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Effect of left ventricular function on diagnostic accuracy of FDG SPECT

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Objectives: Fluorine-18 fluorodeoxyglucose (FDG) SPECT has emerged as an alternative to dedicated PET imaging. However, it remains uncertain whether FDG SPECT is an as accurate for viability assessment as FDG PET in patients with severely reduced left ventricular function. The aim of the study was to assess the diagnostic accuracy of FDG SPECT in a head-to-head comparison with FDG PET, and divide the patients according to the severity of left ventricular dysfunction. ***Methods:*** A total of 47 patients, with a history of myocardial infarction underwent FDG/perfusion (^{99m}Tc-sestamibi or ^{201}Tl) SPECT as well as FDG/^{13}N-ammonia PET. The patients were divided into 2 subgroups based on the left ventricular ejection fraction (LVEF) (35% cutoff). The left ventricular myocardium was divided into 13 segments, and each segment was classified as viable or scar using a semi-quantitative scoring system based on defect severity and the presence or absence of perfusion-FDG mismatch. ***Results:*** Of the 47 patients studied, 23 had LVEF < 35% (low LVEF group; mean 25 ± 7%), whereas the remaining 24 had LVEF ≥ 35% (high LVEF group; mean 47 ± 6%). In the low LVEF group, 213 segments (71%) were dysfunctional, as compared to 102 (33%) in the high LVEF group. The agreement for detection of viability between PET and SPECT in the low LVEF group was 82% (kappa 0.63), which was not different from the agreement in the high LVEF group (85%, kappa 0.66, p = 0.42 versus low LVEF group). ***Conclusions:*** The results indicate that FDG SPECT can be used for tissue viability assessment regardless of the severity of left ventricular dysfunction.

Key words: SPECT, PET, ^{18}F-FDG, myocardial viability

INTRODUCTION

MYOCARDIAL VIABILITY assessment continues to represent an important issue for the patients with coronary heart disease and left ventricular dysfunction, because viable tissue is likely to recover in function after restoration of myocardial blood flow. Metabolic imaging using ^{18}F-fluorodeoxyglucose (FDG) and PET has played a major role to differentiate viable from scarred tissue.[1–3] However, its restricted availability and high cost limit wide clinical use of cardiac PET imaging for viability assessment. Furthermore, the camera time for PET viability studies is frequently limited even in PET centers, to meet the high demand for oncology studies.

FDG SPECT with ultra-high energy collimators has emerged as an alternative technique to FDG PET for the assessment of myocardial viability.[4] Despite its limited physical performance as compared with PET, published data support the use of FDG SPECT as a reliable diagnostic technique for viability assessment.[5,6] However, it still

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remains uncertain whether FDG SPECT can reliably differentiate viable from scarred myocardium independent of the severity of left ventricular (LV) dysfunction. In patients with severely depressed LV function, accurate assessment of the extent of viable tissue may become a more critical issue, because these patients are at higher risk for peri-operative complications associated with surgical revascularization.[7]

Thus, the aim of the study was to determine whether the diagnostic accuracy of FDG SPECT would differ between patients with severely and mild-to-moderately reduced left ventricular function using FDG PET as a reference standard for tissue viability.

MATERIALS AND METHODS

Patients

We studied 47 patients (41 men, 6 women, mean age 64 years) with chronic myocardial infarction and reduced global or regional LV function. Of these, 27 patients at The Medical & Pharmacological Research Center Foundation, Ishikawa, Japan (Center 1), and the remaining 20 patients were imaged at Free University, Amsterdam, Netherlands (Center 2). In order to come to a meaningful analysis on the influence of LV function, data from previous studies were included.[5,8] All patients underwent both FDG SPECT and FDG PET imaging within 2 months. None of the patients had cardiac events (unstable angina, myocardial infarction, decompensated heart failure) during the study period. The mean left ventricular ejection fraction (LVEF), as assessed by radionuclide ventriculography or gated-SPECT, was 36 ± 13% (range: 7–60%).

Informed consent, based on the guidelines of each institutional human study committee, was obtained prior to participation in the study.

