Left ventricular dyssynchrony assessment by phase analysis from gated PET-FDG scans

Aju P. Pazhenkottil, MD,[a] Ronny R. Buechel, MD,[a] Rene Nkoulou, MD,[a] Jelena-Rima Ghadri, MD,[a] Bernhard A. Herzog, MD,[a] Lars Husmann, MD,[a] Mathias Wolfrum, MD,[a] Silke M. Küest, MD,[a] Michael Fiechter, MD,[a,b] Oliver Gaemperli, MD,[a] and Philipp A. Kaufmann, MD[a,b]

Background. **The outcome of patients with severe ischaemic left ventricular (LV) dysfunction is determined by the extent of myocardial viability and the presence of LV dyssynchrony. We aimed at assessing both parameters from the same imaging method, i.e. gated positron emission tomography (PET) F18-fluorodeoxyglucose (FDG) scans.**

Methods. **Phase analysis from Emory Cardiac Toolbox was applied on gated PET-FDG scans to assess histogram bandwidth and standard deviation (SD) as a measure of LV dyssynchrony in 30 heart failure patients (mean ejection fraction: 30.2% ± 13.8%) referred for the evaluation of myocardial viability. Cut-off values from single-photon emission computed tomography myocardial perfusion imaging (SPECT-MPI) best predicting cardiac resynchronization therapy (CRT) response served as standard of reference (bandwidth < 135°; phase SD < 43°). Severe LV dyssynchrony was diagnosed if both SPECT-MPI values were above these limits. Intraclass correlation and clinical agreement in detection of severe LV dyssynchrony by PET vs SPECT were assessed.**

Results. **There was a significant correlation between PET-FDG and SPECT-MPI for bandwidth ($r = 0.88$, $P < .001$) and phase SD ($r = 0.88$, $P < .001$) resulting in an excellent clinical agreement between the two methods of 93%.**

Conclusions. **Accurate LV dyssynchrony assessment by phase analysis of gated PET-FDG scans is feasible, allowing assessing myocardial viability and severe LV dyssynchrony in one scan. (J Nucl Cardiol 2011;18:920–5.)**

Key Words: Left ventricular dyssynchrony • phase analysis • myocardial perfusion imaging • myocardial viability

INTRODUCTION

Coronary artery disease (CAD) is one of the leading causes of morbidity and mortality in western countries. Patients with extensive coronary artery disease (CAD) are at higher risk to develop heart failure and left ventricular (LV) dysfunction.

In patients with severe ischaemic LV dysfunction revascularization of viable segments guided by myocardial PET-FDG findings has been shown to improve outcome.[1-4] Recently, it has been shown that not only myocardial viability but also severe LV dyssynchrony is an independent predictor of perioperative outcome.[5,6] Therefore, it has been advocated that the assessment of myocardial viability and LV dyssynchrony should be a routine part of the preoperative evaluation of these patients.[5]

Moreover, studies showed that the presence of LV dyssynchrony as well as the extent of scar tissue and viable myocardium is directly related to the response to cardiac resynchronization therapy (CRT). Therefore, it has been stated that the evaluation for viability and LV dyssynchrony should be considered in the selection process for CRT.[7-10]

For the accurate assessment of LV dyssynchrony, different imaging methods, such as tissue Doppler imaging, multigated blood pool ventriculography

From the Cardiac Imaging,[a] University Hospital Zurich, Zurich, Switzerland; and Zurich Center for Integrative Human Physiology,[b] University of Zurich, Zurich, Switzerland.

Aju P. Pazhenkottil and Ronny R. Buechel shared first authorship.

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Reprint requests: Philipp A. Kaufmann, MD, Cardiac Imaging, University Hospital Zurich, Ramistrasse 100, 8091 Zurich, Switzerland; *pak@usz.ch*.

