Scintigraphic Evaluation of Endocarditis

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Abstract: *Introduction:* Infective endocarditis (IE) is a very heterogeneous condition for several reasons. The diagnosis can be notoriously difficult. A delay in diagnosis can have severe consequences. Even proper application of the Duke criteria cannot solve all cases. For this reason, positron emission tomography / computer tomography (PET/CT) with 18F-fluorodesoxyglucose (18FDG) has been proposed in the 2015 guidelines of the European Society of Cardiology. What has been the effect of these guidelines thus far?

Methods: A probe of the literature has been performed in PubMed, from 2016 on using the search terms "endocarditis AND PET"

Results: One hundred items were identified, of which 41 documents could be retained. However, only 16 were original series, mostly with low numbers. The other manuscripts were editorials, comments, reviews and "image vignettes". PET/CT increased the sensitivity of the Duke criteria in cases of prosthetic valve endocarditis (PVE), but in a much lesser degree in native valve endocarditis (NVE). Patient preparation should be standardized in order to reduce the uptake of 18FDG by the myocardium. This includes low carbohydrate – high fat diet, fasting and unfractionated heparin administration. Furthermore, image acquisition and processing (quantification, correction for attenuation, taking into account implanted metallic materials) should also be standardized. Effects of antibiotics (negative imaging results before cure) and inflammation (especially healing after operation and use of biological glue materials) should be taken into account. Radiolabeled white blood cell scintigraphy could be a valuable adjunct in these cases. The detection of extra-cardiac foci (especially tumors which can serve as port of entry and septic emboli) is an additional advantage.

Conclusion: PET/CT seems a valuable tool to increase the accuracy in diagnosing IE, especially PVE. Early postoperative cases must be interpreted with caution. To confirm the value of PET/CT, the major centers should standardize their method. This allows comparison of results of larger patient groups, which could be collected in the International Collaboration of Endocarditis – Prospective Cohort Study. Nuclear cardiologists should also be included in "endocarditis teams.

Keywords: Infective endocarditis, Positron emission tomography, Native valve, Valve prosthesis, Duke criteria.

INTRODUCTION

Infective endocarditis (IE) is a very heterogeneous condition. Well-known variables are the causative agents, the site and severity of the infection. The latter includes presence or absence of paravalvular involvement, abscesses, fistulae, chordal rupture, valve perforation and heart block as sign of intra-cardiac destruction. This can lead to congestive heart failure, which is one of the strongest predictors of poor outcome [1]. Other variables are the effect on other organs through septic emboli. This can lead to devastating complications such as stroke but can also remain silent. Last but not least, IE can occur as native valve endocarditis (NVE) or after the implantation of prosthetic valves, prosthetic valve endocarditis (PVE) or electronic cardiac devices cardiac device related IE (CDRIE). The outcome of IE depends highly on timely and adequate intervention and can be influenced by other factors such as referral and treatment bias [1]. The diagnosis of IE can be notoriously difficult. The ESC added in their guidelines the need for an "endocarditis team" and suggested also the use of nuclear imaging [2]. Positron emission tomography (PET) with 18-fluoro-desoxyglucose (18-FDG) as marker for increased metabolism can serve such as in inflammation, infection and malignancies [3]. Another method is labeling of white blood cells (WBC)] with a radionuclide tracer which is considered as more specific for infection [4]. The question to answered is in how far these guidelines had already an effect on management of IE.

METHODS

A small screening probe through PubMED from 2016 to 2018 was performed using the search terms "endocarditis AND PET". Case studies, congenital heart defects and no free access manuscripts were excluded. Included were all papers (original articles, reviews, meta-analyses, editorials, technical comments) dealing with native IE (NVE), prosthetic valve IE (PVE) and cardiac electronic device related IE (CDRIE).

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RESULTS

With these search terms, one hundred items were found. Forty-one documents could be retained. Of these, only 16 were original articles. There were 9 reviews, 7 editorials, two meta-analyses and 7 manuscripts of another type. The original articles are listed in Table **1**. Most of them are smaller series: eleven articles have less than 100 patients, five of them are larger. Most of them are retrospective and observational and are aimed to assess the added value of PET/CT scan. One paper does not focus on IE but on the uptake pattern after valve replacement [5]. Nevertheless, this paper has been included because this offers valuable information about interpreting