Imaging Procedure

All patients underwent FDG SPECT combined with perfusion imaging using rest injected ^{201}Tl or ^{99m}Tc-sestamibi. PET imaging with FDG and ^{13}N-ammonia was also performed within 2 months of the SPECT study.

Imaging Protocol at Center 1

Twenty-seven patients underwent PET imaging with ^{13}N-ammonia and FDG, followed by ECG-gated dual-isotope SPECT with FDG and ^{99m}Tc-sestamibi on a single day, as previously described.[8,9] Each patient received oral glucose (50 g) loading approximately 1 hour prior to FDG administration. Short-acting insulin was administered in known or suspected diabetic subjects with hyperglycemia to enhance myocardial uptake of FDG; this was required in 15 of 27 patients.

PET imaging was performed using Advance scanner (General Electric Medical Systems, Milwaukee, WI, USA). After a 15 minute transmission scan, PET images were acquired over 5 to 10 minutes beginning 5 minutes after an intravenous injection of ^{13}N-ammonia (740 MBq). After completion of ^{13}N-ammonia data acquisition, 370 MBq of FDG was injected and 40 minutes thereafter imaging (for 15 minutes) was started.

Immediately after the completion of the PET study, 800 MBq of ^{99m}Tc-sestamibi was injected intravenously. This activity of ^{99m}Tc would provide a ^{99m}Tc/^{18}F ratio of 3.49/1 in the heart at the time of imaging, resulting in limited (<6%) down scatter of ^{18}F to the ^{99m}Tc window. Thirty minutes after injection, ECG-gated imaging was performed using a dual-head SPECT camera in a 90 degree geometry equipped with ultra-high energy, parallel hole collimators designed for 511 keV acquisition (Millennium VG, General Electric Medical Systems, Milwaukee, WI, USA). Images were recorded over 180 degrees from the 45 degree right anterior oblique to the 45 degree left posterior oblique in a 64 × 64 matrix with an acquisition time of 30 seconds per projection in 3 degree increments, resulting in a total of 60 projection data. At each position, 8 ECG gated frames per cardiac cycle were acquired. Energy windows were centered on 511 keV ± 10% for ^{18}F and 140 keV ± 10% for ^{99m}Tc. Image reconstruction was performed using a Butterworth filter with a cutoff frequency of 0.4, order 10. Summed data of all frames were generated as the non-gated images for image interpretation.

Imaging Protocol at Center 2

Twenty patients underwent both PET and SPECT within 2 months (mean 34 days) in a manner previously described.[5] In brief, PET imaging was performed using an ECAT951 PET scanner (Siemens, Erlargen, Germany). After injection of 370 MBq of ^{13}N-ammonia, dynamic imaging was performed for 15 minutes. Dynamic FDG PET was performed during hyperinsulinemic euglycemic clamping after injection of 185 MBq of FDG. For both ^{13}N-ammonia and FDG data, the last frame was used for analysis.

Perfusion SPECT was obtained 15 minutes after injection of 111 MBq of ^{201}Tl at rest using a dual-head SPECT camera (Vertex, ADAC laboratories, Milpitas CA, USA) over 360 degrees, collecting 64 projections for 30 seconds each. After the ^{201}Tl study, FDG SPECT was performed during hyperinsulinemic euglycemic clamping. FDG (185 MBq) was injected after 60 minutes of clamping, and 45 minutes thereafter imaging was started. For imaging, the same camera system as described for ^{201}Tl acquisition was used; the system was now equipped with ultra-high energy collimators for 511 keV data acquisition.

Data Analysis

Visual interpretation of the SPECT and PET images was performed by 2 experienced observers using a 13-segment model[5] and 4-point scoring system (1 = normal, 2 = mildly reduced tracer uptake, 3 = severely reduced tracer

