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Special issue
on hybrid PET in infection and inflammation

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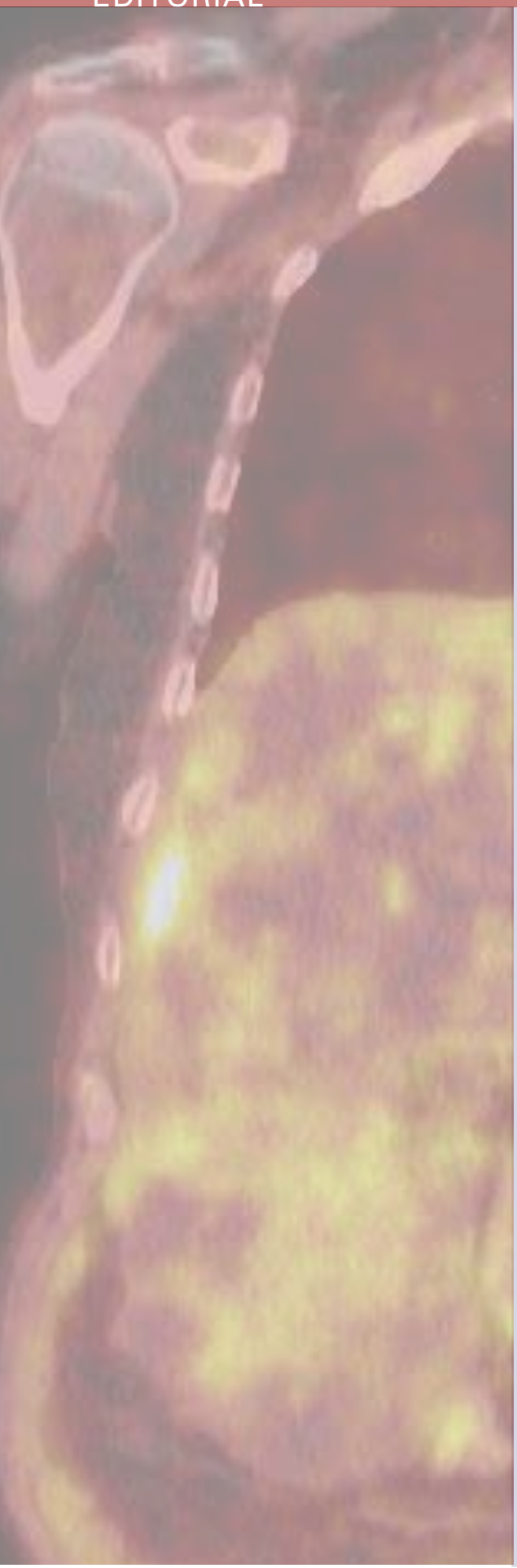
Hybrid PET/(CT/MR) in infectious and inflammatory diseases

Despite its relative short history, nuclear medicine is playing an important role in the diagnosis of infectious and inflammatory diseases. In this regard, already in the 1970s, planar imaging with labelled white blood cell scintigraphy was proven successful. Non-specific radiolabelled compounds, such as ^{67}Ga-citrate, polyclonal human immunoglobulin (HIG), or more specific like anti-E-selectin, anti-granulocyte antibodies, cytokines, ciprofloxacin or antimicrobial peptides were either less successful or are still under research.
Furthermore, the introduction of new techniques like SPECT led to higher sensitivity to detect infectious and inflammatory diseases, and hybrid camera techniques such as SPECT/CT helped to improve both the specificity and the diagnostic accuracy, due to the synergy of the anatomical and pathophysiological information it provides.
Since 2002, hybrid clinical PET/CT systems (PET + multislice CT) are available. The combination of high sensitivity PET images fused with high resolution CT images has gained an almost immediate widespread clinical acceptance for diagnosis, staging and re-staging as well as prediction of response to treatments in oncology.
In the USA the costs of PET/(CT) scans are reimbursed by the Centers for Medicare and Medicaid Services (CMS). In the opinion of the CMS National Coverage Determination there are clear indications for ^{18}F-FDG PET/CT, besides oncology, in diseases of the heart and the brain (i.e. myocardial perfusion, seizures and the differential diagnosis of frontotemporal dementia and Alzheimer's disease). Apparently, the non-specificity of FDG is very well recognised, but so far the use of FDG PET/CT in infectious and inflammatory diseases is not reimbursed. This lack of reimbursement in the USA is most likely the reason that a large proportion of publications that report on the use of ^{18}F-FDG PET/CT in diagnosing infectious and inflammatory diseases, originate from Europe.

Because infectious and inflammatory conditions form a very heterogeneous group of diseases, and patients may present with a variety of symptoms, diagnosis can be an important problem to the clinician. Usually, after initial laboratory tests, various conventional imaging procedures are consulted (X-ray, ultrasound, CT and/or MRI) to reveal anatomical changes. However, in the early stages of disease, morphologic changes or abnormalities may be absent, so anatomic imaging modalities have a rather low sensitivity for early stage disease. In addition, these techniques usually provide information on a limited part of the body, and e.g. the use of total body MRI is not widespread. Moreover, when morphologic changes are found after surgery or other therapeutic interventions, differentiation of infection/inflammation from residual changes is limited. Performing ^{18}F-FDG PET/CT in an early stage of disease may be beneficial for an early diagnosis.
However, it remains a challenge to define when the benefits of a hybrid PET/CT outweigh the costs.

In this special issue of the TvNG readers will learn more about the work of Dutch colleagues on infectious and inflammatory issues. The first contribution is by Kouijzer et al from Radboud University Medical Center (UMC) Nijmegen. They claim ^{18}F-FDG PET/CT is cost-effective in patients with 'fever of unknown origin' (FUO) because an adequate and early diagnosis in FUO limits the number of non-contributing, often invasive, tests and the duration of hospitalisation. Note: a first attempt to describe the cost-effectiveness of ^{18}F-FDG PET/CT in 'inflammation of unknown origin' was



published in a previous issue of this journal (TvNG. 2015;37(2):1409-11).
Vos et al, also attached to Radboud UMC Nijmegen, describe the value of ^{18}F-FDG PET/CT in metastatic infectious disease and suggest it should be performed in all patients with high risk Gram-positive bacteraemia.
Scholtens from Meander Medical Center at Amersfoort reports on the value of ^{18}F-FDG PET/CT in cardiovascular infection and endocarditis.
Van der Laken, from VUMC Amsterdam, discusses the use of ^{18}F-FDG and ^{18}F-fluoride PET/CT next to MRI in the field of rheumatology, bearing in mind that the efficacy of expensive biologicals (€€20.000/patient/year) is only 50-70%. Also clinical results with ^{11}C-PK11195 PET as a marker of (activated) macrophages are discussed.
Note: of particular interest for daily clinical practice is a recent overview by Glaudemans et al from UMC Groningen on pitfalls and limitations of hybrid imaging in infection and inflammation (Sem Nucl Med. 2015;45:500-12).

Hybrid PET/MRI is a different ball game: it presents soft tissue contrast better and causes less radiation exposure in simultaneous imaging settings, theoretically resulting in improved matching of the images. Voo et al from Maastricht UMC also recognise a certain downside; MRI protocols increase workflow complexity and are, compared with CT, time-consuming and requiring more patient compliance. However, based on their positive first clinical experiences, it is likely that hybrid PET/MRI will become a valuable imaging approach in the diagnosis of many cardiovascular diseases, including inflammatory pathologies such as myocarditis, cardiac sarcoidosis, or large vessel vasculitis.

New developments in radiochemistry and e.g. peptide chemistry will hopefully result in more selective tracers with high specific activity.
As inflammation is a nonspecific process (e.g. occurring both in malignancy and infection), a tracer that may differentiate between inflammation and infection is regarded to be the 'Holy Grail'. However, so far such a tracer has not been established.
Aarntzen and Boerman, affiliated with Radboud UMC Nijmegen, discuss the main categories of clinical available techniques for in vivo immune cell imaging. They highlight the current developments envisioned to have clinical impact in the upcoming years.

Hopefully, this special issue contributes to the increasing insight that hybrid nuclear medicine offers powerful non-invasive techniques for visualisation of infectious and inflammatory disorders. Especially the use of whole body imaging that enables the determination of both localisation and the number of infectious/inflammatory foci. Results of hybrid nuclear medicine investigations may therefore play a crucial role in 'specialised' or 'personalised' medicine.

Hans Balink, MD, PhD
Guest editor

• On the cover, a hybrid ^{18}F-FDG PET/CT image of a 61-year-old man known with multiple liver cysts and renal cysts and a renal transplant in the right fossa iliaca. The CRP value was125 mg/L. Subfebrile body temperatures. Blood cultures were positive for Escherichia coli and Enterococcus faecalis. After initial Ciproxin, which was later followed by Augmentin without clinical improvement, ^{18}F-FDG PET/CT showed pathological uptake at the margin of a lateral localised liver cyst (black arrow). In consequence of the rising CRP levels with an infected liver cyst, intravenous application of cefotaxime was started for 4 weeks, after which the patient gradually recovered.

The value of ^{18}F-FDG PET/CT in fever of unknown origin

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Abstract

Kouijzer IJE, Vos FJ, Oyen WJG, Bleeker-Rovers CP. The value of ^{18}F-FDG PET/CT in fever of unknown origin. Fever of unknown origin (FUO) was commonly defined as fever higher than 38.3°C on several occasions during at least three weeks with uncertain diagnosis after a number of obligated investigations. FUO remains a clinical challenge as no diagnosis is reached in up to 50% of cases. FDG PET and FDG PET/CT are valuable imaging techniques for the evaluation of FUO. FDG PET/CT facilitates anatomical localisation of focally increased FDG uptake, thereby guiding further diagnostic tests to achieve a final diagnosis in FUO. With FDG PET/CT becoming widely available, FDG PET/CT should be a routine procedure in the evaluation of FUO. **Tijdschr Nucl Geneesk 2015; 37(4):1469**

Introduction

Fever of unknown origin (FUO) remains a challenging diagnostic problem in medicine. In 1961, Petersdorf and Beeson firstly defined the definition of FUO as an illness of more than three weeks duration with fever higher than 38.3°C (101°F) on several occasions and diagnosis uncertain after one week of study in the hospital (1). In 1992, this definition of FUO has been modified by removing the requirement that the evaluation must take place in the hospital and by excluding immunocompromised patients as these patients need an entirely different diagnostic and therapeutic approach (2, 3). The quantitative criterion of a diagnosis uncertain after one week has been changed in 2007 to a qualitative criterion that requires a number of diagnostic procedures to be performed (4).

The potential causes of FUO include a broad spectrum of diseases: infectious diseases, non-infectious inflammatory disorders, and malignancies. In the clinical analysis of a patient with FUO it is essential to first identify diagnostic clues by taking a complete history and performing a physical examination followed by laboratory tests, chest radiography, and abdominal ultrasonography. With these diagnostic clues, a limited list of probable diagnoses can be made. If subsequently a hypothesis for the cause of FUO can be established, a further focused diagnostic work-up can be performed to prove or refute the hypothesis. When diagnostic clues are absent or misleading, FUO should be further evaluated using a standard diagnostic protocol (4).

Imaging in FUO

Imaging techniques may help to identify the possible causes of FUO. Anatomic imaging modalities such as CT and MRI require anatomic changes in tissue secondary to inflammation before detection is possible and therefore in many cases are not able to detect early stages of disease. Also, anatomic changes caused by cured disease or surgery may result in false-positive interpretation of the images. In addition, anatomic imaging techniques include only a limited area of the body and do not provide information about other areas being a major disadvantage if the potential cause of fever is not clear. Whole body scintigraphic imaging techniques may play an important role in the diagnosis of FUO, because they are performed as whole body imaging examinations and the radiotracers used are able to detect inflammatory processes in the body in an early stage before anatomic changes appear. Conventional scintigraphic methods are ^{67}Ga-citrate scintigraphy and ^{111}In-labelled or ^{99m}Tc-labelled leukocyte scintigraphy. However, these imaging techniques have their limitations, such as handling of potentially infected blood products (labelled leukocyte scintigraphy), high radiation burden (^{67}Ga-citrate scintigraphy and ^{111}In-labelled leukocyte scintigraphy), instability of the labelling (^{99m}Tc-labelled leukocyte scintigraphy), and their relatively long time span between injection and diagnosis (^{67}Ga-citrate scintigraphy).

^{18}F-fluorodeoxyglucose (FDG) positron emission tomography combined with computed tomography (PET/CT) has become an established imaging procedure in oncology and has successfully entered the field of clinical infectious diseases (5). Imaging is normally performed as early as sixty minutes after injection of FDG. Normal uptake may obscure pathologic foci in some organs and tissues. High accumulation of FDG

is always observed in the brain and also frequently present in the myocardium. Because of FDG excretion into the urine, visualisation of renal and pelvic abnormalities may be disturbed. Diffuse or discrete uptake in the gastrointestinal tract may result from peristalsis and is physiological (6). When comparing FDG PET/CT and conventional scintigraphy, advantages of FDG PET/CT are higher resolution, higher sensitivity in chronic low-grade infections, and higher accuracy in the central skeleton, as well as the short time period between injection of the radiotracer and the imaging procedure (7). As for many conventional scintigraphic techniques, the mechanisms responsible for FDG uptake do not allow differentiation among infection, sterile inflammation, and malignancy. However, in FUO, this appears to be an advantage rather than a disadvantage as all of these disorders are presented in patients with FUO. Therefore, FDG PET/CT can be used to guide additional diagnostic tests to arrive at the final diagnosis. Although FDG PET/CT is a relatively expensive imaging technique and the availability may still be more limited in some countries as compared with anatomical imaging techniques and conventional scintigraphy, it can be cost-effective in the diagnostic work-up of FUO when used at an early stage. It helps to establish an early diagnosis reducing hospitalisation days owing to a substantial number of routine diagnostic purposes and the repetition of unnecessary and unhelpful tests (8).

FDG PET in FUO

In FUO, several studies investigated the role of FDG PET (not combined with CT): three retrospective and six prospective studies in 396 patients with FUO (table 1). Two prospective studies compared FDG PET with ^{67}Ga-citrate scintigraphy in patients with FUO and found FDG PET to be helpful in 55% (9) and 41% (10) of patients. Kjaer et al. (11) compared ^{111}In-granulocyte scintigraphy with FDG PET in 19 patients with FUO. FDG PET was only helpful in 16% and sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were 50%, 46%, 30%, and 67%, respectively. Seshadri et al. (12) compared FDG PET with ^{111}In-granulocyte scintigraphy in 23 patients with FUO. FDG PET was helpful in 52% of patients with FUO. For FDG PET, sensitivity was 86%, specificity was 78%, PPV was 86%, and NPV was 78%. A small retrospective study in 16 patients with FUO showed that FDG PET led to the final diagnosis in 11 patients (69%) (13). Bleeker-Rovers et al. (14) retrospectively studied the contribution of FDG PET in 35 patients with FUO and concluded that FDG PET was helpful in 37% of patients. Sensitivity, specificity, PPV, and NPV were 93%, 90%, 87%, and 95%, respectively. Buysschaert et al. (15) performed a large prospective study of 74 patients with FUO of whom 39 patients (53%) had a final clinical diagnosis. FDG PET was helpful in 49% of these 39 patients. Bleeker-Rovers et al. (16) showed that FDG PET was helpful in 66% of patients with a final diagnosis and in 33% of all patients. Sensitivity, specificity, PPV, and NPV were 88%, 77%, 70%, and 92%, respectively. In a Japanese multicentre retrospective study, Kubota et al. (17) analysed the diagnostic results of FDG PET for FUO according to four groups of final diagnosis: infection; arthritis, vasculitis, or other autoimmune or collagen disease; tumour or granuloma; and other or unknown diagnosis of FUO. Sensitivity was highest in the tumour or granuloma group (100%, 7/7), followed by the infection group (89%, 24/27), the autoimmune group (65%, 11/17), and the other or unknown group (0%, 0/1). Overall helpfulness of FDG PET was 51%.

Comparing these studies about the role of FDG PET in FUO is rather challenging. In most of the studies the exact definition of FUO was different from the internationally accepted definition. Also, in four studies, the patient population was highly selected as not all patients with FUO referred to the hospital were recruited, but only those patients referred to the Nuclear Medicine Department (9, 17), patients referred for ^{111}In-granulocyte scintigraphy because of FUO by the Department of Infectious Diseases (11), and patients referred for FDG PET because of FUO by the Department of Internal Medicine (15). In the study of Kubota et al. an FDG PET/CT scanner was used in some cases, but the exact number of patients who underwent FDG PET/CT was not mentioned (17). Only the prospective study by Bleeker-Rovers et al. (16) used the standard definition of FUO and included all patients presenting with FUO to the hospital.

The two prospective studies of Meller et al. (9) and Blockmans (10) et al. compared FDG PET with ^{67}Ga-citrate scintigraphy in a total of 78 patients with FUO. FDG PET was superior to ^{67}Ga-citrate scintigraphy because the diagnostic value is at least similar to that of ^{67}Ga-citrate scintigraphy and the results are available within hours instead of days. Kjaer et al. compared FDG PET with ^{111}In-granulocyte scintigraphy in 19 patients with FUO. ^{111}In-granulocyte scintigraphy was concluded to be superior to FDG PET because of the high percentage of false-positive FDG PET images (37%) (11). However, in many patients included in this study no efforts were undertaken to confirm the abnormalities found on FDG PET. Specificity of FDG PET could have been increased if these additional examinations were performed (18). It is questionable whether this relatively high percentage of false positive results is sufficient justification to reject FDG PET as a valuable diagnostic technique in patients with FUO.

FDG PET/CT in FUO

Eleven retrospective studies and one prospective study have investigated the role of FDG PET/CT in 540 patients with FUO (table 2). Keidar et al. (19) investigated the value of FDG PET/CT in a prospective study of 48 patients with FUO. In 22 patients (46%), FDG PET/CT identified the underlying etiology of FUO. Sensitivity for FDG PET/CT was 100%, specificity was 81%, PPV was 81%, and NPV 100%. In this prospective study, FDG PET/CT was considered less helpful for the

Table 1. Literature on FDG PET in patients with FUO.

reference	study design	FUO definition	conclusion
Seshadri et al. (12)	prospective (n=23) comparison with ^{111}In-granulocyte	temp >38.3°C >3 weeks; no diagnosis after 1 week in-hospital investigation	FDG PET helpful in 52%, sensitivity 86%, specificity 78%, PPV 86%, NPV 78%
Kubota et al. (17)	retrospective (n=81)	temp >38.0°C >2 weeks; no diagnosis after certain obligated initial investigation	FDG PET helpful in 51%, sensitivity 81%, specificity 75%
Bleeker-Rovers et al. (16)	prospective (n=70)	temp >38.3°C >3 weeks; no diagnosis after certain obligated initial investigation	FDG PET helpful in 33%, PPV 70%, NPV 92%
Buysschaert et al. (15)	prospective (n=74)	temp >38.3°C >3 weeks; no diagnosis after 3 days in hospital or 3 outpatient visits; and referral for FDG PET/CT	FDG PET helpful in 26%
Kjaer et al. (11)	prospective (n=19) comparison with ^{111}In-granulocyte	temp >38.3°C >3 weeks; no diagnosis after 1 week in-hospital or outpatient evaluation; and referral for ^{111}In-granulocyte scintigraphy	FDG PET helpful in 16%, sensitivity 50%, specificity 46%, PPV 30%, NPV 67%
Bleeker-Rovers et al. (14)	retrospective (n=35)	temp >38.3°C >3 weeks; no diagnosis after 1 week in-hospital or outpatient evaluation	FDG PET helpful in 37%, PPV 87%, NPV 95%
Lorenzen et al. (13)	retrospective (n=16)	temp >38.0°C >3 weeks; increased ESR and CRP; inconclusive diagnostic tests	FDG PET helpful in 69%, PPV 92%, NPV 100%
Blockmans et al. (10)	prospective (n=58) comparison with ^{67}Ga	temp >38.3°C >3 weeks; no diagnosis after 3 days in-hospital investigations	FDG PET helpful in 41%, FDG PET superior to ^{67}Ga
Meller et al. (9)	prospective (n=20) comparison with ^{67}Ga	temp >38.3°C >3 weeks; no diagnosis after 1 week of diagnostic workup; and referral to nuclear medicine department	FDG PET helpful in 55%, PPV 92%, NPV 75%, FDG PET superior to ^{67}Ga

ESR = erythrocyte sedimentation rate, CRP = C-reactive protein, PPV = positive predictive value, NPV = negative predictive value

Table 2. Literature on FDG PET/CT in patients with FUO.

reference	study design	FUO definition	conclusion
Gafter-Gvili et al. (29)	retrospective (n=112)	temp >38.3°C >3 weeks; no diagnosis after 3 days or 1 week in-hospital or outpatient evaluation	FDG PET/CT helpful in 66%, sensitivity 72.2%, specificity 57.5%, PPV 74.2%, NPV 53.5%
Tokmak et al. (30)	retrospective (n=21)	temp >38.0°C >3 weeks; no diagnosis after 1 week in-hospital investigation	FDG PET/CT helpful in 60%, accuracy 90.5%, sensitivity 93.8%, specificity 80%
Kim et al. (28)	retrospective (n=48)	not defined	FDG PET/CT helpful in 52%, sensitivity 92%, specificity 23%
Crouzet et al. (27)	retrospective (n=79)	temp >38.3°C >3 weeks; no diagnosis after certain obligated initial investigation	FDG PET/CT helpful in 57%, sensitivity 98%, specificity 87%
Pedersen et al. (26)	retrospective (n=22)	temp >38.3°C >3 weeks; no diagnosis after 3d in-hospital investigation	FDG PET/CT helpful in 45%, PPV 83%, NPV 50%
Pelosi et al. (25)	retrospective (n=24)	temp >38.3°C >3 weeks; no diagnosis after certain obligated initial investigation	FDG PET/CT helpful in 46%
Sheng et al. (24)	retrospective (n=48)	not defined	FDG PET/CT helpful in 67%, sensitivity 89%, specificity 33%, PPV 80%, NPV 50%
Kei et al. (23)	retrospective (n=12)	temp >38.3°C >3 weeks; no diagnosis after 3 days in-hospital or 2 weeks outpatient evaluation	FDG PET/CT helpful in 42%
Ferda et al. (22)	retrospective (n=48)	not defined	FDG PET/CT helpful in 54%, sensitivity 97%, specificity 75%
Federici et al. (21)	retrospective (n=10)	temp >38.3°C >3 weeks; no diagnosis after 1 week in-hospital investigation	FDG PET/CT helpful in 50%
Balink et al. (20)	retrospective (n=68)	not defined	FDG PET/CT helpful in 56%
Keidar et al. (19)	prospective (n=48)	temp >38.3°C >3 weeks; no diagnosis after 1 week in-hospital investigation	FDG PET/CT helpful in 46%, sensitivity 100%, specificity 81%, PPV 81%, NPV 100%

PPV = positive predictive value, NPV = negative predictive value

diagnostic process than FDG PET/CT was in the retrospective studies. Balink et al. (20) retrospectively analysed 68 patients with FUO and in these patients FDG PET/CT was helpful in 56% of all patients. Federici et al. (21) investigated the role of FDG PET/CT in ten patients with FUO and in four patients with unexplained prolonged inflammatory syndrome. FDG PET/CT was helpful for 50% of patients with FUO. In 48 patients with FUO, Ferda et al. (22) concluded FDG PET/CT to be helpful in 54%. Sensitivity was 97% and specificity was 75%. Kei et al. (23) retrospectively included 12 patients with FUO and observed a helpfulness of 42% for FDG PET/CT. In the study of Sheng et al. (24) a final diagnosis was established for 36 (75%) patients with FUO. For FDG PET/CT, sensitivity was 89%, specificity was 33%, PPV was 80%, and NPV was 50%. In the retrospective study of Pelosi et al. (25) including 24 patients with FUO, FDG PET/CT was helpful in 46% of all patients. Pedersen et al. (26) concluded FDG PET/CT to be helpful in 45% in a study of 22 patients with FUO. Crouzet et al. (27) investigated the value of FDG PET/CT in 79 patients with FUO. FDG PET/CT was helpful in 57%, sensitivity and specificity were 98% and 87%, respectively. In a retrospective study of Kim et al. (28) including 48 patients with FUO, FDG PET/CT was helpful in 52%. In this study, sensitivity was 92% and specificity was 23% for FDG PET/CT. In a retrospective study of Gafter-Gvili et al. (29) 112 patients with FUO were included. FDG PET/CT was helpful in 74 patients (66%). Sensitivity, specificity, PPV, and NPV of FDG PET/CT were 72.2%, 57.5%, 74.2%, and 53.5%, respectively. Tokmak et al. (30) retrospectively included 50 patients with FUO. Of these patients, 25 underwent FDG PET/CT and 21 were appropriate for analysis. FDG PET/CT was helpful in 15 patients (60%). The accuracy, sensitivity, and specificity of this imaging modality were 90.5%, 93.8%, and 80%, respectively.

