Aus der Klinik und Poliklinik für Nuklearmedizin
Klinik der Universität München
Direktor: Prof. Dr. med. Peter Bartenstein

Gated ^{99m}Tc-tetrofosmin SPECT and gated ^{18}F-FDG PET for the Assessment of Left Ventricular Myocardial Dyssynchrony and its Impact of the Left Ventricular Function – A Functional Imaging Study

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Frank Philipp Walter Graner

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Berichterstatter:	Priv.-Doz. Dr. med. Sebastian Lehner
Mitberichterstatter:	Prof. Dr. Andrei Todica
	Priv.-Doz. Dr. Ludwig Weckbach
Dekan:	Prof. Dr. med. Thomas Gudermann
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Affidavit

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Table of Contents

Abbreviation

BW	Bandwidth
CAD	Coronary artery disease
CRT	Cardiac resynchronization therapy
CT	Computed tomography
CVD	Cardiovascular disease
DC	Dyssynchrony Cohort
ECG	Echocardiography
EKG	Echokardiography
ECTb	Emory Cardiac Toolbox
EDV	End diastolic volume
ESV	End systolic volume
FDG-PET	^{18}F-fluorodeoxyglucose positron emission tomography
HF	Heart failure
IHD	Ischemic heart disease
KHK	Koronare Herzerkrankung
LV	Left ventricular
LVEF	Left ventricular ejection fraction
LVMD	Left ventricular mechanical dyssynchrony
MMI	Myocardial metabolic imaging
MPS	Myocardial perfusion scintigraphy
MRI	Magnetic resonance imaging
PET	Positron emission tomography
QGS	Quantitative Gated SPECT
RC	Reference Cohort
ROC	Receiver Operating Characteristic
SCD	Sudden cardiac deaths
SD	Standard deviation
SPECT	Single-photon emission computed tomography
VF	Ventricular fibrillation
4DM	4DM SPECT

List of Publications

This cumulative dissertation consists out of two published manuscripts:

Paper I:

Graner FP, Fischer M, Ilhan H, Bartenstein P, Todica A, Lehner S. **Assessment of left ventricular function with gated myocardial perfusion SPECT and gated myocardial FDG PET in patients with left ventricular mechanical dyssynchrony**. Q J Nucl Med Mol Imaging. 2021 Dec 9. doi: 10.23736/S1824-4785.21.03398-7. Epub ahead of print. PMID: 34881846.

Paper II:

Lehner S, **Graner FP**, Fischer M, Ilhan H, Bartenstein P, Todica A. **The assessment of left ventricular mechanical dyssynchrony from gated ^{99m}Tc-tetrofosmin SPECT and gated ^{18}F-FDG PET by QGS: a comparative study**. J Nucl Cardiol. 2021 Jul 19. doi: 10.1007/s12350-021-02737-0. Epub ahead of print. PMID: 34282536.

1. Your Contribution to the Publications

1.1 Contribution to Paper I

As first author of this paper, I was given the opportunity to lead the overall direction and planning of this subsequent research study which is based on the primary study presented in Paper II. I envisioned the original idea and design of this study in close consultation with my mentor and included all other authors in the further execution of the project. I was responsible for the complete data collection and database design as starting point for all following analyses. Furthermore, under the supervision and guidance of my mentor, I was involved in processing the data, performing the analysis, and designing the figures. I substantially contributed to the interpretation of the results and development of the manuscript. Together with my mentor, and the other authors, I was mainly responsible for drafting and writing the manuscript.

1.2 Contribution to Paper II

As second author of this manuscript I contributed substantially to the design of this research study. I was exclusively responsible for the entire data acquisition including all imaging and medical data. I designed the study database for the entire project. Based on the collected data, I was involved in the analysis and the interpretation of the results and contributed to the drafting of the manuscript. Together with the other authors I offered critical feedback of and revision to the manuscript for its final version.

2. Introduction

Cardiovascular disease (CVD) is the leading cause of global mortality and is one of the main contributors to massive health, and health-economic, burdens.[1] In 2019, CVD caused an estimated 18.6 million deaths-- one-third of all deaths globally. In particular, ischemic heart disease (IHD), also referred to as coronary artery disease (CAD), is one of the most prevalent forms of CVD and every year accounts for around half of all deaths from CVD. For the last two decades, CAD has not only been the prominent reason for mortality but is also one of the main causes of morbidity, and subsequent diminishing quality of life, as a chronic disability, for an increasing number of people.[2, 3]

In more than 50% of all sudden cardiac deaths (SCD), the underlying cause of death is ventricular fibrillation (VF). Numerous cases of SCD in the general population occur in individuals without prevalent cardiovascular disease.[4] Consequently, it is a challenge to detect high-risk individuals in the community because of the heterogeneous pathophysiology within CVD. The prerequisite for healthy cardiac function is primarily connected to the highly synchronized function of the myocardium – also called the functional syncytium. This function is often compromised in many cardiac pathologies, including CAD, and leads to malignant arrhythmias, such as VF.[5]

Non-invasive modern imaging techniques such as echocardiography (ECG), magnetic resonance imaging (MRI), computed tomography (CT), single-photon emission computed tomography (SPECT), and positron emission tomography (PET) play a key role in further diagnosis today. These techniques are valuable in forecasting and in risk stratification for treatment planning in patients with heart failure (HF).[6] In particular, optimized cardiac vitality diagnostics, as performed in nuclear medicine imaging, offer the possibility of non-invasively assessing biochemical and physiological processes in vivo and localizing their pathological changes. By utilizing these optimized diagnostics, treatment and therapy have shown the most beneficial outcome for this specific patient population.[7]

Currently, the non-invasive standard test within nuclear medicine diagnostic imaging for patients with CAD or HF is myocardial perfusion scintigraphy (MPS). MPS can assess left ventricular perfusion and identify stress-induced ischemia and scarring.[8] Another well-recognized non-invasive imaging technique for the quantification of myocardial metabolism and perfusion is PET. Myocardial metabolic imaging (MMI) with ^{18}F-fluorodeoxyglucose PET (FDG-PET) is the gold standard to determine the degree and level of viable myocardium.[9]

Through the combination of static and ECG-gated MPS imaging, an evaluation of left ventricular (LV) end diastolic volume (EDV), end systolic volume (ESV) as well as LV ejection fraction (LVEF) is possible.[10] In addition, ECG-gated FDG-PET presents the unique potential of combining LV function and myocardial metabolism assessments by generating additional prognostic information in a single PET test.[11]

In the early 2000's, several computer software packages were clinically validated to provide phase analysis of ECG-gated MPS imaging as well as additional parameters, such as wall motion and thickening analysis, for the evaluation of LV mechanical dyssynchrony (LVMD). More recently, this fully automated assessment was also extended to ECG-gated FDG PET. The most clinically used and commercially available software packages are Quantitative Gated SPECT (QGS, Cedars-Sinai, Los Angeles, California), the Emory Cardiac Toolbox (ECTb, Emory University, Atlanta, Georgia) or 4DM SPECT (4DM, Michigan University, Ann Arbor, Michigan).[12, 13]

LVMD reflects the level of left ventricular contractile dyssynchrony and shows a discrepancy in the timing of mechanical contraction, or relaxation, between different segments of the left ventricle. As LVMD can impact one or both phases of the cardiac cycle, it is important to understand that systolic and diastolic LVMD have various underlying factors and mechanisms.[14, 15] Therefore, phase analysis of LVMD in patients with HF not only adds incremental prognostic information but also provides an additional tool to select patients for cardiac resynchronization therapy (CRT) and monitor their outcome.[12, 16] As, unfortunately, one third of all patients who undergo CRT implantation are considered "non-responders," it is critical to include phase analysis information of LVMD as part of the decision support for this therapy. This is particularly true as there is

more and more evidence that the results of LVMD phase analysis via MPS and FDG-PET lead to a better selection of patients for CRT. Therefore, this additional tool not only boosts the efficacy of this medical procedure and leads to a better patient outcome, but also improves the cost-efficiency from a health economic standpoint.[13, 16]

Therefore, the further investigation of the prognostic value of LVMD phase analysis for both gated MPS and gated FDG-PET seems rather salient particularly since, even after more than 15 years, the amount of available evidence is still limited. Additionally, most of the evidence consists of gated MPS data, while only a small amount includes gated FDG-PET data.

In our joint publication with the title “The Assessment of Left Ventricular Mechanical Dyssynchrony from gated ^{99m}Tc-tetrofosmin SPECT and gated ^{18}F-FDG PET by QGS – A Comparative Study” we investigated, using a novel approach, how well results from QGS phase analysis can predict LVMD by using gated MPS and FDG-PET. We then further examined the limits of this method in addition to the extent to which the modalities match.

Various studies have concluded the uncertainty as to which phase analysis parameters best predict LVMD in patients with HF. Additionally, these studies have shown that the normal values vary among different commercially available software programs.[17] Therefore, to further advance and evolve published research from the last few years in this specific field,[18-21] we focused with this retrospective study on a comprehensive assessment of the phase analysis parameters Bandwidth (BW), Phase Standard Deviation (Phase SD), and Entropy between SPECT and PET datasets to further analyze standing evidence between both imaging modalities.

As a novel approach of this joint research project, we also looked further into MMI. In doing so, we assessed the diagnostic accuracy of gated FDG-PET phase analysis values. Whereas the gated MPS reference standard typically serves as SPECT datasets reference values, we calculated specific gated FDG-PET cut-off values. These PET dataset specific parameters BW, Phase SD, and Entropy can lead to an optimization of the diagnostic performance.

The study population for our joint publication was selected from the database that was specifically created as part of this doctoral thesis. The database includes over 200 patients with a history of CAD, who were referred to the department of Nuclear Medicine, LMU for diagnostic imaging and the assessment

of myocardial viability. Our study population consisted of 93 subsequent patients. The study population was divided into two groups depending on whether patients were identified as synchronous or dyssynchronous. As reference standard for these cohorts, we used gated MPS with published QGS reference phase analysis values of BW (17.0 – 63.7°), Phase SD (4.4 – 26.5°), and Entropy (44.0 – 63.7%).[18] We analyzed the data in two ways. In the first analysis, only patients with three pathological phase analysis parameters were assigned to the dyssynchronous cohort. While in the second analysis, patients with only two pathological parameters were assigned to the dyssynchronous cohort. The imaging datasets of both cohorts for gated SPECT and gated PET were successfully processed with QGS as described in previous literature.[18]. Figure 1 shows an example of the displayed QGS phase analysis results for the essential parameters.

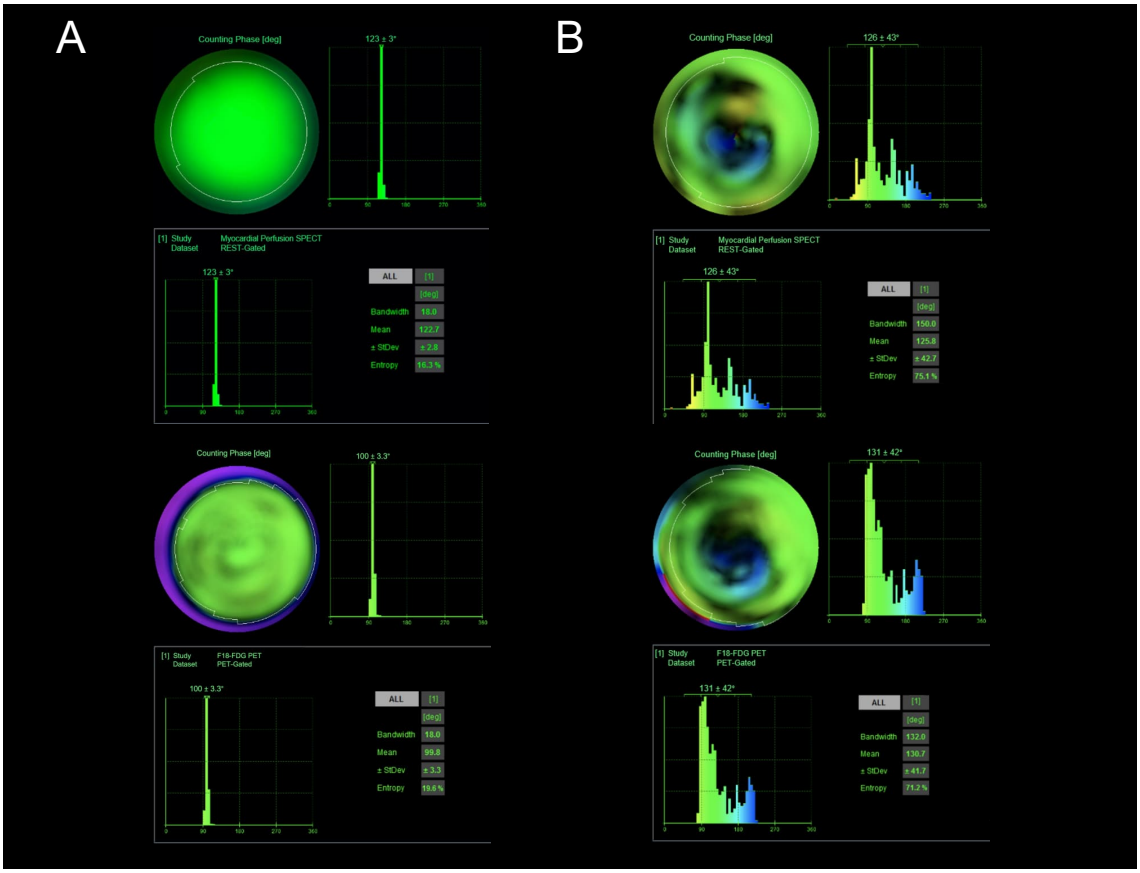

Figure 1 Phase analysis with QGS. Panel A shows the SPECT (upper image) and PET (lower image) phase analysis of the same patient without dyssynchrony. Panel B shows the SPECT (upper image) and PET (lower image) phase analysis of the same patient with dyssynchrony.[22]

Based on the results presented in our joint publication, we showed, in comparison to the currently published data, that the concordance of the phase analysis

for gated SPECT and gated PET is suboptimal. Consequently, both procedures cannot be considered interchangeable at the present time. (Table 1).