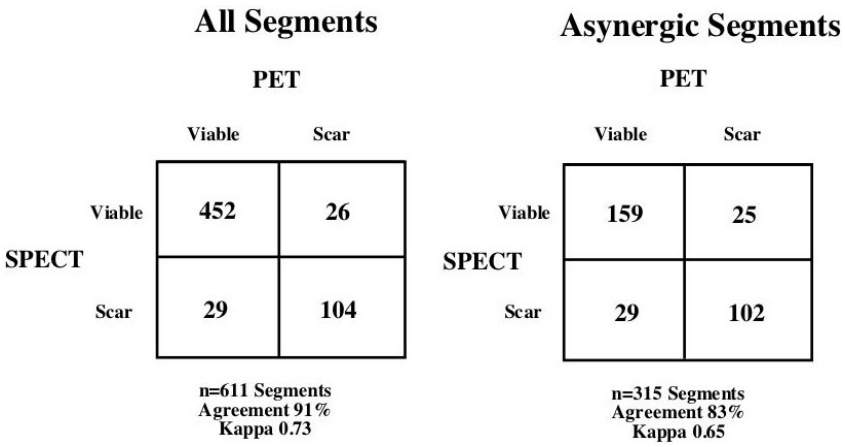

Fig. 1 Agreement of viability assessment between FDG SPECT and PET in all (*left*) and dysfunctional (*right*) segments.

uptake, 4 = absent tracer uptake). Disagreements in interpretation were resolved by consensus. Tissue viability on SPECT or PET was assessed by the combined interpretation of perfusion and FDG activity as previously described.[2] A segment was considered viable if myocardial perfusion was normal or mildly reduced (perfusion score ≤2) or if severely reduced or absent perfusion (perfusion score ≥3) was associated with a perfusion/metabolism mismatch (perfusion score minus ^{18}F-FDG score was ≥1). Conversely, a segment with severely reduced or absent perfusion (perfusion score ≥3) without increased ^{18}F-FDG uptake was considered to represent scar tissue.

Regional Contractile Function

Regional contractile function was assessed from either 2D echocardiography (n = 20) or gated-SPECT (n = 27). Each segment was visually classified using a 3-point scoring system (1 = normal, 2 = hypokinesia, 3 = a- or dyskinesia), as previously described.[5]

Statistical Analysis

Data were expressed as mean ± 1 standard deviation (SD). The evaluation of agreement of viability between FDG SPECT and PET was performed using a kappa statistic. Differences in proportions were analyzed using Chi-square test. Statistical significance was defined as $p < 0.05$.

RESULTS

Overall Results

All 47 patients had FDG images of good quality. From a total of 611 segments in 47 patients, PET identified 481 (79%) segments as viable and 130 (21%) as nonviable. SPECT identified 478 (78%) segments as viable and 133 (22%) as nonviable. The overall agreement of viability between PET and SPECT was 91% with a kappa statistic of 0.73 (Fig. 1).

Of these 611 segments, 315 (52%) showed regional dysfunction on echocardiography or gated-SPECT. Of these, PET identified 188 (60%) segments as viable and 127 (40%) as nonviable. SPECT identified 184 (58%) segments as viable and 131 (42%) as nonviable. As illustrated in Figure 1, the agreement of viability between PET and SPECT in the dysfunctional segments was 83% with a kappa statistic of 0.65. However, there were segments showing discordant results between PET and SPECT (i.e., 29 segments were viable by PET but nonviable by SPECT; another 25 segments were nonviable by PET but viable by SPECT). Of the 29 segments that were viable only by PET, 18 were located in the anterior wall (including apex) and the remaining 11 were in the inferior wall. Of the 25 segments that were viable only by SPECT, 15 were located in the anterior wall (including apex) and the remaining 10 were in the inferior wall.

Diagnostic Accuracy of FDG SPECT in the Low and High LVEF Groups

Of a total of 47 patients, 23 (49%) had LVEF < 35% (low LVEF group; mean 25 ± 7%), whereas the remaining 24 (51%) had LVEF ≥ 35% (high LVEF group; mean 47 ± 6%). The low LVEF group had 213 (71%) dysfunctional segments, while the high LVEF group had 102 (33%) dysfunctional segments ($p < 0.0001$). When only the patients with low LVEF were analyzed, PET identified 120 (56%) viable and 93 (44%) nonviable segments, while SPECT identified 111 (52%) viable and 102 (48%) nonviable segments. Of the 102 dysfunctional segments from the high LVEF group, PET identified 68 (67%) viable and 34 (33%) nonviable segments, while SPECT identified 73 (72%) viable and 29 (28%) nonviable segments. As shown in Figure 2, the agreement of viability between PET and SPECT in this low LVEF group was 82% with a kappa statistic of 0.63, which was similar to that for the high LVEF group (85%, kappa statistic 0.66, $p = 0.42$ versus the low LVEF group). When the results for