In these studies investigating the value of FDG PET/CT in patients with FUO, helpfulness of FDG PET/CT ranges between 42% and 67%. However, comparing these studies is again difficult. In five of the eleven retrospective studies, the definition of FUO was not further specified (20, 22, 24, 25, 28). Also, in three studies not all included patients underwent FDG PET/CT, because a protocol for FDG PET/CT was lacking (26, 28, 30). Also, in two studies the exact imaging technique of FDG PET/CT was not described (26, 28). In one study, patients were selected from patients with fever who were readmitted on the Department of Infectious Diseases and not from the total number of FUO patients (26). This leads to selection bias. The study of Keidar et al. (19) was the only study with a long-term follow-up of 12-36 months as part of the study. Unfortunately, the authors did not mention the precise duration of follow-up per patient. In all other studies no long-term follow-up was part of the study.

Comparing FDG PET and FDG PET/CT in patients with FUO, overall helpfulness for all studies investigating the role of FDG PET in FUO was 40% (corrected for study population) and overall helpfulness for all studies investigating the role of FDG PET/CT in FUO was 57% (corrected for study population). The difference in helpfulness of FDG PET and FDG PET/CT may be due to the fact that fused images with CT result in precise anatomical localisation of small lesions and better differentiation between physiological and pathological metabolic foci. However, studies investigating FDG PET/CT in patients with FUO were often retrospective which leads to bias. For a more exact assessment of the value of FDG PET/CT in the evaluation of FUO, a large prospective study using a structured diagnostic protocol with long-term follow-up would be more helpful.

Conclusions

Conventional scintigraphic techniques should be replaced by FDG PET/CT in the evaluation of patients with FUO. FDG PET and FDG PET/CT are valuable imaging techniques for the workup of FUO. It can be expected that FDG PET/CT is cost-effective in patients with FUO, because an adequate and early diagnosis in FUO limits the number of non-contributing and often invasive tests and duration of hospitalisation. Therefore, FDG PET/CT should become a routine procedure early in the evaluation of FUO.

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References

1. Petersdorf RG, Beeson PB. Fever of unexplained origin: report on 100 cases. Medicine. 1961;40:1-30
2. Petersdorf RG. Fever of unknown origin. An old friend revisited. Archives of internal medicine. 1992;152(1):21-2
3. de Kleijn EM, Vandenbroucke JP, van der Meer JW. Fever of unknown origin (FUO). I A. prospective multicenter study of 167 patients with FUO, using fixed epidemiologic entry criteria. The Netherlands FUO Study Group. Medicine. 1997;76(6):392-400
4. Bleeker-Rovers CP, Vos FJ, de Kleijn EM, Mudde AH, Dofferhoff TS, Richter C, et al. A prospective multicenter study on fever of unknown origin: the yield of a structured diagnostic protocol. Medicine. 2007;86(1):26-38
5. De Winter F, Vogelaers D, Gemmel F, Dierckx RA. Promising role of 18-F-fluoro-D-deoxyglucose positron emission tomography in clinical infectious diseases. European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology. 2002;21(4):247-57
6. Meller J, Sahlmann CO, Scheel AK. 18F-FDG PET and PET/CT in fever of unknown origin. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2007;48(1):35-45
7. Bleeker-Rovers CP, Boerman OC, Rennen HJ, Corstens FH, Oyen WJ. Radiolabeled compounds in diagnosis of infectious and inflammatory disease. Current pharmaceutical design. 2004;10(24):2935-50
8. Becerra Nakayo EM, Garcia Vicente AM, Soriano Castrejon AM, Mendoza Narvaez JA, Talavera Rubio MP, Poblete Garcia VM, et al. [Analysis of cost-effectiveness in the diagnosis of fever of unknown origin and the role of (18)F-FDG PET-CT: a

proposal of diagnostic algorithm]. Analisis de costo-efectividad en el diagnostico de fiebre de origen desconocido y el papel de la (18)F-FDG PET-TC: propuesta de algoritmo diagnostico. Revista espanola de medicina nuclear e imagen molecular. 2012;31(4):178-86
9. Meller J, Altenvoerde G, Munzel U, Jauho A, Behe M, Gratz S, et al. Fever of unknown origin: prospective comparison of [18F]FDG imaging with a double-head coincidence camera and gallium-67 citrate SPET. European journal of nuclear medicine. 2000;27(11):1617-25
10. Blockmans D, Knockaert D, Maes A, De Caestecker J, Stroobants S, Bobbaers H, et al. Clinical value of [(18)F]fluoro-deoxyglucose positron emission tomography for patients with fever of unknown origin. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2001;32(2):191-6
11. Kjaer A, Lebech AM, Eigtved A, Hojgaard L. Fever of unknown origin: prospective comparison of diagnostic value of 18F-FDG PET and 111In-granulocyte scintigraphy. European journal of nuclear medicine and molecular imaging. 2004;31(5):622-6
12. Seshadri N, Sonoda LI, Lever AM, Balan K. Superiority of 18F-FDG PET compared to 111In-labelled leucocyte scintigraphy in the evaluation of fever of unknown origin. The Journal of infection. 2012;65(1):71-9
13. Lorenzen J, Buchert R, Bohuslavizki KH. Value of FDG PET in patients with fever of unknown origin. Nuclear medicine communications. 2001;22(7):779-83
14. Bleeker-Rovers CP, de Kleijn EM, Corstens FH, van der Meer JW, Oyen WJ. Clinical value of FDG PET in patients with fever of unknown origin and patients suspected of focal infection or inflammation. European journal of nuclear medicine and molecular imaging. 2004;31(1):29-37
15. Buysschaert I, Vanderschueren S, Blockmans D, Mortelmans L, Knockaert D. Contribution of (18)fluoro-deoxyglucose positron emission tomography to the work-up of patients with fever of unknown origin. European journal of internal medicine. 2004;15(3):151-6
16. Bleeker-Rovers CP, Vos FJ, Mudde AH, Dofferhoff AS, de Geus-Oei LF, Rijnders AJ, et al. A prospective multi-centre study of the value of FDG-PET as part of a structured diagnostic protocol in patients with fever of unknown origin. European journal of nuclear medicine and molecular imaging. 2007;34(5):694-703
17. Kubota K, Nakamoto Y, Tamaki N, Kanegae K, Fukuda H, Kaneda T, et al. FDG-PET for the diagnosis of fever of unknown origin: a Japanese multi-center study. Annals of nuclear medicine. 2011;25(5):355-64
18. Bleeker-Rovers CP, Corstens FH, Van Der Meer JW, Oyen WJ. Fever of unknown origin: prospective comparison of diagnostic value of (18)F-FDG PET and (111)In-granulocyte scintigraphy. European journal of nuclear medicine and molecular imaging. 2004;31(9):1342-3; author reply 4.
19. Keidar Z, Gurman-Balbir A, Gaitini D, Israel O. Fever of unknown origin: the role of 18F-FDG PET/CT. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2008;49(12):1980-5
20. Balink H, Collins J, Bruyn GA, Gemmel F. F-18 FDG PET/CT in the diagnosis of fever of unknown origin. Clinical nuclear medicine. 2009;34(12):862-8
21. Federici L, Blondet C, Imperiale A, Sibilia J, Pasquali JL, Pflumio F, et al. Value of (18)F-FDG PET/CT in patients with fever of unknown origin and unexplained prolonged inflammatory syndrome: a single centre analysis experience. International journal of clinical practice. 2010;64(1):55-60
22. Ferda J, Ferdova E, Zahlava J, Matejovic M, Kreuzberg B. Fever of unknown origin: a value of (18)F-FDG PET/CT with integrated full diagnostic isotropic CT imaging. European journal of radiology. 2010;73(3):518-25
23. Kei PL, Kok TY, Padhy AK, Ng DC, Goh AS. [18F] FDG PET/CT in patients with fever of unknown origin: a local experience. Nuclear medicine communications. 2010;31(9):788-92
24. Sheng JF, Sheng ZK, Shen XM, Bi S, Li JJ, Sheng GP, et al. Diagnostic value of fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography in patients with fever of unknown origin. European journal of internal medicine. 2011;22(1):112-6
25. Pelosi E, Skanjeti A, Penna D, Arena V. Role of integrated PET/CT with [(1)(8)F]-FDG in the management of patients with fever of unknown origin: a single-centre experience. La Radiologia medica. 2011;116(5):809-20
26. Pedersen TI, Roed C, Knudsen LS, Loft A, Skinhoj P, Nielsen SD. Fever of unknown origin: a retrospective study of 52 cases with evaluation of the diagnostic utility of FDG PET/CT. Scandinavian journal of infectious diseases. 2012;44(1):18-23
27. Crouzet J, Boudousq V, Lechiche C, Pouget JP, Kotzki PO, Collombier L, et al. Place of (18)F-FDG-PET with computed tomography in the diagnostic algorithm of patients with fever of unknown origin. European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology. 2012;31(8):1727-33
28. Kim YJ, Kim SI, Hong KW, Kang MW. Diagnostic value of 18F-FDG PET/CT in patients with fever of unknown origin. Internal medicine journal. 2012;42(7):834-7
29. Gafter-Gvili A, Raibman S, Grossman A, Avni T, Paul M, Leibovici L, et al. [18F]FDG PET/CT for the diagnosis of patients with fever of unknown origin. QJM : monthly journal of the Association of Physicians. 2015;108(4):289-98
30. Tokmak H, Ergonul O, Demirkol O, Cetiner M, Ferhanoglu B. Diagnostic contribution of (18)F-FDG PET/CT in fever of unknown origin. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases. 2014;19:53-8

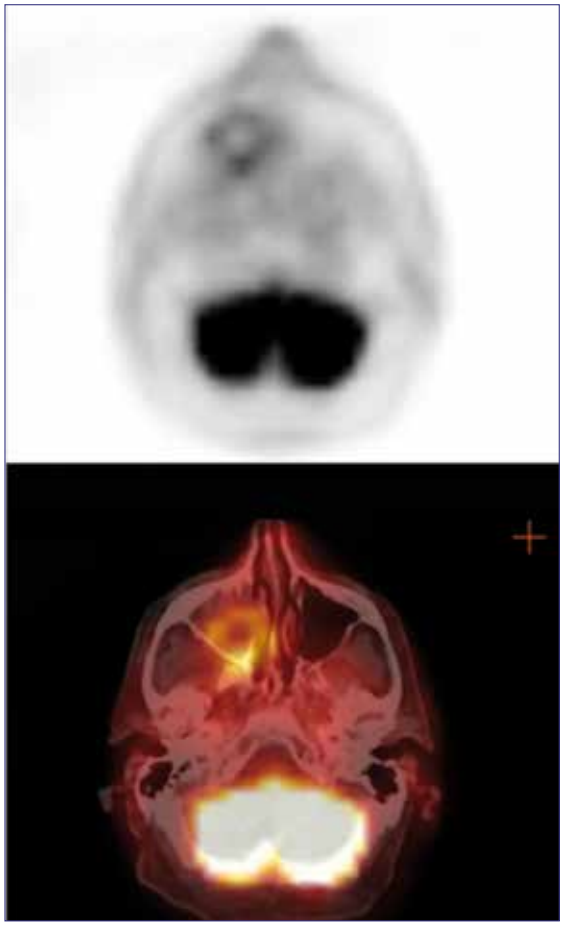

Figure 1

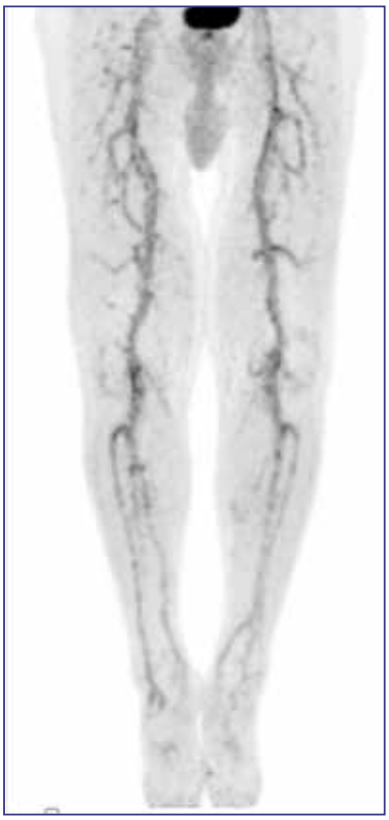

Figure 2

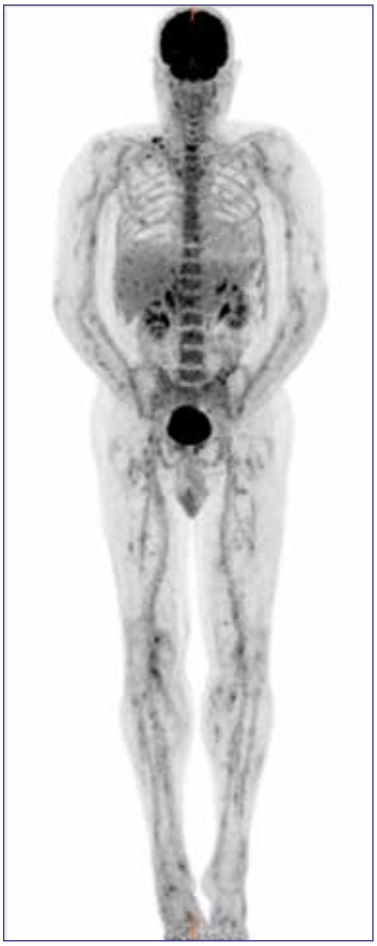

Figure 3

Figure 1. A 68-year-old man presented with fever and malaise. Physical examination showed no abnormalities. The erythrocyte sedimentation rate was increased with normal leukocyte rate, normal creatinine level, and liver function tests. FDG PET/CT showed pathologic FDG uptake in the right maxillary sinus. This patient was diagnosed with chronic sinusitis and was referred to the otorhinolaryngologist. After treatment his fever disappeared.

Figure 2. A 75-year-old man presented with weight loss, night sweats, fever, and recent vision loss of the left eye. Physical examination was normal. The erythrocyte sedimentation rate was increased, with normal leukocyte count, creatinine level, and liver function. FDG PET/CT showed pathologic FDG uptake in the large arteries in both legs. He was diagnosed with large vessel vasculitis and was treated with high dosage corticosteroids. His fever disappeared.

Figure 3. A 65-year-old man presented with fever and myalgia. Physical examination showed no abnormalities. The erythrocyte sedimentation rate was increased, with normal leukocyte count, creatinine level, and liver function. FDG PET/CT showed irregular FDG uptake with hotspots in large, medium, and small arteries. He was diagnosed with polyarteritis nodosa. Treatment was started with high dosage corticosteroids and cyclophosphamide.

The value of ^{18}F-FDG PET/CT in metastatic infectious disease

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Abstract

Vos FJ, Kouijzer IJE, Oyen WJG, Bleeker-Rovers CP. The value of ^{18}F-FDG PET/CT in metastatic infectious disease. Clinically silent metastatic infectious foci are a well-known complication in one third of patients with Gram-positive bacteraemia. Delayed detection of these metastatic foci can result in increased morbidity, relapse of infection and death due to incomplete eradication.FDG PET/CT has proved to be helpful in delineation of these clinically silent metastatic infectious foci resulting in early treatment adjustment and therefore decreased relapse rates and mortality.
A cost effectiveness analysis showed incremental costs of routine FDG PET/CT is well within the acceptable range. Even in a subgroup of patients with infective endocarditis, introduction of FDG PET/CT searching for extracardiac metastatic infectious foci tends to diminish relapse rates. New generation PET-scanners and adjusted protocols are promising in the detection of infectious endocarditis itself, especially concerning prosthetic valves. **Tijdschr Nucl Geneesk 2015; 37(4):1476**

Introduction

Multifocal infection is an important complication of Gram-positive bacteraemia. It is known that complicating infectious foci occur in approximately one third of patients with *Staphylococcus aureus* and *Streptococcus species* bacteraemia (SAB and SSB) (1,2,3). In high risk patients with SAB, endocarditis is found in 19-32% when routine echocardiography is performed (4,5). In clinical settings in which echocardiography is performed symptom-based, e.g. because of the presence of cardiac murmurs, endocarditis is revealed in only 5-13% of patients with high risk SAB, missing a significant part of endocarditis cases (3,4,6). In native valve endocarditis (NVE), which is in fact a metastatic infectious focus in itself, extracardiac foci play an important role in treatment failure (4,7). In 42-59% of patients with endocarditis, clinically relevant metastatic infectious foci are present (1,6). Up to 32% of metastatic infectious foci lack localising signs and symptoms, thereby increasing the risk of remaining undiagnosed and (partly) untreated. As infection-related mortality is significantly higher among patients with complicating infectious foci, increased morbidity and mortality can be influenced favourably by early recognition and treatment of these clinically silent metastatic infectious foci (1,3,8,9). Patients at high risk for the presence of complicated disease are relatively easy to identify using a set of clinical parameters (table 1) (3, 6, 10, 11).
To date there are no guidelines describing a diagnostic protocol for the detection of metastatic infectious foci in patients with Gram-positive bacteraemia, except for the recommendation to perform echocardiography in patients with SAB (5). Since conventional radiological techniques only visualise a fixed part of the body, they are almost always used for symptom-guided imaging. During the last decade, whole body scanning using ^{18}F-FDG PET/CT has emerged as an important imaging technique in infectious diseases, especially in infections which are difficult to diagnose, for example vascular graft infections and spondylodiscitis (12).
In general, sensitivity of ^{18}F-FDG PET/CT in diagnosing infections compares favourably to other diagnostic modalities, since it reveals early metabolic changes instead of anatomical changes. Lower specificity due to ^{18}F-FDG accumulation in conditions involving leukocyte activation other than infection (e.g. vasculitis and malignancy), may be a potential drawback, but can often be overcome by correlation with previous history and additional imaging techniques (13).
A growing number of case reports and case series appeared in literature in which ^{18}F-FDG PET/CT delineated clinically important, but unsuspected metastatic infectious foci. Studies on the subject are scarce, but promising (14). Two studies on the use of ^{18}F-FDG PET/CT in bloodstream infections were published, with an additional third study in 2012 on the cost-effectiveness of routine ^{18}F-FDG PET/CT in high risk patients with Gram-positive bacteraemia (table 2), six studies address the performance of ^{18}F-FDG PET/CT in clinically suspected infective endocarditis (table 3), and five study the use of ^{18}F-FDG PET/CT in the detection of extracardiac foci in endocarditis (table 4). These studies will all be discussed in this concise review.

Table 1. Clinical criteria for the identification of patients at risk for metastatic infectious disease.

community acquisition of infectious disease
signs of infection >48 hours before initiation of appropriate treatment
positive blood cultures >48 hours after initiation of appropriate treatment
fever >72 hours after initiation of appropriate treatment

Table 2. Literature on the value of ^{18}F-FDG PET/CT in metastatic infectious disease.

reference	study design (N study / control)	aim	outcome
Vos et al. (2)	prospective matched control (115/230)	outcome: relapse rate, mortality	Se 100%, Sp 87%, PPV 89%, NPV 100% relapse rate (SAB) 1.4-8.9% (p=0.04) mortality 19.1-32.2% (p=0.01)
Bleeker-Rovers et al. (15)	retrospective (40)	detecting clinically relevant new foci	PPV 91%, NPV 100% relevant new foci in 45%
Vos et al. (16)	prospective matched control (115/230)	cost analysis routine PET/CT	cost-effective/ incremental costs due to treatment of clinically relevant foci

Se = sensitivity
Sp = specificity
PPV = positive predictive value
NPV = negative predictive value
SAB = *Staphylococcus aureus* bacteraemia

Table 3. Literature on the value of ^{18}F-FDG PET/CT in patients with clinically suspected infective endocarditis.

reference	study design (N type of endocarditis)	aim	outcome
Kouijzer et al. (21)	prospective (NVE 66/PVE 66)	detecting endocarditis	Se 39%, Sp 93%, PPV 64%, NPV 82%
Rouzet et al. (25)	prospective (PVE 39)	detecting endocarditis	Se 93%, Sp 71%, PPV 68%, NPV 94%
Ricciardi et al. (26)	retrospective (NVE 7 / PVE 20)	detecting endocarditis	PVE, Se PET/CT 85%, TTE 69%, Duke criteria 77% (p<0.001)
Graziosi et al. (27)	prospective (cardiac device related 27)	detecting endocarditis	Se 63%, Sp 86%, PPV 77%, NPV 76%
Saby et al. (28)	prospective (PVE 72)	detecting endocarditis	Se 73%, Sp 80%, PPV 85%, NPV 67%, increases accuracy of modified Duke criteria
Pizzi et al. (29)	prospective (PVE 92)	detecting endocarditis	Se 87%, Sp 92.1%, PPV 93.6%, NPV 84.3% increases accuracy of modified Duke criteria

Se = sensitivity
Sp = specificity
PPV = positive predictive value
NPV = negative predictive value
NVE = native valve endocarditis
PVE = prosthetic valve endocarditis
TTE = transthoracic echocardiography

Table 4. Literature on the value of ^{18}F-FDG PET/CT in extracardiac metastatic infectious disease in patients with infective endocarditis.

reference	study design (N)	aim	outcome
van Riet et al. (30)	prospective (25)	detecting clinically relevant extracardiac new foci in endocarditis	clinically relevant new foci in 7/25 (28%)
Bonfigliolo et al. (31)	prospective (71)	detecting clinically relevant extracardiac new foci in endocarditis	clinically relevant new foci in 17/71 (24%)
Kestler et al. (32)	prospective matched control (47)	detecting extracardiac foci, evaluating relapse rate	Se 100%, Sp 80%, PPV 90%, NPV 100%, relapse rate from 9.6% to 4.2% (p=0.25)
Asmar et al. (33)	prospective (72)	detecting clinically relevant extracardiac new foci in endocarditis	clinically relevant new foci in 11/72 (15%)
Orvin et al. (34)	prospective (40)	detecting clinically relevant extracardiac new foci in endocarditis	extracardiac foci in 42.5%, treatment modified in 35%

Se = sensitivity PPV = positive predictive value
Sp = specificity NPV = negative predictive value

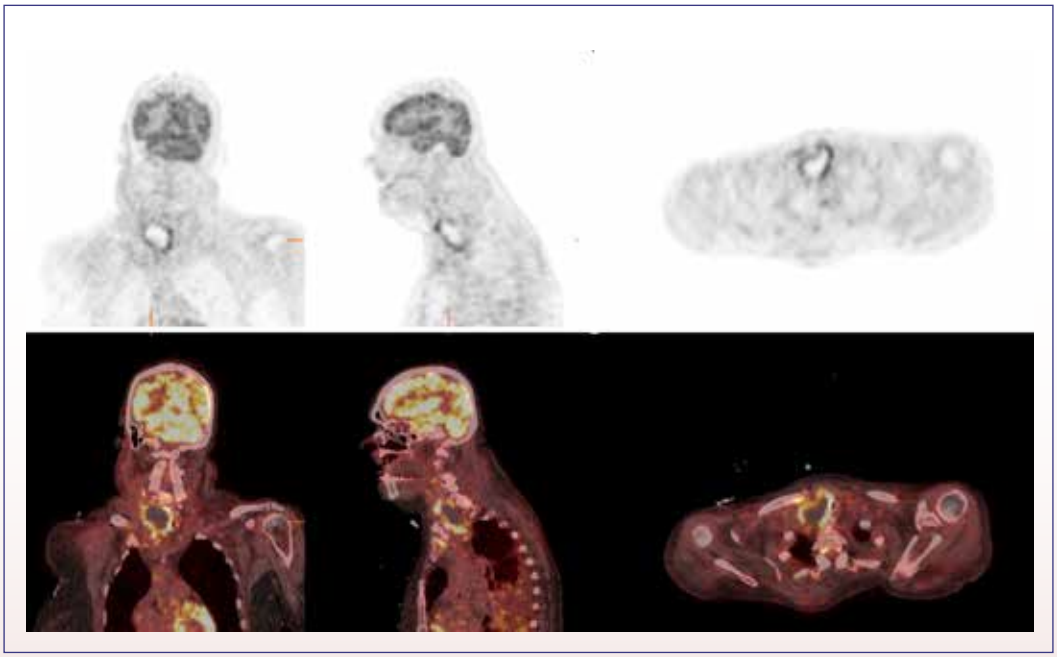

Figure 1. An 68-year old woman admitted with a chronic Staphylococcus aureus infection of an arthrodesis of her right foot. Despite extensive debridement and high dose flucloxacillin she remained febrile. Routine examination including chest X-rays did not show any abnormalities. ^{18}F-FDG PET/CT revealed a large retrosternal abscess, which was subsequently drained.