	SPECT	PET	p
BW (°)	94 ± 55	104 ± 53	0.022
Phase SD (°)	26 ± 16	30 ± 17	0.004
Entropy (%)	58 ± 15	58 ± 15	0.601

Table 1 BW and Phase SD differed significantly between SPECT and PET.[22]

For the evaluation of the gated FDG-PET cut-off values, Receiver Operating Characteristic (ROC) analysis showed that Entropy reveals to be the best predictor of dyssynchrony (Figure 2). The optimized cut-off point is 63%.

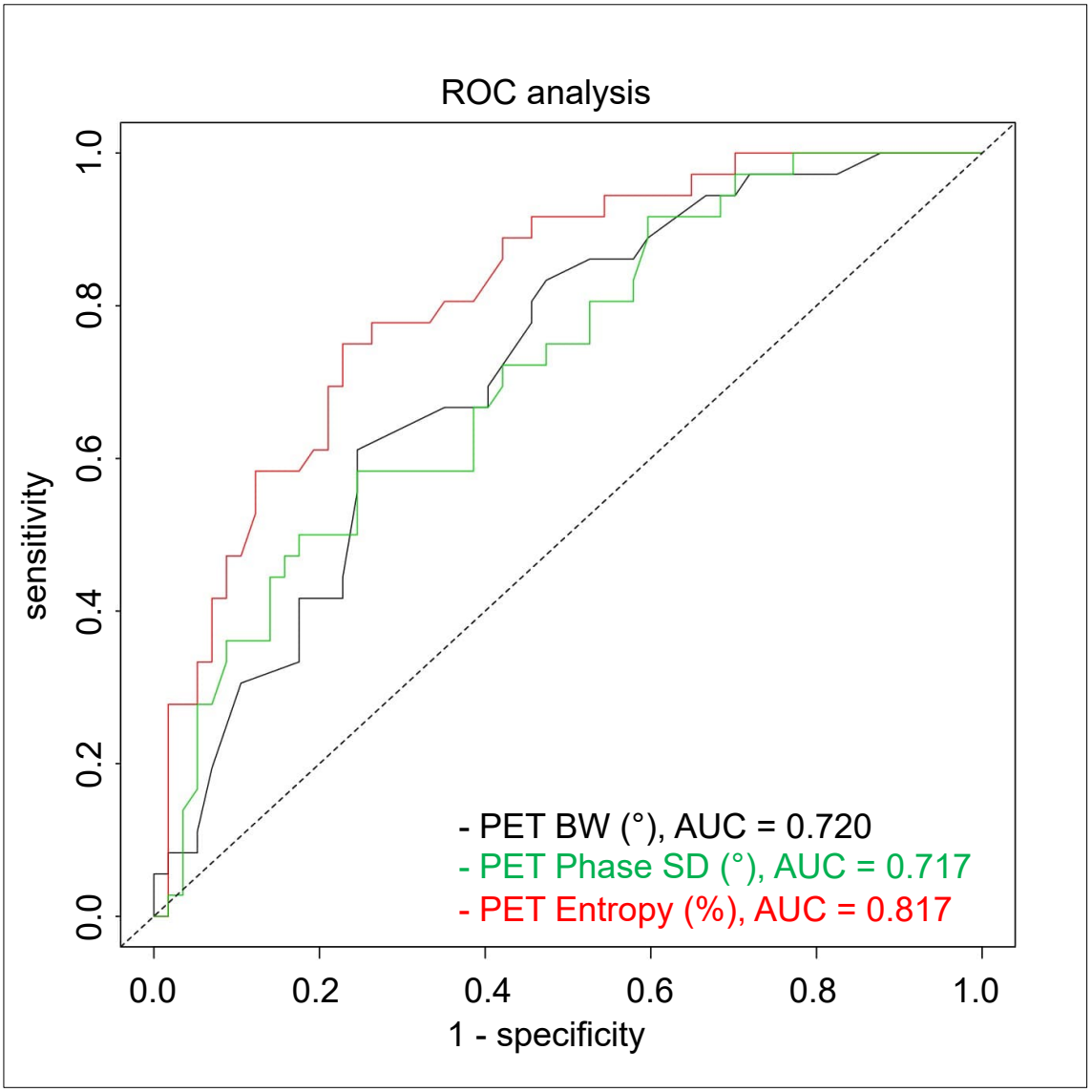

Figure 2 ROC analysis for PET BW, Phase SD and Entropy to predict dyssynchrony (criterion for dyssynchrony three pathological phase analysis parameters).[22]

For this evaluation of the diagnostic performance of gated FDG-PET, we applied the gated MPS reference standard, as currently there is only published QGS reference data for gated MPS available. We are aware that gated FDG-PET reference standard data might ultimately demonstrate to be the more accurate method.

Despite this, we are confident in our evaluation of the analysis of gated FDG-PET performance because, instead of only depending on visual assessment alone, our evaluation adds objective criteria for dyssynchrony.

Furthermore, with this method we were able to provide preliminary data which gave more insight into which PET parameters might be useful for assessing dyssynchrony.

In summary, as discovered by the findings of our joint research, both diagnostic imaging methods cannot be treated as equivalent and clearly have some limitations. To move forward with the determination of reference ranges and cut-off values, particularly in PET imaging, it will require more specific research to provide more accuracy and reliability in this field. Additionally, as there is more and more indication that PET imaging also offers improved image quality, as well as higher diagnostic accuracy as compared to SPECT imaging, a closer look at both imaging techniques, in relation to LV function in LVMD patients, appears to be a next subject matter for research.

In my first author publication “Assessment of left ventricular function with gated myocardial perfusion SPECT and gated myocardial FDG-PET in patients with left ventricular mechanical dyssynchrony,” I further investigated the implicated link between LVMD and LV function. It appears that there is currently no study which simultaneously compares the performance of gated MPS and gated FDG-PET in patients with LVMD. As we had the opportunity to build on the results of our previous joint study, it seemed natural to investigate this topic further.

The capability to analyze LV function with gated MPS, and also in recent years with gated FDG-PET, as part of the LV phase analysis, with the commercially available software packages, pushed our research to study further the diagnostic results in patients with LVMD. In addition to the QGS phase analysis from gated SPECT and PET datasets, it is also possible, to estimate left ventricular

end diastolic volume (EDV) and end systolic volume (ESV), as well as left ventricular ejection fraction (LVEF).[10, 13] Therefore, Figure 3 is an example of the QGS software showing not only the parameters BW, Phase SD, and Entropy as descriptions of myocardial synchrony but also the parameters EDV, ESV, and LVEF as descriptions of LV myocardial function for SPECT and PET datasets.

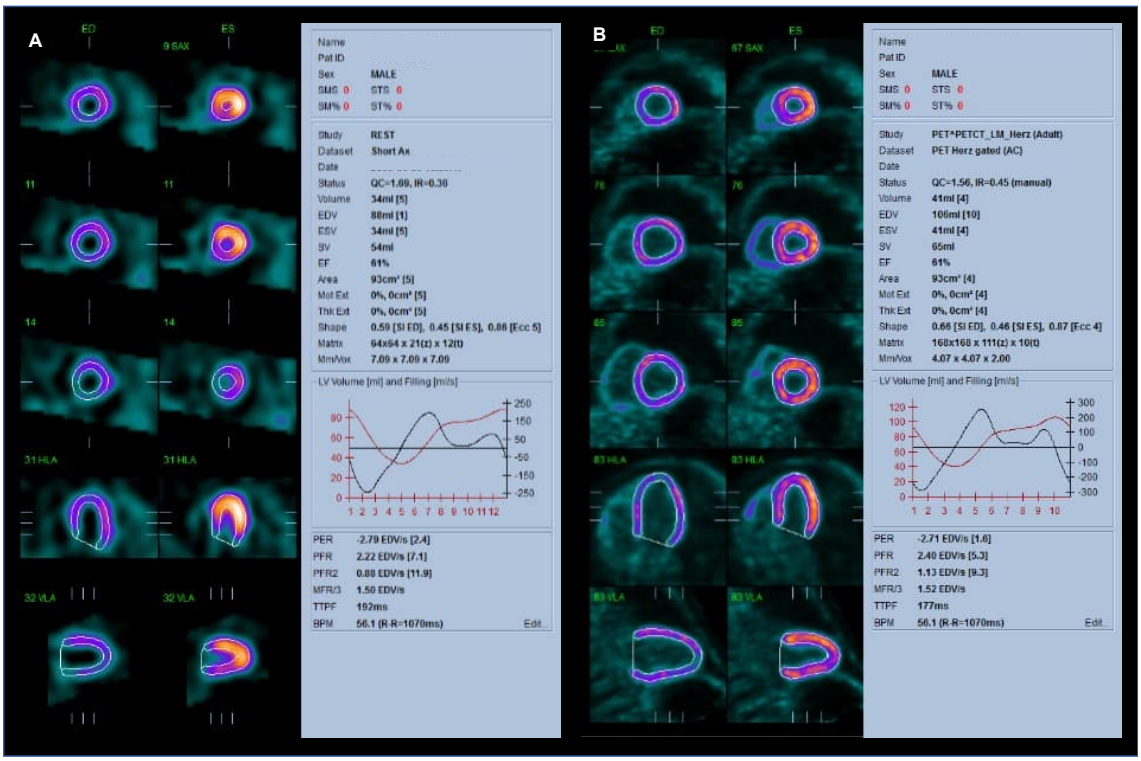

Figure 3 Representative images of gated MPS (A) and gated FDG PET (B). In each panel the left column shows end systole, the middle column end diastole, and the right column the left ventricular functional parameters. Note that PET detects a proportionally larger EDV and ESV as compared to SPECT, probably due to superior image resolution and reduced partial volume effects. LVEF is equal.[23]

Based on the already available results of the QGS phase analysis for LVMD and LV function, and as there is not, to our knowledge, any research that looks at possible agreement between gated MPS and gated FDG-PET, we thought that it would be of additional interest to further investigate the correlation between these two imaging modalities.

We hypothesized that in both imaging techniques patients diagnosed with LVMD should show increased EDVs and ESVs but also a reduced LVEF compared to patients with a ventricular synchrony. Therefore, QGS phase analysis of LVMD and LV function should show progressively higher EDV, ESV, and progressively lower LVEF in direct correlation with severity of LVMD. We also assumed we would receive the same diagnostic results for both, gated MPS

and FDG-PET, in patients who received both scans contemporaneously. However, we also expected differences in both methods based on superior spatial resolution of FDG-PET and therefore, in addition to other factors, a reduction of partial volume effects.

The study population for this retrospective study was also selected from the existing database described for the previous study. Following the same published references values (BW, Phase SD, and Entropy) from the QGS gated MPS datasets phase analysis,[18] we divided the patient population into two cohorts. Patients who had pathological results of all three reference values were assigned to the cohort with LVMD (DC) while all other patients were assigned to the reference cohort without LVMD (RC).

In our study we were able to confirm our hypothesis. We showed that, as expected, EDVs and ESVs were significantly higher and LVEF significantly lower in gated MPS and gated FDG-PET phase analysis results for patients in the DC group compared to the RC group (Table 2). Therefore, gated SPECT and gated PET are valuable diagnostic tools to evaluate LV function in patients with LVMD.