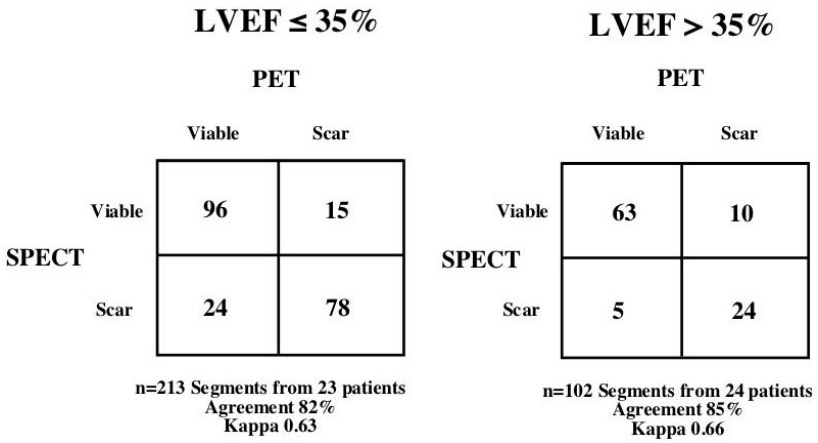

Fig. 2 Agreement of viability assessment between FDG SPECT and PET in patients with left ventricular ejection fraction (LVEF) of <35% (*left*) and ≥35% (*right*).

each imaging center was separately analyzed, there were no significant differences in the agreement of viability between the low and high LVEF group in any center (center 1, 86% for the low LVEF group and 91% for the high LVEF group, NS; center 2, 79% for the low LVEF group and 77% for the high LVEF group, NS).

DISCUSSION

To the best of our knowledge, this is one of the largest studies directly comparing FDG SPECT and PET for the assessment of myocardial viability, and pooling the data, enabling subgroup analysis. The major findings in this study were that (1) there was a good overall agreement of viability between FDG SPECT and PET, and that (2) the agreement of viability did not differ between the patients with mildly and severely reduced LV function.

Metabolic Imaging Using SPECT Techniques

In this study, we used FDG PET as a reference technique to be compared with FDG SPECT, because FDG PET is currently regarded as the metabolic gold standard of tissue viability in patients with coronary heart disease and LV dysfunction.[1–3] Our results showed that the agreement of viability between FDG SPECT and PET occurred in 91% of all and 83% of dysfunctional segments. To date, several studies have been published comparing FDG SPECT and PET in the literature. Burt et al.[10] first compared FDG SPECT and PET in the same 20 patients and reported that both SPECT and PET were equally effective for the assessment of tissue viability. The following studies have also reported good agreements of viability between FDG SPECT and PET.[5,8,11–13] In the current study, pooling data from two centers allowed us to compare FDG SPECT and FDG PET in a large number of patients, confirming the good agreement between PET and SPECT imaging. A recent study by Slart et al.[14] also reported a good agreement of viability between FDG SPECT and PET in an even larger number of patients (n = 58), but they used a different imaging protocol (stress perfusion imaging for both SPECT and PET) and did not address the effect of left ventricular function on diagnostic accuracy.

Despite the good agreement of viability between PET and SPECT observed in this study, there were still some segments showing discordant results. These discordant segments were located in both the anterior and inferior wall, and no specific over- or underestimation of viability by SPECT was observed, suggesting that the lack of attenuation correction with SPECT did not markedly affect the diagnostic accuracy. This may be because we relied not only on tracer uptake but also on the presence or absence of perfusion/metabolism mismatch. More importantly, we already know the normal myocardial distribution of FDG and flow tracer on SPECT images[9] and the visual assessment by expert observers readily considers the effect of photon attenuation in interpreting the SPECT images.

