in central panels, SPECT images in right panels). SPECT images demonstrate a clear focus of uptake in the right heart, identified as endocarditis of the native tricuspid valve by the superimposed SPECT/CT images (central panels). Endocarditis of the mechanical prosthesis, the expected site of infection before performing ^{99m}Tc-HMPAO-WBC, was therefore excluded.

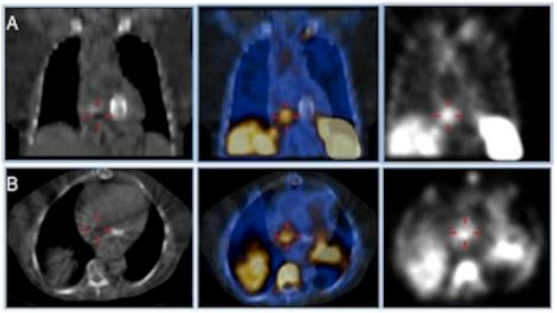
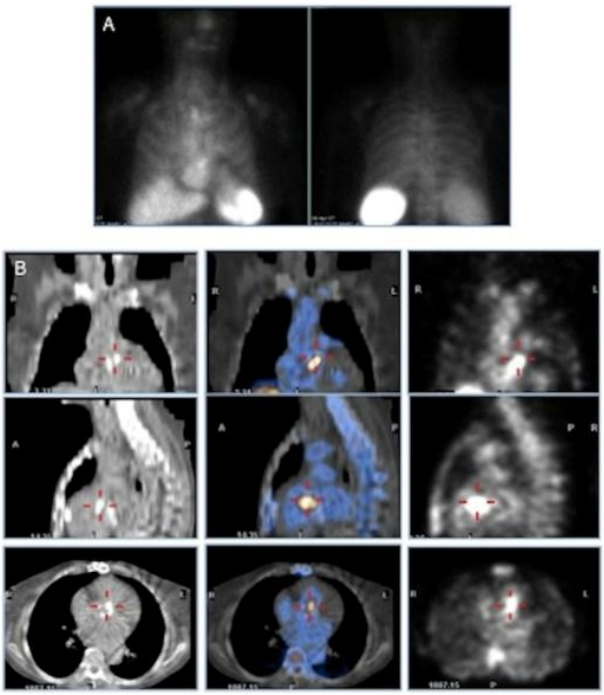


Figure 3. ^{99m}Tc-HMPAO-WBC scintigraphy demonstrating the value of SPECT/CT for precisely localizing the site of infection. (A) Planar anterior and posterior views (anterior in left panel, posterior in right panel), where focal uptake of radiolabeled WBCs mimic sternal osteomyelitis. (B) Coronal, sagittal, and transaxial CT sections in left panels, fused SPECT/CT sections in middle panels and SPECT sections in right panels. The tomographic images correctly localize uptake of ^{99m}Tc-HMPAO-WBCs at the mitral valve prosthesis.



^{99m}Tc-HMPAO-WBC SPECT/CT was therefore true positive in 46/51 and false negative in 5/51 cases. The 5 false negative findings for IE at ^{99m}Tc-HMPAO-WBC scintigraphy occurred in patients with small valve vegetations (<6 mm) and in the presence of

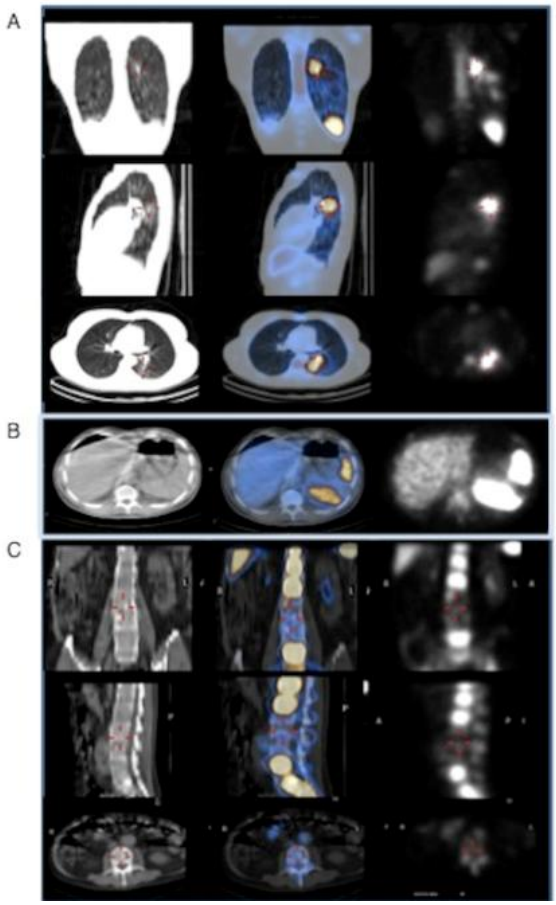
infection from *Enterococcus* (n=4) or *Candida* (n=1); all such patients were under high-dose antimicrobial therapy at the time of scintigraphy. There were no false positive scans for infection of the cardiac valves.

Although both planar and stand-alone SPECT images were sufficiently accurate to detect the presence of infection involving the heart in the majority of the patients (there were in fact only 4 false negative planar scans due to accumulation of the radiolabeled leukocytes hidden by the sternum or the ribs), only after co-registration with CT it was possible to precisely discriminate the localization of ^{99m}Tc-HMPAO-WBC uptake (i.e. especially mitral *versus* aortic valves, given their proximity, metal devices, or surgical stitches/clips) from any non-cardiac site of infection in the mediastinal space. Out of the total 89 sites of increased ^{99m}Tc-HMPAO-WBC uptake in the chest, fused SPECT/CT imaging demonstrated heart valve localization in 44 cases, as opposed to non-cardiac-valve localizations due to infection of aortic graft (n=11), sternum osteomyelitis (n=13), mediastinitis (n=3), and lung infection (n=17). For areas with focal ^{99m}Tc-HMPAO-WBC uptake located outside the thorax, major impact of the SPECT/CT findings was observed for infection sites in the CNS and head-and-neck lesions, as well as to discriminate between bone infection and soft tissue infection. In particular, the exact sites of ^{99m}Tc-HMPAO-WBC accumulation were diagnosed as CNS, nasal and maxillary sinus infections (in 3 and 5 cases, respectively), spleen embolism (n=4) or bone, soft tissue or prosthetic joint infections (22 cases overall, involving spine in 10 cases).