	RC SPECT	**DC SPECT**	**p**
EDV (ml)	189 ± 99	255 ± 97	<0.001
ESV (ml)	123 ± 88	202 ± 82	<0.001
LVEF (%)	40 ± 16	25 ± 9.1	<0.001
	RC PET	**DC PET**	**p**
EDV (ml)	194 ± 76	244 ± 111	0.042
ESV (ml)	130 ± 76	191 ± 100	0.002
LVEF (%)	37 ± 16	26 ± 10	<0.001

Table 2 Comparison of SPECT and PET derived left ventricular function between the RC and the DC.[23]

We also demonstrated in the combined cohort (RC and DC) that a more severe course of LVMD correlates with an increasingly reduced ventricular function as demonstrated by increased ESV, EDV, and decreased LVEF. The strongest association was for the dyssynchrony parameter Entropy as shown in Table 3. While generally in good agreement, gated MPS and gated FDG PET show differences, when mean values of EDV, ESV, and LVEF are compared. As previ-

ously discussed, and learned from repeated measurements or therapy monitoring, both methods should not be used interchangeably.

		SPECT	
	BW	**Phase SD**	**Entropy**
EDV	R=0.40, p<0.001	R=0.36, p<0.001	R=0.43, p<0.001
ESV	R=0.53, p<0.001	R=0.49, p<0.001	R=0.55, p<0.001
LVEF	R=-0.63, p<0.001	R=-0.61, p<0.001	R=-0.72, p<0.001
		PET	
	BW	**Phase SD**	**Entropy**
EDV	R=0.50, p<0.001	R=0.45, p<0.001	R=0.50, p<0.001
ESV	R=0.55, p<0.001	R=0.51, p<0.001	R=0.60, p<0.001
LVEF	R=-0.60, p<0.001	R=-0.57, p<0.001	R=-0.79, p<0.001

Table 3 Correlation between parameters of dyssynchrony and parameters of left ventricular function in the combined cohort of all patients (RC + DC) for SPECT and PET.[23]

Limitations for this study are similar to those mentioned in our other study. Because of the lack of any external gold standard, we assigned patients to each cohort by means of gated SPECT phase analysis and available published reference values. Also, patients who did not meet all three criteria for LVMD were assigned the RC group. However, this patient cohort can also not be considered healthy controls as they were referred for cardiac diagnostic imaging to the department of Nuclear Medicine. Therefore, the RC group may not be the optimal group to which to compare. Additionally, the inclusion criteria for the DC group could be debated as dyssynchrony has a wide range from mild to severe and therefore not all three parameters may be out of the normal range.

Nonetheless, our research opens the potential for further investigation in this specific field and also requires further validation of the results in a prospective study approach. Reiterating the results of both studies we conclude that in a complementary manner, not only phase analysis results of QGS for gated MPS but also of gated FDG-PET can add additional value and contribute to the already existing diagnostic results.

For this novel research approach of objective analysis of dyssynchrony, we do not simply rely on a visual or semi-quantitative assessment of LVMD, but on established and published reference values for SPECT. This subsequently turns this method of gated MPS into an even better gold or reference standard.

3. Zusammenfassung:

Weltweit stellen Herz-Kreislauf-Erkrankungen die häufigste Todesursache dar. Die koronare Herzkrankheit (KHK) ist eine der am weitesten verbreiteten Arten von Herz-Kreislauf-Erkrankungen, die jährlich für etwa die Hälfte aller Todesfälle verantwortlich ist. Daher ist KHK einer der Hauptverursacher massiver gesundheitlicher und gesundheitsökonomischer Belastungen im Gesundheitswesen. Eine der Hauptfaktoren für Morbidität und Mortalität von KHK ist die linksventrikuläre mechanische Dyssynchronie (LVMD). Die klinische Diagnose von LVMD kann auch als Maß für den Grad der Erkrankung herangezogen werden und bestimmt somit auch den weiteren Behandlungsverlauf. Derzeit ist für Patienten mit KHK die EKG-getriggerte Myokardperfusionsszintigraphie (MPS) die Standarduntersuchung innerhalb der nuklearmedizinischen diagnostischen nicht-invasiven Bildgebung. Ein weiteres anerkanntes nicht-invasives Bildgebungsverfahren für die myokardiale metabolische Bildgebung (MMI) ist die EKG-getriggerte ^{18}F-Fluordeoxyglukose-PET (FDG-PET) Untersuchung.

Derzeit existieren mehrere Computersoftwareprogramme zur Auswertung der Phasenanalyse von LVMD für die EKG-getriggerte MPS-Bildgebung, wie auch die EKG-getriggerten FDG-PET. Für unsere Forschung verwendeten wir die Software „Quantitative Gated SPECT“ (QGS, Cedars-Sinai, Los Angeles, Kalifornien). Die Ergebnisse der Phasenanalyse von LVMD bei EKG-getriggerter MPS und EKG-getriggerter FDG-PET bei Patienten mit Herzinsuffizienz (HI), bieten ein zusätzliche Möglichkeit Patienten für eine kardiale Resynchronisationstherapie (CRT) gezielter auszuwählen und somit eine Verbesserung des weiteren Krankheitsverlauf, aber auch eine Verbesserung der Kosteneffizienz zu erreichen.

In unserer gemeinsamen Publikation haben wir das Potenzial der EKG-getriggerten FDG-PET Phasenanalyse im Vergleich zur EKG-getriggerten -MPS Phasenanalyse untersucht und uns mit möglichen Cut-off-Werten zur Definition von Dyssynchronie für die FDG-PET befasst. Wir haben die Phasenanalyseparameter Bandwidth (BW), Phase Standard Deviation (Phase SD) und Entropie zwischen SPECT- und PET-Datensätzen analysiert. Basierend auf den Ergebnissen konnten wir nur eine mäßige Übereinstimmung zwischen SPECT und

PET zur Identifizierung einer Dyssynchronie erkennen. Die Entropie war der eindeutig der beste PET-Parameter zur Vorhersage von Dyssynchronie. Der optimierte Cut-off-Wert für die Entropie betrug 63 %.

In meiner Erstautoren-Publikation haben wir die Beziehung zwischen LVMD und LV-Funktion untersucht. Wir konnten zeigen, dass LVMD mit einem signifikant höheren enddiastolischen Volumen (EDV) und endsystolischen Volumen (ESV), sowie einer signifikant reduzierten linksventrikulären Ejektionsfraktion (LVEF) für EKG-getriggerte MPS und EKG-getriggerte-FDG-PET-Bildgebung verbunden ist. Darüber hinaus haben wir validiert, dass ein zunehmender Schweregrad von LVMD mit einem zunehmenden EDV und ESV sowie einer abnehmenden LVEF einhergeht. Die stärkste Übereinstimmung konnte bei dem Dyssynchronieparameter Entropie gezeigt werden.

Beide Studien zeigen, dass man mit den Ergebnissen der Phasenanalyse von QGS für EKG-getriggertes MPS und EKG-getriggertes FDG-PET nicht nur die LVMD beurteilen kann, sondern dass auch eine gute Korrelation mit der LV-Funktion besteht. Darüber hinaus konnten wir zeigen, dass die beiden Methoden derzeit noch nicht austauschbar verwendet werden können, obwohl sie prinzipiell das gleiche messen. Die Festlegung von Referenzbereichen und Cut-off-Werten ist aufgrund eines fehlenden externen Goldstandards schwierig. Es gibt daher Einschränkungen für beide Studien. Dennoch ist dieser neuartige Forschungsansatz der objektiven Analyse von Dyssynchronie ein guter Weg, um tiefer in die Phasenanalyse beider bildgebender Verfahren einzutauchen und somit die klinische Leistungsfähigkeit dieser Methoden zu erweitern.

4. Abstract (English):

Globally, cardiovascular disease (CVD) is the leading cause of mortality. Coronary artery disease (CAD) is one of the most prevalent types of CVD and annually accounts for around half of all CVD deaths. Therefore, CAD is one of the main contributors to massive health, and health-economic, burdens. A major factor in the morbidity and mortality of CAD is Left Ventricular Mechanical Dyssynchrony (LVMD). LVMD can also be used as a measure of disease burden and, potentially, clinical outcome Currently, the non-invasive standard test within nuclear medicine diagnostic imaging for patients with CAD is ECG-gated myocardial perfusion scintigraphy (MPS). Another well-recognized non-invasive imaging technique for myocardial metabolic imaging (MMI) is ECG-gated ^{18}F-fluorodeoxyglucose PET (FDG-PET).

Several computer software packages are currently available to provide phase analysis of ECG-gated MPS imaging and also ECG-gated FDG PET for the evaluation of LVMD. For our analyses we used Quantitative Gated SPECT (QGS, Cedars-Sinai, Los Angeles, California). Phase analysis of LVMD in patients with heart failure (HF) provides an additional tool to select patients for cardiac resynchronization therapy (CRT). The results of LVMD phase analysis of MPS and FDG-PET leads to a better selection of patients for CRT improving both treatment efficacy and cost efficiency.

In our joint publication we investigated the performance of gated FDG PET phase analysis as compared to gated MPS as well as looked at possible cut-off values for FDG PET to define dyssynchrony. We analyzed the phase analysis parameters Bandwidth (BW), Phase Standard Deviation (Phase SD), and Entropy between SPECT and PET datasets. Based on the results we could only find moderate agreement between SPECT and PET to identify dyssynchrony. Entropy was the best single PET parameter to predict dyssynchrony. The optimized cut-off value for Entropy was 63%.

In my first author publication we further investigated the relationship between LVMD and LV function. We were able to show that LVMD is linked to significantly higher end diastolic volume (EDV) and end systolic volume (ESV) as well

as a significantly reduced left ventricular ejection fraction (LVEF) for MPS and gated FDG PET imaging. Additionally, we validated that the increasing severity of LVMD is associated with increasing EDV and ESV as well as a decreasing LVEF. The association was strongest for the dyssynchrony parameter Entropy.

Both studies show that phase analysis results of QGS for gated MPS and gated FDG-PET not only assess LVMD but also demonstrate a good correlation with LV function. Furthermore, we demonstrated that the methods cannot be used interchangeably, even though in principle both measure the same parameters. Establishing reference ranges and cut-off values is difficult due to the lack of an external gold standard. There is, however, limitation for both studies. Nevertheless, this novel approach of objective analysis of dyssynchrony, is a great way forward to dive deeper into the phase analysis of both imaging techniques and thus to expand the clinical efficiency of these methods.

5. Paper I

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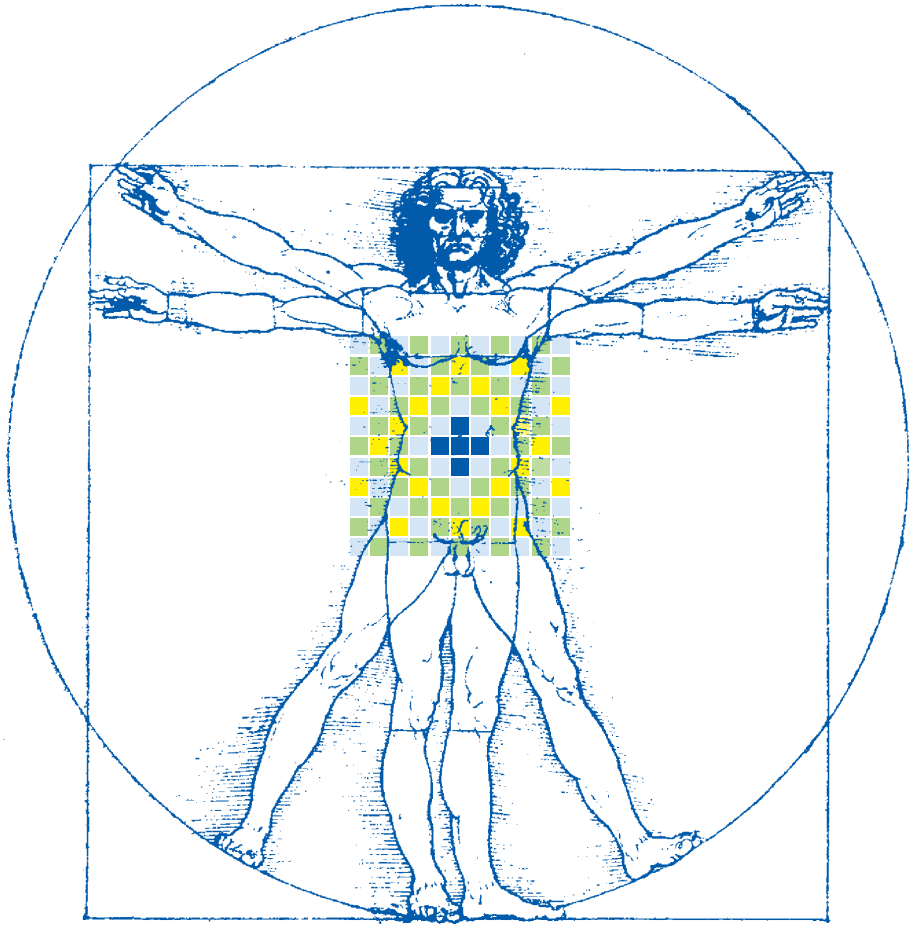
ASSESSMENT OF LEFT VENTRICULAR FUNCTION WITH GATED MYOCARDIAL PERFUSION SPECT AND GATED MYOCARDIAL FDG PET IN PATIENTS WITH LEFT VENTRICULAR MECHANICAL DYSSYNCHRONY