Effect of Left Ventricular Function on Diagnostic Accuracy of FDG SPECT

In addition to the limited number of patients studied with both FDG PET and SPECT, virtually no data are available in patients with depressed LV function. In particular, in these patients, with severely reduced LV function, the presence and extent of viable myocardium is a critical issue, since these patients have a poor prognosis when managed medically, but at the same time have a high event rate when undergoing surgical revascularization. In this view, our results are important, since they demonstrate that the agreement of viability assessment between FDG SPECT and PET in patients with depressed LVEF was comparable to that of patients with a more preserved LV function.

Methodological Considerations and Limitations

In this study, data from two imaging laboratories were

combined. Therefore, the imaging protocols differ in some details, which is frequently an issue in studies performed at different locations. These differences include oral glucose loading versus insulin clamping, dual-isotope versus single-isotope acquisition for FDG SPECT, and wall motion evaluation by gated-SPECT versus 2D echocardiography. Concerning the FDG protocol, it has been demonstrated that the insulin clamp technique does not alter FDG uptake patterns when compared to the glucose loading protocol, although it results in good image quality.[15] In this study, all patients had FDG images of good quality. This is likely due to the fact that short-acting insulin was injected in 56% of patients who were studied after oral glucose loading.

Concerning dual- versus single-isotope SPECT, it has been suggested that the down scatter from FDG to the ^{99m}Tc window may unfavorably affect the ^{99m}Tc-sestamibi perfusion images.[13] However, the contribution of down scatter will be minimal if the ratio of ^{99m}Tc to ^{18}F is 3.2 or higher.[16] In the current study, this ratio was 3.49 at the time of imaging. On the other hand, scatter from ^{99m}Tc to ^{18}F is not that much of an issue since ^{18}F has a much higher photon energy. Concerning wall motion assessment by gated-SPECT or 2D echocardiography, various studies have shown a good agreement between both techniques for the assessment of wall motion.[17,18] Finally, when the data from both centers were separated, and the results from patients with low and high LVEF were compared again, the results were similar.

One additional limitation needs to be emphasized: functional outcome data after revascularization were not obtained, and although good agreement between PET and SPECT was demonstrated, a head-to-head comparison between PET and SPECT in patients who undergo revascularization is needed.

CONCLUSION

In patients with severely depressed LV function, the presence and extent of myocardial viability becomes a critical issue to determine whether or not to proceed to revascularization. The current results lend further support to the contention that FDG SPECT can be used to assess viability, even in this subset of patients.