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acquisition (MUGA) and magnetic resonance imaging (MRI) have been developed. For long time, MUGA has been seen as the most accurate and reproducible non-invasive technique.[11] Lately, phase analysis based on Fourier harmonic function on gated single-photon-emission computed tomography myocardial perfusion imaging (SPECT-MPI) has been suggested as a suitable option for LV dyssynchrony assessment.[12,13]

As PET-FDG is considered the most specific tool for evaluation of viable tissue in ischaemic LV dysfunction where LV dyssynchrony has emerged as independent predictor of outcome, the assessment of the latter by gated PET-FDG appears pertinent. Thus, the aim of this study was to validate the assessment of LV dyssynchrony from phase analysis from gated PET-FDG scans vs previously established phase analysis from gated SPECT-MPI as standard of reference.[12,13]

MATERIALS AND METHODS

This study includes 30 consecutive patients with known CAD who were referred for evaluation of viable myocardium by SPECT-MPI/PET-FDG because of severe ischaemic LV dysfunction. Patients were included if they had signed informed consent authorizing their records to be included in our research registry.

SPECT-MPI Image Acquisition and Interpretation

The SPECT-MPI acquisition was performed approximately 1 hour after injection of 900 MBq ^{99m}Tc-tetrofosmin at rest on a Ventri dual-head camera (Ventri, GE Healthcare) with a low-energy, high-resolution collimator, a 20% symmetric window at 140 keV, a 64 × 64 matrix, and an elliptic orbit with step-and-shoot acquisition at 3° intervals over 180° arc (45° right anterior oblique to 45° left posterior oblique) with 30 steps (60 views). Scan time was set to 25 seconds per frame for stress and rest, resulting in a total acquisition time of 14 minutes 52 seconds (including inter-step rotation time) for each scan as recommended by the American Society of Nuclear Cardiology (ASNC).[14] Images were reconstructed on a dedicated workstation using a standard iterative reconstruction algorithm with Ordered Subset Expectation Maximization (OSEM) with 2 iterations and 10 subsets. Standard short as well as vertical, and horizontal long axis, and polar maps of perfusion encompassing the entire left ventricle were analysed using QGS/QPS software. Effective radiation dose for the SPECT-MPI study was calculated as ^{99m}Tc-tetrofosmin activity times 7.9 mSv/GBq.

PET-FDG Image Acquisition and Interpretation

Myocardial viability scans were acquired on a PET/CT scanner using 250 MBq of FDG. All patients were advised to fast for at least 6 hours before PET examination and received a standardized oral glucose load.[15] After FDG injection, patients rested for 1 hour before image acquisition. Images were acquired on a Discovery (LS/RX) PET/CT scanner (GE Healthcare). CT attenuation maps were used for AC as previously reported.[16] Acquired images were reconstructed using attenuation weighted-OSEM iterative reconstruction (2 iterations and 8 subsets). FDG uptake polar maps were equally derived using the Cedars QPS/QGS software package as for SPECT-MPI. Effective radiation dose for PET-FDG study was calculated as FDG activity times 0.019 mSv/MBq.

Assessment of LV Dyssynchrony by SPECT-MPI and PET-FDG

The Emory Cardiac Toolbox software (Emory University/Syntermed, Atlanta, GA) for phase analysis and assessment of LV dyssynchrony from SPECT-MPI has been extensively validated.[12,13,17] The software was applied on both, gated PET-FDG and SPECT-MPI scans to assess phase histogram bandwidth and standard deviation (SD), which are the two parameters best allowing determination of presence vs absence of LV dyssynchrony. The previously established optimal cut-off value for the prediction of response to CRT, i.e. 135° for histogram bandwidth and 43° for phase SD,[17] were used in this study. Severe LV dyssynchrony was considered to be present if both the parameters were above the cut-off value. All images were analysed by a reader who was blinded to the history of the patient.

Statistical Analysis

All statistical analyses were performed using SPSS software (SPSS 15.0, Chicago, IL, USA). Quantitative variables were expressed as mean ± standard deviation, and categorical variables were expressed as frequencies and percentages. Means of histogram bandwidth and phase SD assessed by the two different imaging methods PET-FDG vs SPECT-MPI were compared using Wilcoxon signed-rank test. Intraclass correlation of the two parameters, histogram bandwidth and phase SD, from PET-FDG vs SPECT-MPI was performed. In addition, clinical agreement and Bland-Altman (BA) limits of agreement were calculated. A P value of $<.05$ was considered to indicate statistical significance.