F.P. GRANER, M. FISCHER, H. ILHAN, P. BARTENSTEIN, A. TODICA, S. LEHNER



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ORIGINAL ARTICLE

Assessment of left ventricular function with gated myocardial perfusion SPECT and gated myocardial FDG PET in patients with left ventricular mechanical dyssynchrony

Frank P. GRANER [1], Maximilian FISCHER [2], Harun ILHAN [1], Peter BARTENSTEIN [1], Andrei TODICA [1], Sebastian LEHNER [1, 3] *

[1]Department of Nuclear Medicine, University Hospital Munich, Ludwig-Maximilians-University Munich, Munich, Germany; [2]Department of Cardiology, University Hospital Munich, Ludwig-Maximilians-University Munich, Munich, Germany; [3]Ambulatory Health Care Center Dr. Neumaier & Colleagues, Radiology, Nuclear Medicine, Radiation Therapy, Regensburg, Germany

*Corresponding author: Sebastian Lehner, Department of Nuclear Medicine, University Hospital Munich, Ludwig-Maximilians-University Munich, Marchioninistraße 15, 81377 Munich, Germany. E-mail: sebastian.r.lehner@icloud.com

ABSTRACT

BACKGROUND: Left ventricular mechanical dyssynchrony (LVMD) and left ventricular function are intertwined. Gated myocardial perfusion SPECT (MPS) and gated fluorodeoxyglucose positron emission computed tomography (FDG PET) is an elegant way for repeated assessment of myocardial dyssynchrony and myocardial function. To the knowledge of the authors at the time this manuscript was prepared, there was no comprehensive evaluation of the interplay of LVMD and left ventricular function as measured by gated MPS and gated FDG PET; as well as no evaluation of the agreement between the two methods.

METHODS: Patients were assigned to the reference cohort (RC) and the dyssynchrony cohort (DC) based on the phase analysis results of gated MPS datasets. Subsequently left ventricular function was analyzed.

RESULTS: We demonstrated that LVMD as detected by gated MPS is associated with a significantly higher end-diastolic volume (EDV) and end-systolic volume (ESV) as well as a significantly reduced left ventricular ejection fraction (LVEF) both in gated MPS and gated FDG PET imaging. In the RC and the DC SPECT and PET showed good agreement and generally high linear correlations with regard to left ventricular volumes and LVEF. In the combined cohort (RC and DC) increasing amounts of LVMD were associated with increasing left ventricular volumes as well as a decreasing LVEF. The association was strongest for the dyssynchrony parameter Entropy.

CONCLUSIONS: We demonstrated that gated SPECT and gated PET are useful tools in the evaluation of left ventricular function in patients with LVMD as detected by gated MPS. Increasing amounts of dyssynchrony were associated with an increasingly reduced myocardial function. For repeated measurements or therapy monitoring, the methods should not be used interchangeably.

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KEY WORDS: Ventricular function, left; Perfusion imaging; Entropy.

Myocardial perfusion scintigraphy (MPS) in SPECT (single-photon emission computed tomography) technique has become a standard examination for the non-invasive assessment of left ventricular perfusion and the detection of stress-induced ischemia and scarring in patients with known or suspected coronary artery disease or heart failure.[1] Static MPS images are routinely complemented by ECG-gated MPS images to evaluate left ventricular end diastolic (EDV) and end systolic volumes (ESV) as well as left ventricular ejection fraction (LVEF).[2] Additional parameters, such as wall motion and thickening analysis are available. In recent years, the ability to conduct left ventricular phase analysis for the detection of left ventricular mechanical dyssynchrony (LVMD) has been added to virtually all major commercially available software packages.[3] The ability to analyze left ventricular function and synchrony has also been extended to gated positron emission computed tomography (PET) scans.[4]

It has long been purported that LVMD and left ventricular function are intertwined.[5] Phase analysis has been employed to select heart failure patients for cardiac resynchronization therapy and monitor its outcome.[4] Furthermore, it could be demonstrated that a reduction in LVMD after myocardial infarction is associated with an improved left ventricular function.[6]

Gated MPS and gated ^{18}F-fluorodeoxyglucose (FDG) PET are an elegant way for repeated and reliable simultaneous assessment of myocardial dyssynchrony and myocardial function, while providing a plethora of additional useful parameters at the same time.[7]

To the knowledge of the authors at the time this manuscript was prepared, there was no comprehensive evaluation of the interplay of LVMD and left ventricular function as measured by gated MPS and gated FDG PET; as well as no comparison of the agreement between the two methods.

As such, in the present study we hypothesized the following:

- patients with LVMD show increased EDVs and ESVs as well as a reduced LVEF as compared to their synchronous counterparts measured by gated MPS and gated FDG PET;
- LVMD and left ventricular function are correlated in a way that increased LVMD will lead to increased EDV and ESV as well as a decreased LVEF as measured by gated MPS and gated FDG PET;
- gated MPS and gated FDG PET carried out in the same patient within a narrow time frame should lead to identical diagnostic results;
- differences between both methods are to be expected due to superior spatial resolution of FDG PET and therefore, among other factors, a reduction of partial volume effects.

Materials and methods

Study population

Based on previously published reference values[8] for BW, Phase SD and Entropy as calculated by the Quantitative Gated SPECT software (QGS, Cedars-Sinai, Los Angeles, CA, USA) for gated MPS datasets, patients were assigned to one of two groups as follows: patients simultaneously yielded pathological results of all three parameters were assigned to the cohort with LVMD (DC) while all other cases were assigned to the reference cohort without LVMD (RC).

The RC consisted of 57 patients (50 male, mean age 65±11 years, mean weight 87±24 kg, mean injected ^{99m}Tc-tetrofosmin/^{99m}Tc-MIBI dose 429±160 MBq, mean injected ^{18}F-FDG dose 269±44 MBq).

The DC consisted of 36 patients (33 male, mean age 64±12 years, mean weight 86±19 kg, mean injected ^{99m}Tc-tetrofosmin/^{99m}Tc-MIBI dose 417±140 MBq, mean injected ^{18}F-FDG dose 265±59 MBq).

Both cohorts consisted of consecutive patients that presented at our department for the evaluation of myocardial viability, primarily in a setting of ischemic cardiomyopathy.

Gated MPS was carried out on a dedicated SPECT/CT system (Symbia, Siemens Medical Systems, Erlangen, Germany) and a triple-head SPECT camera (Prism 3000 XP; Philips/InterMedical, formerly Picker, Cleveland, OH, USA). Gated MPS scans were conducted under resting conditions. On average, 17 days after the gated MPS scan in the RC and 16 days after the gated MPS scan in the DC, an FDG PET/CT scan was performed (Biograph 64, Siemens Medical Systems, Erlangen, Germany; and GE Discovery 690, GE Healthcare, Chicago, IL, USA).

This retrospective study was conducted with the approval of the local ethics committee (Ethikkommission der Medzinischen Fakultät der LMU München).

SPECT imaging

The tracer was injected intravenously for rest MPS, the scans were started approximately 45 minutes after the injection. One camera was a dual-head hybrid SPECT/CT camera (Symbia, Siemens Medical Systems), a parallel hole LEHR collimator was used with a symmetrical 20% energy window centered at 140 keV. Detector heads formed a 90° angle, during the scan, they performed a rotation of 180° divided into 64 rotational steps with every step lasting 23 seconds. Images were ECG-gated at 12 emission frames for each cardiac cycle. Images were then reconstructed as static and gated images. The second camera used was triple-head SPECT camera system (Prism 3000 XP; Philips/InterMedical, formerly Picker, Cleveland, OH, USA). Imaging was performed as described above: Three detector heads formed a 120° angle, a 360° rotation was performed, 20 steps were used per head with a scan duration of 60 seconds per detector head. The scan was performed with ECG-gating. Each head was equipped with a LEHR collimator, the 20% symmetrical energy window was centered at 140 keV. Images were then reconstructed as static and gated images.

PET/CT Imaging

64-slice CT integrated PET/CT systems were used for cardiac FDG PET/CT (Biograph 64, Siemens Medical Systems; and GE Discovery 690, GE Healthcare). Patients

were pretreated with 250 mg acipimox approximately two hours before the scan. FDG was injected intravenously approximately half an hour before the scan.

Oral glucose loading was performed in non-diabetic patients. Diabetic patients were treated according to a modified protocol of the American Society of Nuclear Cardiology.[9] One hour before the scan, patients were given a light meal and were instructed to inject their regular insulin dose. Two syringes were prepared with 20% glucose solution (0.2 g per kg bodyweight), one of these syringes contained an additional dose of insulin (0.2 dose units per kg bodyweight). Under continuous monitoring of blood glucose levels, the contents of the syringes were injected over the course of eight minutes. After the glucose peak was reached, FDG was injected.

The PET/CT scan commenced approximately 30 minutes later. A low-dose spiral CT (120 keV, 11 mAs) was acquired for attenuation correction, afterwards a 20-minute emission scan with ECG-gating was performed. The PET images were reconstructed as static and gated images (matrix size 168×168, zoom factor 1).

Image analysis

Gated MPS and gated FDG PET were analyzed with QGS (Cedars-Sinai, Los Angeles, CA, USA) as described previously.[8, 10] All datasets were loaded into the software, which uses and automated algorithm for the delineation of the myocardium. Proper recognition of the myocardium as well as time-volume curves of the left ventricle were verified visually and, if necessary, minor manual adjustments were made.

The QGS software displays the parameters BW, Phase SD and Entropy as representations of myocardial synchrony and the parameters EDV, ESV and LVEF as representations of left ventricular myocardial function for SPECT and PET datasets (Figure 1).

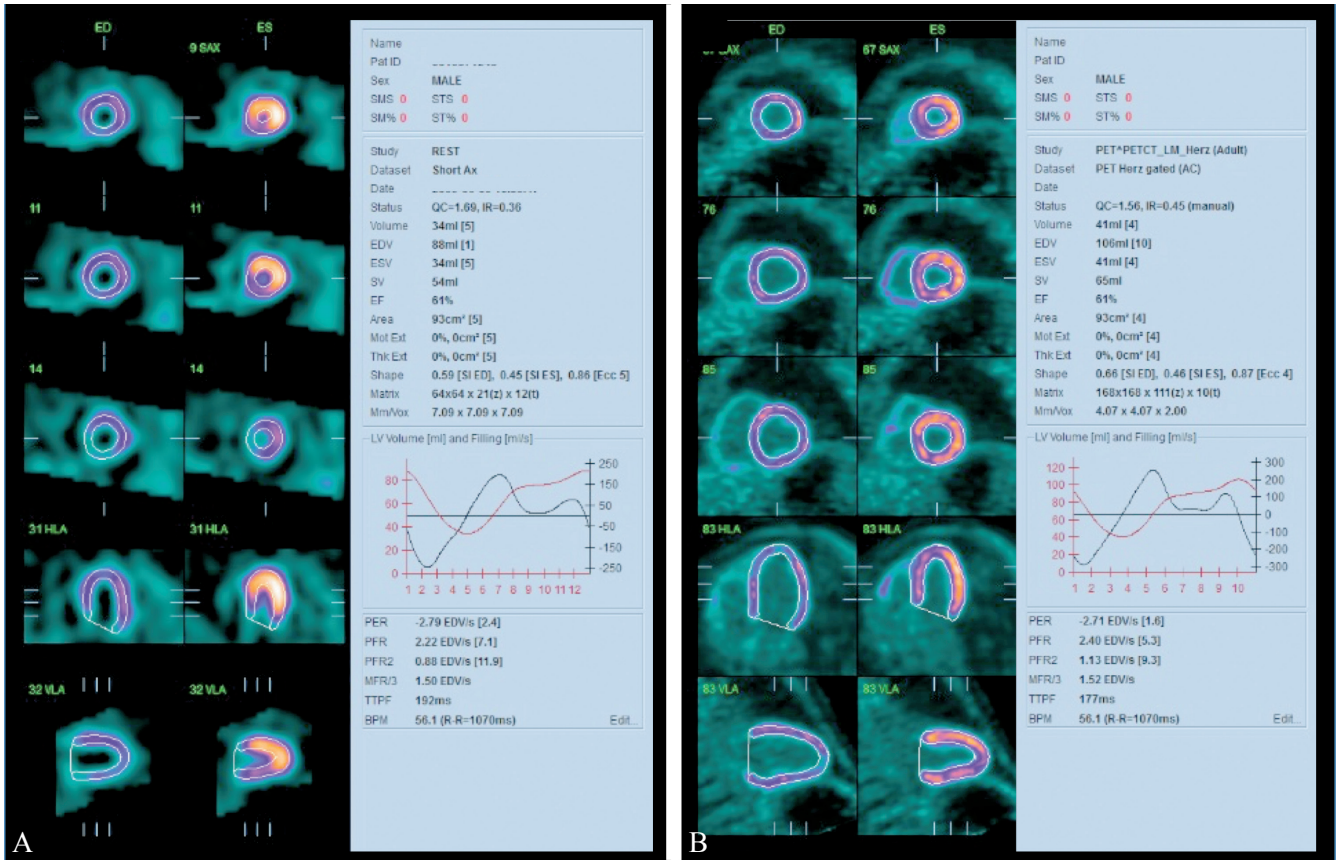

Figure 1—A) Representative images of gated MPS; and B) gated FDG PET.
In each panel the left column shows end systole, the middle column end diastole and the right column the left ventricular functional parameters. Note that PET detects a proportionally larger EDV and ESV as compared to SPECT, probably due to superior image resolution and reduced partial volume effects. LVEF is equal.