Septic embolism was detected in 41% of patients (Figure 4).

Figure 4. Examples of septic embolism at different sites as detected by ^{99m}Tc-HMPAO-WBC SPECT/CT. (A) Patient with septic embolism in the left lung (coronal, sagittal and transaxial CT sections in left panels, fused SPECT/CT sections in middle panels, and SPECT sections in right panels). (B). Patient with spetic embolism in the spleen, where infection shows as a photopenic area in the splenic parenchyma (transaxial CT section in left panel, fused

SPECT/CT section in center panel, SPECT in right panel). (C) Patient with septic embolism in the spine (coronal, sagittal and transaxial CT sections in left panels, fused SPECT/CT sections in middle panels, and SPECT sections in right panels). Similarly as in the case of the spleen, infection shows as a photopenic area which in this patient involves two vertebral bodies.



Three cases interpreted as septic embolism at ^{99m}Tc-HMPAO-WBC scintigraphy were instead false-positive, due to active vasculitis of the aortic arch, an isolated vertebral metastasis from prostate cancer, and an osteoporotic vertebral crush, respectively. There were 8 false negative scans for extracardiac infection, due to kidney (n=3) or cerebral septic embolism (n=5) (all detected by the CT or MRI imaging).

Table 3 correlates the SPECT/CT results and the Duke classification in the 51 patients with final diagnosis of IE. Most of the added value from the ^{99m}Tc-HMPAO-WBC scan for decision-making was seen in patients in whom the Duke criteria yielded "possible" IE.

Table 3. Results of ^{99m}Tc-HMPAO-WBC scintigraphy in patients with final diagnosis of IE, stratified according to Duke criteria.

		Positive scan			Negative scan
		cardiac only	cardiac and extracardiac	extracardiac only	
Duke criteria	Definite IE (24/51)	9	11*	0	4
	Possible IE (25/51)	13	11[#]	1*	0
	Rejected IE (2/51)	1	1*	0	0

(*) with septic embolism consequent to IE; ([#]) 8 patients with septic embolism, 1 with vasculitis, and two false-positive scans due to vertebral crush and metastasis from prostate cancer.

Table 4 shows the correlation between echocardiographic and ^{99m}Tc-HMPAO-WBC scintigraphic findings. The scan was particularly valuable in patients with negative and/or difficult-to-interpret echocardiographic findings due to several circumstances, such as mechanical valve implants or the presence of huge calcifications (in a diabetic patient undergoing dialysis). Furthermore, 3 patients were falsely positive at echocardiography but correctly negative at ^{99m}Tc-HMPAO-WBC scintigraphy: these patients had marantic vegetations.

Table 4. Results of ^{99m}Tc-HMPAO-WBC scintigraphy in patients with final diagnosis of IE, stratified according to echocardiography (ECHO).

		Positive scan	Negative scan
ECHO	positive (40/51)	35	5
	negative (11/51)	11	0

Table 5 correlates the results of ^{99m}Tc-HMPAO-WBC scintigraphy and blood culture. The most striking result was a positive scan observed in patients with negative blood culture; such high negative fraction of false-negative result of the blood culture could be linked to high-dose antibiotic therapy.

Table 5. Results of ^{99m}Tc-HMPAO-WBC scintigraphy in patients with final diagnosis of IE, stratified according to blood culture.

		Positive scan			Negative scan
		cardiac only	cardiac and extracardiac	extracardiac only	
Blood culture	positive (32/51)	15	14*	0	3
	negative (19$^{\#}$/51)	8	9§	1	1

(*) 11/14 with septic embolism consequent to IE and two false-positive scans due to vertebral crush; ($^{\#}$) during antibiotic therapy in 44/64 patients; (§) 8/9 with septic embolism consequent to IE and one false-positive scan due to vasculitis.

Table 6 shows results of all the diagnostic procedures in patients without IE. Out of the 50/80 patients without IE who exhibited a positive ^{99m}Tc-HMPAO-WBC scintigraphy (only at extracardiac sites), the scan correctly classified such patients as having either osteomyelitis (n=22), peripheral vascular graft infection (n=12), lung infection (n=7), mediastinitis (n=5), or cholecystitis (n=2). In 2 cases focal uptake of the radiolabeled leukocytes in the spine was falsely positive for infection, as it was due to vertebral crush

caused by osteoporosis in one case, by metastasis from a melanoma with unknown primary site in the other case.

Table 6. Results of all the diagnostic procedures in the 80 patients without IE (ECHO = echocardiography).

		^{99m}Tc-HMPAO-WBC scintigraphy	
		Positive scan*	Negative scan
ECHO	positive (n = 3/80)	0	3
	negative (n = 77/80)	0	77
Blood culture	positive (n = 35/80)	26	9
	negative (n = 45/80)	24	21
Dukes criteria	Definitive IE (n = 4)	4	0
	Possible IE (n =30)	19	11
	Rejected IE (n =46)	27	19

*all patients presented only with extracardiac sites of radiopharmaceutical uptake.

DISCUSSION

The diagnosis of IE is becoming progressively more challenging due to a variety of factors. These include the indiscriminate use of antimicrobial agents in some clinical settings, the increased proportion of individuals with predisposing and/or underlying conditions (i.e., frail and elderly, immunosuppressed persons), as well the increasing number of interventional cardiovascular procedures and placement of valve prosthesis, intravascular, or cardiac devices. Mortality of IE remains high when this condition is undiagnosed, therefore not adequately treated (*14*). Early diagnosis and prompt institution of appropriate antibiotic therapy reduce septic embolism and mortality (*15*); therefore, the identification of patients at highest risk of death may offer the opportunity to change the course of the disease and improve prognosis.