RESULTS

In all 30 patients phase analysis of Emory Cardiac Toolbox was applied successfully using rest MPI scans and PET-FDG scans, respectively. Baseline characteristics of the entire study population are given in Table 1. The SPECT and FDG exams were performed in a time range between December 2007 and January 2010. The mean injected activity was 925 ± 12 MBq for the rest ^{99m}Tc-Tetrofosmin SPECT-MPI study and 252 ± 20 MBq for the PET-FDG study resulting in a total radiation dose of 7.3 ± 1.0 mSv for the SPECT-MPI scan and 4.8 ± 0.4 mSv for the FDG exam, respectively.

SPECT-MPI revealed a perfusion defect in 27 patients. Of these, 19 patients had at least partially preserved FDG uptake, indicating dysfunctional but viable tissue.

Mean histogram bandwidth by SPECT-MPI and PET-FDG was 168.7° ± 78.4° and 168.0° ± 66.7° (P = n.s.), respectively. Mean phase SD by SPECT-MPI and PET-FDG was 52.7° ± 23.2° and 57.3° ± 27.0° (P = n.s.).

SPECT-MPI identified severe LV dyssynchrony in 18 patients with a mean histogram bandwidth of 225.2° ± 36.7° and a mean phase SD of 68.7° ± 11.3°. Normal LV synchronicity or mild LV dyssynchrony was found in 12 patients with a mean bandwidth of 83.9° ± 32.8° and a phase SD of 28.7° ± 13.1°. In 13 of these 18 patients there was a flow-metabolism mismatch, i.e. a perfusion defect in SPECT but preserved FDG uptake in PET in at least one segment. PET-FDG scans revealed severe LV dyssynchrony in 20 patients among which the 18 patients identified by SPECT-MPI. Mean histogram bandwidth was 204.9° ± 44.1° and mean phase SD was 68.7° ± 17.0°. Mean values of normal or mild findings by PET-FDG were 94.2° ± 34.0° and 34.5° ± 15.1° for histogram bandwidth and SD, respectively. An example of dyssynchrony assessment from SPECT-MPI vs PET-FDG is illustrated in Figure 1.

Table 1. Baseline characteristics of study population (n = 30)

Male	22 (73.3%)
Age (years)	
Mean ± SD (range)	64 ± 14 (35–83)
Body mass index (kg/m^2)	
Mean ± SD (range)	25.8 ± 3.7 (20.7–34.9)
Ejection fraction (%)	
Mean ± SD, (range)	30.2 ± 13.8 (11–55)
Hypertension	17 (57%)
Dyslipidemia	10 (33%)
Diabetes	8 (27%)
Smoking	16 (53%)
Positive family history	6 (20%)

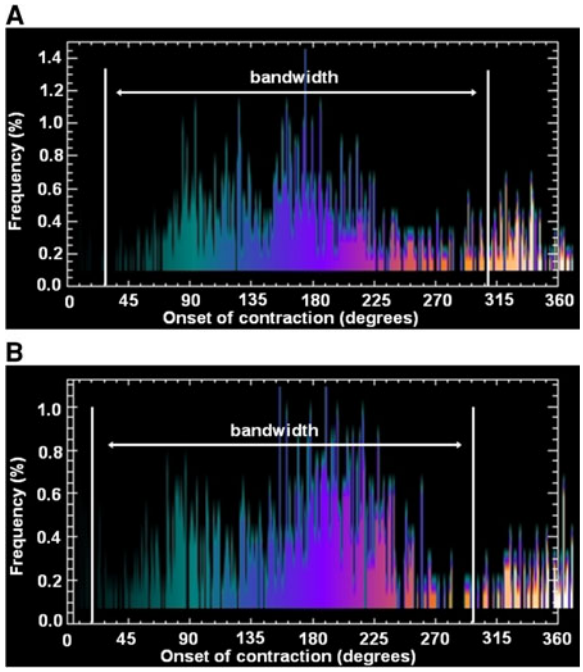

Figure 1. Phase analysis of gated SPECT-MPI (**A**) and PET-FDG (**B**) in a patient with severe LV dyssynchrony reveals comparable results for histogram bandwidth (281° and 280°) and phase SD (79° and 81°), respectively.