^{18}F-FDG PET/CT for the detection of infectious metastatic foci in bacteraemia

It has been suggested that early treatment adjustment in the presence of clinically silent infectious foci might lead to a decrease in relapse rate, due to the fact that a smaller amount of foci would remain untreated (2, 8). This concept of early detection of metastatic infectious foci using ^{18}F-FDG PET/CT was evaluated in two studies. In a retrospective cohort of forty patients with bloodstream infection, ^{18}F-FDG PET revealed a clinically relevant new focus in 45% of cases, even though a median of four conventional diagnostic tests had been performed prior to ^{18}F-FDG PET (15). In the second study, 115 non-neutropenic patients with Gram-positive bacteraemia were prospectively included (2). Patients with positive blood cultures growing *Staphylococcus aureus, Streptococcus species* or *Enterococcus species* were included when a clinical risk factor was present (table 1) and were then evaluated by ^{18}F-FDG PET/CT within two weeks after the first positive blood culture. Results were compared with a matched historical control group of 230 patients in whom no ^{18}F-FDG PET/CT was performed. Diagnostic procedures were only performed symptom-guided in this group. Significantly more patients were diagnosed with metastatic foci in the study group (68% versus 36%). Of note, in the ^{18}F-FDG PET/CT group almost 40% of patients showed multifocal disease, compared to 27% of controls. Possible foci detected with ^{18}F-FDG PET/CT included endovascular, ocular and pulmonary foci, osteomyelitis, infected joint prosthesis and epidural abscesses. In more than half of the patients diagnosed with endocarditis another metastatic infectious focus was found, often leading to adjustment of therapy. ^{18}F-FDG PET/CT was the first to delineate infectious foci in approximately one third of patients. Relapse rates decreased from 7.4% to 2.6 % among study patients (p=0.09), and from 8.9% to 1.4% in patients with *Staphylococcus aureus* (*p*=0.04). Overall mortality after six months decreased significantly from 32% to 19% in the ^{18}F-FDG PET/CT group. In conclusion, the addition of ^{18}F-FDG PET/CT to the work-up of high risk patients with Gram-positive bacteraemia is a valuable technique that results in lower mortality rates.
A cost-effectiveness analysis on the use of ^{18}F-FDG PET/CT in patients with Gram-positive bacteraemia was also performed (16). Alongside the clinical study, healthcare related costs were collected, influencing total costs due to the addition of ^{18}F-FDG PET/CT (2). The diagnostic regimen incorporating ^{18}F-FDG PET/CT resulted in an increase of incremental costs of EUR 6.303 due to more in-hospital treatment of clinically relevant metastatic infectious foci. The increase of costs was mainly due to admission days (mean EUR 4.421). Costs per mortality case prevented were EUR 48.325 and are well within the range that is considered to be efficient by Dutch guidelines. Cost-effectiveness would further improve when patient management should be based on ^{18}F-FDG PET/CT abnormalities alone, without the confirmation by conventional radiological techniques that was obligatory in the study. It was concluded that costs should not be a reason to leave the ^{18}F-FDG PET/CT out of the work-up of metastatic infectious disease.

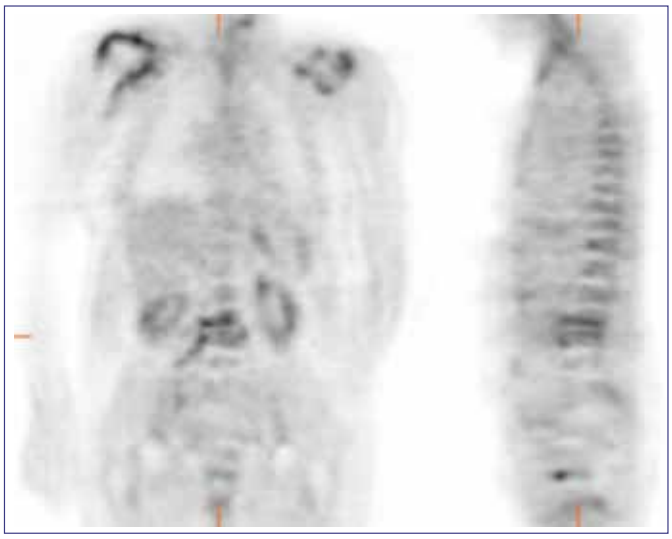

Figure 2. A 57-year old woman was admitted with Staphylococcus aureus mitral valve endocarditis and subsequent multifocal spondylodiscitis and septic arthritis of both shoulders requiring prolonged treatment and drainage.

^{18}F-FDG PET/CT in diagnosing endocarditis

To date, one should distinguish studies trying to establish infective endocarditis and studies aiming to detect extracardiac metastatic infectious foci complicating infectious endocarditis.
Currently, ^{18}F-FDG PET/CT is not incorporated in guidelines for the diagnosis of infective endocarditis (17). Infective endocarditis is diagnosed using the revised Duke criteria based on both clinical and microbiological findings and echocardiography (17). Sensitivity of the Duke criteria is a limitation in clinical practice. Although case reports and small case series suggest a promising role for the detection of infective endocarditis, ^{18}F-FDG PET/CT is frequently considered unsuitable in detecting infective endocarditis, mainly due to physiological cardiac ^{18}F-FDG uptake and small lesion size (13, 18-20). A recent study investigated the diagnostic value of ^{18}F-FDG PET/CT in detecting infectious endocarditis in 72 patients with definite endocarditis (26). All patients underwent both ^{18}F-FDG PET/CT and echocardiography. Infectious endocarditis was defined according to the revised Duke criteria. For ^{18}F-FDG PET/CT, sensitivity was only 39%, specificity was 93%, positive predictive value (PPV) was 64%, and negative predictive value (NPV) was 82%. Because of this low sensitivity, it was concluded that ^{18}F-FDG PET/CT is currently unsuitable for diagnosing endocarditis, but its high specificity is indeed promising (21). Newer (time-of-flight) PET/CT scanners have improved resolution and there is promising evidence that a 'low carbohydrate, fat allowed' diet will adequately suppress cardiac ^{18}F-FDG uptake (22, 23). Furthermore, delayed imaging could increase the diagnostic

accuracy of ^{18}F-FDG PET/CT concerning the detection of small intracardiac infectious foci, as demonstrated by a case report recently published (24). These improvements may increase sensitivity as is suggested in five recent studies, which are discussed below.

All studies compared ^{18}F-FDG PET/CT with modified Duke criteria in patients with both NVE and prosthetic valve endocarditis (PVE). Especially in PVE, ^{18}F-FDG PET/CT improves diagnostic accuracy (25-29). Performance of ^{18}F-FDG PET/CT was compared separately with radiolabelled leucocyte scintigraphy in 39 patients with clinically suspected PVE and inconclusive echocardiography results (25). The final diagnosis was made by an expert panel based on the modified Duke criteria after a follow-up of three months. Positive and negative predictive value (PPV and NPV) were 68% and 94% for ^{18}F-FDG PET/CT and 100% and 81% for leucocyte scintigraphy. ^{18}F-FDG PET/CT showed higher sensitivity than leucocyte scintigraphy. The authors stated that ^{18}F-FDG PET/CT was the preferred imaging technique. Ricciardi et al. retrospectively examined 27 patients with suspected infective endocarditis (26). In this study, the majority of patients had PVE (20 patients). ^{18}F-FDG PET/CT showed a sensitivity of 85% , versus 69% for transoesophageal echocardiography and 77% for the Duke criteria. In the study of Graziosi et al., that prospectively included 27 patients with an implanted cardiac device related infective endocarditis (CDE), the performance of ^{18}F-FDG PET/CT was evaluated (27). Of 10 patients with a positive ^{18}F-FDG PET/CT, infective endocarditis was proven in 7. In 17 patients with a negative examination, 4 scans were false negative (since the patients met the modified Duke criteria). Some patients had a technically suboptimal examination. Still ^{18}F-FDG PET/CT increased the diagnostic accuracy of the modified Duke criteria. In a large prospective study, 72 consecutive patients with suspected PVE were analysed (28) and received an ^{18}F-FDG PET/CT at admission. The addition of abnormal ^{18}F-FDG uptake around the prosthetic valve as a new major criterion significantly increased the sensitivity of the modified Duke criteria at admission (70% versus 97%), due to a significant reduction in the number of possible PVE cases from 40 to 23 (56% versus 32%, $p < 0.0001$).
In the most recent study, 92 patients with suspected PVE or CDE were prospectively included (29), supporting the addition of the abovementioned ^{18}F-FDG uptake as a diagnostic criterion. Echocardiography, ^{18}F-FDG PET/CT and cardiac CT angiography (CTA) were performed. A final diagnosis was reached by the infective endocarditis unit. ^{18}F-FDG PET/CT and echocardiography were concordant in 54% of cases. Diagnostic performance of ^{18}F-FDG PET/CT was better than the modified Duke criteria in diagnosing PVE (PPV 93.6% versus 92.9%, NPV 84.3 versus 84.3%). Further improvement was reached using the Duke criteria combined with PET/CTA (PPV 92.8%, NPV 88.3%). It substantially reduced the rate of doubtful cases from 20% to 8%.

^{18}F-FDG PET/CT for the detection of extracardiac metastatic infectious foci in endocarditis

The first study on the use of ^{18}F-FDG PET/CT in detecting extracardiac metastatic infectious foci in patients with infective endocarditis was published in 2010 (30). This small prospective study among 24 patients with 25 episodes of definite infectious endocarditis, the value of ^{18}F-FDG PET/CT in diagnosing septic embolisms was investigated. Standard work-up in this study consisted of investigation of the skin for superficial embolism, fundoscopy for retinal embolism, duplex examination of suspected vessels, echography, and CT on indication. ^{18}F-FDG PET/CT was performed in all patients and revealed a septic embolism in 11 episodes (44%). In 7 positive cases (28%) there was no clinical suspicion on the presence of metastatic infectious foci prior to ^{18}F-FDG PET/CT. The second study investigated 71 patients with suspected infectious endocarditis (31). ^{18}F-FDG PET/CT detected unexpected extracardiac septic embolisms in 17 patients (24%), which were confirmed using conventional techniques. Spondylodiscitis and pulmonary embolism were most often leading to possible changes in therapeutic management.

In the study of Kestler et al., ^{18}F-FDG PET/CT was able to detect septic embolisms in 57% of the 47 patients with definite infectious endocarditis (32), compared to only 18% in a matched control group of 94 patients with definite endocarditis without ^{18}F-FDG PET/CT evaluation ($p<0.01$). In 55% of true positive patients, ^{18}F-FDG PET/CT was the first to delineate extracardiac foci. Intravascular or endovascular prosthetic infection, septic pulmonary embolism, and one case of infected soft tissue around the pacemaker led to a change in therapeutic management. The routine use of ^{18}F-FDG PET/CT was associated with a twofold reduction in the number of relapses (9.6 versus 4.2%, p=0.25). In another study by Asmar et al., ^{18}F-FDG PET/CT was added to the regular work-up in 72 patients with infective endocarditis (33). A total number of 114 lesions were detected of which 65 were true positive and 25 were first detected by ^{18}F-FDG PET/CT. In 11 of 72 patients (15%) foci were considered clinically relevant. The most recent study also aimed to evaluate the clinical impact of ^{18}F-FDG PET/CT on medical management (34). In 40 consecutive patients with confirmed infective endocarditis according to the Duke criteria, ^{18}F-FDG PET/CT was performed within fourteen days from diagnosis. Extracardiac foci were found in 17 patients (42%), of which 8 patients experienced no symptoms. Treatment was modified in 14 of 40 (35%) patients.

Conclusions

In patients with Gram-positive bacteraemia or endocarditis thorough history taking, physical examination, and close observation should delineate high risk patients based on a set of clinical criteria (table 1). Studies show that in a large portion of patients asymptomatic metastatic infectious foci are

present. In high risk patients with Gram-positive bacteraemia, a structured diagnostic protocol including echocardiography and ^{18}F-FDG PET/CT aimed at the detection of these asymptomatic foci, improves outcome as both relapse rate and mortality decrease. A cost-effectiveness analysis shows incremental costs due to in-hospital treatment of clinically relevant metastatic foci are well within the acceptable range, due to a decrease in relapse rates and subsequent readmissions and tailored treatment duration in patients without metastatic infectious foci. Therefore, ^{18}F-FDG PET/CT should be performed in all patients with high risk Gram-positive bacteraemia.

In patients with infective endocarditis, routine use of ^{18}F-FDG PET/CT in order to delineate extracardiac foci also tends to improve outcome. Besides, new generation ^{18}F-FDG PET/CT scanners and protocols are promising in detecting infective endocarditis itself, opening doors for the incorporation of ^{18}F-FDG PET/CT in diagnostic endocarditis guidelines.

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References

1. Vos FJ, Kullberg BJ, Sturm PD, et al. Metastatic infectious disease and clinical outcome in Staphylococcus aureus and Streptococcus species bacteremia. Medicine. 2012;91:86–94
2. Vos FJ, Bleeker-Rovers CP, Sturm PD, et al. 18F-FDG PET/CT for detection of metastatic infection in Gram-positive bacteremia. J Nucl Med. 2010;51:1234–40
3. Jensen AG, Wachmann CH, Espersen F, et al. Treatment and outcome of Staphylococcus aureus bacteremia: a prospective study of 278 cases. Arch Intern Med. 2002;162:25–32
4. Vos FJ, Bleeker-Rovers CP, Sturm PD, et al. Endocarditis: effects of routine echocardiography during Gram-positive bacteraemia. Neth J Med. 2011;69:335-40
5. Fowler VG Jr, Li J, Corey GR, et al. Role of echocardiography in evaluation of patients with Staphylococcus aureus bacteremia: experience in 103 patients. J Am Coll Cardiol. 1997;30:1072-8
6. Fowler VG Jr, Sanders LL, Sexton DJ, et al. Outcome of Staphylococcus aureus bacteremia according to compliance with recommendations of infectious diseases specialists: experience with 244 patients. Clin Infect Dis. 1998;27:478-86
7. Hill EE, Herijgers P, Claus P, et al. Infective endocarditis: changing epidemiology and predictors of 6-month mortality: a prospective cohort study. Eur Heart J. 2007;28:196-203
8. Jensen AG. Importance of focus identification in the treatment of Staphylococcus aureus bacteraemia. J Hosp Infect. 2002;52:29-36
9. Rieg S, Peyerl-Hoffmann G, de With K, et al. Mortality of S. aureus bacteraemia and infectious diseases specialist consultationVa study of 521 patients in Germany. J Infect. 2009;59:232-9
10. Lesens O, Hansmann Y, Storck D, Christmann D. Risk factors for metastatic infection in patients with Staphylococcus aureus bacteremia with and without endocarditis. Eur J Intern Med. 2003;14:227–31
11. Fowler VG Jr, Olsen MK, Corey GR, et al. Clinical identifiers of complicated Staphylococcus aureus bacteremia. Arch Intern Med. 2003;163:2066-72
12. Kumar R, Basu S, Torigian D, et al. Role of modern imaging techniques for diagnosis of infection in the era of 18F-fluorodeoxyglucose positron emission tomography. Clin Microbiol Rev. 2008;21:209-24
13. Bleeker-Rovers CP, Vos FJ, van der Graaf WT, Oyen WJ. Nuclear medicine imaging of infection in cancer patients (with emphasis on FDG-PET). Oncologist. 2011;16:980-91
14. Kouijzer IJ, Bleeker-Rovers CP, Oyen WJ. 18F-FDG PET/CT for the Detection of Septic Embolisms in Patients with Infectious Endocarditis. J Nucl Med. 2014;55:1045-6
15. Bleeker-Rovers CP, Vos FJ, Wanten GJ, et al. 18F-FDG PET in detecting metastatic infectious disease. J Nucl Med. 2005;46:2014-9
16. Vos FJ, Bleeker-Rovers CP, Kullberg BJ, Adang EM, Oyen WJ. Cost-effectiveness of routine 18F-FDG PET/CT in high-risk patient with Gram-positive bacteremia. J Nucl Med. 2011;52:1673–78
17. Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis. 2000;30:633–8
18. Vind SH, Hess S. Possible role of PET/CT in infective endocarditis. J Nucl Cardiol. 2010;17:516–9
19. Yeh CL, Liou JY, Chen SW, Chen YK. Infective endocarditis detected by 18F-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography in a patient with occult infection. Kaohsiung J Med Sci. 2011;27:528–31
20. Millar BC, Prendergast BD, Alavi A, Moore JE. 18FDG-positron emission tomography (PET) has a role to play in the diagnosis and therapy of infective endocarditis and cardiac device infection. Int J Cardiol. 2013;167:1724–36
21. Kouijzer IJE, Vos FJ, Janssen MJR, et al. The value of 18F-FDG PET/CT in diagnosing infectious endocarditis. Eur J Nucl Med Mol Imaging. 2013;40:1102–7
22. Balink H, Hut E, Pol T, Flokstra FJ, Roef M. Suppression of 18F-FDG myocardial uptake using a fat allowed carbohydrate-restricted diet. J Nucl Med Technol. 2011;39:185–9
23. Coulden R, Chung P, Sonnex E, et al. Suppression of myocardial 18F-FDG uptake with a preparatory 'Atkins-style' low-carbohydrate diet. Eur Radiol. 2012;22:2221–8
24. Caldarella C, Leccisotti L, Treglia G, et al. Which is the optimal acquisition time for FDG PET/CT images in patients with infectious endocarditis? J Nucl Cardiol. 2013;20:307–9
25. Rouzet F, Chequer R, Benali K, et al. Respective performance of 18F-FDG PET and radiolabeled leukocyte scintigraphy for the diagnosis of prosthetic valve endocarditis. J Nucl Med. 2014;55:1980-5
26. Ricciardi A, Sordillo P, Ceccarelli L, et al. 18-Fluoro-2-deoxyglucose positron emission tomography-computed tomography: an additional tool in the diagnosis of prosthetic valve endocarditis. Int J Infect Dis. 2014;28:219-24
27. Graziosi M, Nanni C, Lorenzini M, et al. Role of ^{18}F-FDG PET/

CT in the diagnosis of infective endocarditis in patients with an implanted cardiac device: a prospective study. Eur J Nucl Med Mol Imaging. 2014;41:1617-23
28. Saby L, Laas O, Habib G, et al. Positron emission tomography/computed tomography for diagnosis of prosthetic valve endocarditis: increased valvular 18F-fluorodeoxyglucose uptake as a novel major criterion. J Am Coll Cardiol. 2013;61:2374-82
29. Pizzi MN, Roque A, Fernández-Hidalgo N, et al. Improving the Diagnosis of Infective Endocarditis in Prosthetic Valves and Intracardiac Devices with 18F-FDG PET/CT-Angiography: Initial Results at an Infective Endocarditis Referral Center. Circulation. 2015 Aug 14 [Epub ahead of print]
30. Van Riet J, Hill EE, Gheysens O, et al. (18)F-FDG PET/CT for early detection of embolism and metastatic infection in patients with infective endocarditis. Eur J Nucl Med Mol Imaging. 2010;37:1189-97
31. Bonfiglioli R, Nanni C, Morigi JJ, et al. ^{18}F-FDG PET/CT diagnosis of unexpected extracardiac septic embolisms in patients with suspected cardiac endocarditis. Eur J Nucl Med Mol Imaging. 2013;40:1190-6
32. Kestler M, Muñoz P, Rodríguez-Créixems M, et al. Role of (18) F-FDG PET in Patients with Infectious Endocarditis. J Nucl Med. 2014;55:1093-8
33. Asmar A, Ozcan C, Diederichsen AC, Thomassen A, Gill S. Clinical impact of 18F-FDG PET/CT in the extra cardiac work-up of patients with infective endocarditis. Eur Heart J Cardiovasc Imaging. 2014;15:1013-9
34. Orvin K, Goldberg E, Bernstine H, et al. The role of 18F-FDG PET/CT imaging in early detection of extra-cardiac complications of infective endocarditis. Clin Microbiol Infect. 2015;21:69-76

^{18}F-FDG PET/CT in cardiac implant infection and endocarditis

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Abstract

Scholtens AM. ^{18}F-FDG PET/CT in cardiac implant infection and endocarditis. ^{18}F-fluorodeoxyglucose positron emission tomography combined with computed tomography (FDG PET/CT) has shown clear value in diagnosing infectious disease, with many recent reports extolling its value in cardiovascular infection specifically. Its ability to show infectious activity, image the entire body and change clinical decision making have garnered it a place in the most recent European Society of Cardiology guidelines on endocarditis. This narrative review discusses the current knowledge and possible future perspectives on FDG PET/CT in cardiovascular infection. **Tijdschr Nucl Geneesk 2015; 37(4):1483**

Introduction

^{18}F-fluorodeoxyglucose positron emission tomography combined with computed tomography (FDG PET/CT) has been of increasing interest in the diagnostic workup of infectious and inflammatory disorders, including cardiovascular infection.

Infectious endocarditis (IE) is an inflammation of the inner lining of the heart due to bacterial, fungal or viral infection which may involve the mural endocardium, native valvular apparatus, prosthetic valves and leads from pacemakers or defibrillators. Additionally, implantable device pockets or left ventricular assist device (LVAD) components are also possible infectious foci.

The clinical diagnosis of IE is often difficult, with the modified Duke Criteria (originally intended as a tool to retrospectively analyse the prevalence of IE) relying on results from echocardiography, blood cultures and predisposing factors. However, blood cultures can be negative in up to one in three cases due to previous antibiotic therapy or causative pathogens that are not cultured through normal techniques and the presence of cardiovascular implants such as prosthetic valves may hamper echocardiography.

Early diagnosis is imperative to ensure adequate treatment through antibiotics, lead extraction or even surgery to remove infectious foci. As IE can develop from septicaemia based on other infectious foci, and conversely is prone to develop metastatic infection itself, it is also important to look beyond the heart in search of pockets of disease. In this light, FDG PET/CT shows great promise as an adjunct to current diagnostic protocols based on its whole-body approach.