Because of the ability to detect endocardial vegetations (*16*), abscess (*17*) as well as intra-cardiac complications (i.e., valve perforation and chordal rupture) (*18*), echocardiography is the indirect method of choice for investigating patients with clinical suspicion of IE (*19,20*). Furthermore, some echocardiographic features such as vegetation size (higher risk for lesions >10 mm in diameter and for vegetations that are increasing in size), number (multiple) and features (mobile but pedunculated, noncalcified, prolapsing) (*20*) may be also used to predict the potential embolic burden of IE. However, the presence of prosthetic valves consistently decreases sensitivity and specificity of echocardiography, to about 20% for TTE and around 90% (in the hands of an experienced operator) for TEE (*8*). In approximately 15% of the cases, echocardiography can be false positive (because thickened valves, nodules, or valvular calcifications are misinterpreted as vegetations) (*4*), while a similar proportion can be false negative (*4*). Thus, echocardiographic findings alone cannot always definitely confirm nor exclude the clinical suspicion of IE. Since echocardiography represent the backbone of Duke criteria, this suboptimal diagnostic accuracy translates into a relatively high proportion of the cases classified as "possible" IE; yet, about 24% of such cases are eventually diagnosed to have indeed IE (*5*).

Additional potentially misleading factors in the Duke's classification include some well-known pitfalls in blood culture (antimicrobial treatment, subacute right-sided and mural endocarditis (*21*), fungi, slow-growing and difficult to identify organisms) (*22*), and ambiguous symptoms without any of the classical stigmata of valvular infection.

A functional imaging modality such as radionuclide imaging, capable of characterizing specific features of the endocardial vegetations, may contribute to solve clinical dilemmas in such conditions. In our experience, when the results of ^{99m}Tc-HMPAO-WBC scintigraphy were associated with either a positive echocardiography or a positive blood culture no cases of IE went undiagnosed. In particular, the radiolabeled leukocyte scan facilitated the diagnosis of IE in challenging situations for echocardiography, as in the

presence of mechanical prosthetic valve, anuloplasty rings, calcifications, and/or nonbacterial thrombotic vegetations. Furthermore, ^{99m}Tc-HMPAO-WBC scintigraphy allowed to exclude valve infection in patients with concomitant risk factors, non-diagnostic echocardiographic findings, positive blood cultures (37% of the cases in our series), or to identify other focal infections different from IE (as occurred in 38% of the overall 131 patients). ^{99m}Tc-HMPAO-WBC scintigraphy can therefore be considered as the second-line test of choice in patients with prosthetic valve/device, fever, positive blood cultures and equivocal TTE/TEE findings.

This study confirms that ^{99m}Tc-HMPAO-WBC scintigraphy is a crucial imaging modality also for localizing sites of infection in patients with symptoms and signs and laboratory findings of sepsis (increased ESR, CRP, and WBC count) (*12*) with either a positive or a negative blood culture. In these patients generally neither TEE nor TTE are used for screening purposes (*4*) and, therefore, the heart region should always be carefully evaluated when analysing the ^{99m}Tc-HMPAO-WBC scan.

The possibility of acquiring whole-body images and additional planar and SPECT/CT spot images constitutes an invaluable aid for detecting septic embolism and metastatic sites of infection, as observed in our patients population. In particular, septic embolism was detected even in the absence of the typical echocardiographic predictors of systemic embolism (*8*,*20*).

These results refer only to patients with IE arising on native and prosthetic valves since we intentionally excluded patients with device related infection. In fact, we consider not possible to apply the same diagnostic algorithm intended for IE to this different clinical entity.

Specific methodology-related issues must be properly addressed in order to ensure adequate scintigraphic acquisitions. Images should be acquired in time-mode, compensating for isotope decay at each time point. In case of equivocal findings at 6 hours SPECT/CT imaging of the thorax, images should be repeated also at 24 hours. Images should be analysed using the same scale frame to easily identify any focal area of activity that increases over time

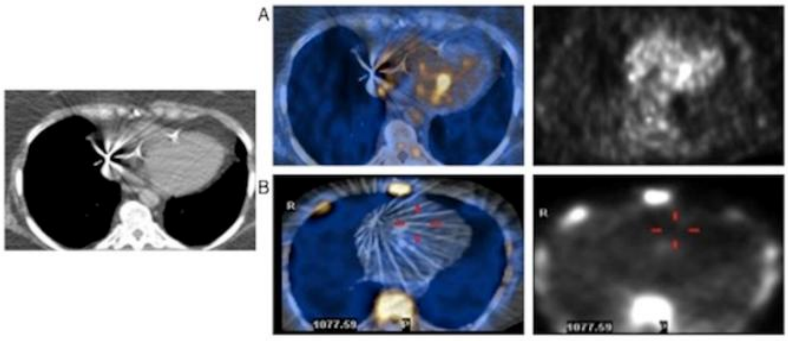
or modifies its shape from early to late images. Both CT-attenuation corrected and non-corrected images should be always inspected side by side, to minimise metal-related artefacts. Quantitative analysis of target/background (T/B) ratios was not necessary in these patients. SPECT/CT is mandatory to correctly interpret and localize sites and extension of radiolabeled leukocyte uptake indicating infection (*23*), to discriminate involvement of the heart valve or prosthesis from uptake around the prosthesis. Furthermore, in cases with positive scintigraphy in the cardiac region SPECT/CT imaging can discriminate endocardial infections from all other possible causes of post-surgical fever, i.e., mediastinitis, osteomyelytis of the sternum or ribs, wound infections.