There was a significant correlation between SPECT-MPI data and PET-FDG scans for histogram bandwidth ($r = 0.88$, $P < .001$) and phase SD ($r = 0.88$, $P < .001$) (Figure 2). Sensitivity, specificity, PPV and NPV on a per-patient base were 100%, 83%, 90% and 100% for data sets from PET-FDG compared to SPECT-MPI as standard of reference. This resulted in an agreement of the two methods of 93%.

DISCUSSION

This study investigates the use of PET-FDG scans to assess severe LV dyssynchrony in patients with ischaemic LV dysfunction referred for preoperative evaluation prior to CABG surgery. Our results reveal that LV dyssynchrony assessment from PET-FDG scans is feasible and accurate. This allows using the same scans performed for viability assessment also for assessment of LV dyssynchrony, which has recently shown to be an independent predictor of perioperative outcome in CABG surgery of patients with severe ischaemic LV dysfunction.

There are several therapeutic strategies, which have been considered for the treatment of patients with ischaemic heart failure. As the value of medical therapy

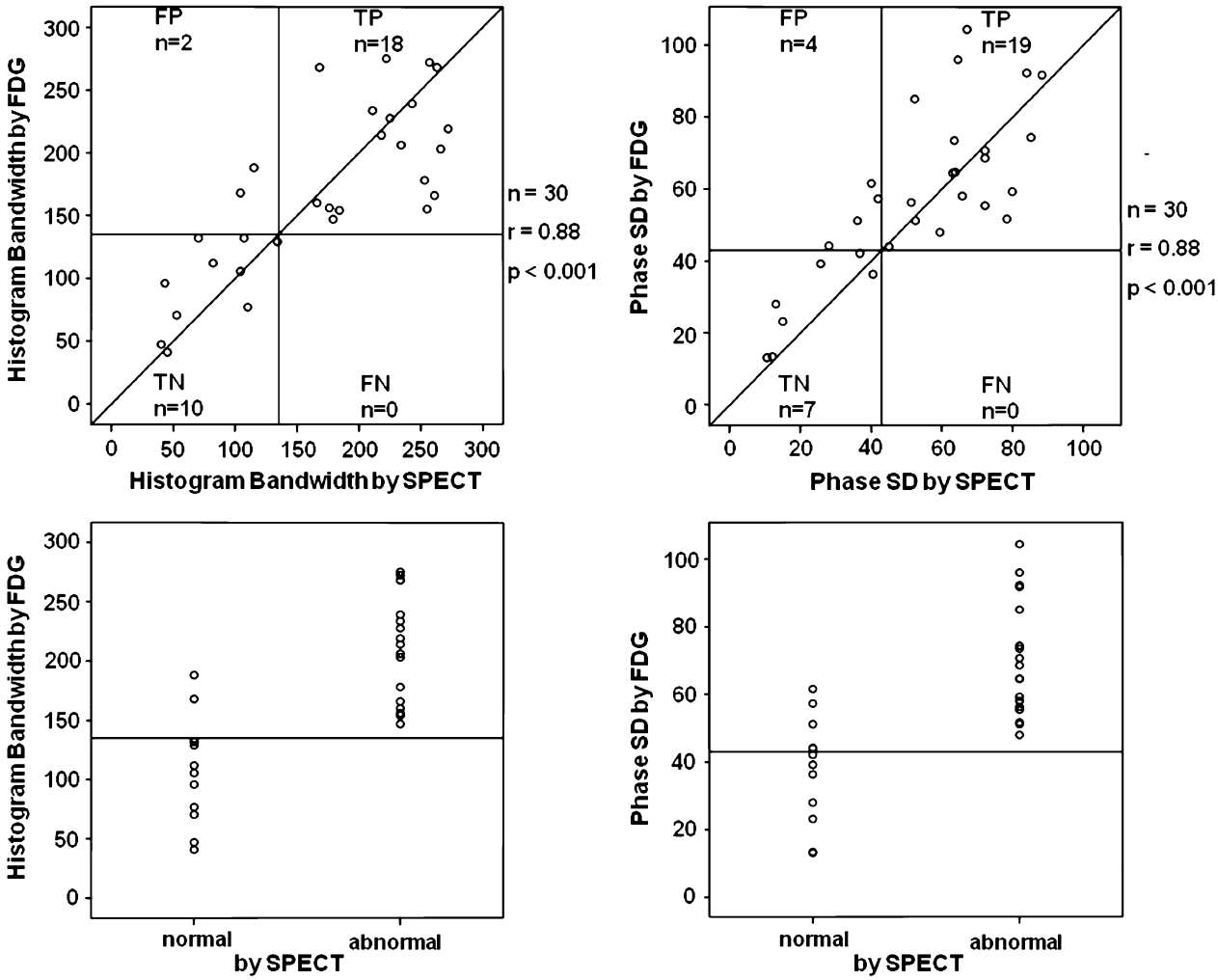

Figure 2. Correlation of histogram bandwidth (*left*) and phase SD (*right*) values between PET-FDG vs SPECT-MPI (*upper panel*) and accuracy of PET-FDG to predict LV dyssynchrony (*lower panel*). Values greater than 43° (for phase SD) and 135° (for histogram bandwidth) from SPECT-MPI were considered abnormal (according to Henneman et al[17]).

remains questionable,[3,18] other modalities such as coronary revascularization and resynchronization have gained importance as valuable treatment option in these patients. CABG surgery improves survival in patients with chronic CAD, and the presence of viability has been considered as one of the most important parameters of preoperative evaluation. Recently, a poor outcome in patients undergoing CABG surgery has been associated with the presence of severe LV dyssynchrony.[5,6] Therefore, it has been suggested that both, viability as well as LV dyssynchrony should be routinely assessed before CABG surgery.[5]

CRT is an established therapy for patients with advanced heart failure. The technique improves heart failure symptoms, exercise capacity, and LV function, with a reduction in morbidity and mortality.[19,20] However, 20%-30% of all patients receiving a CRT do not respond. The search of reasons for nonresponse to CRT has gained importance in recent investigations. The presence of LV dyssynchrony as well as the extent of scar tissue and viable myocardium has been identified as key parameters directly related to the response to CRT[7-10] suggesting that the evaluation of patient selection for CRT should include these parameters.