Table 1: The Original Series

Author	n	Type	Aim	Conclusion
Amrawi 2016 [35]	35	CDRIE	Search for septic embolism	emboli in 10/35 (sometimes clinically silent or not visible on CT)
Fagman 2016 [19]	27	8 PVE 19 controls retr. cc.	comparison with non-infected valve prostheses	AUC = 0.90
Granados 2016 [9]	21 29 30	NVE PVE CDIE prosp.	evaluate diagnostic accuracy of PET/CT in suspected IE	limited value in NE PET-CT is a valuable adjunct for doubtful cases other foci and neoplasms
Jimenez-Ballvé 2016 [18]	41	PVE/ CDRIE	usefulness of PET/CT interpretation criteria	AUC = 0.71 importance of patient preparation
Salomaki 2016 [7]	23	PVE 16 NVE 7	search for paravalv. infection	PET/CT sensitive in PVE but limited value in NVE
Kokalova 2017 [36]	13	PVE	evaluation of PET	high spec, sens. and PPV low NPV; reveals extra cardiac foci
Kouijzer 2017 [38]	273	Q-fever	diagnostic value of PET/CT	PET/CT provides important diagnostic and prognostic information in Q fever
Machelart 2017 [31]	10	Bentall graft infection	use of PET/CT during follow-up	impact of PET on clinical management is unclear
Mathieu 2017 [5]	51	non-infected prosthetic heart valves*	features of PET/CT uptake pattern	often homogenous mild-to-moderate tracer accumulation
Pizzi 2017 [39]	25	cong. HD with prosthesis prospective	value PET/CTA in complex anatomy	Duke criteria are low sens. and NPV; PET/CTA improves these with accuracy
Scholtens 2017 [27]	13	PVE	60' v. 150' imaging improves accuracy?	late imaging is prone to false +: caution!
Ariaans 2018 [37]	234 379	before SBC after SBC	effect of SBC for S. aureus bacteremia	PET and TEE have added value
Diemberger 2018 [6]	105	CDRIE, prosp. obs.	evaluate extended CDIE by PET/CT on survival	survival improves by correct identification CDRIE by PET/CT
Gomes 2018 [40]	176	obs. NVE, PVE & CDRIE	comparing echo, CTA & PET/CT	modalities are complementary for these conditions
kouijzer 2018 [14]	88	NVE retrosp.	value of PET/CT	negative PET/CT does not exclude NVE useful for extra-cardiac
Swart 2018 [21]	160 77	PVE suspected controls* blinded	improving accuracy & performance; excluding conf.	low inflammatory activity (prolonged antibiotic) is a confounder

Abbreviations: cc. case control; CDRIE: cardiac device related infective endocarditis; conf.: confounders; cong. HD: congenital heart disease; echo: echocardiography NVE: native valve endocarditis; NPV: negative predictive value; obs.: observational; paravalv.: paravalvular; PET/CT: positron emission tomography / computer tomography; PPV: positive predictive value; prosp.: prospective; PVE: prosthetic valve endocarditis; retr.: retrospective; SBC: structured bedside consultation; sens.: sensitivity; spec.: specificity; SUV: standard uptake value; TBR: target-to-background-ratio; TEE: transesophageal echocardiography.
* indication for PET/CT: oncologic, suspected but at hindsight excluded PVE, vasculitis.
NOTE: TBR = SUV max valve / SUV mean blood pool.

postoperative PET/CT images. Several issues are addressed for this interesting imaging modality.

Increase in Accuracy by PET/CT

Most important is the added value of PET/CT in different types of IE (NVE, PVE and CDRIE). The reason is the numbers of false positive and false negatives of the Duke criteria for IE. Late recognition of this condition can lead to increased mortality. Correct identification improves survival in patients with electronic cardiac implants and IE [6]. PET/CT leads to an increased sensitivity, especially in patients with PVE [7-13]. Adding PET/CT could increase the sensitivity of the modified Duke criteria to about 90%. A negative PET/CT does not exclude the presence of NVE [14] because its sensitivity is low [4]. The reason could be the low number of inflammatory cells in vegetation in NVE [4]. PVE is associated with perivalvular involvement and tissue destruction and clearly has an added value for pseudo-aneurysms and abscesses [11]. With PET/CT, up to 90% of the undecided cases of PVE could be reclassified [15] and misdiagnosis can be reduced [16]. These methods should not replace the more classic imaging techniques but should be integrated into decision algorithms [15, 17]. Using PET/CT could increase the area under the curve in the receiver-operator-curve analysis to 0.71 [18] and even 0.90 [19, 20] in PVE. Prolonged antibiotic treatment in patients with PVE, however, leads to lowered inflammatory activity, which could serve as a confounder [21]. In cases of doubt, PET/CT could be complemented with WBC scintigraphy [4]. It is also important to keep in mind that echocardiography or cardiac CT is needed to document vegetation in PVE [2, 11].

Patient Preparation

The use of 18-FDG is based on metabolic trapping of this radiolabeled agent since it cannot be further processed. This is more outspoken in metabolic active tissues. In physiologic conditions, this is for example the myocardium. For this reason, patient preparation is needed. This includes a low carbohydrate – high fat diet, and administration of unfractionated heparin, to suppress the myocardial 18-FDG uptake [16, 18, 22, 23]. The image processing should make use of the maximum standard uptake value (SUV-max) and of target to background ratio (TBR), taking into account both parameters show a great variability of overlap between patients with and without PVE. Cut-off values at 4.4 [24] or lower [21] have been proposed. Correction of attenuation [25] should be performed and the proximity of metallic prosthetic material, if present, should be taken into account. The timing of imaging-taking is considered as useful [2, 26, 27], but not by all [24].