As FDG PET/CT has been incorporated into the latest European Society of Cardiology Guidelines for the management of infective endocarditis (1) its use will likely increase as treating physicians become more aware of the technique, which makes it all the more important that the nuclear medicine community develops a standardised acquisition, interpretation and reporting protocol for this indication.

This work borrows from and expands upon our recent review (2).

Patient preparation

As the physiological uptake of FDG in the myocardium is highly variable, adequate suppression is key in differentiating physiological from pathological metabolic activity. Normal uptake in the myocardium is dependent upon serum insulin, glucose and free fatty acid (FFA) levels, with elevated insulin and glucose levels increasing cardiac glucose consumption and increased FFA levels with decreased insulin and glucose levels shifting cardiac metabolism away from glucose, substituted by FFA metabolism.

It is generally agreed that prolonged fasting is effective in decreasing myocardial glucose metabolism, with a low-carbohydrate diet (LCD) the day before to intensify the effect. Other additional measures include fat-rich meals to elevate FFA levels or intravenous heparin administration (15-50 IU/kg) before radiotracer injection, which induces lipolysis and elevates serum FFA levels as much as fivefold (3). A combination of these measures may be synergistic, and we have good experiences with combining LCD, 12-hour fast and heparin pre-administration.

Valvular endocarditis

Native valve endocarditis

The available data suggest that FDG PET/CT is relatively ill-equipped to reliably visualise native valve endocarditis

(NVE)(4). It is likely that this is attributable to the way NVE usually manifests: small masses -vegetations- form at the site of damage on valve surfaces, with microorganisms nestling in these fibrin-rich masses. White blood cell (WBC) invasion of these vegetations is uncommon (5). Although the relative absence of white blood cells is not yet fully understood, it may explain why FDG PET/CT performs less well in NVE: The primary basis of FDG uptake in infection lies in increased glucose transporter expression in WBCs which then migrate to the infectious process. The paucity in cellular response of the immune system to infected vegetations directly leads to diminished signal on FDG PET/CT. Added to this is the small size of most vegetations, which may render them below the resolution threshold of current scanners.

Prosthetic valve endocarditis

In prosthetic valve endocarditis (PVE) the cellular immune system plays a larger role, although FDG PET/CT alone may miss vegetations in PVE for the same reasons as in NVE (6). Saby et al. showed a powerful role for FDG PET/CT in conjunction with the modified Duke Criteria to more accurately assess PVE (7). Although radiolabelled WBC scintigraphy has a higher specificity, its sensitivity is relatively poor (8). Also, it is a relatively cumbersome technique requiring multiple days and the handling of blood products compared to the relatively simple single-day protocol for FDG PET/CT.

Due to the likelihood of vegetations being non-FDG-avid, a negative FDG PET/CT finding should not rule out solitary vegetations and transthoracic or transoesophageal echocardiography (TTE/TEE) or CT angiography (CTA) should be performed for this purpose (6). On high quality scanners FDG PET/CT and CTA of the valves may even be performed in the same session.

Implantable devices

Cardiac implantable electronic device infection

Cardiac implantable electronic devices (CIEDs) such as pacemakers or implantable defibrillators typically consist of the device itself implanted in a subcutaneous pocket and one or multiple leads running to the heart. Either of these components may be involved in infection, which usually necessitates the removal of the device.

CIED pocket infection

^{18}F-FDG PET/CT seems adept at diagnosing infection of the CIED pocket (9-11), distinguishing between deep pocket infection where the device itself is involved and superficial infection of the soft tissues above (but not involving) the device and its pocket. The latter can be treated with antibiotics alone without device removal (10), giving FDG PET/CT a potential to guide therapy in these cases.

Lead infection

Diagnosing lead infection with FDG PET/CT is more challenging than pocket infection, probably due at least in part to smaller lesion size, which may fall below the threshold of PET/CT. There is large variation in the reported sensitivities for lead infection detection (24 to 100%) (9,11), likely based on differences in antibiotic use and imaging protocols. Interestingly, the study with the lowest initial sensitivity saw it rise from 24 to 61% when imaging was repeated at a later time point (3 hrs post injection), allowing for background activity in the blood pool to decrease and thus raising the contrast between lesions and background (11).

Left ventricular assist devices

LVADs are basically pumps implanted to perform the circulatory function of the heart, often as a bridge-to-transplant. These relatively large devices are comprised of in- and outflow cannulas typically implanted through the apex of the heart and the ascending aorta, the actual pump and a driveline which is particularly prone to infection as it pierces the skin. Very little evidence exists regarding FDG PET/CT in LVAD infection, with one small series acting as proof-of-concept next to case reports (12,13).

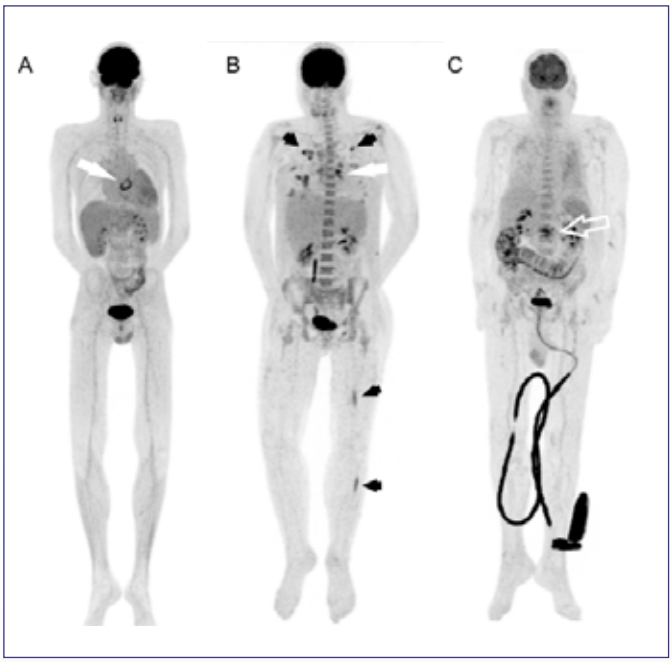

Figure 1. FDG PET/CT maximum intensity projection (MIP) images of three patients with suspected prosthetic heart valve (PHV) endocarditis. Scan A shows intense uptake surrounding the mitral PHV (white arrow), proven to be infected after surgical removal, without any other foci of infection. Scan B shows intense uptake near the aortic PHV (white arrow) as well as in multiple metastatic infectious foci in the lungs and muscles of the left leg (black arrows). Scan C shows no uptake near the aortic PHV and TEE showed no vegetations, ruling out PHV endocarditis. It does show intense uptake between L2 and L3 due to spondylodiscitis as the focus of infection (open white arrow).

Extracardiac infectious foci

Arguably the greatest asset of FDG PET/CT imaging is the ability to image the entire body in a single imaging session. A number of studies have demonstrated FDG PET/CT shows more foci of infection than routine clinical and imaging workup, often before any symptoms have arisen and with therapeutic consequences (14-17), illustrated in figure 1. The lungs, spleen and the musculoskeletal system are most often reported as extracardiac foci of infection. The brain and the urinary tract are more difficult to interpret in light of their physiologically high activity (due to high uptake and excretion, respectively) and the often small size of lesions.

Potential confounders

A number of circumstances may lead to misreading of FDG PET/CT in the context of cardiac infectious disease, with possible false positive and false negative interpretations.

False positive confounders

- A minimal amount of activity surrounding prosthetic heart valves is likely a normal variant, based on mild foreign body reactions.
- Inadequate suppression of myocardial glucose metabolism may be quite focal, with activity in the basal septum potentially misdiagnosed as valvular infection.
- Complicated surgery with hematoma can be hard to distinguish from abscess formation, especially when antibiotic therapy has been initiated.
- Foreign body reactions, especially to surgical adhesives as sometimes used in cardiothoracic surgery, can be extremely active on FDG PET/CT and nearly impossible to distinguish from infection (18).
- Lipomatous hypertrophy of the interatrial septum is potentially highly FDG-avid and close to the aortic valve.
- Myocardial ischaemia leads to higher uptake of FDG (as fatty acid metabolism is not possible in hypoxic regions) and may lie adjacent to valves, especially the mitral valve.
- Sterile granulomatous disease such as sarcoidosis can mimic focal infection.
- Beam hardening artefacts near cardiac devices and leads may be propagated to the attenuation correction, leading to artefactually high activity on AC PET images.

False negative confounders

- Vegetations may be negative on FDG PET/CT, as explained above.
- Adequate antibiotic therapy may suppress infectious activity below the threshold of FDG PET/CT although the causative pathogen has not been fully eradicated (19).

A non-exhaustive list of these confounders, their effects and possible considerations during image interpretation is presented in table 1.

Future perspectives

For FDG PET/CT to grow further in IE and CIED infection, it is important that we are aware of normal variations and the limits of the technique. As vegetations may be missed and normal myocardium may not be optimally suppressed, adding diagnostic CTA of the valve(s) and heart and using the contrast agent administered there to further clarify the low-dose CT images of FDG PET/CT may further enhance the diagnostic yield. Although this would mean a significant increase in the radiation burden of such a hybrid imaging protocol, the potential morbidity and mortality of IE and CIED infection justify this. Also, comprehensive imaging early in the course of the disease may limit additional imaging and its radiation burden at a later stage.

Cessation of antibiotics before FDG PET/CT imaging may be indicated when infectious parameters have decreased significantly, so as to minimise false negative findings; on the other hand, it could be argued that if infectious parameters are decreasing there is no further indication for imaging. It is probably wise to discuss with referring physicians that imaging performed in the early stages, preferably before or very shortly after antibiotic therapy is started, has a greater likelihood of being diagnostically accurate and may affect treatment choice.

As dual time point imaging has been proposed to improve sensitivity for lead infections, it may be worthwhile to evaluate in a wider scope of cardiovascular infection. Structures other than leads should be interpreted with some caution, as non-infectious inflammation may also become more prominent on later images and lead to false positive interpretations.
A unified protocol across different centres with patient preparation to suppress myocardial glucose metabolism and comparable acquisition and post-processing parameters would allow for a pooled analysis of a larger body of patients, which in turn would further elucidate the strengths and weaknesses beyond the basic level of evidence available today.

Conclusion

FDG PET/CT has added value in the diagnostic workup of IE and CIED infection, to evaluate the local extent of disease and to determine distant metastatic infectious foci especially. Its inability to reliably image vegetations, however, makes additional anatomical imaging of the valve a necessity. Careful interpretation of findings during antibiotic therapy and when known confounding factors are present, as well as unified imaging protocols are important factors in further developing the technique in the context of cardiovascular infectious disease.

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Table 1. Potential confounders in FDG PET/CT imaging for cardiovascular.

potential confounder	effect	considerations
antibiotic therapy	possible underestimation of the presence of infectious foci	Have laboratory and clinical parameters of infection decreased since antibiotics were started? If no, FDG PET/CT is likely still appropriate. If yes, consider postponing FDG PET/CT until after cessation of therapy or when signs and symptoms return.
attenuation correction artefact	high-density objects may give rise to beam-hardening artefacts on low-dose CT, which are propagated to the density map used for PET attenuation correction, leading to false active areas	Both attenuation corrected and raw uncorrected images should be used to interpret possible infectious foci, especially near dense structures such as implantable devices. PHVs usually do not have the density needed to lead to correction artefacts.
granulomatous disease	sterile inflammation mimicking infection	Granuloma directly adjacent to the valve is difficult to distinguish from infection. Intense activity that extends into the myocardium, especially near the basal septum, but not the perivalvular or perivascular fat planes may be due to granulomatous disease such as sarcoidosis or inadequate suppression (see below).
inadequate suppression of myocardial glucose metabolism	difficult interpretation of uptake surrounding valves	Activity in obviously unsuppressed myocardium reaching to the valvular plane per continuitatem is less likely to be based on infection, as is activity in the myocardium that does not involve the valvular plane.
myocardial ischaemia	in the ischemic state there is inadequate oxygen for fatty acid metabolism; metabolism is necessarily shifted to glucose consumption which leads to uptake of FDG	Focal uptake in myocardium corresponding to the arterial bed of one or more coronaries and most profound in the subendocardial region may be due to ischaemia, especially in patients with high risk of or known cardiovascular disease.
normal uptake near prosthetic heart valves (PHVs)	difficulty distinguishing physiological activity from low grade infection	Likely normal variants: - in mechanical PHVs minimal to moderate uptake surrounding the ring. - in biological PHVs nearly symmetrical uptake near the struts where the leaflets are fastened.
surgical adhesive	sterile inflammation mimicking infection	Has surgical adhesive been applied? This may give rise to an especially active inflammatory response and should be interpreted cautiously.
vegetations	only minimal cellular inflammatory response to pathogens nestled in the fibrin-rich mass of vegetations	FDG PET/CT is not capable of ruling out infected vegetations, and should be accompanied by adequate echocardiography or CT angiography of the valves.

References

1. Authors/Task Force Members, Habib G, Lancellotti P, Antunes MJ, et al. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC) Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J. 2015 Aug 29
2. Rewers KI, Scholtens AM, Thomassen A, Hess S. The Role of 18F-FDG PET/CT in Infectious Endocarditis and Cardiac Device Infection. Current Molecular Imaging. 2014;3:216-24
3. Persson E, Nordenstrom J, Nilsson-Ehle P, Hagenfeldt L, Wahren J. Plasma lipolytic activity and substrate oxidation after intravenous administration of heparin and a low molecular weight heparin fragment. Clin Physiol. 1990;10:573-83
4. Ricciardi A, Sordillo P, Ceccarelli L, et al. 18-Fluoro-2-deoxyglucose positron emission tomography-computed tomography: an additional tool in the diagnosis of prosthetic valve endocarditis. Int J Infect Dis. 2014;28:219-24
5. Cabell CH, Abrutyn E, Karchmer AW. Cardiology patient page, Bacterial endocarditis: the disease, treatment, and prevention. Circulation. 2003;107:185-7
6. Tanis W, Scholtens A, Habets J, et al. CT angiography and (18)F-FDG-PET fusion imaging for prosthetic heart valve endocarditis. JACC. Cardiovasc Imaging 2013;6:1008-13
7. Saby L, Laas O, Habib G, et al. Positron emission tomography/computed tomography for diagnosis of prosthetic valve endocarditis: increased valvular 18F-fluorodeoxyglucose uptake as a novel major criterion. J Am Coll Cardiol. 2013;61:2374-82
8. Rouzet F, Chequer R, Benali K, et al. Respective performance of 18F-FDG PET and radiolabeled leukocyte scintigraphy for the diagnosis of prosthetic valve endocarditis. J Nucl Med. 2014;55:1980-5
9. Ploux S, Riviere A, Amraoui S, et al. Positron emission tomography in patients with suspected pacing system infections may play a critical role in difficult cases. Heart Rhythm. 2011;8:1478-81
10. Sarrazin JF, Philippon F, Tessier M, et al. Usefulness of fluorine-18 positron emission tomography/computed tomography for identification of cardiovascular implantable electronic device infections. J Am Coll Cardiol. 2012;59:1616-25
11. Leccisotti L, Perna F, Lago M, et al. Cardiovascular implantable electronic device infection: delayed vs standard FDG PET-CT imaging. J Nucl Cardiol. 2014;21:622-32
12. Tlili G, Picard F, Pinaquy JB, Domingues-Dos-Santos P, Bordenave L. The usefulness of FDG PET/CT imaging in suspicion of LVAD infection. J Nucl Cardiol. 2014;21:845-8
13. Kim J, Feller ED, Chen W, Dilsizian V. FDG PET/CT imaging for LVAD associated infections. JACC Cardiovasc Imaging. 2014;7:839-42
14. Van Riet J, Hill EE, Gheysens O, et al. (18)F-FDG PET/CT for early detection of embolism and metastatic infection in patients with infective endocarditis. Eur J Nucl Med Mol Imaging. 2010;37:1189-97
15. Bonfiglioli R, Nanni C, Morigi JJ, et al. (18)F-FDG PET/CT diagnosis of unexpected extracardiac septic embolisms in patients with suspected cardiac endocarditis. Eur J Nucl Med Mol Imaging. 2013;40:1190-6
16. Asmar A, Ozcan C, Diederichsen AC, Thomassen A, Gill S. Clinical impact of 18F-FDG PET/CT in the extra cardiac work-up of patients with infective endocarditis. Eur Heart J Cardiovasc Imaging. 2014;15:1013-9
17. Kestler M, Munoz P, Rodriguez-Creixems M, et al. Role of (18) F-FDG PET in Patients with Infectious Endocarditis. J Nucl Med. 2014;55:1093-8
18. Schouten LR, Verberne HJ, Bouma BJ, van Eck-Smit BL, Mulder BJ. Surgical glue for repair of the aortic root as a possible explanation for increased F-18 FDG uptake. J Nucl Cardiol. 2008;15:146-7
19. Scholtens AM, van Aarnhem EE, Budde RP. Effect of antibiotics on FDG PET/CT imaging of prosthetic heart valve endocarditis. Eur Heart J Cardiovasc Imaging. 2015;16:1223

De waarde van PET voor inflammatoire reumatische ziektebeelden

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Abstract

Van der Laken CJ. De waarde van PET voor inflammatoire reumatische ziektebeelden.
Geavanceerde beeldvormende technieken zijn veelbelovend voor de vroeg diagnostiek en therapie monitoring van diverse inflammatoir reumatische ziekten. Het spectrum van diagnostiek verschuift naar de zeer vroege stadia van de ziektebeelden om vroegtijdig behandeling te kunnen opstarten en daarmee irreversibele schade te voorkomen. Beeldvorming krijgt ook een steeds belangrijkere positie in de therapie monitoring en predictie van therapie uitkomst. In de afgelopen 10-15 jaar zijn met succes diverse biologicals als behandeling voor meerdere inflammatoir reumatische ziekten (reumatoïde artritis, spondyloartritis, artritis psoriatica en een aantal systeemziekten) in de klinische praktijk gebracht. Ondanks het belangrijke potentieel van deze middelen is het effectiviteitspercentage 50-70%. Dit betekent dat het gekozen middel bij een subgroep niet aanslaat, terwijl de kosten aanzienlijk zijn (circa € 20.000/patiënt/jaar). De gedachte is dat de ziekten een heterogene pathogenese hebben en dat therapie op maat zou kunnen bijdragen tot het verhogen van de effectiviteit en het verlagen van de kosten. Beeldvorming zou niet alleen kunnen bijdragen tot stratificatie van therapie, maar ook om het behandelingsdoel remissie te bereiken. Dit laatste door sensitieve monitoring van (verandering van) inflammatoire ziekte activiteit.
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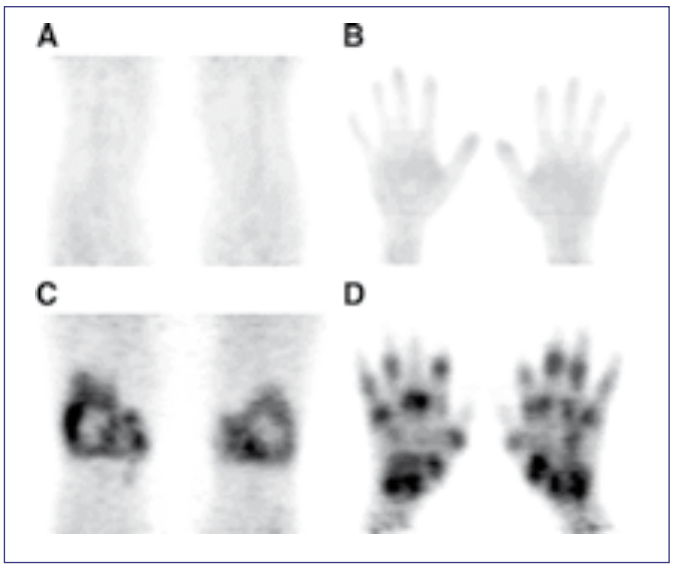
Geavanceerde beeldvormende technieken zijn veelbelovend voor de vroege diagnostiek en therapiemonitoring van diverse inflammatoire reumatische ziekten. Het spectrum van de diagnostiek verschuift naar de zeer vroege stadia van de ziektebeelden om vroegtijdig behandeling te kunnen opstarten en daarmee irreversibele schade te voorkomen. Beeldvorming krijgt ook een steeds belangrijkere positie in de therapiemonitoring en predictie van therapie-uitkomst. In de afgelopen 10 tot 15 jaar zijn met succes diverse biologicals als behandeling voor meerdere inflammatoire reumatische ziekten (reumatoïde artritis, spondyloartritis, artritis psoriatica en een aantal systeemziekten) in de klinische praktijk gebracht. Ondanks het belangrijke potentieel van deze middelen is het effectiviteitspercentage 50-70%. Dit betekent dat het gekozen middel bij een subgroep niet aanslaat, terwijl de kosten aanzienlijk zijn (circa 20.000 euro per patiënt per jaar). De gedachte is dat de ziekten een heterogene pathogenese hebben en dat therapie op maat zou kunnen bijdragen tot het verhogen van de effectiviteit en het verlagen van de kosten. Beeldvorming zou niet alleen kunnen bijdragen tot stratificatie van therapie, maar ook om het behandelingsdoel remissie te bereiken. Dit laatste door sensitieve monitoring van (verandering van) inflammatoire ziekteactiviteit.

Naast de toenemende bewijsvoering dat echografie en MRI een belangrijke rol kunnen spelen om te voldoen aan hierboven geschetste klinische behoeften, lijkt er ook een meerwaarde voor positron emissie tomografie (PET) weggelegd, als hybride techniek met computer tomografie (CT) of magnetische resonantie imaging (MRI) (1-4). De hoge sensitiviteit van de PET techniek om inflammatie op moleculair niveau op te sporen, de mogelijkheid het signaal te kwantificeren, whole body imaging en de mogelijkheid specifieke tracers te gebruiken, maken deze techniek onderscheidend ten opzichte van echografie en MRI.
In de huidige klinische praktijk van de reumatoloog wordt de PET scan vooral gebruikt bij de diagnostiek van grote vaten vasculitis, door beoordeling van ontstekingsactiviteit in alle grote vaten, afgebeeld op de whole body scan, alsmede bij de diagnostische work-up van een verhoogde bloedbezinkingssnelheid door onbekende oorzaak (BSE eci). Binnen het kader van wetenschappelijk onderzoek wordt onder meer door onze groep veel onderzoek gedaan naar de mogelijkheden van PET voor vroegdiagnostiek en therapiemonitoring van reumatoïde artritis, spondyloartritis en grote vaten vasculitis. Hieronder worden de bevindingen met PET bij deze ziektebeelden samen gevat.