No false positive findings were found, particularly in patients with early IE evaluated within the first two months from the surgical procedure, suggesting that adequate acquisition protocol and interpretation criteria can optimize specificity of the scan also in this clinical setting. On the other hand, the false negative scans observed in presence of IE sustained by *Candida* spp. or *Enterococcus* spp. may be explained by the ability of these micro-organisms (as well as others such as *S. epidermis*) of forming a "biofilm" that results in resistance to antimicrobial treatment and escape from the host defence mechanisms (*24*). Additionally, altered neutrophil recruitment at the primary site of IE by *E. faecalis* extracellular proteases constitute a further mechanism of innate immune response impairment (*25*). Such mechanisms might reduce sensitivity of scintigraphy with radiolabeled leukocytes in patients with IE. However, in our experience the reduced sensitivity of ^{99m}Tc-HMPAO-WBC scintigraphy was counterbalanced by the association with echocardiography.

Both false negative and false positive findings were also observed in our patients' group regarding distant septic embolism. In particular, the typical ^{99m}Tc-HMPAO-WBC scintigraphic pattern of spleen embolism and spondilodiscitis represented by a cold spot (*26*) may be also present in other benign or malignant conditions. Thus, despite highly suggestive for septic embolism, such finding in patients with IE should be confirmed with additional

diagnostic imaging, as MRI. Finally, it is reasonable to assume that the availability of new generation SPECT/CT scanners with a more advanced CT component will further increase diagnostic accuracy, particularly when evaluating the CNS and bone. Alternatively, PET/CT imaging may be proposed to improve spatial resolution. In this regard, preliminary data have demonstrated significant uptake of [^{18}F]FDG both in infected endocardial vegetations and at metastatic sites of infection (*27-30*). However, [^{18}F]FDG uptake is observed in a variety of benign and malignant conditions such as inflammation or tumours (*31*), thus reducing its specificity. Moreover, special caution should be employed when interpreting of [^{18}F]FDG uptake in the cardiac region, due to the high number of possible causes other than IE for a positive scan: recent thrombi (*32*), soft atherosclerotic plaques (*33*), vasculitis (*34*), primary and metastatic cardiac tumors (*35*,*36*), or simply post-surgical inflammatory reaction (*37*). In the clinical routine, focal areas of [^{18}F]FDG uptake at heart site in the absence of IE are quite commonly observed (unpublished data, Figure 5).

Figure 5. False positive [^{18}F]FDG PET/CT result in a patient with fever. The area of increased [^{18}F]FDG uptake suspected for endocarditis at a mitral valve mechanical prosthesis (A, central panel fused transaxial PET/CT and right panel PET stand alone) turned out to be negative in the ^{99m}Tc-HMPAO-WBC SPECT/CT (B; central panel fused transaxial SPECT/CT and right panel SPECT) clinical follow-up confirmed the absence of infection. Left column, CT transaxial image.



The possibility of efficient radiolabelling of autologous leukocytes with positron emitting radionuclides can be expected to change the whole scenario of PET imaging for patients with suspected IE. In this regard, intense [^{18}F]FDG-WBC uptake at the valve site has been described for the only patient with IE ever reported up to now (*38*). Unfortunately, the physical half-life of ^{18}F is too short to encompass the whole kinetics of leukocyte migration into sites of infection, thus making a major limit for the use of this method in this clinical setting.

CONCLUSION

In conclusion, our experience supports the use of scintigraphy with ^{99m}Tc-HMPAO-WBC in patients with high clinical suspicion of IE, in order to confirm the diagnosis in doubtful circumstances and/or to detect sites of septic embolism. The rate of misdiagnosed IE can be reduced with the use of ^{99m}Tc-HMPAO-WBC (a) in patients with high clinical suspicion but inconclusive echocardiographic findings; (b) for the differential diagnosis between septic and sterile vegetations detected at echocardiography; (c) when echocardiographic, laboratory and clinical data are contradictory, as also to exclude valve involvement (especially of a prosthetic valve) during febrile episodes, sepsis or post-surgical infections.

SPECT/CT is necessary to demonstrate and localize ^{99m}Tc-HMPAO-WBCs at native or prosthetic valves, thus confirming the diagnosis of IE. Furthermore, whole-body images followed by additional planar and SPECT/CT spot images allow to detect distant sites of septic embolism, thus constituting an invaluable aid of this scintigraphic procedure. Negative results in presence of a typical echocardiographic pattern for IE should be carefully evaluated, since false negative findings due to limited spatial resolution or non-leukocyte recruiting microorganisms can be encountered.

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Chapter 2

Clinical impact of of ^{99m}Tc-HMPAO-labeled leukocytes scintigraphy in the diagnostic workup of high risk patients with suspected device related infections

ABSTRACT

Use of cardiovascular implantable electronic device has increased significantly over the last decade due to growing evidence of improved quality of life and survival among certain groups of patients. The infection rate of cardiac device varies widely between 1% and 7% and is associated with significant morbidity and mortality. The aim of this study is the investigation of the potential of ^{99m}Tc-HMPAO autologous leukocyte SPECT/CT in patients with suspected device infection to determine the performances of this functional tests to guide clinical decisions. Methods: We assessed the value of ^{99m}Tc-HMPAO-WBC scintigraphy including SPECT/CT acquisitions in a series of 63 consecutive patients with known or suspected cardiac device infections. ^{99m}Tc-HMPAO-WBC scintigraphy results were correlated with transthoracic (TTE) or transesophageal (TEE) echocardiography and the Duke criteria. Results: Scintigraphy was true positive in 30/32 and false negative in 2/30. There were no false positive scans for CDIE infection. Sites of WBC uptake consistent with additional infections (n=38) are also reported, with particular attention to the presence of concomitant infectious endocarditis (n=6) cases and distant embolisms (n=15). Conclusions: Our results supports the use of scintigraphy with ^{99m}Tc-HMPAO-WBC in patients with high clinical suspicion of CIED infection. ^{99m}Tc-HMPAO-WBC scan results particularly useful in the evaluation of the pocket and the lead portion between pocket and superior cava debouchment, traits which remain unexplored by TEE.