Inflammation V. Infection

Infection and inflammation of other causes such as postoperative healing and foreign body reaction should be discerned because of their different management and outcome. Scintigraphic techniques, based on radiolabeled WBC can serve as complement for distinction between sterile inflammation and infection [4, 15, 25, 28]. Although PET/CT has the advantage of detecting cells with high metabolic activity and has a short acquisition time, the technique does not distinguish inflammation from infection. IE is more probable in presence of an intense and focal perivalvular uptake of 18-FDG but biological surgical glues and suture material [25, 29] can also produce this effect. Sterile postoperative inflammation at the border between the host tissue and prosthetic material can exists for some months in an animal model [26], and sometimes even for years on PET/CT imaging [25]. Moreover, without proper preparation, the adjacent myocardium also shows a high uptake [4]. Nevertheless, PET/CT allows a reclassification of possible IE into definitive IE or rejection of the diagnosis [4]. Radiolabeled WBC accumulate in areas of bacterial infection such as IE and shows high sensitivity (up to 90%) and a 100% specificity. These inflammatory cells are absent in vegetation, which are usually small [4]. WBC scintigraphy has the disadvantage of handling blood products in-vitro and a longer preparation time. As for PET/CT, WBC scintigraphy can also detect metastatic infections due to septic emboli [28]. This is important in postoperative situations where early PVE is suspected. One series studied non-infected prosthetic valves [5] thereby providing useful imaging data: inflammation as part of a healing process often shows a homogenous, mild-to-moderate and steady accumulation of the tracer [29]. This can be important in situations with suspected early PVE in the first weeks after valve replacement. Waiting to perform PET/CT does not solve the problem of false positive imaging, hence there is no reason to wait according to some authors [26], but not to others [29]. However, on the one hand, one should be aware for suture material [29], and surgical adhesive material [2, 13, 25, 29], which show more intense accumulation.

On the other hand, the level of inflammation in true IE can be lowered by prolonged use of antibiotics [21, 30], which can result in false negative results on PET/CT. Moreover, it is not clear if PET/CT can be used to assess the effect of antibiotics [15]. Especially in early postoperative PVE, foreign body reaction and a low degree of inflammation due to antibiotic treatment are not always easy to distinguish [4, 24]. In certain conditions, such as infection of a Bentall graft, the added value of PET/CT is unclear [31]. Remission of "hot spots" does not equal cure of IE [2]. Some other sources might cause false interpretation. One of the more known anomalies is lipomatous interatrial hypertrophy [2, 24, 32]. Correlation of these metabolic data with anatomical findings in CT such as abscesses, fistulae, pseudo-aneurysms and thickening of leaflets, and vegetation is invaluable in the distinction of IE [29].

Extra-Cardiac Foci

One of the extra bonuses of PET/CT are the extra-cardiac foci. These included the possible mechanisms of development of IE. Malignancies, especially those of the digestive tract could serve as port of entry for bacteria [33, 34] such as streptococcus gallolyticus and enterococci. The included original series [9, 14, 35, 36] also mention the detection of extra-cardiac manifestations of the disease. Even in patients without clinical suspicion, up to 65%of the cases show such possible emboli [37]. In a meta-analysis, this has been 17% [12]. The use of PET/CT is especially useful for those patients in whom an MRI is not possible because of a previously implanted cardiac electronic device [15, 30].

CONCLUSIONS

PET/CT is a useful imaging method for inflammatory cardiovascular conditions and it complements more conventional imaging methods [11]. PET/CT shows the combined metabolic and anatomical data. Still, in the last years only a few large series of over 100 patients have been published; most series are small, observational and retrospective and therefore prone to bias (3). Randomized controlled trials are difficult to design for ethical reasons. Larger multicenter based series over some expanded time are needed, in order to collect enough data. A standardized method for patient preparation, imaging acquisition and processing is needed. This can best be undertaken through the International Collaboration on Endocarditis – Prospective Control Study ICE-PCS. Pitfalls such as inflammatory repair in the early postoperative period and low inflammation – without cure – after prolonged antibiotic treatment can lead to misinterpretations. Moreover, the method is useful in patients with PVE, but much less with NVE.

It was also remarkable to see more reviews, editorials and comments of several types compared to original series between 2016 and 2018. This stresses even more the need for prospective multicenter collection of data over an extended period. Only two larger series could be identified. One series showed the value of the structured bedside consult in cases of bacteremia with S. aureus [37] and also showed the value of PET/CT, even in patients with suspected PVE in the early postoperative course. Standardization of every step in the PET/CT protocol is mandatory. The method can be incorporated in decision algorithms for NVE and PVE separately [15, 17], by specially assigned "endocarditis teams" [4].

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