As described above patients were assigned to the RC and DC based on published QGS rest reference values for BW, Phase SD and Entropy.[8]

Statistical analysis

All variables are reported as mean±standard deviation (SD) except for gender. Statistical analyses were performed with the commercial statistics software Wizard 2 (Version 2.0.4 [250], Evan Miller; https://www.evanmiller.org/).

The Shapiro-Wilk Test was used to test for normal distribution. To test for differences between two independent samples, the χ^2 test, Student's *t*-test and the Mann-Whitney Test were used, where appropriate.

Pearson's *r* was calculated as a measure of linear correlation between two datasets, scatter diagrams and Bland-Altman plots were used for visualization. P values <0.05 were considered statistically significant.

Results

Between the RC and the DC, we found no significant differences with regard to gender (P=0.549), age (P=0.978), weight (P=0.647), administered dose for SPECT imaging (P=0.837) and administered dose for PET imaging (P=0.677).

In the RC SPECT showed an EDV of 189±99 mL, an ESV of 123±88 mL and a LVEF of 40±16 mL. In the DC SPECT showed an EDV of 255±97 mL, an ESV of 202±82 mL and a LVEF of 25±9.1%. EDV and ESV were significantly elevated in the DC as compared to the RC, LVEF was significantly reduced in the DC as compared to the RC (P<0.001 for all parameters).

In the RC PET showed an EDV of 194±76 mL, an ESV of 130±76 mL and a LVEF of 37±16 mL. In the DC PET showed an EDV of 244±111 mL, an ESV of 191±100 mL and a LVEF of 26±10%. EDV and ESV were significantly elevated in the DC as compared to the RC (P=0.042 and P=0.002 respectively), LVEF was significantly reduced in the DC as compared to the RC (P<0.001).

In the RC SPECT EDV and PET EDV did not differ significantly (P=0.053) and showed a high linear correlation (*R*=0.88, P<0.001). SPECT ESV and PET ESV differed significantly (P=0.004) but showed a high linear correlation (*R*=0.86, P<0.001). SPECT LVEF and PET LVEF did not differ significantly (P=0.091) and showed a high linear correlation (*R*=0.85, P<0.001).

In the DC SPECT EDV and PET EDV did not differ significantly (P=0.414) and showed a high linear correlation (*R*=0.72, P<0.001). SPECT ESV and PET ESV did not differ significantly (P=0.197) and showed a high linear correlation (*R*=0.86, P<0.001). SPECT LFEV and PET LVEF did not differ significantly (P=0.521) and showed a high linear correlation (*R*=0.73, P<0.001).

Table I, II give an overview of the results.

An analysis of the pooled group from the RC and the DC (Table III) revealed that there is a positive correlation between the three dyssynchrony parameters BW, Phase SD and Entropy and the parameters of left ventricular function EDV and ESV for SPECT and for PET. As well as a negative correlation between the three parameters of dyssynchrony and LVEF. The highest correlations were observed between parameters of dyssynchrony and LVEF with high Entropy best predicting a low LVEF (Figure 2).

While the correlation between SPECT and PET for the assessment of left ventricular function showed a good lin-

TABLE I.—*Comparison of SPECT and PET derived left ventricular function between the RC and the DC.*

Variables	RC SPECT	DC SPECT	RC PET	DC PET	P
EDV (mL)	189±99	255±97			<0.001
ESV (mL)	123±88	202±82			<0.001
LVEF (%)	40±16	25±9.1			<0.001
EDV (mL)			194±76	244±111	0.042
ESV (mL)			130±76	191±100	0.002
LVEF (%)			37±16	26±10	<0.001

TABLE II.—*Comparison left ventricular function in the RC and the DC between SPECT and PET.*

Variables	RC SPECT	RC PET	DC SPECT	DC PET	P	R
EDV (mL)	189±99	194±76			0.053	0.88
ESV (mL)	123±88	130±76			0.004	0.86
LVEF (%)	40±16	37±16			0.091	0.85
EDV (mL)			255±97	244±111	0.414	0.72
ESV (mL)			202±82	191±100	0.197	0.86
LVEF (%)			25±9.1	26±10	0.521	0.73

TABLE III.—*Correlation between parameters of dyssynchrony and parameters of left ventricular function in the combined cohort of all patients (RC+DC) for SPECT and PET.*

Variables	BW	Phase SD	Entropy
SPECT			
EDV	*R*=0.40, P<0.001	*R*=0.36, P<0.001	*R*=0.43, P<0.001
ESV	*R*=0.53, P<0.001	*R*=0.49, P<0.001	*R*=0.55, P<0.001
LVEF	*R*=-0.63, P<0.001	*R*=-0.61, P<0.001	*R*=-0.72, P<0.001
PET			
EDV	*R*=0.50, P<0.001	*R*=0.45, P<0.001	*R*=0.50, P<0.001
ESV	*R*=0.55, P<0.001	*R*=0.51, P<0.001	*R*=0.60, P<0.001
LVEF	*R*=-0.60, P<0.001	*R*=-0.57, P<0.001	*R*=-0.79, P<0.001

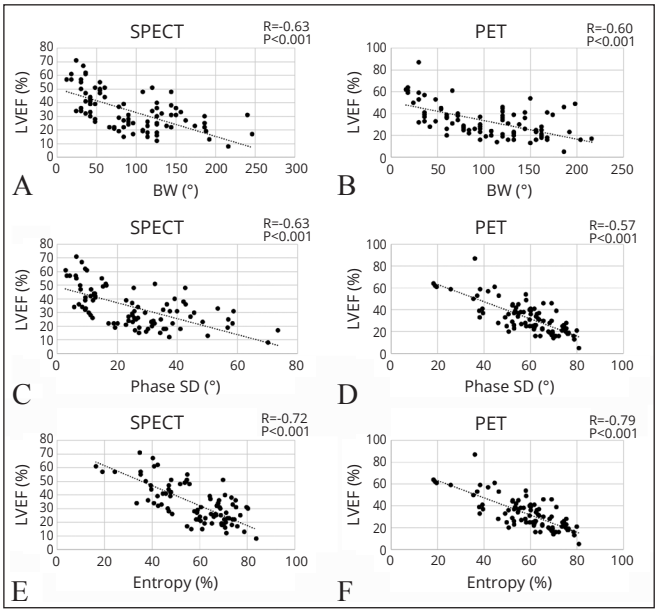

Figure 2.—A-F) Negative correlation between parameters of dyssynchrony and LVEF for SPECT and PET.

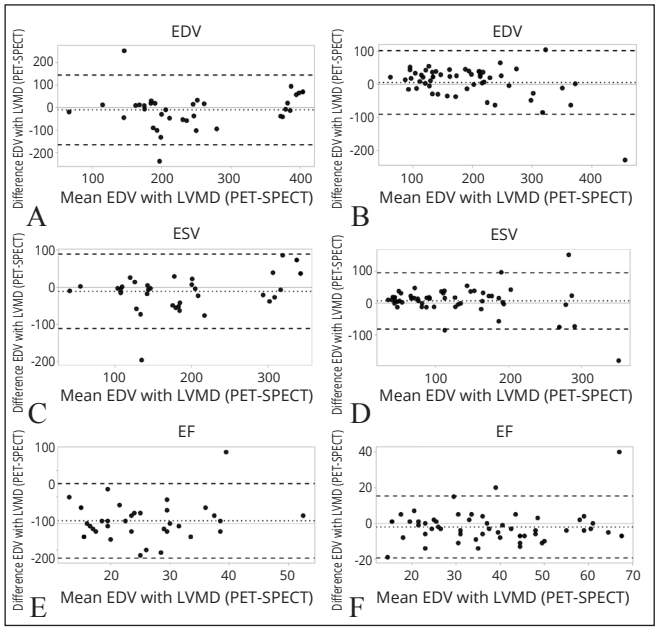

Figure 3.—A-F) Bland-Altman plots to compare SPECT *vs*. PET for the assessment of left ventricular function in patients with and without LVMD.

ear correlation, Bland-Altman plots revealed that all three parameters (EDV, ESV and LVEF) show some variability, which is more pronounced, when LVMD is present (Figure 3).

Discussion

In our study we demonstrated that LVMD as detected by gated MPS is associated with a significantly higher EDV and ESV as well as a significantly reduced LVEF both in gated MPS and gated FDG PET imaging. In the RC and the DC SPECT and PET showed good agreement and generally high linear correlations with regard to left ventricular volumes and LVEF. In the combined cohort (RC and DC) increasing amounts of LVMD were associated with increasing left ventricular volumes as well as a decreasing LVEF. The association was strongest for the dyssynchrony parameter Entropy.

In our study, patients were assigned to the RC and the DC based on the phase analysis results of gated MPS datasets with the software QGS and published reference values for the parameters BW, Phase SD and Entropy as detected by QGS in a reference cohort.[8] Patients were assigned to the DC, if all three parameters were outside of the reference range, otherwise they were assigned to the RC. We opted for this approach for the lack of an external gold standard. PET might eventually prove to be the superior method for the detection of dyssynchrony, due to higher count rates and increased spatial resolution,[4] however reliable data on normal ranges are lacking especially for FDG PET and no definite consensus has been reached on what can be regarded as normal.[4]

The RC and the DC were matched with regard to gender, age, weight and the administered radiopharmaceutical doses for SPECT and PET imaging. Both cohorts showed a strong preference of men, which reflects the higher prevalence of heart diseases in males in the German population.[11]

Our study also demonstrated that the presence of LVMD is closely associated with increased left ventricular volumes as well as a significantly reduced LVEF. It has long been established that the presence of LVMD is correlated with impaired left ventricular function and that the reduction of LVMD leads to improved left ventricular function and the reduction of morbidity and mortality.[4-6] Furthermore, different software packages as well as gated SPECT and gated PET have been compared to each other and other methods, such as MRI, for the evaluation of left ventricular function.[12]

However, at the time this manuscript was prepared, to the knowledge of the authors, there was no study that simultaneously compared the performance of gated MPS and gated FDG PET in patients with LVMD.

The findings of our study are in line with Foley *et al.*[13] that analyzed dyssynchrony in heart failure patients with

MRI and found a positive correlation with EDV and ESV as well as a negative correlation with LVEF. That study also found that dyssynchrony was more likely to be present in patients with reduced ejection fraction and elongated QRS duration, emphasizing the interdependence of left ventricular function and synchronicity of myocardial contraction.

A 2019 study that was conducted in a cohort of patients with end-stage renal disease, myocardial dyssynchrony was evaluated with gate MPS.[14] The study found similar correlations between parameters of phase analysis and LVEF as well as left ventricular volume as we did. However, no comparison with gated-PET was made.

Past comparisons of left ventricular function between gated PET and gated SPECT demonstrated that, while both methods generally show good agreement, the calculated values cannot be used interchangeably.[12]

A current study compared gated MPS, gated FDG PET, and cardiac MRI as well as different software packages for the evaluation of left ventricular function in patients with prior myocardial infarction.[15] The study found that while all methods delivered comparable results, they should not be used interchangeably on a per-patient basis.