INTRODUCTION

Use of cardiovascular implantable electronic device (permanent pacemakers, implantable cardioverter/defibrillator or cardiac resynchronization therapy device with or with-out defibrillators, CIED) has increased significantly over the last decade due to growing evidence of improved quality of life and survival among certain groups of patients (*1,2,3*). Associated complications, particularly infections have increased disproportionally higher than newly implanted devices (*4,5,6,7*). The infection rate of cardiac device varies widely between 1% and 7% (*8,9*) and is associated with significant morbidity and mortality (*10,11,12*). A cost analysis in a large cohort of about 200000 patients revealed that incremental cost for the management of CIED infection is about $ 28676 to $ 53349 (compared to 12468 to 36851 for uncomplicated devices), with nearly half of the current incremental cost for intensive care (13). Therefore, strategies to shorten the time to explantation, including expedited diagnosis are needed.

Staphylococci are the mean etiological agents (60-80%). Gram negative bacilli represent 5-10% of cases and another 10% are negatives cultures. Rarely fungi or mycobacteria are involved. CIED related infection may occur either as a surgical site infection within 1 year after implantation (*14*) or as late-onset lead endocarditis (*15*). Infections rarely respond to conservative management with antibiotics (*16,17,18*) and usually require complete removal of all hardware (*19*).Clinical challenges begins at time of diagnosis because patients with CIED can present with a variety of manifestations. The decision whether to medically treat or remove the device represent an additional important medical decision as does the selection of the most appropriate test to deter mine the response to the antimicrobial treatment and the most suitable time to implant a new device after the removal of the infected one.

The diagnosis is generally reached using microbiological tests (blood cultures and culture of exudates of the pocket) and transthoracic or transesophageal echocardiography

(TTE, TEE). Results of these investigations may be also used to define patients likelihood to have infection according to the Duke criteria (*20*,*21*). However, in case of CIED infections the application of the Duke criteria as they have originally created for the diagnosis of infectious endocarditis is troublesome; therefore implementation of the criteria have been proposed (*22*). Even introducing those corrections, there is the possibility to underestimate the extent of the infection (*23*).

In the recent years, the use of [^{18}F]FDG PET/CT has been proposed as a tool to improve the diagnosis of CIED infections, potentially impact on patients' management (*24*,*25*,*26*). In fact, a functional imaging modality able to demonstrate through the localization of a metabolic-related radiopharmaceutical the presence and the extent of active infection might find a place in the diagnostic algorithm of CIED infections. The peculiar possibility to follow radiolabeled leukocytes recruitment over time at site of infections as well as the high spatial resolution nowadays achievable using hybrid SPECT/CT equipment makes this imaging modality a suitable candidate for imaging patients with suspected CIED infections, as already demonstrated in a number of other clinical conditions (*27*). Therefore, the aim of this study is the investigation of the potential of ^{99m}Tc-HMPAO autologous leukocyte SPECT/CT in patients with suspected device infection to determine the performances of this functional tests to guide clinical decisions.

MATERIAL AND METHODS

Patient Population

Sixty-three patients (47 men and 16 women, mean age 68,6 ± 13,9; median age 70, range 27-87) were referred for ^{99m}Tc-HMPAO WBC for the evaluation of known or suspected cardiac device infections between June 2007 and December 2010. Patients main clinical features and type of devices are reported in Table 1.

Table 1. Type of cardiac devices and main clinical features of the patients included in the study (PM = pace-maker; ICD = implantable cardioverter defibrillator; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein).

Type of device	single-chamber PM	dual-chamber PM	temporary PM	single-chamber ICDs	dual-chamber ICDs
	30/63 (48%)	17/63 (27%)	2/63 (3%)	9/63 (14%)	5/63 (8%)
Infection rate	12/30 (40%)	7/17 (41%)	1/2 (50%)	7/9 (78%)	3/5 (60%)
Risk factors	Diabetes	Renal failure	Long term corticoid use	Previous infection	Recent invasive procedures
	17/63 (27%)	11/63 (17%)	7/63 (11%)	8/63 (13%)	30/63 (48%)
Fever	Present	Absent			
	35/63 (55%)	28/63 (45%)			
Time from device implant (last procedure, months)	≤ 1	1-3	4-12	> 12	After device removal
	8/63 (13%)	13/63 (21%)	18/63 (28%)	22/63 (35%)	2/63 (3%)
Infection rate	6/8 (75%)	5/13 (38%)	8/18 (44%)	13/22 (59%)	-
Local inflammation signs/symptoms	Pain	Tenderness	Erythema	Purulent drainage	
Blood tests	ESR	PCR	Leukocytosis		
	49/63 (77%)	42/63 (67%)	29/63 (46%)		
Blood culture	Positive	Negative			
	27/63 (43%)	36/63 (57%)*			

* during antibiotic therapy in 25/56 patients; 4 patients presented either positive EC or pocket culture.

The interval between last implantation procedure and symptoms was less than 1 month in 7/56 patients, 1 to 3 months in 12/56, 4 to 12 months in 17/56, more than 1 year in 20/56.

A total of 75 scintigraphies were performed since 10 patients have repeated studies (8 with two scans, 2 with three scans). Patients were referred for a baseline scan in 56 cases while 19 examinations were required for the evaluation of patient response to antibiotic therapy and used to define its discontinuation. All patients underwent clinical examination, blood tests including WBC counts, C-reactive protein, erythrocyte sedimentation rate, acute phase proteins, electrophoresis, urine-analysis, either TTE, TEE or both. Three sets of blood cultures including at least one aerobic and one anaerobic from a peripheral vein were performed for all patients (*28*). For patients referred for a diagnostic scan, clinical signs and symptoms including the presence of pain, tenderness, erythema and purulent drainage at pocket site as well laboratory, and echocardiography results were collected. All patients evaluated to assess response to antibiotic therapy presented negative clinical examination, no symptoms/signs or persistent infection, negative blood tests, negative echocardiography and negative blood cultures.