Reumatoïde artritis (RA)

Diagnostiek van (vroege) RA

De meest gebruikte tracer in de klinische praktijk is ^{18}F-fluoro-2-deoxy-D-glucose (^{18}F-FDG), een glucosederivaat dat opgenomen wordt in metabool actieve processen zoals ontstekingen. Visualisatie van artritisactiviteit is zeer goed mogelijk (figuur 1). De semi-kwantitatieve opname van ^{18}F-FDG, uitgedrukt in standardized uptake values (SUVs), in gewrichten bleek te correleren met gevalideerde klinische meetmethoden om de ziekteactiviteit van RA vast te stellen middels een Disease Activity Score (DAS) (4). Ook

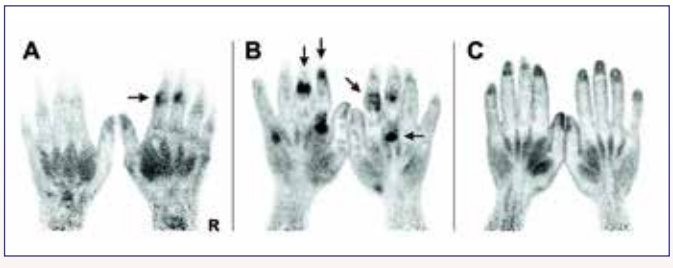


Figuur 1 (4). ^{18}F-FDG PET scans van een gezonde vrijwilliger (A en B) en een RA patiënt met actieve ziekte (C en D). (A) 3D scan met normale distributie in de knie. (B) Normale distributie in handen en polsen. (C) RA knieën. (D) RA handen en polsen.

correleerden gesimplificeerde visuele scoresystemen van ^{18}F-FDG (gradatie van 0 tot 4) met de klinische symptomen van artritis (5-7).
De distributie van ^{18}F-FDG opname in gewrichten kan helpen bij de differentiatie van RA versus spondyloartritis (SpA) activiteit in perifere gewrichten. ^{18}F-FDG opname in RA gewrichten wordt typisch geobserveerd in het synoviale weefsel, terwijl de ^{18}F-FDG opname in SpA gewrichten vooral waargenomen wordt in de entheses als uiting van enthesitis (6,8).
Ondanks de veelbelovende resultaten die tot op heden bereikt zijn met ^{18}F-FDG PET in de beeldvorming van RA, is differentiatie van artritis ten gevolge van RA en artrose lastig (9-11). De beeldvorming van ^{18}F-FDG PET is zeer sensitief doch weinig specifiek, hetgeen bepaald wordt door het gebruik van de aspecifieke tracer ^{18}F-FDG. Immers, ^{18}F-FDG wordt in ieder metabool actief proces opgenomen. Data van een ^{18}F-FDG PET studie lieten zien dat de kwantitatieve opname van ^{18}F-FDG in ontstoken gewrichten bij RA niet verschilde van die bij artrose (9). Wel was het aantal PET positieve gewrichten bij RA hoger dan bij artrose.
De specificiteit van de beeldvorming van RA met PET zou kunnen worden verhoogd door het gebruik van tracers die specifiek binden aan receptoren in RA synovium.
Aangezien RA gekenmerkt wordt door proliferatie van synoviaa§l weefsel in gewrichten, is ^{11}C-methylcholine (choline is een precursor voor synthese van fosfolipiden) als tracer onderzocht voor visualisatie van RA (12). De absolute opname van ^{11}C-choline in RA gewrichten lag in dezelfde range als die van ^{18}F-FDG, doch de 'uptake rate' van ^{11}C-choline was achtmaal hoger.

Een andere interessante target om artritis te visualiseren is de macrofaag. Macrofagen spelen vanaf de eerste fase van de ontwikkeling van artritis tot en met geavanceerde stadia van RA een belangrijk rol (13,14). De 'translocator protein 18 kDa' (TSPO) die in het bijzonder tot expressie komt op (geactiveerde) macrofagen, is succesvol als target gebruikt middels de tracer ^{11}C-PK11195 voor visualisatie van artritis en vasculitis (15,16; figuur 2).
De gewrichtsopname van deze macrofagentracer op de ^{11}C-PK11195 PET scan in RA patiënten bleek goed te correleren met de mate van macrofageninfiltratie in de sublining van het synovium (15). In deze studie was in enkele klinisch niet ontstoken gewrichten ook een PET signaal aanwezig, hetgeen kon duiden op detectie van subklinische artritis. Vervolgens bleek dat zeer vroege subklinische artritis bij patiënten met artralgie en een positief anti-CCP met PET kan worden opgespoord. Alle patiënten met een positieve PET scan kregen binnen achttien maanden RA (17). Ondanks de succesvolle bevindingen met macrofagen-targeting in RA, wordt de detectie van meer subtiele artritis beperkt door de peri-articulaire achtergrondbinding van ^{11}C-PK11195. Er zijn momenteel nieuwe macrofagentracers in ontwikkeling welke een lagere achtergrondbinding tonen (18 ,19). De veelbelovende bevinding van vroege detectie van RA, gebruik makende van de meest optimale macrofagentracer, wordt binnenkort gevalideerd in een grotere multicenter studie.

Predictie en monitoren van therapeutische effecten
Diverse ^{18}F-FDG PET studies hebben laten zien dat PET een gevoelige methode is om veranderingen van ziekteactiviteit bij RA te monitoren (6,7,20). ^{18}F-FDG PET veranderingen in gewrichten correleerden met zowel veranderingen in klinische ziekteactiviteit als serum-inflammatiemarkers (21,22). Daarnaast werd de predictieve waarde van ^{18}F-FDG PET voor de uitkomst van infliximab (anti-tumornecrosefactor) therapie aangetoond. Vroege ^{18}F-FDG PET veranderingen van



Figuur 2. ^{11}C-(R)-PK11195 PET scans van handen en polsen in (A) een anti–CCP–positieve patiënt met artralgie, (B) een RA patiënt met evidente klinische artritis in verscheidene hand- en polsgewrichten en (C) een gezonde vrijwilliger. Pijlen duiden de gewrichten met tracer opname aan, welke afwezig is in de gezonde vrijwilliger. Deze tracer toont ook achtergrondopname in de intrinsieke handmusculatuur, beenmerg en weke delen rondom de nagels.

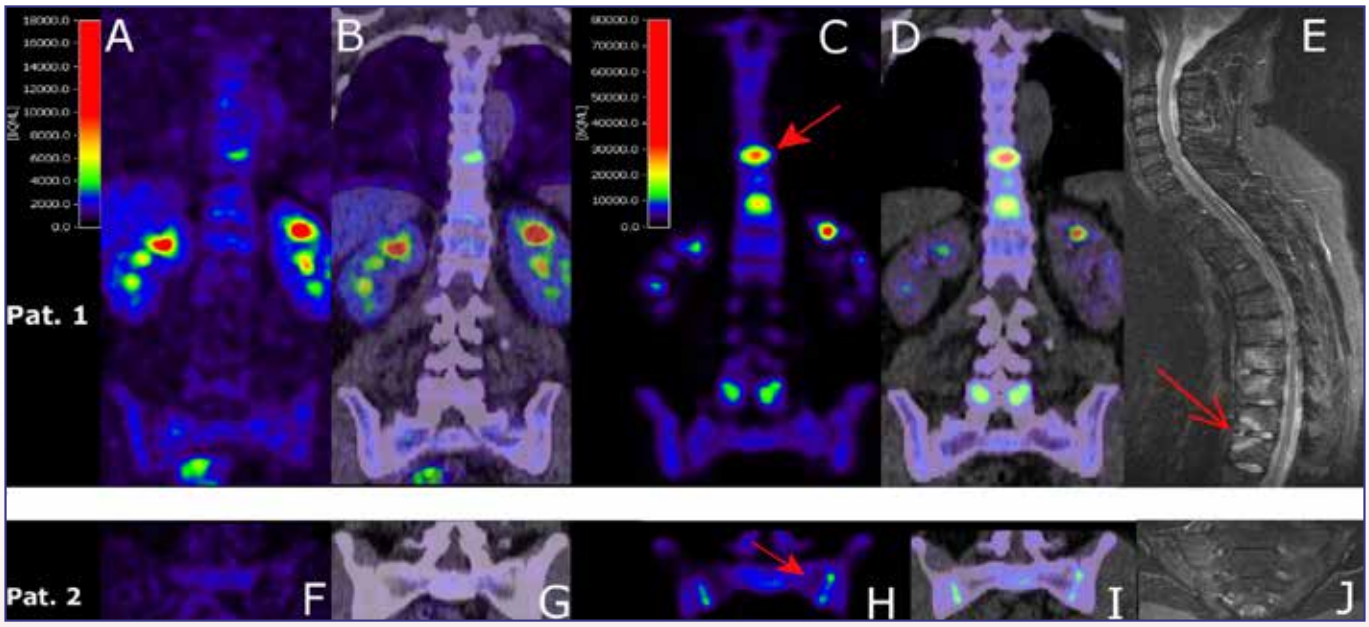
gewrichten, reeds tussen 0 tot 2 weken, bleken de klinische uitkomst (DAS 28 score) op 4 en 5 maanden te voorspellen (23). In tegenstelling tot de predictieve waarde van PET voor de therapie-uitkomst, werd er geen correlatie gevonden tussen BSE, C-reactief proteïne (CRP) 0 tot 2 weken, en klinische ziekteactiviteit op 4 tot 5 maanden na start van infliximab therapie.
In een RA cohort in klinische remissie bleek dat mensen met een cumulatief hogere ^{11}C-PK11195 PET score van hand- en polsgewrichten vaker een exacerbatie van RA kregen binnen drie jaar klinische follow-up, dan mensen met een lage PET score (24). Daarnaast wijzen de resultaten van deze studie op een hogere specificiteit van PET met macrofagen- targeting dan MRI in de predictie van exacerbatie van RA later in de tijd. Inmiddels zijn deze resultaten bevestigd in een cohort met vroege RA, welke na initiële behandeling in klinische remissie was gebracht (25). Deze resultaten tonen aan dat PET ook subklinische artritis bij patiënten met een lage klinische ziekteactiviteit kan opsporen en een rol zou kunnen spelen in toekomstige predictie van het ziektebeloop en hiermee in stratificatie van de behandeling. Dit is momenteel onderwerp van verdere studies, waaronder verdere ontwikkeling van specifieke tracers gericht op diverse inflammatoire targets.

Spondyloartritis (SpA)

MRI is onlangs geïncludeerd in de nieuwe ASAS-classificatiecriteria voor SpA (26) en fungeert heden in de dagelijkse klinische praktijk als gouden standaard voor de detectie van sacroiliitis. Echter, de rol van MRI voor de diagnostiek van vroege SpA is nog onzeker. PET/CT zou hier additionele waarde kunnen hebben.
Case reports met ^{18}F-FDG PET/CT lieten zien dat de techniek potentiële waarde zou hebben voor het opsporen van aseptische spondylodiscitis (27).
Er zijn aanwijzingen dat het 'targeten' van botformatie ('hallmark' voor SpA) met ^{18}F-fluoride PET/CT een alternatieve mogelijkheid biedt voor de beeldvorming van ziekteactiviteit van SpA (28,29). Een opnameratio van SI-gewrichten/sacrum > 1.3 leverde een sensitiviteit van 80% en een specificiteit van 77% op (28). In een pilotstudie lijkt de ^{18}F-fluoride tracer superieur aan ^{18}F-FDG en ^{11}C-PK11195 voor de visualisatie van ziekteactiviteit in de wervelkolom en SI-gewrichten. Daarnaast werden meer hot spots op ^{18}F-fluoride PET/CT dan op MRI in beeld gebracht, hetgeen een indicatie is dat deze PET benadering informatie aan het MRI beeld kan toevoegen (29; figuur 3). Momenteel lopen grotere ^{18}F-fluoride PET/CT studies om de verdere waarde van deze techniek voor diagnostiek en therapiemonitoring van SpA te kunnen bepalen.

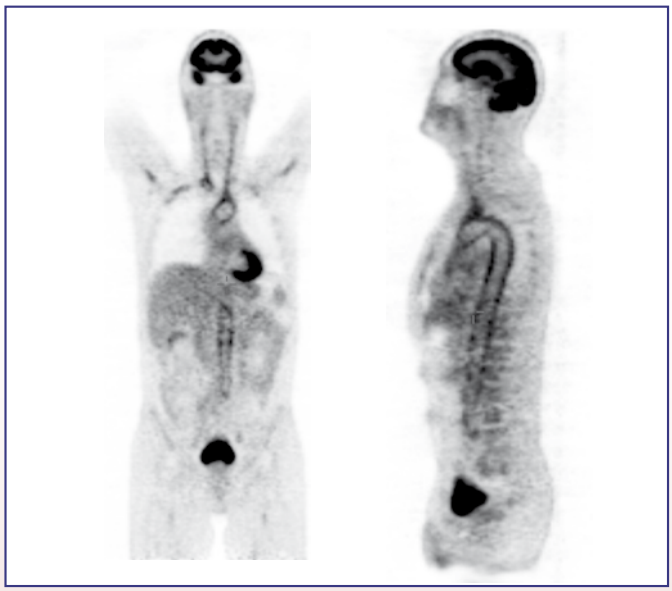
Grote vaten vasculitis

Er zijn twee typen grote vaten vasculitiden: arteritis temporalis (en in het verlengde van dit spectrum polymyalgia rheumatica) en Takayasu arteritis. Bij beide kunnen aorta en/of afgeleide



Figuur 3. ^{18}F-FDG en ^{18}F-fluoride PET-CT en MRI scans van patiënten 1 (a-e) en 2 (f-j). Coronale PET (a, c, f, h) en PET/CT (b, d, g, i) scans met ^{18}F-FDG (a, b, f, g) en ^{18}F-fluoride (c, d, h, i). Multipele hotspots worden getoond; twee voorbeelden zijn aangeduid middels rode gesloten pijlen (c, h). Sagittale MRI scan (short-tau inversion recovery, STIR) van de wervelkolom (e) en coronale/oblique MRI (STIR) van SI gewrichten (j). Multipele laesies met toegenomen signaal (beenmergoedeem) worden getoond; een voorbeeld is aangeduid middels een open pijl.

arteriën betrokken zijn. Er is een opmars van ^{18}F-FDG PET/CT voor de diagnostiek van grote vaten vasculitis omdat het arteria temporalis biopt (als gouden standaard voor diagnostiek van arteriitis temporalis) negatief kan zijn en het geen informatie geeft over de betrokkenheid van andere grote vaten. De hoge 'relapse rate' van grote vaten vasculitis (50-60%) lijkt onder meer samen te hangen met vasculitis in de aorta en de aftakkingen hiervan. Tenslotte wordt de prognose van grote vaten vasculitis negatief beïnvloed door de ontwikkeling van aneurysmata (arteritis temporalis) of stenosen (Takayasu) en is vroegtijdige opsporing en behandeling van grote vaten vasculitis derhalve cruciaal.
De combinatie van hoge sensitiviteit van ^{18}F-FDG om inflammatie te detecteren, kwantificeren en whole body imaging maken de ^{18}F-FDG PET/CT techniek een geschikte techniek om vasculitis over het gehele lichaam op te sporen (figuur 4). Uit diverse studies komt naar voren dat ^{18}F-FDG PET/CT een goede sensitiviteit (57-96%) en specificiteit (80-96%) heeft om grote vaten vasculitis op te sporen (30,31). Differentiatie tussen vasculitis en atherosclerose kan lastig zijn. Een visuele lineaire of lange segmentele opname van ^{18}F-FDG in de vaatwand lijkt het meest indicatief voor vasculitis. De hoogste 'interobserver agreement' voor het bepalen van betrokkenheid van grote vaten bij patiënten met arteritis temporalis werd recent behaald wanneer hogere vasculaire ^{18}F-FDG opname dan lever opname als diagnostisch criterium werd gebruikt (32).
De rol van ^{18}F-FDG PET/CT voor de diagnostiek van Takayasu arteritis is nog niet uitgekristalliseerd. Voor de initiële diagnose wordt veelal MRI en CT-angiografie gebruikt.



Figuur 4. ^{18}F-FDG PET scans in sagitale en coronale richting van een patiënt met grote vaten vasculitis (arteritis temporalis) welke evidente opname in de vaatwand van onder meer de aorta laat zien.

De prevalentie van grote vaten vasculitis bij polymyalgia rheumatica, in het bijzonder de betrokkenheid van de arteria subclavia, werd in 31% van de polymyalgia rheumatica patiënten gevonden (33-35). De daadwerkelijke incidentie van vasculitis bij polymyalgia rheumatica moet nog worden vastgesteld in grote prospectieve studies.
Onder behandeling met prednison is afname van ^{18}F-FDG in aangedane vaatsegmenten in meerdere studies gerapporteerd, alhoewel veranderingen in het PET signaal niet altijd synchroon liepen met de klinische response (36-37). Dit kan samenhangen met het gebrek aan consensus over de klinische definitie van ziekteactiviteit en behoefte aan evaluatiemethoden van ^{18}F-FDG opname in de vaatwand(en). ^{18}F-FDG PET/CT lijkt geen waarde te hebben voor het voorspellen van een exacerbatie van grote vaten vasculitis na een aanvankelijke respons op prednison (35,38). Dit hangt onder meer samen met vaatwand remodelling, welke in het beloop van de vasculitis optreedt.
Tenslotte bleek grote vaten vasculitis op whole body ^{18}F-FDG PET/CT aanwezig in 24% van een cohort patiënten met verhoogde BSE eci, waarna deze patiënten succesvol met prednison konden worden behandeld (39).

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Referenties

1. Ostergaard M, Peterfy C, Conaghan P, et al. OMERACT Rheumatoid Arthritis Magnetic Resonance Imaging Studies. Core set of MRI acquisitions, joint pathology definitions, and the OMERACT RA-MRI scoring system. J Rheumatol. 2003; 30:1385-6
2. Iagnocco A, Naredo E, Wakefield R, et al. Responsiveness in rheumatoid arthritis. a report from the OMERACT 11 ultrasound workshop. J Rheumatol. 2014;41:379-82
3. Palmer WE, Rosenthal DI, Schoenberg OI, et al. Quantification of inflammation in the wrist with gadolinium-enhanced MR imaging and PET with 2-[F-18]-fluoro-2-deoxy-D-glucose. Radiology. 1995;196:647-55
4. Beckers C, Ribbens C, Andre B, et al. Assessment of disease activity in rheumatoid arthritis with (18)F-FDG PET. J Nucl Med. 2004;45:956-64
5. Kubota K, Ito K, Morooka M, et al. Whole-body FDG PET/CT on rheumatoid arthritis of large joints. Ann Nucl Med. 2009; 23:783-91
6. Vijayant V, Sarma M, Aurangabadkar H, et al. Potential of (18)F-FDG-PET as a valuable adjunct to clinical and response assessment in rheumatoid arthritis and seronegative spondyloarthropathies. World J Radiol. 2012; 4:462-8
7. Goerres GW, Forster A, Uebelhart D, et al. F-18 FDG whole-body PET for the assessment of disease activity in patients with rheumatoid arthritis. Clin Nucl Med. 2006;31:386-90
8. Taniguchi Y, Arii K, Kumon Y, et al. Positron emission tomography/computed tomography: a clinical tool for evaluation of enthesitis in patients with spondyloarthritides. Rheumatology. 2010;49:348-54
9. Elzinga EH, van der Laken CJ, Comans EF, et al. 2-Deoxy-2-[F-18] fluoro-D-glucose joint uptake on positron emission tomography images: rheumatoid arthritis versus osteoarthritis. Mol Imaging Biol.

2007; 9:357-60
10. Wandler E, Kramer EL, Sherman O, et al. Diffuse FDG shoulder uptake on PET is associated with clinical findings of osteoarthritis. AJR Am J Roentgenol. 2005;185:797-803
11. Houseni M, Chamroonrat W, Zhuang H, Alavi A. Facet joint arthropathy demonstrated on FDG-PET. Clin Nucl Med. 2006;31:418-9
12. Roivainen A, Parkkola R, Yli-Kerttula T, et al. Use of positron emission tomography with methyl-11C-choline and 2-18F-fluoro-2-deoxy-D-glucose in comparison with magnetic resonance imaging for the assessment of inflammatory proliferation of synovium. Arthritis Rheum. 2003; 48:3077-84
13. Kraan MC, Versendaal H, Jonker M, et al. Asymptomatic synovitis precedes clinically manifest arthritis. Arthritis Rheum. 1998;41:1481-8
14. Haringman J, Gerlag D, Zwinderman A, et al. Synovial tissue macrophages: a sensitive biomarker for response to treatment in patients with rheumatoid arthritis. Ann Rheum Dis. 2005;64:834-8
15. van der Laken CJ, Elzinga EH, Kropholler MA, et al. Noninvasive imaging of macrophages in rheumatoid synovitis using 11C-(R)-PK11195 and positron emission tomography. Arthritis Rheum. 2008;58:3350-5
16. Lamare F, Hinz R, Gaemperli O, et al. Detection and quantification of large-vessel inflammation with 11C-(R)-PK11195 PET/CT. J Nucl Med. 2011;52:33-9
17. Gent YY, Voskuyl AE, Kloet RW, et al. Macrophage positron emission tomography imaging as a biomarker for preclinical rheumatoid arthritis: findings of a prospective pilot study. Arthritis Rheum. 2012;64:62-6
18. Gent YY, Weijers K, Molthoff CF, et al. Evaluation of the novel folate receptor ligand [18F]fluoro-PEG-folate for macrophage targeting in a rat model of arthritis. Arthritis Res Ther. 2013;15:R37
19. Gent YY, Weijers K, Molthoff CF, et al. Promising potential of new generation translocator protein tracers providing enhanced contrast of arthritis imaging by positron emission tomography in a rat model of arthritis. Arthritis Res Ther. 2014;16:R70
20. Okamura K, Yonemoto Y, Arisaka Y, et al. The assessment of biologic treatment in patients with rheumatoid arthritis using FDG PET/CT. Rheumatology (Oxford). 2012; 51:1484-91
21. Roivainen A, Hautaniemi S, Mottonen T, et al. Correlation of 18F-FDG PET/CT assessments with disease activity and markers of inflammation in patients with early rheumatoid arthritis following the initiation of combination therapy with triple oral antirheumatic drugs. Eur J Nucl Med Mol Imaging. 2013; 40:403-10
22. Beckers C, Jeukens X, Ribbens C, et al. (18)F-FDG PET imaging of rheumatoid knee synovitis correlates with dynamic magnetic resonance and sonographic assessments as well as with the serum level of metalloproteinase-3. Eur J Nucl Med Mol Imaging. 2006; 33:275-80
23. Elzinga EH, van der Laken CJ, Comans EF, et al. 18F-FDG PET as a tool to predict the clinical outcome of infliximab treatment of rheumatoid arthritis: an explorative study. J Nucl Med. 2011;52:77-80
24. Gent YY, Ahmadi N, Voskuyl AE, et al..Detection of Subclinical Synovitis with Macrophage Targeting and Positron Emission Tomography in Patients with Rheumatoid Arthritis without Clinical Arthritis. J Rheumatol. 2014 Nov;41:2145-52
25. Gent YY, Ter Wee MM, Vokuyl AE et al. Subclinical synovitis detected by macrophage PET, but not MRI, is related to short-term flare of clinical disease activity in early RA patients: an explorative study. Arthritis Res Ther 2015, sept 25; 17:266.
26. Rudwaleit M, van der Heijde D, Landewé R, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis. 2009;68):777-83
27. Wendling D, Blagosklonov O, Streit G, et al. FDG PET/CT scan of inflammatory spondylodiscitis lesions in ankylosing spondylitis, and short term evolution during anti-tumour necrosis factor treatment. Ann Rheum Dis. 2005;64:1663-5
28. Strobel K, Fischer DR, Tamborrini G, et al. 18F-fluoride PET/CT for detection of sacroiliitis in ankylosing spondylitis. Eur J Nucl Med Mol Imaging. 2010;37:1760-5
29. Bruijnen ST, van der Weijden MA, Klein JP, et al. Bone formation rather than inflammation reflects Ankylosing Spondylitis activity on PET-CT: a pilot study. Arthritis Res Ther. 2012;14:R71
30. Besson FL, Parienti JJ, Bienvenu B, et al. Diagnostic performance of F-18 fluorodeoxyglucose positron emission tomography in giant cell arteritis: a systematic review and meta-analysis. Eur J Nucl Med Mol Imaging. 2011;38:1764-72
31. Fuchs M, Briel M, Daikeler T, et al. The impact of 18F-FDG PET on the management of patients with suspected large vessel vasculitis. Eur J Nucl Med Mol Imaging. 2012;39:344-53
32. Lensen KJ, Comans EFI, Voskuyl AE, et al. Large-vessel vasculitis: interobserver agreement and diagnostic accuracy of 18F-FDG PET/CT. BioMed Res Int. 2015;2015:914692
33. Blockmans D, Maes A, Stroobants S, et al. New arguments for a vasculitic nature of polymyalgia rheumatica using positron emission tomography. Rheumatology. 1999;38:444-47.
34. Blockmans D, Stroobants S, Maes A, Mortelmans L. Positron emission tomography in giant cell arteritis and polymyalgia rheumatica: evidence for inflammation of the aortic arch. Am J Med. 2000;108:246-249.
35. Blockmans D, De Ceuninck L, Vanderschueren S, et al. Repetitive 18-fluorodeoxyglucose positron emission tomography in isolated polymyalgia rheumatica: a prospective study in 35 patients. Rheumatology. 2007;46:672-77.
36. Meller J, Strutz F, Siefker U, et al. Early diagnosis and follow-up of aortitis with [(18)F]FDG PET and MRI. Eur J Nucl Med Mol Imaging. 2003;30:730-36.
37. Scheel AK, Meller J, Vosshenrich R, et al. Diagnosis and follow up of aortitis in the elderly. Ann Rheum Dis. 2004;63:1507-10.
38. Blockmans D, de Ceuninck L, Vanderschueren S, et al. Repetitive 18F-fluorodeoxyglucose positron emission tomography in giant cell arteritis: a prospective study of 35 patients. Arthritis Rheum. 2006;55:131-37.
39. Lensen KJ, Voskuyl AE, van der Laken CJ, et al. 18F-fluorodeoxyglucose positron emission tomography in elderly patients with an elevated erythrocyte sedimentation rate of unknown origin. PLoS One. 2013;8:e58917.