REFERENCES

1. Tillisch J, Brunken R, Marshall R, Schwaiger M, Mandelkern M, Phelps M, et al. Reversibility of cardiac wall-motion abnormalities predicted by positron tomography. *N Engl J Med* 1986; 314: 884–888.
2. vom-Dahl J, Eitzman DT, Al-Aouar ZR, Kanter HL, Hicks RJ, Deeb GM, et al. Relation of regional function, perfusion, and metabolism in patients with advanced coronary artery disease undergoing surgical revascularization. *Circulation* 1994; 90: 2356–2366.
3. Tamaki N, Kawamoto M, Tadamura E, Magata Y, Yonekura Y, Nohara R, et al. Prediction of reversible ischemia after revascularization. Perfusion and metabolic studies with positron emission tomography. *Circulation* 1995; 91: 1697–1705.
4. Bax JJ, Visser FC, van Lingen A, Huitink JM, Kamp O, van Leeuwen GR, et al. Feasibility of assessing regional myocardial uptake of ^{18}F-fluorodeoxyglucose using single photon emission computed tomography. *Eur Heart J* 1993; 14: 1675–1682.
5. Bax JJ, Visser FC, Blanksma PK, Veening MA, Tan ES, Willemsen TM, et al. Comparison of myocardial uptake of fluorine-18-fluorodeoxyglucose imaged with PET and SPECT in dyssynergic myocardium. *J Nucl Med* 1996; 37: 1631–1636.
6. Bax JJ, Cornel JH, Visser FC, Fioretti PM, van Lingen A, Huitink JM, et al. Prediction of improvement of contractile function in patients with ischemic ventricular dysfunction after revascularization by fluorine-18 fluorodeoxyglucose single-photon emission computed tomography. *J Am Coll Cardiol* 1997; 30: 377–383.
7. Haas F, Haehnel CJ, Picker W, Nekolla S, Martinoff S, Meisner H, et al. Preoperative positron emission tomographic viability assessment and perioperative and postoperative risk in patients with advanced ischemic heart disease. *J Am Coll Cardiol* 1997; 30: 1693–1700.
8. Matsunari I, Kanayama S, Yoneyama T, Matsudaira M, Nakajima K, Taki J, et al. Electrocardiographic-gated dual-isotope simultaneous acquisition SPET using ^{18}F-FDG and ^{99m}Tc-sestamibi to assess myocardial viability and function in a single study. *Eur J Nucl Med Mol Imaging* 2005; 32: 195–202.
9. Matsunari I, Kanayama S, Yoneyama T, Matsudaira M, Nakajima K, Taki J, et al. Myocardial distribution of (18)F-FDG and (99m)Tc-sestamibi on dual-isotope simultaneous acquisition SPET compared with PET. *Eur J Nucl Med Mol Imaging* 2002; 29: 1357–1364.
10. Burt RW, Perkins OW, Oppenheim BE, Schauwecker DS, Stein L, Wellman HN, et al. Direct comparison of fluorine-18-FDG SPECT, fluorine-18-FDG PET and rest thallium-201 SPECT for detection of myocardial viability. *J Nucl Med* 1995; 36: 176–179.
11. Chen EQ, MacIntyre WJ, Go RT, Brunken RC, Saha GB, Wong CY, et al. Myocardial viability studies using fluorine-18-FDG SPECT: a comparison with fluorine-18-FDG PET. *J Nucl Med* 1997; 38: 582–586.
12. Srinivasan G, Kitsiou AN, Bacharach SL, Bartlett ML, Miller-Davis C, Dilsizian V. [^{18}F]fluorodeoxyglucose single photon emission computed tomography: can it replace PET and thallium SPECT for the assessment of myocardial viability? *Circulation* 1998; 97: 843–850.
13. Fukuchi K, Katafuchi T, Fukushima K, Shimotsu Y, Toba M, Hayashida K, et al. Estimation of myocardial perfusion and viability using simultaneous ^{99m}Tc-tetrofosmin—FDG collimated SPECT. *J Nucl Med* 2000; 41: 1318–1323.
14. Slart RH, Bax JJ, de Boer J, Willemsen AT, Mook PH, Oudkerk M, et al. Comparison of (99m)Tc-sestamibi/(18)FDG DISA SPECT with PET for the detection of viability in patients with coronary artery disease and left ventricular dysfunction. *Eur J Nucl Med Mol Imaging* 2005; 32: 972–979.

15. Knuuti MJ, Nuutila P, Ruotsalainen U, Saraste M, Harkonen R, Ahonen A, et al. Euglycemic hyperinsulinemic clamp and oral glucose load in stimulating myocardial glucose utilization during positron emission tomography. *J Nucl Med* 1992; 33: 1255–1262.
16. Delbeke D, Videlefsky S, Patton JA, Campbell MG, Martin WH, Ohana I, Sandler MP. Rest myocardial perfusion/metabolism imaging using simultaneous dual-isotope acquisition SPECT with technetium-99m-MIBI/fluorine-18-FDG. *J Nucl Med* 1995; 36: 2110–2119.
17. Chua T, Kiat H, Germano G, Maurer G, van Train K, Friedman J, Berman D. Gated technetium-99m sestamibi for simultaneous assessment of stress myocardial perfusion, postexercise regional ventricular function and myocardial viability. Correlation with echocardiography and rest thallium-201 scintigraphy. *J Am Coll Cardiol* 1994; 23: 1107–1114.
18. Cwajg E, Cwajg J, Keng F, He ZX, Nagueh S, Verani MS. Comparison of global and regional left ventricular function assessed by gated-SPECT and 2-D echocardiography. *Rev Port Cardiol* 2000; 19 Suppl 1: I39–I46.