Final diagnosis of CIED infections, or exclusion of this condition and identification of an alternative cause of disease was defined based on the final microbiological (n = 24) or clinical diagnosis (n = 8), with clinical follow-up of 12 months for all patients. All patients without microbiological diagnosis repeated ^{99m}Tc-HMPAO WBC scintigraphy at the end of the antibiotic treatment. Based on these combined parameters, CIED infections were confirmed in 32 out of the 63 patients (see Table 2). *Staphylococcus* spp. was the microorganism more frequently responsible for the infection (12/28), followed by *Streptococcus* spp. (3/28), *Enterococcus* spp. (3/28), *Enterobacteriaceae* spp. (2/28); *P. Aeruginosa* (2/28)*; Micrococcus* and *Candida* were found in 1/30 patients each.

Infection occurred most frequently in single-chamber ICDs (7/9) and dual-chamber ICDs (3/5); single and dual chamber PM have similar infection rate (12/30 versus 7/17). One

out of the two temporary PM presented infection. Infection was prevalent early after implant (5/8 of patients evaluated <1 month and 5/13 cases studied 1-3 months after implantation, respectively). Semi-late and late infection were observed in 8/18 patients studied 4-12 months and 13/22 patients > 12 months from the procedure. Of interest, 3/5, 5/8 and 11/13 infections were after the second procedure (Table 1).

Radiopharmaceutical preparation and imaging acquisition protocol

Autologous radiolabeled WBCs were prepared according to the EANM Guidelines for the labeling of leukocytes with ^{99m}Tc-HMPAO (*29,30*). Radiolabelling efficiency was always between 70-85%, and viability of the radiolabelled leukocytes was always tested by the Tripan blue exclusion test before reinfusion.

Whole body and spot planar images were obtained after 30 minutes (early), then 4-6 and 20-24 hours (delayed images) after reinfusion of 370-555 MBq of ^{99m}Tc-HMPAO-WBC. SPECT/CT of the chest was performed in all patients at 6 hours and repeated at 24 hours in case of negative or doubtful imaging at 6 hours. Images were acquired using a dual-head, variable-angle SPECT/CT gamma camera (Hawkeye, GE Healthcare). The low-dose CT transmission scan was acquired for 16 seconds over 220° for each transaxial slice. The full FOV consisting of 40 slices was completed in 10 minutes. The transmission data were reconstructed using filtered back-projection to produce cross-sectional images. Resolution of the CT scan was 2.2 mm and localization images were produced with a 4.5-mm pixel size, similar to the nuclear medicine emission images. The CT scans were reconstructed into a 256×256 matrix. The SPECT component of the same FOV was acquired using a 128×128 matrix, 360° rotation, 6° angle step, and 40/60-sec-per-frame acquisition time at 6 and at 24 hours, respectively. Both CT-attenuation corrected and non-corrected SPECT images were evaluated in the coronal, transaxial, and sagittal planes, as well as in tridimensional maximum intensity projection (MIP) cine mode. Matching pairs of x-ray transmission and radionuclide

emission images were fused using the Xeleris software, and hybrid images of overlying transmission and emission data were generated.

Interpretation criteria

All images were revaluated, independently, by two experienced nuclear physicians aware of the patients' clinical history and of the results of prior conventional imaging tests reviewed the planar scans and the SPECT/CT images, with regard to the presence and location of any focus of abnormal radioactivity accumulation indicating infection. Preliminary analysis of the SPECT/CT images included visual inspection to exclude misregistration between the SPECT and the CT components.

The scintigraphic studies were classified as negative when no sites of abnormal uptake were observed at SPECT/CT images, or positive for infection when at least one focus of abnormal uptake characterized by time-dependent increase in radioactivity from early planar to delayed images was observed (*31*). This time-dependent pattern of uptake is especially relevant for the transvenous portions of the lead and cardiac region, considering that physiologic accumulation of radiolabeled leukocytes in the bone marrow (as in the clavicle and sternum, overlying vessels and the heart) early after reinfusion can interfere with interpretation of the planar images. When present, focal uptake indicating infection was further classified as pertaining to the heart and/or to extracardiac sites. Positive scans were categorized as follow: a) isolated pocket infection; b) isolated lead infection at either intravascular or intracardiac portion of the lead; c) pocket and lead infection (either intravascular or intracardiac portion); d) extracardiac sites of infection consistent with embolism; e) other infections.

Data Analysis

Results of ^{99m}Tc-HMPAO-WBC scintigraphy were correlated with those of TEE, blood culture, the Duke criteria classification and the risk factor category classification (this latter only for diagnostic scan). The ability to detect or to exclude the presence of CIED

infections was defined based on the final microbiological or clinical diagnosis. Furthermore, the ability to identify septic emboli was considered, in order to assess the ability of ^{99m}Tc-HMPAO-WBC scintigraphy to define disease burden.

For the site-based analysis results of the planar, stand-alone SPECT and SPECT/CT images were compared. Stand-alone SPECT and SPECT/CT were considered contributory when they provided data that could not be obtained from the assessment of planar images concerning the presence of infection or its precise location. The contribution of SPECT/CT was considered with special attention to the possibility of anatomically localizing the exact site of infection, particularly for vessels and the heart region. The patient-based performance of SPECT/CT was compared for the different clinical indications, namely device infection or evaluation of the response to antibiotic treatment.

Statistical analysis

All values are expressed as median and range, as customary for nonparametric data.

RESULTS

By adopting the interpretation criteria described above for scintigraphic detection of infection, it was possible to classify all the scans as either frankly positive or frankly negative, therefore without any equivocal result at scintigraphy.

With these criteria for interpretation of the diagnostic ^{99m}Tc-HMPAO-WBC scintigraphies, images were totally negative in 30/75 cases. At least one abnormal area with focal uptake of the radiolabeled leukocytes was detected in 45 out of the 75 scans.