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Hybrid PET/MR imaging in the diagnosis of cardiovascular diseases: feasibility and initial results

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Abstract

Vöö S, Gerretsen S, Gommers S, Mottaghy FM. Hybrid PET/MR imaging in the diagnosis of cardiovascular diseases: feasibility and initial results. Hybrid imaging including PET/CT and SPECT/CT have seen a great success in clinical routine. With the recent advent of PET/MR scanners, expectations that PET/MR would replicate that success are accordingly high. The combination between the high spatial resolution and detailed morphologic characterisation of MR with the molecular/functional PET imaging is expected to result in an increased diagnostic accuracy or even in the creation of additional demands for hybrid imaging. As a new imaging modality that has been recently introduced on the market, there is still a limited PET/MR experience in the field of nuclear cardiology and inflammation and many applications still need to be validated. However, based on positive first clinical experience, it is likely that the hybrid PET/MR will become a valuable imaging approach in the diagnosis of many cardiovascular diseases, including inflammatory pathologies such as myocarditis, cardiac sarcoidosis, or large vessel vasculitis.

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Introduction

Hybrid PET/MR emerges as an imaging modality with great potential in diagnosis of cardiovascular diseases. The ability to fuse images from two or more modalities is always interesting, but to acquire them simultaneously or within a narrow window of a few seconds to minutes is exciting as it opens the potential of utilising the various functional parameters into a single study.

Both PET and MR imaging have independently gained wide acceptance for the diagnosis of cardiovascular diseases, such as for the assessment of perfusion and tissue viability in patients with ischaemic cardiomyopathies, cardiac sarcoidosis, or large vessel vasculitis (LVV). PET is a sensitive imaging tool able to image multiple metabolic parameters depending on the radiotracer used. On the other hand, MR imaging is able to provide excellent anatomic detail and is able to deliver multimodal physiologic, functional imaging parameters in the same time.

In the hybrid PET/MR, the major advantage of MR over CT as an adjunct to PET include the fact that MR provides a high anatomic detail without exposing the patient to radiation. MR imaging currently represents the gold standard for the assessment of left ventricular function and offers features such as myocardial ischaemia, oedema, or interstitial tissue infiltration. Continuous motion correction provided by MR imaging may improve substantially the quantification of regional PET tracer uptake.

On the downside, MR increases workflow complexity compared with CT. CT is fast and easy to perform, while MR protocols are time-consuming and require more patient compliance. The electromagnetic fields needed for MR also restrict its use on patients with pacemakers, implantable cardioverter defibrillators and mechanical heart valves, which is a major disadvantage in cardiac imaging.

PET/MR is entering routine clinical practice at present. Access to co-registered, almost simultaneous physiologic and metabolic measurements have already made PET/MR the most sophisticated quantitative imaging modality to date. The expectation remains that the PET/MR system will exploit superior tissue contrast inherent in the MR component of the machine and the multi-parametric functional information provided by PET in cardiac disease state (1). Yet, cardiovascular PET/MR applications are in their infancy and there are still no clear clinical indications or 'killer' cardiovascular applications yet defined for the use of the integrated PET/MR. Moreover, it is still not clear whether PET/MR will be able to offer added value or generate an additional demand for imaging studies that PET/CT cannot satisfy. The present paper looks briefly at the potential of this new technology, presents initial literature, and shares our first experience in Maastricht University Medical Centre of using PET/MR in imaging cardiovascular diseases.

Cardiac PET/MR

PET/MR in ischaemic cardiomyopathies

Currently, the role of PET/MR in evaluating suspected or known coronary artery disease is limited in view of the established relatively cheap competing modalities such as stress echo, CT calcium score/CT angiography, and myocardial perfusion scintigraphy.

However, ^{18}F-FDG PET has become a commonly used technique in nuclear cardiology to identify injured, yet

viable myocardium (hibernating or stunned myocardium) that is prone to benefit for the functional recovery after revascularisation. Based on meta-analyses, the sensitivity and specificity of ^{18}F-FDG PET to predict functional recovery after revascularisation are approximately 92% and 63%, respectively (2).
Obviously, there are some drawbacks when using ^{18}F-FDG PET for viability imaging. The myocardial uptake of ^{18}F-FDG may be reduced in diabetic patients, which might result in poor image quality. Furthermore, PET has a relatively low spatial resolution. MR with the late-gadolinium enhancement (LGE) approach evolved as a possible alternative approach for viability assessment. This technique makes use of the property of gadolinium chelates to accumulate in increased extracellular spaces, such as scarred myocardium (3). The uptake of gadolinium chelates into fibrotic/scarred tissue is insulin independent. Another advantage of MR is the far higher spatial resolution of approximately 1-3 mm, which allows an accurate differentiation between transmural and non-transmural infarction (4). Additionally, MR may help in classifying areas of reduced or absent ^{18}F-FDG uptake owing to a thinned myocardial wall (e.g., in the case of heart failure) which are often miscategorised as a scar by PET alone.
Our initial experience, similar to a recently published paper (5), shows a substantial agreement between PET and MR in evaluating viable myocardium after acute myocardial infarction. Yet, there are also limited cases with discordance between ^{18}F-FDG PET and MR findings. For instance, a low locally ^{18}F-FDG uptake, indicating nonviable myocardium, but with a non-transmural LGE signal, indicating rest viable tissue. However, whether this sensitive findings are relevant in the overall functional recovery of these injured myocardial segments in the long-term course after infarction is still unclear.

PET/MR in non-ischaemic cardiomyopathies

Cardiac MR is already an imaging of choice in the management of myocarditis. Using LGE, together with double-inversion-recovery fast spin-echo T2- and T1-weighted sequences, MR may be useful to detect infiltrative processes and oedema in active myocarditis. However, as the infiltrative processes in myocarditis may be diffuse, MR may fail to make the correct diagnosis.
^{18}F-FDG PET may represent a valuable alternative, as ^{18}F-FDG is not only a sensitive marker of inflammation, but also a quantifiable parameter for disease activity that could complement MR in the detection, differential diagnosis, and monitoring of myocarditis. Furthermore, recent evidence suggests that the use of hybrid ^{18}F-FDG PET/MR, performed under fasting conditions, may result in improved diagnosis of myocarditis (6). However, further confirmatory clinical studies are warranted.
In cardiac sarcoidosis, the clinical course of the disease varies from benign to life-threatening with sudden cardiac death and heart failure. Owing to these risks, cardiac involvement by sarcoidosis should be ruled out. Yet, a generally accepted gold standard imaging is missing. The Guidelines of the Japanese Ministry of Health and Welfare, which serves as a worldwide standard for the clinical diagnosis of cardiac sarcoidosis, do not include PET, in contrast to cardiac MR and ^{67}Ga scintigraphy. PET/MR seems a promising imaging approach that might be useful for the initial diagnosis of cardiac sarcoidosis and also for therapy guidance. In order to suppress physiological glucose uptake in the myocardium and substantiate glucose uptake in active inflammatory sites, patients have to follow a strict preparation for the PET study; this consists of a high-fat, low-carbohydrate diet for a period of 24 hours before the examination and intravenous administration of 50 IU/kg body weight of unfractionated heparin 15 minutes before the FDG injection (7). As such, ^{18}FDG PET imaging is increasingly used for an accurate assessment of the inflammatory status in active sarcoidosis. On the other hand, MR allows the exact localisation of fibrotic tissue by T2-weighted oedema imaging or LGE fibrosis imaging. Moreover, a combined approach of myocardial inflammation and perfusion assessment (e.g., ^{13}N-NH3, ^{82}Rb, or MR sequences for myocardial ischaemia) allows for exact staging of the disease: normal perfusion and enhanced ^{18}F-FDG uptake indicates active inflammation, hypoperfusion and high glucose metabolism are suggestive of advanced stage, while reduced/absent perfusion and missing ^{18}F-FDG uptake is indicative for end-stage cardiac sarcoidosis.
First clinical experience on simultaneous PET/MR shows the benefits of combining PET and MR for a higher sensitivity and specificity in diagnosing active cardiac sarcoidosis. This is particularly true in patients with suspected relapse of the disease after previous treatment. Similar to other cases published in the literature (8,9), our data shows a clear benefit of adding ^{18}F-FDG PET to diagnosis as it often identifies active myocardial inflammation within areas of established subepicardial fibrosis, otherwise considered simple 'scar' (figure 1). When considering PET and MR alone, their sensitivity in detecting abnormalities in cardiac sarcoidosis is about 65% and 60%, respectively. In contrast, a recently presented paper shows an increased sensitivity of hybrid PET/MR to 89%-100% (10).
By differentiating between the hypermetabolic active disease and the chronic 'burnt out' disease, PET/MR could therefore have a substantial impact on the diagnosis of cardiac sarcoidosis. At the same time, PET/MR might be helpful for guidance of primary preventive device therapy (avoiding lead placement into fibrosis in case of ICD implantation) (7) and monitoring of disease activity under immunosuppressive therapy (11).
Besides these promising initial results, the potential value of cardiac PET/MR in ischaemic and non-ischaemic cardiomyopathies remains further to be tested. The availability of new specific tracers such as ^{18}F-flutemetamol for cardiac amyloidosis, ^{64}Cu-labelled macrophage targeted nanoparticles for identifying cellular inflammation within the myocardial

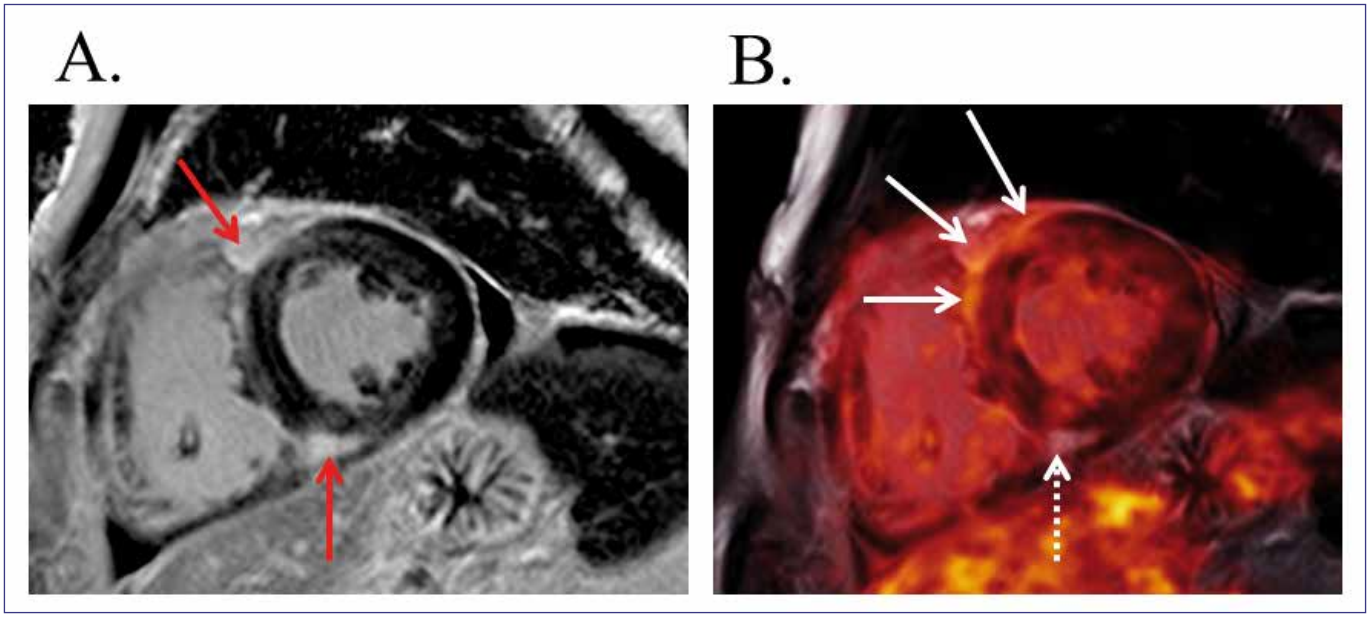

Figure 1. Cardiac ^{18}F-FDG PET/MR in a patient with suspicion of relapse of cardiac sarcoidosis. To suppress physiological glucose uptake in the myocardium, the patient was prepared with a high-fat, low-carbohydrate diet for a period of 24 hours before the examination and was intravenously administered 50 IU/kg body weight of unfractionated heparin 15 minutes before the FDG injection. (A) LGE MR images showing a patchy LGE enhancement (red arrows), suggestive for fibrous tissue. (B) FDG uptake on PET (white arrow) within the area of LGE enhancement on MR, indicative for active inflammation in sarcoidosis. However, no FDG uptake in inferoseptal area of LGE enhancement (dotted-line white arrow), most likely a "burnt out" sarcoidosis lesion as scar.

healing after infarction, or ^{18}F-integrin ($\alpha v\beta 3$) for targeting inflammation are currently exploited.

Vascular PET/MR

Large vessel vasculitis (LVV), including giant cell arteritis and Takayasu's arteritis, is an inflammatory disease that may have serious and life-threatening consequences. ^{18}F-FDG PET has emerged as a powerful imaging modality for the diagnosis of active vessel wall inflammation and therapy monitoring of LVV (12). Besides inflammation, vessel wall changes and vessel stenosis are important factors that have major impact on prognosis and therapy management. This is particularly true if we consider that arterial stenosis and aneurysms occur in 98% and 27% of patients with Takayasu's arteritis (13). Besides vasculitis of the supra-aortal arteries, patients with giant cell arteritis present atypical aortic involvement and thoracic aneurysms in 18% and 11% of which 50% develop further aortic dissection leading to a death rate of 78% (14). Nowadays PET is routinely performed in combination with CT as a hybrid PET/CT examination. However, regarding soft tissue contrast, CT is clearly inferior to MR, which has been also shown to sensitively detect vessel wall changes in LVV and accurately evaluate the luminal stenosis.
On this basis, the hybrid PET/MR using ^{18}F-FDG emerges as a potential imaging tool for the diagnosis and monitoring of LVV. First results on PET/MR in LVV show that the hybrid ^{18}F-FDG PET/MR in vasculitis is feasible (figure 2). PET reveals more vascular regions involved in inflammatory processes than MR alone. Consequently, the inflammatory extent demonstrated by PET alone correlates significantly with C-reactive protein (CRP). But the combination of PET and MR data shows an even stronger correlation with CRP, which is reasonable since MR may detect further vessel regions with morphological vasculitis changes missed by PET likely due to its limited spatial resolution (15). Furthermore, MR detects vessel narrowing, occlusions, or aneurysmatic transformation even in the absence of ^{18}F-FDG positive inflammation. Indeed, these findings indicated by MR alone could have been sites of disease that are no longer active. Therefore, the combination of PET with MR seems to represent disease extent of LVV in a more reliable way than PET alone. Therefore, the corroborated PET/MR information may have a major impact on the further therapeutic regimen (from immunosuppressive therapy to close follow-up examinations and potential vascular surgery in case of vascular occlusion, stenosis, or aneurysm).

Conclusion

PET/MR is one of the most exciting developments in imaging in recent years. There is scope within cardiovascular imaging for this modality to develop, although widely accepted clinical indications remain to be defined. The growing use of novel PET tracers and functional MR parameters offers great potential benefit for PET/MR in research but also clinical cardiovascular imaging.

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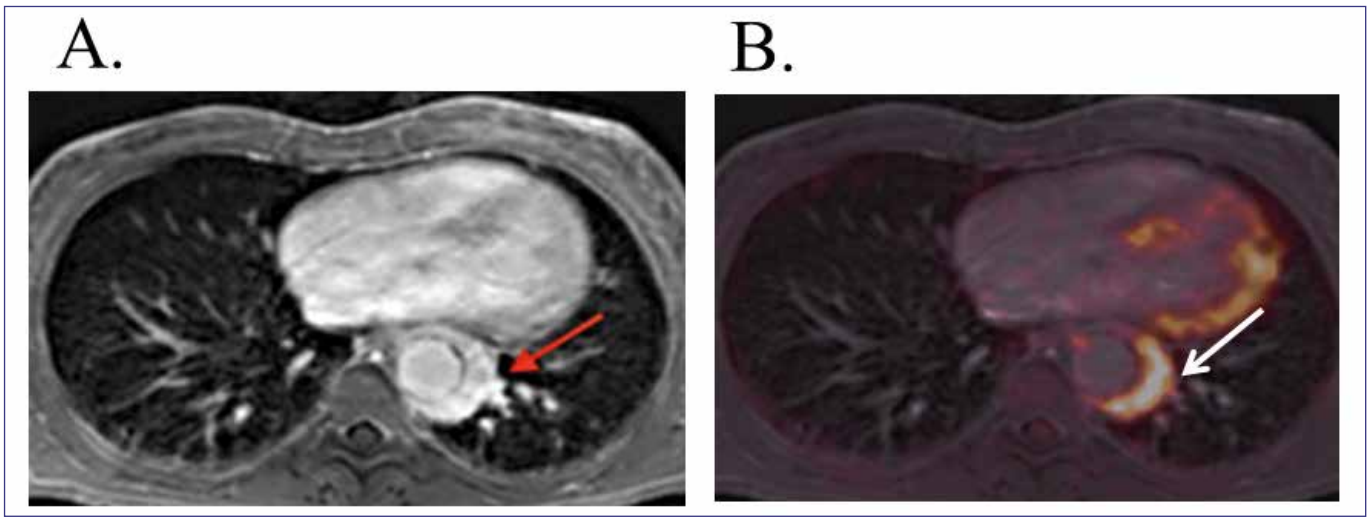

Figure 2. ^{18}F-FDG PET/MR of thoracic descending aorta in a patient with suspicion of active large vessel vasculitis. (A) T2-weighted STIR MR images showing oedema and intense vessel wall thickening (red arrow). (B) Intense FDG uptake on PET at this site in the aortic vessel wall, is indicative for active inflammation and large vessel vasculitis.

References

1. Nekolla SG, Martinez-Moeller A, Saraste A. PET and MRI in cardiac imaging: from validation studies to integrated applications. Eur J Nucl Med Mol Imaging. 2009;36 Suppl 1:S121-30
2. Schinkel AF, Poldermans D, Elhendy A, Bax JJ. Assessment of myocardial viability in patients with heart failure. J Nucl Med. 2007;48:1135-46
3. Klein C, Schmal TR, Nekolla SG, et al. Mechanism of late gadolinium enhancement in patients with acute myocardial infarction. J Cardiovasc Magn Reson. 2007;9:653-8
4. Kim RJ, Wu E, Rafael A, et al. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. N Engl J Med. 2000;343:1445-53.
5. Nensa F, Poeppel TD, Beiderwellen K, et al. Hybrid PET/MR imaging of the heart: feasibility and initial results. Radiology. 2013;268:366-73
6. Nensa F, Poeppel TD, Krings P, Schlosser T. Multiparametric assessment of myocarditis using simultaneous positron emission tomography/magnetic resonance imaging. Eur Heart J. 2014;35:2173
7. Balink H, Hut E, Pol T, et al. Supression of 18F-FDG myocardial uptake using a fat-allowed carbohydrate-restricted diet. J Nucl Med Technol. 2011;39-185-189
8. Schneider S, Batrice A, Rischpler C, et al. Utility of multimodal cardiac imaging with PET/MRI in cardiac sarcoidosis: implications for diagnosis, monitoring and treatment. Eur Heart J. 2014;35:312
9. White JA, Rajchl M, Butler J, et al. Active cardiac sarcoidosis: first clinical experience of simultaneous positron emission tomography--magnetic resonance imaging for the diagnosis of cardiac disease. Circulation. 2013;127:e639-41
10. Wicks E, Menezes L, Pantazis A, et al. Novel hybrid positron emission tomography – magnetic resonance (PET/MR) multi-modality inflammatory imaging has improved diagnostic accuracy for detecting cardiac sarcoidosis. Heart. 2014;100:A1-A138
11. Nensa F, Tezgah E, Poeppel T, et al. Diagnosis and treatment response evaluation of cardiac sarcoidosis using positron emission tomography/magnetic resonance imaging. Eur Heart J. 2015;36:550
12. Pipitone N, Versari A, Salvarani C. Role of imaging studies in the diagnosis and follow-up of large-vessel vasculitis: an update. Rheumatology (Oxford). 2008;47:403-8.
13. Kerr GS, Hallahan CW, Giordano J, et al. Takayasu arteritis. Ann Intern Med. 1994;120:919-29
14. Nuenninghoff DM, Hunder GG, Christianson TJ, et al. Incidence and predictors of large-artery complication (aortic aneurysm, aortic dissection, and/or large-artery stenosis) in patients with giant cell arteritis: a population-based study over 50 years. Arthritis Rheum. 2003;48:3522-31
15. Einspieler I, Thurmel K, Pyka T, et al. Imaging large vessel vasculitis with fully integrated PET/MRI: a pilot study. Eur J Nucl Med Mol Imaging. 2015;42:1012-24

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In vivo imaging of inflammation; what's next?

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Abstract

Aarntzen EHJG, Boerman OC. In vivo imaging of inflammation; what's next? Inflammation results from a highly coordinated action of different cell types and involves many different mediators. Research in the past decade has resulted in a better understanding of the role of inflammation in various disease types, including infection, cancer and autoimmune disorders. In vivo imaging has a potential role in the translation of this knowledge in clinical practice, if we are only able to target the relevant functional processes and fully understand the images we acquire. We will explore the three main domains of inflammation imaging; 1) targeting immune cell metabolism, 2) in vivo targeting of immune cells and 3) the ex vivo labelling of immune cells; and discuss recent imaging protocols and future developments in the in vivo imaging of inflammation. **Tijdschr Nucl Geneesk 2015; 37(4):1498**

Introduction

George de Hevesy first described radionuclide-based imaging in 1935, when he published a letter in Nature on the use of phosphorus-32 (^{32}P) for the study of phosphorus metabolism (1). His and other techniques were later adapted for applications in physiology, biochemistry and, only recently, in molecular imaging. The experiments and clinical studies performed by Scott and Hersey in the early 1970s (2, 3) led to the routine application of radiolabelled leucocytes in clinical practice. The introduction of fluor-18-fluorodeoxyglucose (^{18}F-FDG) at the end of the 1990s gradually pushed cell labelling to the background (figure 1). The increasing need to understand contributions of specific immune cell subsets in auto-immune diseases and complex infections, and our recent understanding of the inevitable role of inflammation in cancer (4) has revived interest in imaging immune cells in vivo.
In this paper, we will discuss the main categories of clinical available techniques for in vivo immune cells imaging and highlight the current developments that we envision to have clinical impact in the upcoming years.