The same statement can be made for the comparison of gated MPS and gated FDG PET for the evaluation of patients with LVMD. In general, the methods show a good agreement for the evaluation of EDV, ESV and LFEV, both in patient cohorts with and without dyssynchrony. However, the mean values usually differ somewhat from one another. In case of ESV in the RC the difference even reached statistical significance (gated MPS: 123±88 mL *vs*. gated FDG PET: 130±76 mL; P=0.004), even though the absolute difference was only 7 mL. These differences might likely be explained by the superior spatial and temporal resolution of PET., Additionally, more suitable software algorithms might be warranted to analyze gated PET images, as current software packages were primarily designed for gated SPECT scans and gated PET was later added.[15] Analysis with Bland-Altman plots revealed that some variability is present between SPECT and PET for the assessment of left ventricular function, which might be clinically relevant. This effect was more pronounced, when LVMD was present. As such, it seems prudent to assume that both methods should not be used interchangeably, especially for repeated measurements or therapy monitoring. This is in line with findings by Wang *et al.*, who advised caution for the interchangeable use of SPECT and PET for the detection of LVMD in certain settings.[16] In contrast, other studies found good correlation between SPECT and PET in that regard,[17] demonstrating the as of yet controversial nature of this subject.

Another interesting observation was made, when BW, Phase SD and Entropy were correlated with EDV, ESV and LVEF. The parameter Entropy – both calculated with SPECT and PET – showed the highest correlations with the parameters of left ventricular function, especially LVEF. This is central for therapy monitoring and risk stratification in heart failure patients, as heart failure with a reduced LVEF leads to significant mortality.[18]

Entropy is a parameter specifically calculated by the QGS software and based on the Shannon Equation from information theory.[19] In brief, the probabilities for the occurrence of each histogram bin from the phase histogram are added and subsequently divided by the logarithmic total number of histogram bins. This yields an Entropy range from 0 to 1 (or 0% to 100%), where 0 represents total order and 1 represents total disorder.

An increasing amount of Entropy was associated with an increasing reduction of LVEF and vice versa. This is especially compelling, since the reduction of LVMD to improve left ventricular function, and subsequently quality of life, exercise capability, and mortality is one of the core principles of cardiac resynchronization therapy.[20] Phase analysis by gated MPS and gated FDG PET might have the potential to become an important tool for patient selection and therapy monitoring.[3, 21]

Limitations of the study

Our study suffers from several limitations of which the reader should be aware. It is a retrospective study, and therefore the findings will need to be validated in prospective studies.

For the lack of an external gold standard, patients were assigned to the RC or DC group by means of gated SPECT phase analysis and published reference values. Gated SPECT might not be the optimal reference standard. Furthermore, the RC is not optimal, because these were not healthy subjects, rather these were patients referred to our institution for further cardiac work-up that did not meet our criteria for the diagnosis of LVMD and were thus assigned to the RC.

Also, our decision to assign patients to the DC only if all three parameters (BW, Phase SD and Entropy) were abnormal, could be challenged. Since dyssynchrony most likely has a broad spectrum from mild to severe and not all parameters might be abnormal at all times. However, for the sake of clarity, our approach seemed reasonable.

Nevertheless, all our findings will have to be validated in future prospective studies.

Perfusion deficits, scars and hibernating myocardium were not included in our analysis, likewise for the sake of focus and clarity. However, these should be addressed in an additional study.

Conclusions

We demonstrated that gated SPECT and gated PET are useful tools in the evaluation of left ventricular function in patients with LVMD as detected by gated MPS. Patients with LVMD showed significantly elevated EDV and ESV as well as a significantly reduced LVEF as compared to patients without LVMD. Increasing amounts of dyssynchrony were associated with an increasingly reduced myocardial function, whereupon Entropy showed the best correlation with the parameters of left ventricular function. While generally in good agreement, gated MPS and gated FDG PET show differences, when mean values of EDV, ESV and LVEF are compared. Consequently, for repeated measurements or therapy monitoring, the methods should not be used interchangeably.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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6. Paper II

The assessment of left ventricular mechanical dyssynchrony from gated ^{99m}Tc-tetrofosmin SPECT and gated ^{18}F-FDG PET by QGS: a comparative study

Sebastian Lehner,[a,b] Frank Philipp Graner,[a] Maximilian Fischer,[c] Harun Ilhan,[a] Peter Bartenstein,[a] and Andrei Todica[a]

[a] Department of Nuclear Medicine, University Hospital, Ludwig-Maximilians-Universität, Munich, Germany
[b] Ambulatory Health Care Center Dr. Neumaier & Colleagues, Radiology, Nuclear Medicine, Radiation Therapy, Regensburg, Germany
[c] Department of Internal Medicine, Cardiology, University Hospital, Ludwig-Maximilians-Universität, Munich, Germany

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Background. **Due to partly conflicting studies, further research is warranted with the QGS software package, with regard to the performance of gated FDG PET phase analysis as compared to gated MPS as well as the establishment of possible cut-off values for FDG PET to define dyssynchrony.**

Methods. **Gated MPS and gated FDG PET datasets of 93 patients were analyzed with the QGS software. BW, Phase SD, and Entropy were calculated and compared between the methods. The performance of gated PET to identify dyssynchrony was measured against SPECT as reference standard. ROC analysis was performed to identify the best discriminator of dyssynchrony and to define cut-off values.**

Results. **BW and Phase SD differed significantly between the SPECT and PET. There was no significant difference in Entropy with a high linear correlation between methods.**
There was only moderate agreement between SPECT and PET to identify dyssynchrony. Entropy was the best single PET parameter to predict dyssynchrony with a cut-off point at 62%.

Conclusion. **Gated MPS and gated FDG PET can assess LVMD. The methods cannot be used interchangeably. Establishing reference ranges and cut-off values is difficult due to the lack of an external gold standard. Further prospective research is necessary. (J Nucl Cardiol 2021)**

Key Words: Gated SPECT • gated PET • left ventricular dyssynchrony • phase analysis • QGS

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This article includes a PowerPoint file that should be made available as ESM on SpringerLink. The authors of this article have provided a PowerPoint file, available for download at SpringerLink, which summarizes the contents of the paper and is free for re-use at meetings and presentations.

The authors have also provided an audio summary of the article, which is available to download as ESM or to listen to via the JNC/ASNC Podcast.

Reprint requests: Sebastian Lehner, Department of Nuclear Medicine, University Hospital, Ludwig-Maximilians-Universität, Marchioninistraße 15, 81377 Munich, Germany; *sebastian.r.lehner@icloud.com*

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Abbreviations	
AUC	Area under the curve
BW	Bandwidth
CRT	Cardiac resynchronization therapy
FDG	^{18}F-fluorodeoxyglucose
HF	Heart failure
LVMD	Left ventricular mechanical dyssynchrony
MPS	Myocardial perfusion SPECT
PET	Positron emission computed tomography
Phase SD	Phase standard deviation
SPECT	Single-photon emission computed tomography

BACKGROUND

The concept of measuring left ventricular mechanical dyssynchrony (LVMD) in heart failure (HF) patients is compelling for its potential use as a tool to select candidates for cardiac resynchronization therapy (CRT) and monitor the outcome.[1,2] While lifesaving in many cases, CRT has unfortunately been prone to a high failure rate of up to 30%, which might be partly explained by the limited amounts of underlying LVMD.[2,3] Phase analysis might help to ameliorate this situation. Other use cases for phase analysis include the assessment of dyssynchrony in coronary artery disease and the assessment of diastolic left ventricular dyssynchrony.[1,3]

Gated myocardial perfusion single-photon emission computed tomography (MPS) and, in recent times, gated ^{18}F-fluorodeoxyglucose positron emission computed tomography (FDG PET) are non-invasive tools that offer simplicity, high reproducibility, and wide availability for the assessment and monitoring of LVMD.[1]

Since its inception in the year 2005, phase analysis of gated MPS datasets has been implemented into all major commercial software packages, such as Quantitative Gated SPECT, the Emory Cardiac Toolbox, or 4DM SPECT, and recently been extended to gated PET datasets.[1,3]

Even though the method has been in use for the better part of 15 years, the amount of available evidence is still limited. Most of the evidence comprises gated SPECT. Data for gated PET have been added.

As of yet, it remains unclear which parameters best measure dyssynchrony, which normal values define synchrony (and to this effect dyssynchrony), and which parameters best predict dyssynchrony in otherwise healthy individuals and HF patients alike. There is a wide variation in numeric evidence between software packages and methods.[4]

In recent years, several groups tried to define normal values for gated SPECT studies using different software packages. One of the most comprehensive of such studies was published in 2018 by Hämäläinen et al.[5] The study aggregated a plethora of reference ranges for many different functional gated MPS values from a rigorously selected normative cohort using the QGS software package. Not many attempts have been made to define phase analysis reference or cut-off values for gated PET. Two studies were published in 2011 and in 2012, both used the Rubidium tracer and employed the Emory Cardiac Toolbox and 4DM SPECT, respectively.[3]

Other studies evaluated the diagnostic performance of gated PET as compared to gated SPECT.

In 2011 Pazhenkottil et al.[6] used the Emory Cardiac Toolbox to compare the diagnostic performance of FDG-PET vs MPS. However, only the parameters BW and Phase SD were analyzed. Furthermore, the used cut-off values to divide the cohort into synchronous and dyssynchronous patients were originally tailored to predict the response following CRT.

In 2013 Wang et al.[7] used QGS to compare phase analysis with FDG-PET and MPS and tried to identify confounders like left ventricular remodeling or poor FDG uptake. However, likewise only the parameters BW and Phase SD were evaluated and no attempt was made to identify dyssynchronous patients to assess the diagnostic performance of FDG-PET or perform an ROC analysis to define possible PET cut-off values.

In 2020 Tian et al.[8] used QGS to compare phase analysis with FDG-PET and MPS. They evaluated BW, Phase SD, and Entropy. However, the used cut-off values to divide the cohort into synchronous and dyssynchronous patients were not specific for the QGS software and partly tailored to predict the response following CRT. No ROC analysis was performed to define possible PET cut-off values for the detection of dyssynchrony.

To make a valuable contribution to this existing body of evidence, the following topics were investigated in our study:

Feasibility of retrospective phase analysis of gated MPS and gated FDG-PET datasets using the QGS software package with a comprehensive comparison of the phase analysis parameters Bandwidth (BW), Phase Standard Deviation (Phase SD), and Entropy between SPECT and PET datasets to validate existing evidence.
Evaluation of the diagnostic performance of gated FDG PET as compared to gated MPS as the reference standard based on reference values specifically

established for SPECT datasets, and the QGS software package and calculation of specific gated FDG-PET cut-off values for the parameters BW, Phase SD, and Entropy to optimize diagnostic performance, which to the knowledge of the authors has not been done before.

MATERIALS AND METHODS

Study Population

Our study population consisted of 93 consecutive patients (83 male, mean age 65 ± 11 years, mean weight 87 ± 22 kg, SPECT left ventricular ejection fraction 34% ± 15%, PET left ventricular ejection fraction 33% ± 15%, mean injected ^{99m}Tc-tetrofosmin/^{99m}Tc-MIBI dose 425 ± 152 MBq, mean injected FDG dose 268 ± 50 MBq). For baseline characteristics see Table 1.

Patients with a history of coronary artery disease were referred to our institution for the assessment of myocardial viability.

An integrated SPECT/CT scanner and a dedicated triple-head SPECT camera system were used for routine MPS under resting conditions. An FDG PET/CT scan was performed on average 17 days after the MPS scan on dedicated PET/CT systems.

This retrospective study was conducted with the approval of the local ethics committee (Ethikkommission der Medizinischen Fakultät der LMU München).

Table 1. Baseline characteristics of the study population.

Baseline characteristics (n = 93)	
Gender (m, f)	83 male
Age (years)	64 ± 11
Weight (kg)	87 ± 22
Dose SPECT (MBq)	425 ± 152
Dose PET (MBq)	268 ± 50
TPD (%)	23 ± 15
Mismatch (%)	6.3 ± 6.3
Scar (%)	16 ± 13
SPECT EDV (mL)	214 ± 103
SPECT ESV (mL)	154 ± 93
SPECT LVEF (%)	34 ± 15
PET EDV (mL)	214 ± 94
PET ESV (mL)	154 ± 91
PET LVEF (%)	33 ± 15

SPECT Imaging

For rest MPS ^{99m}Tc-tetrofosmin was administered intravenously and SPECT scans were commenced 30-45 minutes after the application of the tracer. One camera used in the study, was a dual-head hybrid SPECT/CT camera (Symbia, Siemens Medical Systems, Erlangen, Germany) with a parallel-hole LEHR collimator. The energy window was centered at 140 keV ± 20%; the two detector heads were set at an angle of 90° and covered an arc of 180° at 64 rotational steps. Each single projection lasted 23 seconds. An electrocardiogram R-wave detector was employed for ECG-gating; 12 emission frames were recorded during each cardiac cycle. While images were reconstructed as static and as gated perfusion images, only the gated images were used in the current study, and the static images were used for clinical reporting.

The second camera used was triple-head SPECT camera system (Prism 3000 XP; Philips/InterMedical, formerly Picker, Cleveland, OH). It was equipped with a parallel-hole LEHR collimator. The symmetrical 20% energy window was likewise centered at 140 keV. The three detector heads were set at a 120° angle and performed a 360° rotation with 20 steps per head, each step lasting 60 seconds. ECG-gating was performed as described above. Images were again reconstructed as gated and static images; static images were used for clinical reporting, and gated images were analyzed in the present study.