PET-FDG is the only method for viability assessment which has been shown to improve the outcome of patients when it is used to assist management of severe LV dysfunction.[1] A broad diversity of imaging techniques has been established for LV dyssynchrony assessment, such as echocardiography, especially with

tissue Doppler imaging (TDI) and strain imaging,[21,22] magnetic resonance imaging (MRI) and MUGA radionuclide ventriculography. TDI has emerged as one of the most widely used techniques but may be subject to interobserver variability in part related to observer experience.[23] MUGA radionuclide ventriculography has overcome both of the above-mentioned possible disadvantages but has not been widely used lately. Recently, assessment of LV dyssynchrony by phase analysis of gated SPECT-MPI scans has been established.[12] The evaluation with gated SPECT-MPI scans has potential benefits, such as the automated and reproducible assessment and moreover the possibility to gather information on myocardial perfusion at the same time. This study now shows that PET-FDG, which is used to assess viability, allows assessment of the two key parameters of severe LV dysfunction simultaneously. This enables comprehensive evaluation of patients before CABG surgery.

We acknowledge following limitations: first, this is a single-center study with only a limited population of 30 patients due to the pilot nature of this study. Second, the use of manual base and apex placement may lead to bias, especially in a population which typically has a high prevalence of perfusion defects. However, it has been described earlier that repeatability of phase analysis is higher when using manual placement compared to the automated technique[24] justifying the manual placement tool for phase analysis. In addition, in patients with large fixed defects, the assessment of LV dyssynchrony by phase analysis from SPECT-MPI may be hampered, due to limitations in contour detection. By contrast, many of these segments had preserved FDG uptake potentially allowing better contour detection by PET-FDG scanning. This may have accounted for the fact that in the upper range of LV dyssynchrony there appears to be larger variability between the two methods (see Figure 2).

In conclusion, LV dyssynchrony assessment from PET-FDG scans is feasible and accurate, compared to the standard of reference SPECT-MPI, although our data may not support the interchangeable use of the two methods in patients with large perfusion defects.

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