When considering the 32 patients with final diagnosis of CIED infections, ^{99m}Tc-HMPAO-WBC was true positive in 30/32 (94%). Two false negative scans occurred in patients with CDIE infections by *Candida* and *Enterococcus* (final diagnosis obtained by culture of the leads). Both patients were under high-dose antimicrobial therapy at the time of scintigraphy. A false negative echocardiography, translating in a Duke rejected classification

was present in the first case and a true positive echocardiography and Duke definite classification in the second patient. There were no false positive scans for CIED infection.

Table 2 summarized results of ^{99m}Tc-HMPAO-WBC and of ecocardiography and patients classification according to Duke criteria in cases of final diagnosis of CIED infections.

Table 2. Results of the WBC, echocardiography, Dukes accordingly to the final diagnosis for the 75 studies.

		CDIE infection (n =32)	No CDIE infection (n =43)
WBC	Positive	30/32	0/43
	Negative	2/32	43/43
Echocardiography	Positive	20/32	4/43
	Negative	12/32	39/43
Duke's criteria	Definite	10/32	0/43
	Possible	17/32	10/43
	Rejected	5/32	33/43

Table 3 show results of scintigraphy and echocardiograghy based on time of infection onset. Additionally, in this table results of echocardiography are tabulated based on the site of radiopharmaceutical uptake at ^{99m}Tc-HMPAO-WBC, specifically as involving the pocket (n = 1), the intravascular and/or intracardiac portion of the lead(s), both the pocket and lead(s).

Table 3. Results of scintigraphy and echocardiograghy based on time of infection onset.

Type of infection		Pocket	Leads infection			Pocket plus lead infection			Other infections	No infections
			Intravascular lead	Intracardiac lead	Both leads	Intravascular lead	Intracardiac lead	Both leads		
Very early, ≤ 1 mo (n = 10)		-	-	3	-	1	1	-	-	5
Echo	pos	-	-	1	-	-	1	-	-	-
	neg	-	-	2	-	1	-	-	-	5
Early, 1-3 mo (n = 13)		-	-	3	-	-	1	1	1	7
Echo	pos	-	-	3	-	-	1	-	-	-
	neg	-	-	-	-	-	-	1	1	7
Semi-late, 4-12 mo (n =21)[$]		-	1	6	1	-	-	-	4	9
Echo	pos	-	-	4	1	-	-	-	-	-
	neg	-	1	2	0	-	-	-	4	9
Late, > 12 mo (n =29)		1	-	6	1	1	2	1	10	7
Echo	pos	-	-	3	1	-	2	1	2	2
	neg	1	-	3	-	1	-	-	8	3

[$] including 2 FN scintigraphic results.

Sites of WBC uptake consistent with additional infections (n=38) are also reported, with particular attention to the presence of concomitant infectious endocarditis that was present in 6 cases and distant embolisms (n=15, osteomyelitis in 6 cases, vascular graft and lung in 4 cases each, and 1 spleen). Vascular graft infections (n=2), osteomyelitis (n=6), mediastinitis (n=4), lung infections (n=3) and cholecystitis (n=2) accounts for the other infections. Three cases of ocular and cerebral infections remains undiagnosed. None of the patients with negative WBC for CIED infection and subsequently treated for the primary cause of infection develop CIED infection during the time of the study follow-up.

SPECT/CT images were fundamental to localized WBC accumulation and differentiate infection of the EC, patch infection and endocarditis. Importantly analyzing both the attenuated corrected and the non-attenuated corrected images no false positive results due to artifacts were detected.

DISCUSSION

The use of a CIED have demonstrated significant benefits in terms of reduction of the risk of death and patients better quality of life (*32*). However, infections of the apparatus can darken some of these benefits and recent data point to a disagreeable trend: infection rates are rising faster than implantation rates (*33*). Together with morbidity and even death, infection is also associated with significant financial cost for patients and third-party payers. The estimated average cost of combined medical and surgical treatment of CIED-related infection ranges from $25,000 for permanent pacemakers to $50,000 for implantable cardioverter-defibrillators (*34,35*). Further, in the years after initial implantation, device replacement may become necessary for battery depletion or for upgrades to more complex multilead pacemakers or implantable cardioverter-defibrillator with infection rates higher in replacements compared to initial implantation (*36,37,38*).

Therefore, early recognition of infection and accurate quantification of disease burden that will determine the selection of the best therapeutic strategies are the two base elements for an optimal decision making process.

In our series, CIED infections was first suspected base on clinical and laboratory parameters, subsequently supported by either abnormal echocardiographic findings or local signs and further laboratory tests consistent with infection. Further, to confirm the diagnosis and to define disease burden, all patients performed WBC scintigraphy. Additionally, we also use WBC scintigraphy to evaluate antimicrobial treatment response, to decide its discontinuation.

The use of WBC scintigraphy including SPECT/CT acquisition of the chest, results in high sensitivity (94%) for the detection and the localization of CIDE infection. No false positive result were found, consistent with the specificity of the diagnostic criteria of increased WBC recruitment over time in infectious foci. However, properly due to this specific mechanism false negative findings should be take into account in presence of low-recruiting microorganism (*39,40*), as in our series in the case of CIED sustained by *Candida* spp. and *Enterococcus* spp.

Despite is well known that the majority of infections begin from the pocket by direct contamination during the procedure, we detected infection localized at the only pocket in just one patient. In the majority of the cases pocket infection was associated with catheter leads involvement (7 cases). This data is of importance because of the tendency to underestimate infection extent in patients with localized pocket infections. In fact, local manifestations at the site of pacemaker implantation has been reported associated with infection of the intravascular part of the leads in up to 79% of patients (*41*). The intracardiac portion of the lead was the site more frequently interested by WBC uptake at scintigraphy (24 over a total of 64 sites of uptake) and it is also associated with the highest rate of complications, either infectious endocarditis and/or septic embolism (osteomyelitis, lung, vascular graft) which

were found in for a total of 47% of the cases. This finding may be explained by the relatively high presence of late infections in the patients we studied (semi-late and late account for more of the 50% of the total infections). Infectious endocarditis, present up to 18% of our patients, was associated with high frequency of systemic embolism and metastatic infections (lungs, bone and spleen).