PET/CT Imaging

Cardiac FDG PET/CT was performed on 64-slice CT PET/CT systems (Biograph 64, Siemens Medical Systems, Erlangen, Germany and GE Discovery 690, GE Healthcare, Chicago, USA). Patients received 250 mg Acipimox 120 minutes before the scan, and FDG was administered 30 minutes before the scan.

Non-diabetic patients received an oral glucose load, and diabetic patients were treated according to a modified protocol of the American Society of Nuclear Cardiology.[9] 60 minutes prior to the PET scan, diabetic patients received a light meal and their regular insulin dose. An intravenous catheter was placed into each cubital vein for the injection of glucose and the measurement of blood glucose levels. Over the course of 8 minutes, two syringes filled with 20% glucose solution (.2 g per kg bodyweight), one with additional insulin (.2 dose units per kg bodyweight), were injected. Blood glucose levels were closely monitored. After glucose levels had peaked and started to decline, the FDG was injected. 30 minutes later the patients were placed inside the scanner and a low-dose spiral CT (120

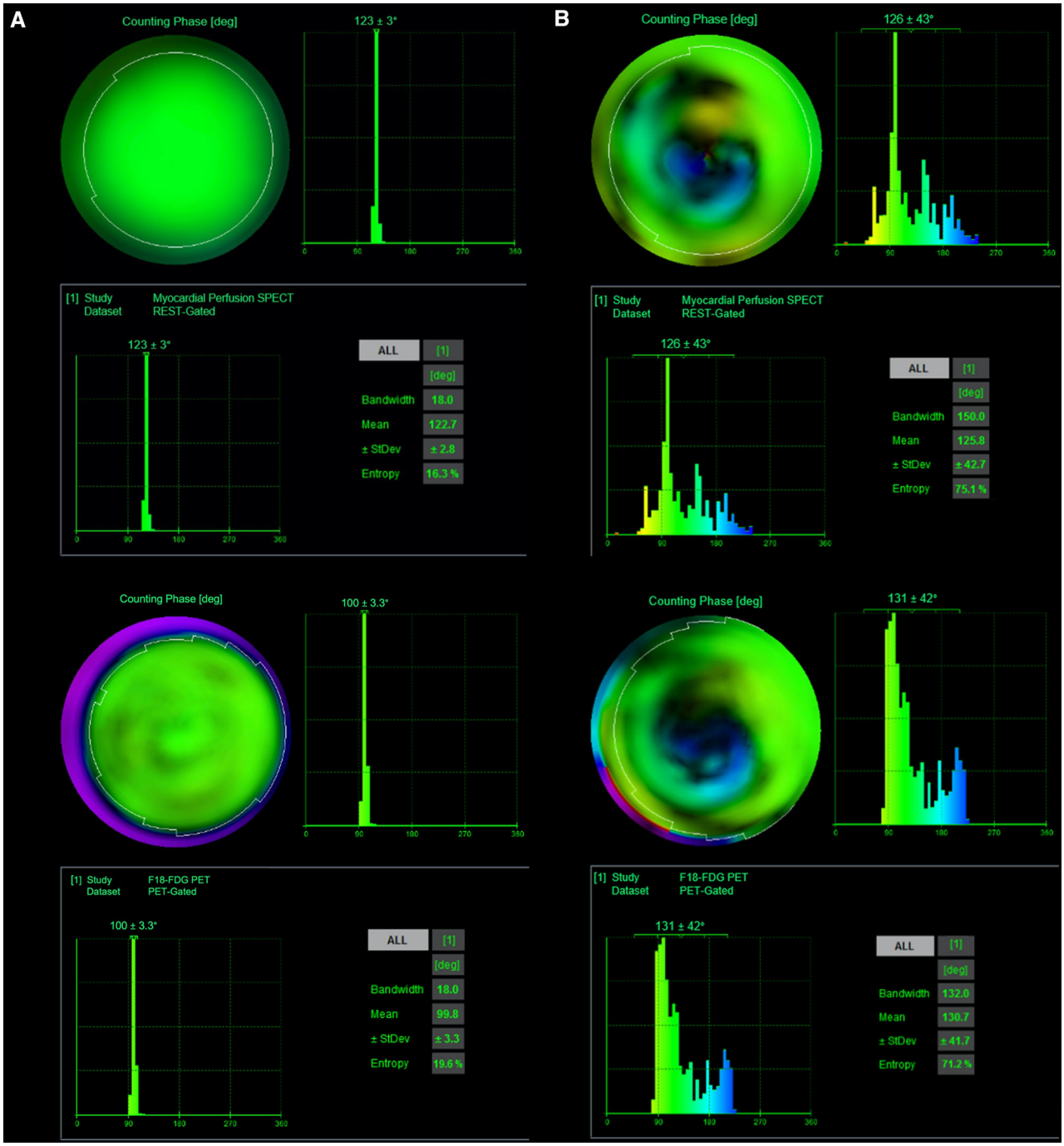

Figure 1. Phase analysis with QGS. **A** shows the SPECT (upper image) and PET (lower image) phase analysis of the same patient without dyssynchrony. **B** shows the SPECT (upper image) and PET (lower image) phase analysis of the same patient with dyssynchrony.

keV, 11 mAs) was acquired for attenuation correction, this was followed by a 20-minute emission scan with ECG-gating. The PET images were reconstructed as static and gated images (matrix size 168 x 168, zoom factor 1). Static images were used for clinical reporting, and gated images were analyzed in the present study.

Table 2. BW and Phase SD differed significantly between SPECT and PET.

	SPECT	PET	p
BW (°)	94 ± 55	104 ± 53	.022
Phase SD (°)	26 ± 16	30 ± 17	.004
Entropy (%)	58 ± 15	58 ± 15	.601

Image Analysis

Gated MPS and gated FDG PET datasets were analyzed with the Quantitative Gated SPECT software (QGS, Cedars-Sinai, Los Angeles, California) as described before.[5] In brief, the datasets were loaded into the software, and the myocardium was delineated by an automatic algorithm. Optimal delineation was visually verified, and minor manual adjustments were made, if necessary. The parameters BW, Phase SD, and

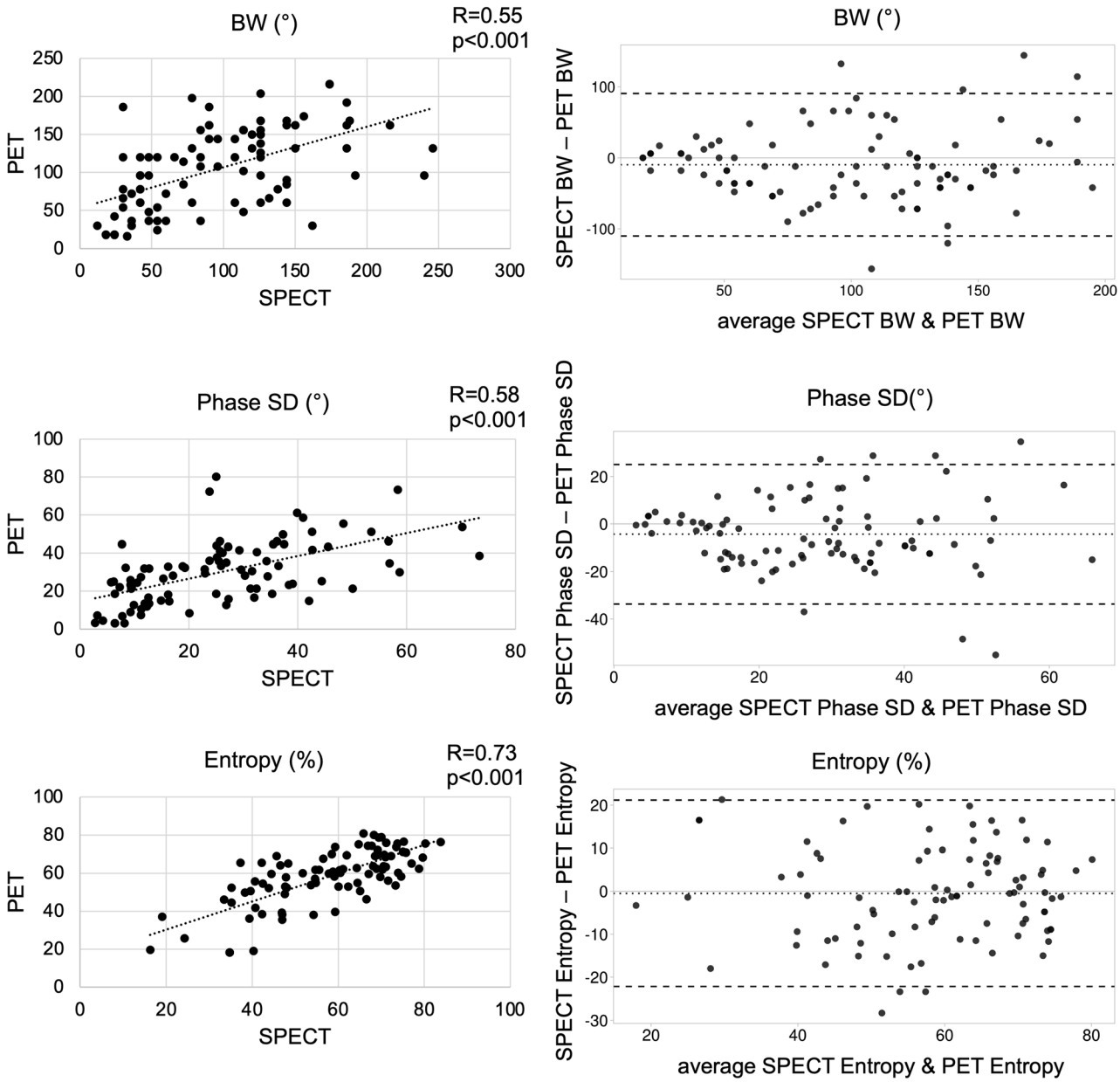

Figure 2. Correlation of BW, Phase SD, and Entropy between PET and SPECT.

Table 3. Contingency table comparing PET to SPECT as standard of reference, criteria for dyssynchrony were three pathological phase analysis parameters.

	SPECT dyssync	SPECT sync	sum
PET dyssync	23	10	33
PET sync	13	47	60
Sum	36	57	93

The calculated sensitivity was 64%, the specificity was 82%, PPV 70%, NPV 78%.

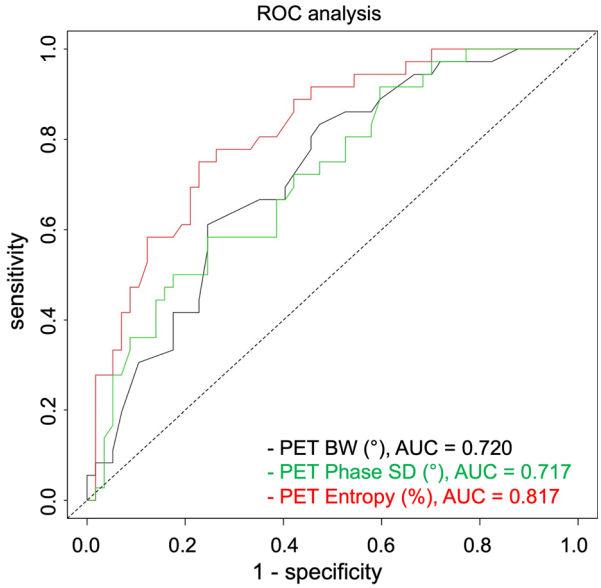

Figure 3. ROC analysis for PET BW, Phase SD, and Entropy to predict dyssynchrony (criterion for dyssynchrony: three pathological phase analysis parameters).

Entropy were calculated and displayed by the software, representing of the amount of myocardial dyssynchrony (Figure 1). Gated SPECT served as the reference standard and patients were diagnosed as synchronous or dyssynchronous based on published QGS rest reference values for BW (17.0-63.7°), Phase SD (4.4-26.5°), and Entropy (44.0%-63.7%).[5] Patients were assigned to the dyssynchronous cohort, when values for all three phase analysis parameters were pathological. Otherwise, they were assigned to the synchronous group. In a second analysis, patients were assigned to the dyssynchronous cohort, if two out of the three phase analysis parameters were pathological. Otherwise, they were assigned to the synchronous group.

Statistical Analysis

All variables are reported as mean ± standard deviation (SD).

Statistics were calculated with the commercial statistics software Wizard 2 (Version 2.0.4 (250), Evan Miller).

The Shapiro–Wilk test was used to test for normal distribution.

The Wilcoxon signed-rank test was used to test for differences in two groups with repeated measurements.