Metabolic tracers

Immune responses require a highly coordinated action of different cell types, involving neutrophils, lymphocytes, macrophages, fibroblasts and endothelial cells. Most of these cells are quiescent, but capable to respond rapidly upon inflammatory stimuli that require production of cytokines, lipid mediators, enzymes and toxins, and increased migratory ability. Glucose is the dominant fuel for these processes and consequently the most widely used tracer for inflammation imaging is ^{18}F-FDG (figure 1 and 3). It targets increased glycolysis, which is the central pathway in virtual all types immune cells that can be involved in infectious and inflammatory disorders.
The role of ^{18}F-FDG PET/CT in imaging infection and inflammation is highlighted in this issue by Kouijzer, Vos and Van der Laken. An example of how imaging with ^{18}F-FDG, as an *early* biomarker for inflammation, can have clinical consequences is provided by studies on cystic fibrosis and idiopathic pulmonary fibrosis. Using dual time point imaging, Umeda et al. found that continued increase of ^{18}F-FDG uptake predicted deteriorated pulmonary function after one year (5). Similarly, the rate of ^{18}F-FDG uptake in the whole lung in stable cystic fibrosis correlates with more rapidly declining lung function, sputum neutrophil counts, and CT scores (6, 7).

Metabolic tracers: what's next?

Fuel meets function

^{18}F-FDG represents a nearly universal tracer for the detection of inflammatory foci, with excellent sensitivity. On the other hand, it inherently lacks specificity for further detailing the type of inflammatory process. A considerable body of literature is now available on the relation between metabolism and cell function in immune cells (see box), which might help in the interpretation of increased ^{18}F-FDG uptake in inflammatory processes. Parameters like distribution pattern of ^{18}F-FDG accumulation, maximum standardised uptake value (SUV_{max}), ^{18}F-FDG accumulation dynamics over time, have been shown to be relevant for localising low virulence infections and guiding treatment (8, 9). However, in discriminating infectious lesions from malignancy or active from inactive tuberculosis lesions, using dual time point imaging with ^{18}F-FDG PET/CT was not successful, demonstrating the complexity of using a tracer with such low specificity (10). Translating knowledge of how 'fuel feeds function' of immune cells into clinical relevant frameworks for disease evaluation will likely result in an improved specificity of ^{18}F-FDG PET/CT.

Imaging immune cell proliferation

The adaptive immune system, comprising mainly of T and B

lymphocytes, is characterised by low frequencies of highly specific cells that undergo rapid expansion once activated. High proliferation rates can result in a more than 1000-fold increase in frequencies of circulating antigen-specific T cells. Although fuelled by glucose, proliferating cells have a high demand for other biosynthetic molecules such as thymidine for increased DNA-synthesis or choline for synthesis of cell membranes. Clinical PET tracers that target these processes have mostly been designed for oncologic applications; ^{18}F-fluorothymidine (^{18}F-FLT) for proliferation and ^{18}F-choline

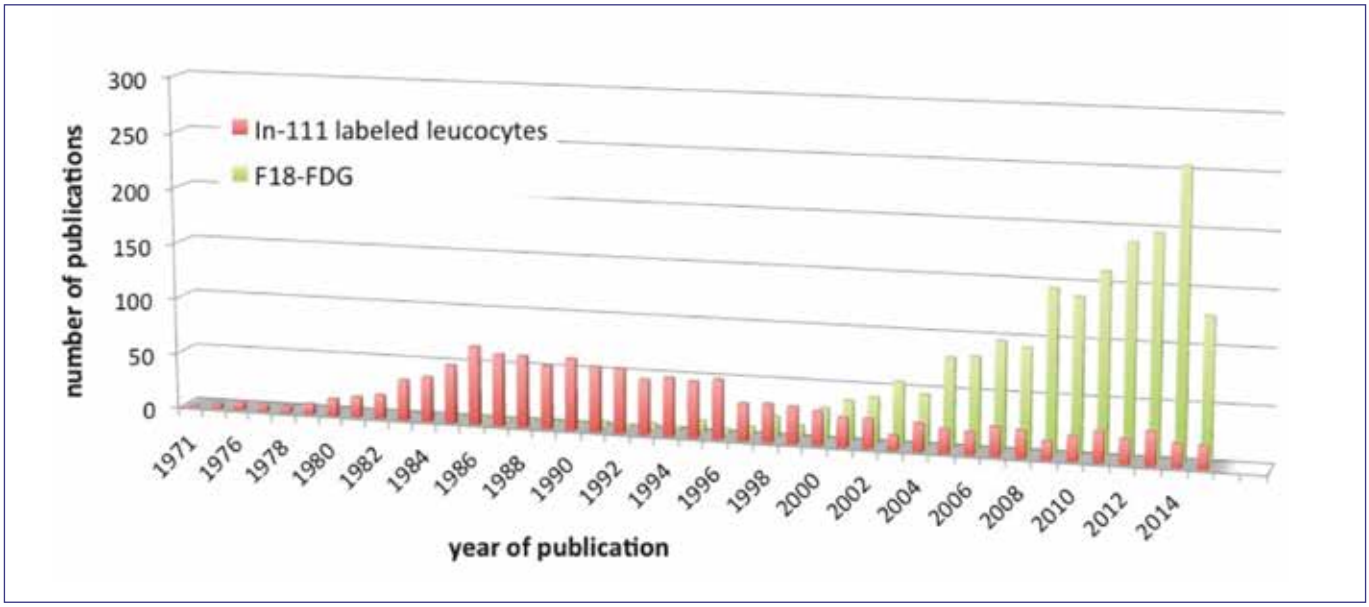


Figure 1. The use of ^{111}In-oxinate labelled leucocytes and ^{18}F-FDG for inflammation imaging in clinical studies in the past decades.

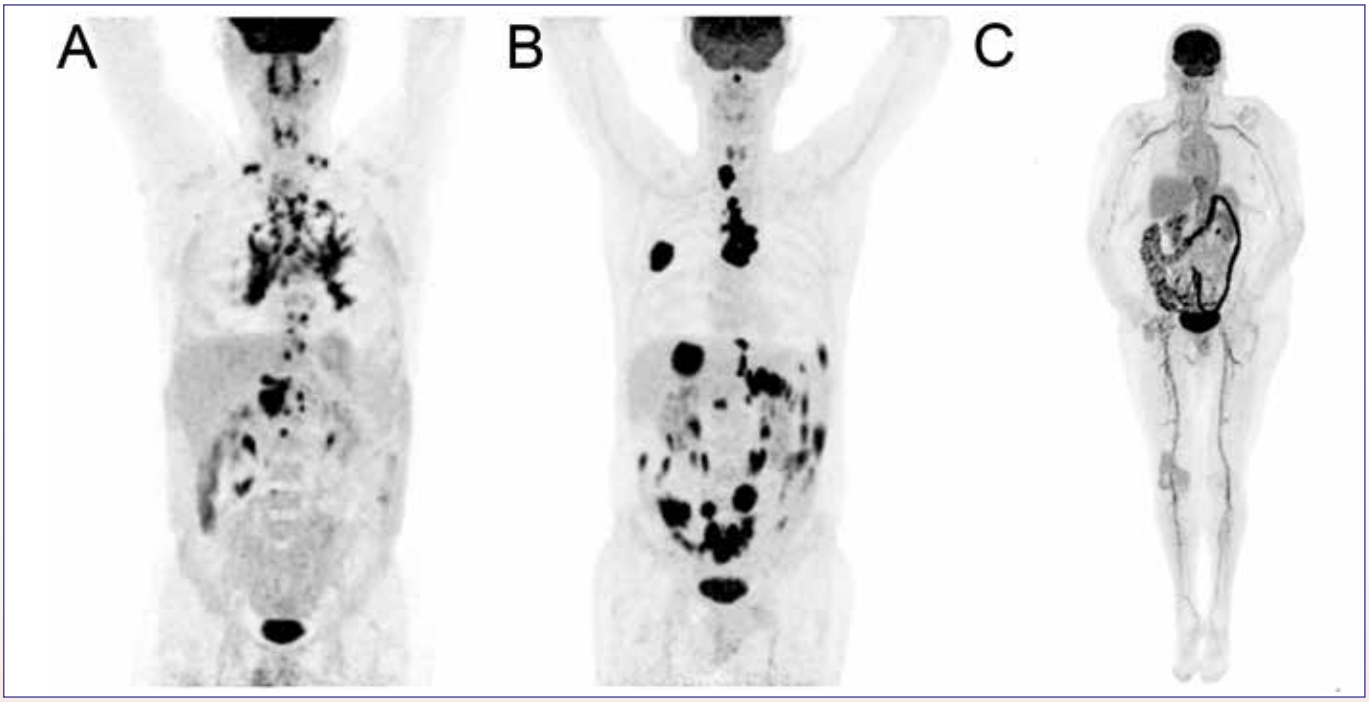
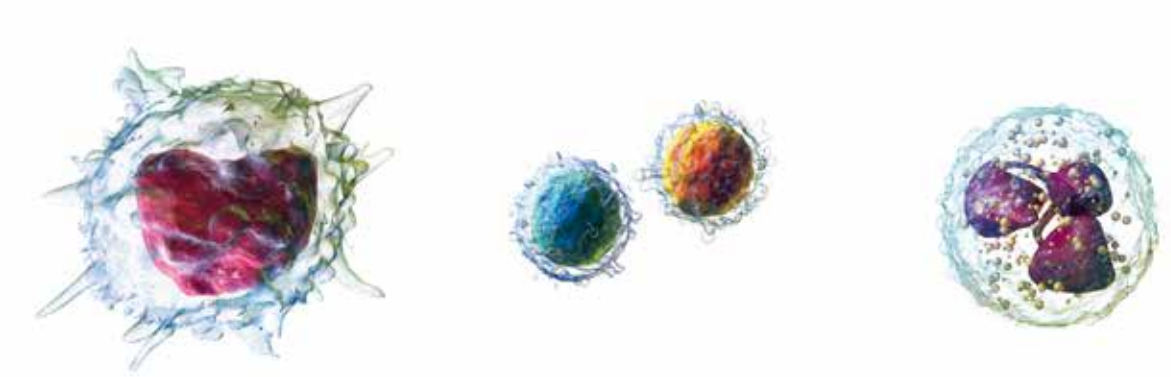


Figure 3. Imaging inflammation and infection in the era of positron-emitting radionuclides. Three typical examples of sarcoidosis (A), tuberculosis (B) and large vessel vasculitis (C), demonstrate the improved sensitivity and image quality. Moreover, the whole body range of scanning in these indications shows a particular distribution pattern that is essential to increase the specificity of ^{18}F-FDG PET/CT.



From left to right; mononuclear phagocytic cells, lymphocytes and neutrophils [with permission from Blausen Medical Communications, Wikimedia].

Why do immune cells exploit the Warburg effect?

Glucose is the main energy source for immune cells, through two metabolic pathways. The first is glycolysis, which is the conversion of glucose to pyruvate in the cytoplasm. Pyruvate can enter the tricarboxylic acid (TCA) cycle, which takes place in the mitochondria: a process called oxidative phosphorylation (32-34). Remarkably, immune cells preferentially use glycolysis to generate ATP, which is less efficient then oxidative phosphorylation, even when oxygen is widely available. This process is known as 'aerobic glycolysis' or the 'Warburg effect'. Immune cells probably switch to this less efficient pathway of ATP-production to be able to meet their high demands for biosynthetic precursors (e.g. lipid, proteins and nucleic acids, that are side-products of glycolysis), required for execution of effector functions.

Neutrophils. Their low number of mitochondria reflects neutrophils' dependency on glycolysis, rather than using oxidative phosphorylation. The reason for neutrophils to stick to glycolysis is their need to produce hydrogen peroxide (H_2O_2) in activated status, which is their main microbial product. Series of clinical studies (35) have confirmed increased ^{18}F-FDG uptake in neutrophil infiltrates by PET/CT. Validation by autoradiography demonstrated increased tritium-deoxyglucose (^{3}H-DG) uptake was dominated by neutrophils. Enhanced glucose uptake occurs upon priming of neutrophils, but is not required for executing the effector functions itself such as the respiratory burst or degranulation (36). Elegant studies in patients with bronchiectasis have shown an increase in neutrophils in the alveolar space, determined by imaging ^{111}In-labelled white blood cells, but no increase in ^{18}F-FDG uptake measured on PET/CT. On the other hand, in lobar pneumonia there is increased ^{18}F-FDG uptake in the lung without evident emigration of ^{111}In-labelled white blood cells in alveolar space (37). These studies confirm that ^{18}F-FDG PET/CT might represent a biomarker for *early* inflammatory processes, reflecting neutrophil activation and priming.

Lymphocytes. In sarcoidosis, which is characterised by lymphocytic infiltration, increased ^{18}F-FDG uptake in lungs is well established (38). Multiple in vitro studies have shown increased glucose metabolism in different stages of functional differentiation of T cells (39). When a naïve T cell encounters its cognate antigen in the proper stimulatory context, it undergoes a transcriptional program that is characterised by proliferation, rapid growth and induction of specialised effector functions. This reprogramming requires metabolic adaption from a catabolic metabolism to an anabolic metabolism because, unlike in the quiescent state, nutrients will not be used for homeostasis, but will be incorporated in biosynthetic precursors required for daughter cells and effector functions. This demand for biosynthetic precursors drives *effector* T cells to increase their glycolysis, even in the presence of sufficient levels of oxygen. To the contrary, T cells destined to become memory cells must maintain catabolic metabolism, underlying their longevity and may postpone their terminal differentiation, so they rely mainly on mitochondrial fatty acid oxidation.

Macrophages. Macrophages are primarily glycolytic (40), with relatively low numbers of mitochondria. In parallel with neutrophils, inflammatory macrophages require radical oxygen species for bacterial killing in phagolysosomes. Indeed, inflammatory macrophages show increased ^{18}F-FDG uptake as demonstrated in multiple clinical studies on atherosclerosis (41) and in alveolar macrophages in fibrotic lung disease (42). However, differentially polarised macrophages may have different metabolic profiles (43). The spectrum of macrophage phenotypes in cancer-related inflammation is currently being explored, but we do not yet fully understand how macrophages initially switch from pro-inflammatory/tumour-suppressing to anti-inflammatory/tumour-promoting or pro-angiogenic/wound-healing phenotypes. It has been suggested that micro-environmental conditions such as hypoxia in the tumour core may mediate this transition, presuming a concurrent metabolic switch in macrophages. In contrast to pro-inflammatory macrophages, pro-tumorigenic macrophages rely on increased mitochondrial capacity for their energy resources, enabling them to thrive in hypoxic conditions deep inside tumours and ischaemic tissues and thereby facilitate angiogenesis.

for membrane synthesis. Increased ^{18}F-choline uptake in lymph nodes is a well-known pitfall for the interpretation of lymph node metastases in cancer patients, mostly studied in prostate cancer. Given the unspecific nature of ^{18}F-choline, its unfavourable physiologic uptake in liver, spleen, intestines and the resulting suboptimal image quality, this tracer will probably not prevail over ^{18}F-FDG for imaging inflammatory foci.
^{18}F-FLT uptake in tumours has been shown to correlate with the fraction of proliferating tumour cells in various types of cancer. Increased ^{18}F-FLT uptake in lymph nodes can represent lymph node metastases, but also is the cause of high rates of false-positives caused by reactive B cell germinal centres (11). At our institute, we have demonstrated in a cell-based vaccination study that increased ^{18}F-FLT uptake in lymph nodes after intranodal injection of antigen-loaded dendritic cells correlated to the magnitude of antigen-specific T and B cell responses as measured by in vitro monitoring. Control injections in contralateral normal lymph nodes showed that the injection alone or the mere presence of dendritic cells did not cause enhanced ^{18}F-FLT uptake in lymph nodes. The SUV_{max} of ^{18}F-FDG in vaccinated lymph nodes did not exceed 4.5 and did not correlate with antigen-specific immune responses measured otherwise (12). So, in our setting ^{18}F-FLT enabled the study of the dynamics of immune responses in vivo.

In vivo targeting of immune cells

The enhanced permeability and retention (EPR) effect and the increased influx of activated lymphocytes in inflamed tissue can be exploited for in vivo targeting of inflammation. A wide variety of inflammatory mediators, receptor-specific proteins and peptides, monoclonal antibodies or cell-specific substrates has been tested to this end (reviewed in (13)).

Radiolabelled cytokines and chemokines

Once activated, T cells express increased numbers of receptors involved in activation signalling and chemotaxis that can be targeted for in vivo imaging. Following their physiological role, these mediators often have high affinity for their cognate receptors expressed on inflammatory cells, which renders them interesting candidates for in vivo imaging. The most investigated receptor is the interleukin (IL)-2 receptor, named CD25, highly expressed on activated T lymphocytes. In the 1980's, IL-2 has been labelled with various isotopes, (i.e. iodine-123, iodine-125, technetium-99m (^{99m}Tc) and ^{18}F) and tested in animal models. Clinical studies using radiolabelled IL-2 involve patients with a wide variety of inflammatory conditions like inflammatory bowel disease, diabetes, atherosclerotic plaques (14-16) and melanoma patients (17). Activated neutrophils, monocytes, and to a lesser extent T lymphocytes, express CXCR1 and CXCR2, the receptors for CXCL8 (IL-8), to facilitate rapid recruitment of neutrophils to inflammatory foci in early stage of inflammation. ^{99m}Tc-CXCL8 was studied in patients with a range of localised infections (18) and in inflammatory bowel disease (Aarntzen E, Hermsen R, Drenth J, Boerman O, Oyen W.J Nucl Med. 2015 Nov 25. pii: jnumed.115.165795. [Epub ahead of print]), demonstrating specific accumulation of ^{99m}Tc-CXCL8 within four hours after injection in inflammatory lesions in direct correlation with disease activity, without significant side effects.
In general, these small biological molecules show rapid targeting with high affinity and rapid clearance from circulation. Moreover, most molecules are internalised by their target cells, all contributing to high target-to-background ratios. Disadvantages include tracer-specific physiological uptake in physiological sites in immune-reactive sites. The tracer is or might be biologically active, which may lead to side effects when higher doses are administered.

Monoclonal antibodies

The main advantage of monoclonal antibodies (mAbs) is the high specificity and affinity for their cognate antigen, addressing the main drawback of ^{18}F-FDG mentioned earlier. Several mAbs for specific cell types have been used, targeting e.g. CD45, CD3, CD4 and CD8 (19). The specific targeting of CD25, expressed on activated lymphocytes in leukaemia patients is especially interesting as anti-CD25 mAbs have been labelled with diagnostic and therapeutic radioisotopes (20). Making ultimate use of the specificity of mAbs, mAbs for (tumour-)antigen-specific cell populations have recently been developed in a preclinical model using OVA-expressing tumours (21).
Due to their large size, mAbs have a long circulation time and slowly accumulate in the target tissue. Disadvantages of radiolabelled mAbs include their sustained background levels and their nonspecific accumulation due to the EPR effect. Moreover, most mAbs have a mouse origin and can lead to the induction of human anti-mouse antibodies (HAMA) that can affect targeting efficiency.

In vivo targeting of immune cells: what's next?

'Smaller bodies'

Considering the high specificity of radiolabelled mAbs, efforts have been made to increase the specific targeting of immune cells by using smaller antibody formats, like 'minibodies', 'diabodies' or 'single-chain variable fragments'. These smaller antibody formats have a more rapid tissue penetration, rapid clearance and generally reveal higher target-to-background ratios. Together with using PET radionuclides such as ^{18}F or gallium (^{68}Ga), these agents could improve image quality to clinically relevant levels, which will boost in vivo inflammation imaging.

Selecting therapeutic targets

Another development in radiolabelled mAbs that will likely affect clinical decision-making is the targeting specific disease processes that might have impact on treatment stratification. For example, antibodies blocking the programmed death 1/ programmed death ligand 1 (PD1/PDL1) axis have shown

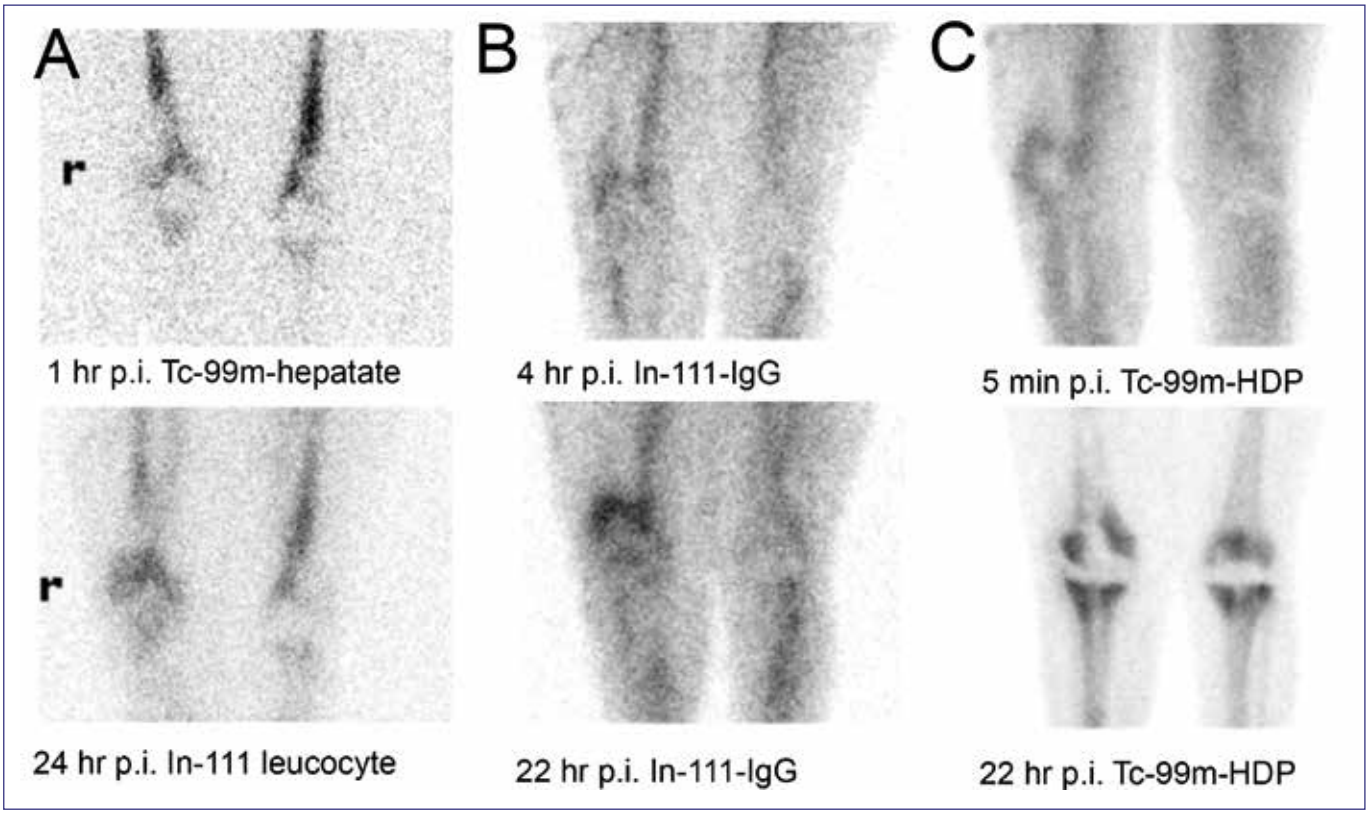


Figure 2. Imaging of inflammation and infection in the era of gamma-emitting radioisotopes. This example shows serial imaging investigations of one patient with total knee prosthesis of the right knee and persistent complaints of pain and dysfunction. In 2007 a leucocyte scan was performed, showing increased leucocyte migration in the right knee above the patella (A). In 2010, a IgG scan showed focal accumulation of IgG over time around the prosthesis (B). Ten months later, in 2010, the bone scan showed increased tracer accumulation in second and late phase, again around the prosthesis (C). All scans are compatible with inflammation, but revision of the knee prosthesis in 2008 and 2010 and subsequent cultures did not show bacterial infection.

impressive results in various types of cancer, and patients with high expression of PDL1 are most likely to benefit from this therapy. Heskamp and colleagues showed that indium-111 (^{111}In)-labelled anti-PDL1 antibody accumulated in PDL1 expressing tumours and did not show specific uptake in tumours with low or no detectable levels of PDL1. Moreover, SPECT/CT and autoradiography showed a heterogeneous distribution of ^{111}In-PDL1 within the tumour, which might be worthwhile to explore in future studies (22).