In this study, we also evaluated the ability of WBC scintigraphy to rule out the device involvement during a febrile episode and sepsis. WBC scintigrafy do exclude the presence of device involvement in 43/75 and SPECT/CT images detected causes infections in 15 cases (vascular graft infections, osteomyelitis, mediastinitis, lung infections and cholecystitis) with sensitivity and specificity of 93% and 91%, respectively.

All patients in our study performed echocardiography as a first line diagnostic test. In our hands, echocardiography results in high specificity 90%, but in a relatively low sensitivity, of about 63%. The typical echocardiographic finding of vegetations on the distal extreme of the lead (*42*) was found in 28% of the patients; however, in up to 10% of patients lead-associated mass, not representing endocarditis was also detected, in line with previous reports (*43,44*). Additionally, in about 40% of patients, we failed to visualize a mass adherent to a lead with TEE, supporting the finding that echocardiography negativity is not sufficient to excluding lead infection (*45,46,47,48*). Vegetations observed in our patients for the concomitant presence of infectious endocarditis (n = 19%) were easily distinguishable from the strands attached to the electrodes that are clinically meaningless. However, the aspect of thickening or sleeve that the lead adopts, in our series reported in 6 cases, may represent a further difficulty for echocardiographic differential diagnosis (*49*). The relatively low sensitivity of echocardiography in our series, should be, therefore, partially explained with the described technical difficulties and partially with the observation that out of the patients with negative TTE/TEE, using WBC scintigraphy we localized infection at the pocket and /or the

intravascular portion of the leads (Table 2 and 3) in 5 cases, with a similar frequency in early and delayed infections.

Therefore, comparing TEE and WBC scans only in patients with infections localized at the intracardiac portion of the leads, the only trait accurately evaluable with echocardiography (in fact, the pocket exploration may results in metal-artifacts and the lead portion between pocket and superior cava debouchment remain unexplored), echocardiography sensitivity increase to 75%.

If we apply the Dukes criteria, which entails the echocardiographic findings, to define the likelihood to present CIED infection we were able to define the presence of infection in 31% and 84% of patients, depending of the inclusion of the only Definite category or both the Definite plus Possible categories. However, using this latter categorization, specificity of 77% should be take into account. This relatively low sensitivity of the Duke criteria may be explained by the fact that for the diagnosis of CIED infections it's not simple possible their application in the format originally created for infectious endocarditis. In fact, beside the described limitation of echocardiography that would benefit from integration with criteria specifically designed for device, the so called minor criteria are just not applicable in this setting. Additionally, the pocket assessment which is one of the clinical parameter important for the diagnosis of CIED infection, is simply not included.

Therefore, due to the difficulties that the diagnosis of CIED infection raise, we proposed the use of functional imaging modalities to increase diagnostic accuracy and perform better a comprehensive clinical assessment in patients at risk of embolism.

The feasibility and the potential usefulness of radiolabeled leukocytes SPECT/CT in the management of infection in a small series of patients with left-ventricular-assist device (LVAD) implantation and infectious endocarditis has been recently shown. Leukocyte SPECT/CT was able to determine the precise anatomic location and extent of a suspected infection, improving patients management (*50,51*). Similarly, preliminary data on the use of

[^{18}F]FDG-PET/CT demonstrated promising results in patients with cardiac device, particularly when the technique is used to rule out device involvement during infection (*52*) and to define the embolic burden (*53,54,55*). In fact, glucose enhanced metabolism in activated leukocytes (*56*), monocyte-macrophages (*57*), CD4(+) T-Lymphocytes (*58*), the basic mechanism of [^{18}F]FDG accumulation in infectious sites, is shared by a number of inflammatory situations (i.e. vasculitis, granulomatosis, sarcoidosis, atherosclerosis) (*59,60,61,62*) as well as post-surgical changes (*63,64*), making the differential diagnosis, especially for early surgical infection, a challenge.

Therefore, potential application of those imaging modalities may be represented by the differential diagnosis between pocket hematoma and purulent collection, fibrous casts or thrombus and active vegetations detected by TEE on leads and the definition of the disease extent as in presence of ascertained pocket infection. Additionally, we also believe results of functional imaging procedure might help clinicians in solving the controversy of the most suitable treatment selection, conservative (antimicrobic agents alone or the removal of just the generator) *versus* full hardware extraction, an example of clinical controversy that has been risen by the availability of new antimicrobial agents that are able to penetrate into biofilm (*65*). Furthermore, since limited data are available for the decision of antibiotic treatment discontinuation and the optimum timing for the placement of a new implantable cardiac device following extraction, these medical decision might be also driven by a negative scan. Indeed, in this series none of the patients with previous CDIE infection whom treatment discontinuation was decided on the base of a negative scan after additional two months of reduced antimicrobial therapy either with or without device replacement, presented infection recurrence during the study follow-up.

CONCLUSION

In conclusion, our experience supports the use of scintigraphy with ^{99m}Tc-HMPAO-WBC in patients with high clinical suspicion of CIED infection. ^{99m}Tc-HMPAO-WBC scan results particularly useful in the evaluation of the pocket and the lead portion between pocket and superior cava debouchment, traits which remain unexplored by TEE. SPECT/CT is necessary to demonstrate and localize ^{99m}Tc-HMPAO-WBCs uptake. Furthermore, whole-body images followed by additional planar and SPECT/CT spot images allow to detect distant sites of septic embolism, thus constituting an invaluable aid of this scintigraphic procedure. False negative findings may be encountered due to limited spatial resolution or non-leukocyte recruiting microorganisms.

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