Ex vivo labelling of immune cells

Specific subsets of immune cells occur in rather small absolute numbers in inflammatory lesions, which is a challenge for in vivo imaging. In an attempt to increase the sensitivity of imaging immune cells, subpopulations of immune cells have been isolated from peripheral blood and labelled ex vivo, before being tracked in vivo. The main advantage of this technique is that the specific activity can be optimised and cell viability and function can be investigated in a systematic way before application in the clinic. Although numerous radionuclides have been used for ex vivo labelling of immune cells, labelling cells with ^{111}In oxinate or tropolonate are the most widely used strategies. ^{111}In chelated by oxinate or tropolonate passively diffuses over the cell membrane and intracellularly associates with proteins in the cytoplasm, resulting in good intracellular retention. Other clinically used strategies such as ^{99m}Tc-hexamethylpropyleneamineoxime (^{99m}Tc-HMPAO) and ^{18}F-FDG show higher leakage from the cell.

The robustness of the ^{111}In-oxinate/tropolonate cell labelling protocols has resulted in routine clinical application of these protocols in leucocytes to image infection and inflammation (23, 24) (figure 2). Also commercial kits are available for leucocyte labelling (25).

Ex vivo labelling of immune cells: what's next?

Development of PET labelling protocols

Although the relatively long half-life of ^{111}In (67 hours) allows longitudinal tracking of labelled cells in processes that typically require multiple days, the low sensitivity and limited spatial resolution of the gamma camera imaging/SPECT is insufficient for more advanced application, referred to in the introduction. Furthermore, gamma camera images are difficult to analyse quantitatively. Recently, several procedures to label cells with

zirconium-89 (^{89}Zr) (half-life 78 hours) have been described (26-28). These methods offer a potential solution to the emerging need for a long half-life PET tracer for quantitative imaging of immune cells exploiting the superior sensitivity and spatial resolution of PET. Although these studies demonstrate comparable labelling efficacy and cell viability for human leucocytes and cell lines, no clinical studies on ^{89}Zr-based cell labelling have been published to date.

Life-long imaging

The ideal technique should allow clinicians to monitor the whole-body tissue distribution of immune cells, to quantify immune cells in a non-invasive and longitudinal fashion. This unmet need can be addressed by using PET reporter gene (PRGs) systems (29). A PRG encodes a protein that mediates the specific accumulation of a PET
reporter probe (PRP) labelled with a positron-emitting radionuclide. PRGs developed to date encode proteins with various activities, including enzymes, transporters, and receptors (29). The most commonly used PRGs are based on herpes simplex virus type 1 thymidine kinase (HSV1-tk). Several PRPs can be used to image cells engineered to express HSV1-tk-based PRGs: 9-[4-^{18}F-3-(hydroxymethyl) butyl]guanine (^{18}F-FHBG), 2′-deoxy-2′-^{18}F-5-ethyl-1-D-arabinofuranosyluracil (^{18}F-FEAU), and 2′-deoxy-2′-^{18}F-5-iodo-1-D-arabinofuranosyluracil (^{18}F-FIAU). To date, HSV1-tk is the only PRG that has been used to image therapeutic cells in patients (30). The main disadvantage of HSV1-tk as a PRG is its immunogenicity, which can lead to immune-mediated elimination of transfected immune cells. The issue of immunogenicity can be solved by replacing the viral kinase with a human orthologue. Campbell and colleagues developed a mutant PRG enzyme, using structure guided enzyme engineering, which is orthogonal to the wild type enzyme regarding its ability to phosphorylate endogenous nucleosides (31). This TK2 double mutant efficiently phosphorylates 2′-deoxy-2′-^{18}F -5-methyl-1-beta-L-arabinofuranosyluracil (L-^{18}F-FMAU) and has lower activity for the endogenous nucleosides thymidine and deoxycytidine than wild type TK2. Imaging studies in mice indicate that the sensitivity of this new human PRG is comparable with that of a widely used PRG based on HSV1-tk. The first clinical studies are eagerly awaited.

Outlook

In vivo imaging has proven to be a valuable tool for the diagnosis and monitoring of infection and inflammation in clinical practice. However, our increasing understanding of the role of immune cells in a wide spectrum of infection, auto-immunity and cancer, raises the bar of expectations for in vivo imaging. The first of three main challenges we face for in vivo imaging of inflammation, is imaging smaller numbers of specific immune cell subsets, which requires optimisation of sensitivity and specificity, for example by exploiting PET over gamma camera and increasing the specific activity per cell. Secondly, in the era of biologicals and monoclonal antibody-based therapies, imaging protocols should target pathways, receptors or cell subsets with direct relevance for treatment. Thirdly, many of the current developments mentioned in this overview will face large hurdles in the translation to clinical practice. The development plan for new imaging protocols should include issues like infrastructure, quality control systems and costs right from the start, in order to increase the efficacy of the translational process.

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References

1. Myers WG. The first radioindicator study in the life sciences with a man-made radionuclide: "Radioactive indicators in the study of phosphorus metabolism in rats, by O. Chievitz and G. Hevesy, reprinted from Nature 136: 754-755, Nov. 9, 1935.". J Nucl Med. 1975;16(12):1106-8.
2. Scott JL, Davidson JG, Marino JV, McMillan R. Leukocyte labeling with 51 chromium. 3. The kinetics of normal lymphocytes. Blood. 1972;40(2):276-81.
3. Hersey P. The separation and 51 chromium labeling of human lymphocytes with in vivo studies of survival and migration. Blood. 1971;38(3):360-71.
4. Quail DF, Joyce JA. Microenvironmental regulation of tumor progression and metastasis. Nat Med. 2013;19(11):1423-37.
5. Umeda Y, Demura Y, Ishizaki T, et al. Dual-time-point 18F-FDG PET imaging for diagnosis of disease type and disease activity in patients with idiopathic interstitial pneumonia. Eur J Nucl Med Mol Imaging. 2009;36(7):1121-30.
6. Chen DL, Atkinson JJ, Ferkol TW. FDG PET imaging in cystic fibrosis. Semin Nucl Med. 2013;43(6):412-9.
7. Amin R, Charron M, Grinblat L, et al. Cystic fibrosis: detecting changes in airway inflammation with FDG PET/CT. Radiology. 2012;264(3):868-75.
8. Husmann L, Sah BR, Scherrer A, et al. 18F-FDG PET/CT for Therapy Control in Vascular Graft Infections: A First Feasibility Study. J Nucl Med. 2015;56(7):1024-9.
9. Barten DG, Delsing CE, Keijmel SP, et al. Localizing chronic Q fever: a challenging query. BMC Infect Dis. 2013;13:413.
10. Treglia G, Taralli S, Calcagni ML, et al. Is there a role for fluorine 18 fluorodeoxyglucose-positron emission tomography and positron emission tomography/computed tomography in evaluating patients with mycobacteriosis? A systematic review. J Comput Assist Tomogr. 2011;35(3):387-93.
11. Troost EG, Vogel WV, Merkx MA, et al. 18F-FLT PET does not discriminate between reactive and metastatic lymph nodes in primary head and neck cancer patients. J Nucl Med. 2007;48(5):726-35.
12. Aarntzen EH, Srinivas M, De Wilt JH, et al. Early identification of antigen-specific immune responses in vivo by [18F]-labeled 3′-fluoro-3′-deoxy-thymidine ([18F]FLT) PET imaging. Proc Nat Acad Sci USA. 2011;108(45):18396-9.
13. Malviya G, Galli F, Sonni I, Signore A. Imaging T-lymphocytes in inflammatory diseases: a nuclear medicine approach. Q J Nucl Med Mol Imaging. 2014;58(3):237-57.

14. Annovazzi A, Bonanno E, Arca M, et al. 99mTc-interleukin-2 scintigraphy for the in vivo imaging of vulnerable atherosclerotic plaques. Eur J Nucl Med Mol Imaging. 2006;33(2):117-26.
15. Signore A, Chianelli M, Annovazzi A, et al. 123I-interleukin-2 scintigraphy for in vivo assessment of intestinal mononuclear cell infiltration in Crohn's disease. J Nucl Med. 2000;41(2):242-9.
16. Signore A, Chianelli M, Ferretti E, et al. New approach for in vivo detection of insulitis in type I diabetes: activated lymphocyte targeting with 123I-labelled interleukin 2. Eur J Endocrinol. 1994;131(4):431-7.
17. Signore A, Annovazzi A, Barone R, et al. 99mTc-interleukin-2 scintigraphy as a potential tool for evaluating tumor-infiltrating lymphocytes in melanoma lesions: a validation study. J Nucl Med. 2004;45(10):1647-52.
18. Bleeker-Rovers CP, Rennen HJ, Boerman OC, et al. 99mTc-labeled interleukin 8 for the scintigraphic detection of infection and inflammation: first clinical evaluation. J Nucl Med. 2007;48(3):337-43.
19. Goldsmith SJ, Signore A. An overview of the diagnostic and therapeutic use of monoclonal antibodies in medicine. Q J Nucl Med Mol Imaging. 2010;54(6):574-81.
20. Zhang M, Yao Z, Zhang Z, et al. The anti-CD25 monoclonal antibody 7G7/B6, armed with the alpha-emitter 211At, provides effective radioimmunotherapy for a murine model of leukemia. Cancer Res. 2006;66(16):8227-32.
21. Griessinger CM, Maurer A, Kesenheimer C, et al. 64Cu antibody-targeting of the T-cell receptor and subsequent internalization enables in vivo tracking of lymphocytes by PET. Proc Natl Acad Sci USA. 2015;112(4):1161-6.
22. Heskamp S, Hobo W, Molkenboer-Kuenen JD, et al. Noninvasive Imaging of Tumor PD-L1 Expression Using Radiolabeled Anti-PD-L1 Antibodies. Cancer Res. 2015;75(14):2928-36.
23. de Vries EF, Roca M, Jamar F, Israel O, Signore A. Guidelines for the labelling of leucocytes with (99m)Tc-HMPAO. Inflammation/Infection Taskgroup of the European Association of Nuclear Medicine. Eur J Nucl Med Mol Imaging. 2010;37(4):842-8.
24. Roca M, de Vries EF, Jamar F, Israel O, Signore A. Guidelines for the labelling of leucocytes with (111)In-oxine. Inflammation/Infection Taskgroup of the European Association of Nuclear Medicine. Eur J Nucl Med Mol Imaging. 2010;37(4):835-41.
25. Signore A, Glaudemans AW, Malviya G, et al. Development and testing of a new disposable sterile device for labelling white blood cells. Q J Nucl Med Mol Imaging. 2012;56(4):400-8.
26. Sato N, Wu H, Asiedu KO, et al. (89)Zr-Oxine Complex PET Cell Imaging in Monitoring Cell-based Therapies. Radiology. 2015;275(2):490-500.
27. Charoenphun P, Meszaros LK, Chuamsaamarkkee K, et al. [(89)Zr]oxinate4 for long-term in vivo cell tracking by positron emission tomography. Eur J Nucl Med Mol Imaging. 2015;42(2):278-87.
28. Bansal A, Pandey MK, Demirhan YE, et al. Novel (89)Zr cell labeling approach for PET-based cell trafficking studies. EJNMMI Res. 2015;5:19.
29. Yaghoubi SS, Campbell DO, Radu CG, Czernin J. Positron emission tomography reporter genes and reporter probes: gene and cell therapy applications. Theranostics. 2012;2(4):374-91.
30. Yaghoubi SS, Jensen MC, Satyamurthy N, et al. Noninvasive detection of therapeutic cytolytic T cells with 18F-FHBG PET in a patient with glioma. Nat Clin Pract Oncol. 2009;6(1):53-8.
31. Campbell DO, Yaghoubi SS, Su Y, et al. Structure-guided engineering of human thymidine kinase 2 as a positron emission tomography reporter gene for enhanced phosphorylation of non-natural thymidine analog reporter probe. J Biol Chem. 2012;287(1):446-54.
32. Palsson-McDermott EM, O'Neill LA. The Warburg effect then and now: from cancer to inflammatory diseases. Bioessays. 2013;35(11):965-73.
33. Pearce EL, Pearce EJ. Metabolic pathways in immune cell activation and quiescence. Immunity. 2013;38(4):633-43.
34. Pearce EL, Poffenberger MC, Chang CH, Jones RG. Fueling immunity: insights into metabolism and lymphocyte function. Science. 2013;342(6155):1242454.
35. Chen DL, Rosenbluth DB, Mintun MA, Schuster DP. FDG-PET imaging of pulmonary inflammation in healthy volunteers after airway instillation of endotoxin. J Appl Physiol (1985). 2006;100(5):1602-9.
36. Jones HA, Cadwallader KA, White JF, et al. Dissociation between respiratory burst activity and deoxyglucose uptake in human neutrophil granulocytes: implications for interpretation of (18) F-FDG PET images. J Nucl Med. 2002;43(5):652-7.
37. Jones HA, Sriskandan S, Peters AM, et al. Dissociation of neutrophil emigration and metabolic activity in lobar pneumonia and bronchiectasis. Eur Respir J. 1997;10(4):795-803.
38. Baydur A. Recent developments in the physiological assessment of sarcoidosis: clinical implications. Curr Opin Pulm Med 2012;18(5):499-505.
39. Fox CJ, Hammerman PS, Thompson CB. Fuel feeds function: energy metabolism and the T-cell response. Nat Rev Immunol. 2005;5(11):844-52.
40. Kubota R, Kubota K, Yamada S, et al. Microautoradiographic study for the differentiation of intratumoral macrophages, granulation tissues and cancer cells by the dynamics of fluorine-18-fluorodeoxyglucose uptake. J Nucl Med. 1994;35(1):104-12.
41. Folco EJ, Sheikine Y, Rocha VZ, et al. Hypoxia but not inflammation augments glucose uptake in human macrophages: Implications for imaging atherosclerosis with 18fluorine-labeled 2-deoxy-D-glucose positron emission tomography. J Am Coll Cardiol. 2011;58(6):603-14.
42. El-Chemaly S, Malide D, Yao J, et al. Glucose transporter-1 distribution in fibrotic lung disease: association with [(1)(8)F]-2-fluoro-2-deoxyglucose-PET scan uptake, inflammation, and neovascularization. Chest. 2013;143(6):1685-91.
43. Mosser DM, Edwards JP. Exploring the full spectrum of macrophage activation. Nat Rev Immunol. 2008;8(12):958-69.

A fungus-like bacterium: Actinomyces

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A 2-year-old girl, currently treated for a recurrent acute lymphatic leukaemia, presented with spiking fever during neutropenia. Although blood cultures and cultures of the bronchoalveolar lavage were negative, especially for Aspergillus, she was treated for a fungal infection based on the results of the ^{18}F-FDG PET/CT scan (left panel figure; A) and clinical symptoms. After two weeks of anti-fungal treatment, her spiking fever and malaise persisted and a follow-up ^{18}F-FDG PET/CT scan was performed (right panel figure; B). This scan showed progressive ^{18}F-FDG avid lesions localised in lungs, spleen, lymph nodes, bone marrow and soft-tissue. Based on the pattern of distribution, the differential diagnosis included disseminated infection (fungal, mould), lymphoma-transformed leukaemia or progressive leukaemia. New biopsies were negative for leukaemia, bronchoalveolar lavage cultures remained negative for Aspergillus but revealed Actinomyces graevenitzii (right panel figure, lower part; B). Her anti-fungal treatment was switched to an anti-bacterial treatment, upon which her fever resolved and her clinical condition improved rapidly.

Actinomyces species are gram-positive rods, however bacteria colonies show branching networks of hyphae-like structures that can be difficult to differentiate from fungi on microscopic evaluation. Remarkably, also the clinical picture and ^{18}F-FDG PET image show strong similarities with fungal infections. This case illustrates that the differential diagnosis of fungal infections should include fungus-like bacteria like the Actinomyces species, especially if a fungal infection is not proven by culture or a polymerase chain reaction test.

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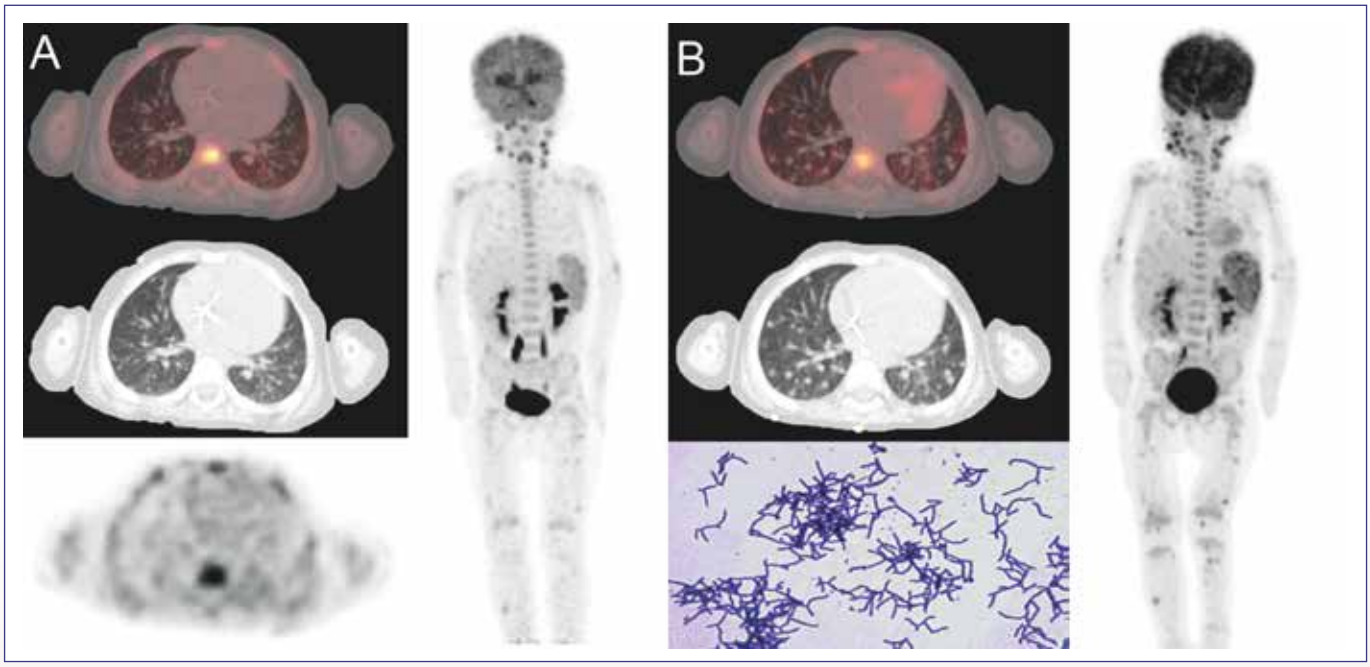

(A) ^{18}F-FDG PET/CT scan showing multiple FDG-avid pulmonary nodules and FDG-avid foci in the spleen, lymph nodes, bone marrow and soft tissue, suspicious of a disseminated infection. (B) Follow-up scan of the same patient after two weeks of anti-fungal treatment, demonstrating progressive widespread FDG-avid lesions, not responding to treatment. Lower panel of (B), a microscopic view of Gram-staining of an Actinomyces species in culture, showing Gram-positive non-spore forming bacteria with branching filamentous structures that resemble a fungal growth pattern.

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2016

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28 - 31 January, 2016. Orlando, USA. www.snmmi.org/mwm2016

Sandwichcursus Acute radiologie en Neuroradiologie
2 - 5 February, 2016. Ede, the Netherlands. www.radiologen.nl

5th international PET/MR Workshop
15 – 19 February, 2016. Tübingen, Germany. http://www.pet-mr-tuebingen.de/

BNMS Spring Meeting 2016
17 – 19 April, 2016. Birmingham, U.K. ww.bnms.org.uk/ann/bnms-annual-spring-meeting/

ISNS Biannual Meeting
30 April – 2 May, 2016. Milaan, Italy. http://isns.info/

Sandwichcursus Cardiovasculaire radiologie en Abdominale radiologie
7 - 10 June, 2016. Ede, the Netherlands. www.radiologen.nl

SNMMI 2016 Annual Meeting
11 - 15 June, 2016. San Diego, USA.
http://www.snmmi.org/MeetingsEvents/EventDetail.aspx?EventID=23024

Symposium Oncologie in perspectief
16 June, 2016. Amsterdam, the Netherlands. www.oncologieinperspectief.avl.nl

5th Balkan Congress of Nuclear Medicine & 13th National Congress of Nuclear Medicine
17 – 20 June, 2016. Thessaloniki, Greece. http://bcnm2016.eu/index.php/en/

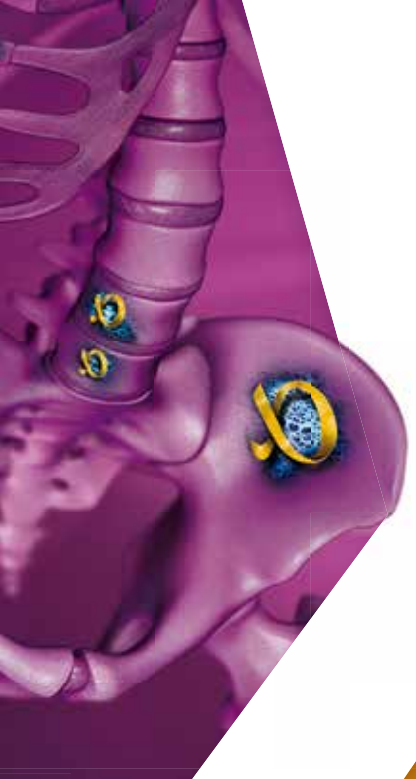
EANM 2016
15 - 19 October, 2016. Barcelona, Spain.
www.eanm.org/congresses_events/future_congresses.php?navId=28

Sandwichcursus Mammaradiologie
1 - 4 November, 2016. Ede, the Netherlands. www.radiologen.nl

RSNA 2016
27 November- 2 December, 2016. Chicago, USA.
https://www.rsna.org/Past_Meetings.aspx

Adreswijzigingen

Regelmatig komt het voor dat wijzigingen in het bezorgadres voor het Tijdschrift voor Nucleaire Geneeskunde op de verkeerde plaats terechtkomen. Adreswijzigingen moeten altijd aan de betreffende verenigingssecretariaten worden doorgegeven. Dus voor de medisch nucleair werkers bij de NVMBR, en voor de leden van de NVNG en het Belgisch Genootschap voor Nucleaire Geneeskunde aan hun respectievelijke secretariaten.
De verenigingssecretariaten zorgen dan voor het doorgeven van de wijzigingen aan de Tijdschrift adresadministratie.
Alleen adreswijzigingen van betaalde abonnementen moeten met ingang van 1 januari 2011 rechtstreeks aan de abonnementenadministratie van Kloosterhof Neer B.V. worden doorgegeven: Kloosterhof Neer B.V., t.a.v. administratie TvNG, Napoleonsweg 128a | 6086 AJ Neer of per E-mail: nucleaire@kloosterhof.nl



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References: 1. Smith MJ *et al.* J R Coll Physicians Lond 2000; 34 (5): 448–51. **2.** Galatola G *et al.* Eur J Gastroenterol Hepatol 1992; 4: 533-7. **3.** Fernández-Bañares F et al. Am J Gastroenterol 2007; 102: 2520–8. **4.** Basumani P *et al.* Gut 2008; 57 (Suppl I): A1-A172.

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