The Mann–Whitney U test was used to test for differences between two groups that were not normally distributed.

Pearson's r was calculated as a measure of linear correlation between two datasets; scatter diagrams and Bland–Altman plots were used for visualization and further analysis.

Kappa was calculated as a measure of agreement between SPECT and PET.

Youden's J statistic was used to calculate cut-off values optimized for sensitivity and specificity in ROC analysis. A z test was used to compare the AUC.

P values $< .05$ were considered statistically significant.

RESULTS

The gated MPS scans as well as the gated FDG PET scans could successfully be analyzed using the QGS software.

Gated MPS revealed a mean BW of 94 ± 55°, a mean Phase SD 26 ± 16°, and a mean Entropy of 58% ± 15%.

Gated FDG PET revealed a mean BW of 104 ± 53°, a mean Phase SD of 30 ± 17°, and a mean Entropy of 58% ± 15%.

Mean BW and mean Phase SD were significantly different between gated MPS and gated FDG PET as shown in Table 2.

BW showed only a moderate correlation between SPECT and PET ($R = .55$, $P < .001$).

Phase SD likewise showed only a moderate correlation between SPECT and PET ($R = .58$, $P < .001$).

Entropy showed a high correlation between SPECT and PET ($R = .73$, $P < .001$).

All parameters showed satisfactory agreement on Bland–Altman plots (Figure 2).

With three pathological phase analysis parameters as the criterion for dyssynchrony, SPECT identified 36 patients with dyssynchrony based on published QGS reference values as described in the methods section. PET identified 33 patients with dyssynchrony based on the same SPECT reference values. With SPECT as a reference standard, PET showed a sensitivity of 64%, a specificity of 82%, a positive predictive value of 70%, and a negative predictive value of 78% (Table 3). SPECT and PET only showed a moderate agreement (kappa .47).

ROC analysis (Figure 3) revealed that the best PET parameter to predict dyssynchrony is Entropy (AUC = .817). BW and Phase SD showed a slightly inferior performance that did not reach statistical significance (AUC = .721 and .717, respectively, P = ns in all comparisons).

Cut-off values for single parameters optimized for sensitivity and specificity using Youden's J statistic were 126° for PET BW (sensitivity 61%, specificity 75%, PPV 61%, NPV 75%), 39° for PET Phase SD (sensitivity 50%, specificity 83%, PPV 64%, NPV 72%), and 63% for PET Entropy (sensitivity 69%, specificity 77%, PPV 66%, NPV 80%).

With two pathological phase analysis parameters as the criterion for dyssynchrony, SPECT identified 46 patients with dyssynchrony based on published QGS reference values as described in the methods section. PET identified 54 patients with dyssynchrony based on the same SPECT reference values. With SPECT as a reference standard, PET showed a sensitivity of 74%, a specificity of 57%, a positive predictive value of 63%, and a negative predictive value of 69% (Table 4). SPECT and PET only showed a fair agreement (kappa .31).

ROC analysis (Figure 4) revealed that the best PET parameter to predict dyssynchrony is Entropy (AUC = .853). BW and Phase SD showed a slightly inferior performance, and the difference did not reach statistical significance (AUC = .778 and .779, respectively, P = ns in all comparisons).

Cut-off values for single parameter optimized for sensitivity and specificity using Youden's J statistic were 126° for PET BW (sensitivity 61%, specificity 83%, PPV 78%, NPV 68%), 33° for PET Phase SD (sensitivity 61%, specificity 85%, PPV 80%, NPV 69%), and 62% for PET Entropy (sensitivity 76%, specificity 83%, PPV 81%, NPV 78%).

DISCUSSION

Phase analysis using the QGS software package was feasible in all gated SPECT and PET datasets and yielded satisfactory results.

The parameters BW and Phase SD differed significantly between the SPECT and PET datasets and only

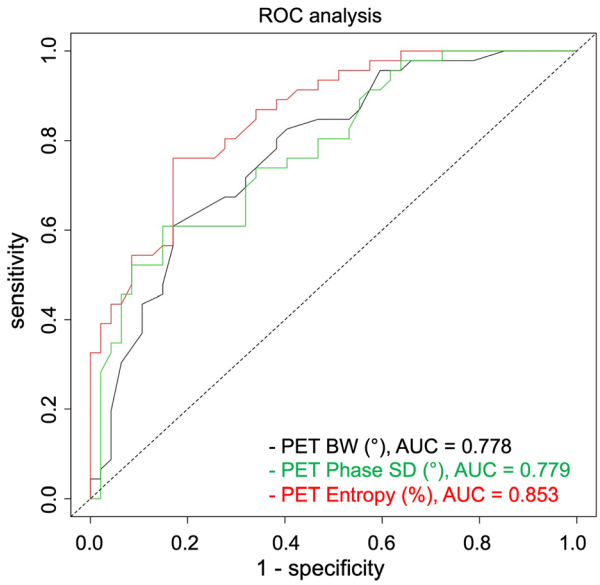

Figure 4. ROC analysis for PET BW, Phase SD, and Entropy to predict dyssynchrony (criterion for dyssynchrony: two pathological phase analysis parameters).

Table 4. Contingency table comparing PET to SPECT as standard of reference, criteria for dyssynchrony were two pathological phase analysis parameters

	SPECT dyssync	SPECT sync	Sum
PET dyssync	34	20	54
PET sync	12	27	39
Sum	46	47	93

The calculated sensitivity was 74%, the specificity was 57%, PPV 63%, NPV 69%.

showed a moderate linear correlation between the methods.

There was no significant difference in Entropy between the SPECT and PET datasets and the parameter showed a high linear correlation between the methods.

All parameters showed satisfactory agreement in the Bland–Altman plots.

With gated SPECT as a reference standard, the diagnostic performance of gated FDG PET proved to be limited with only a moderate agreement between SPECT and PET to detect dyssynchrony on a per patient basis.

ROC revealed that Entropy was the best single PET parameter to predict dyssynchrony overall with a cut-off point at 62% to optimize for sensitivity and specificity.

Retrospective phase analysis could be carried out in all gated MPS and gated PET datasets included in the study and yielded satisfactory results. This is facilitated by the fact that phase analysis in modern software packages is a mostly automatic process that requires little to no interaction by the user and has a high intra- and inter-observer reproducibility.[1] Our experience was in line with published literature and phase analysis parameters could be extracted from all datasets without any problems.

While Pazhenkottil et al. reported no significant differences between gated MPS and gated FDG PET with regard to BW and Phase SD using the Emory Cardiac Toolbox and found a very high linear correlation of those parameters by SPECT and PET,[6] we could not reproduce these results in our study. BW and Phase SD differed significantly between gated MPS and gated FDG PET datasets and showed only a moderate linear correlation. In contrast to BW and Phase SD, Entropy proved to be superior, yielding no significant difference between both methods, and showed a high linear correlation between SPECT and PET. This is very much in line with the results of a study published in 2020 by Tian et al.,[8] which found the same moderate linear correlations of BW and Phase SD between SPECT and PET as we did as well as a high linear correlation of Entropy.

Partly, the different results of the Pazhenkottil study might be explained by the use of a different software package. It could be demonstrated in previous investigations that different software packages yield different results and thus cannot be used interchangeably.[10,11]

In addition to the aforementioned use of different software packages, there are several other confounders of phase analysis that might hamper the comparability not only between studies but also between different patient cohorts.

A systematic review from 2019[4] found a wide variety of normal values in patients with no structural heart disease. Apart from software specific characteristics, other confounding factors were identified, such as age, scanner characteristics, and biophysical profile of the study population or cardiovascular risk factors. A 2012 study by Aljaroudi et al.[12] identified left ventricular function, perfusion defect size, atrial fibrillation, and BMI as additional factors that influence LVMD.

Especially the extent of the myocardial scar tissue seems to be an important factor that is associated with inconsistencies in the evaluation of Phase SD and Entropy.[8] The purported mechanism here is regional count variations.

As such, patient selection might play a crucial role in the expected outcome of phase analysis, and a comparison between our study and the aforementioned studies can only be made with caution, as crucial differences in patient selection are to be expected.

This is also reflected by the fact that in the Pazhenkottil study mean BW was 168.7° and mean Phase SD was 52.7° measured by SPECT as compared to 94° and 26° in our study, respectively, representing a completely different range of LVMD. Also in the Pazhenkottil study, more than half of the patients were identified with severe dyssynchrony, while in our study only approximately one-third of the patients had dyssynchrony at all.

Method-specific characteristics also seem to play an important role: it seems prudent to assume that while gated SPECT and gated PET should generally detect comparable amounts of dyssynchrony, they represent inherently different methods that will invariably lead to differing measurements of the same variable. Especially PET is enjoying several major advantages with regard to increased count rate and highly improved spatial resolution.[3] As such, differing results of the phase analysis parameters were to be expected. A more detailed look at the mean values of BW, Phase SD, and Entropy (Table 1) reveals that even though the difference reached statistical significance, the absolute difference is relatively small: approximately 10° for BW and 4° for Phase SD.

The moderate linear correlations of BW and Phase SD, however, suggest that gated MPS and gated FDG PET scans should not be used interchangeably for the repeated measurements of dyssynchrony, especially for serial therapy monitoring. For the lack of an independent gold standard, it is not possible to determine, which of the methods delivers the more accurate results. This will have to be investigated in future studies with external reference standards.

In summary, phase analysis for the assessment of LVMD (irrespective of the method used) is a complex process, as the results are influenced by a plethora of factors, some of which are impossible to eliminate (e.g.,

TPD, Mismatch and Scar influence-measured LVMD, see Supplement). Nevertheless, to minimize the influence of those factors, it seems advisable to adhere to standardized imaging protocols, to not use the methods interchangeably on follow-up examinations and to have a clear idea of what problems are to be expected in diverse patient populations.

Based on the previously published reference values for gated MPS studies analyzed with QGS[5] and the three-parameter criterion for dyssynchrony, the SPECT method found 36 patients with LVMD. Gated FDG PET yielded 33 patients with dyssynchrony based on the same SPECT reference values. However, at a kappa of only .47 the agreement between the methods was only moderate. This is again in stark contrast to the findings of Pazhenkottil et al., who found an agreement of the methods of 93% based on SPECT cut-off values for BW and Phase SD.[6]

Again, our results are more in line with the findings of Tian et al. that detected a low agreement between the methods at a kappa of .29.[8] The better performance in our study might be due to the use of three and not only two parameters to detect dyssynchrony. Furthermore, we based our evaluation on reference values established especially for QGS in healthy individuals, while Tian et al. based their evaluation on cut-off values established for the prediction of CRT response using the Emory Cardiac Toolbox.

When the criterion for dyssynchrony is based on pathological results in only two instead of three of the phase analysis parameters, the sensitivity of PET increases, while the specificity decreases and the agreement between the SPECT and PET methods deteriorates (kappa .31). This was to be expected, since more dyssynchrony is detected by PET, but not necessarily in the same patients as by the standard of reference SPECT.

One problem that might explain the limited diagnostic performance of gated FDG PET in the detection of LVMD is the lack of a true external gold standard, as the use of gated SPECT as the only reference standard for gated PET is in itself flawed and might be prone to misclassifications. Also gated PET might ultimately prove to be the more accurate method.

Based on the three-parameter criterion, ROC analysis of the gated PET parameters BW, Phase SD, and Entropy revealed that Entropy proved to be the best discriminator between synchronous and dyssynchronous patients as defined by the gated SPECT reference values with an AUC of .817. The optimized cut-off value for Entropy was 63%. The optimized cut-off point for BW was 126° and 39° for Phase SD. These cut-off points were very different from those found in the 2011 and 2012 PET studies by Cooke and Aljaroudi.[3] However, this is most likely explained by the different tracer (Rubidium) and the different software packages (4DM SPECT and Emory Cardiac Toolbox) used in these studies.

Interestingly, when the SPECT reference standard for dyssynchrony was based on the two-parameter criterion, the discrimination of synchronous and dyssynchronous patients by PET actually improved somewhat, with Entropy being the best parameter with an optimized cut-off value of 62% and an AUC of .853.

A possible explanation would be the increased sensitivity of the reference standard for the detection of dyssynchrony and subsequently a higher chance of PET to differentiate between the two patient cohorts.

In the end, it is a striking demonstration that the diagnostic performance of any method aiming to detect LVMD, is also dependent on the definition of LVMD itself.

To objectively determine, whether LVMD is present, and to quantify it, will be one of the ultimate challenges of phase analysis.

NEW KNOWLEDGE GAINED

In contrast to some of the previously published data, we could demonstrate that the agreement between the gated SPECT and gated PET-based phase analysis is not optimal and that the methods cannot simply be used interchangeably, especially for serial imaging and therapy monitoring. Based on reference values for BW, Phase SD, and Entropy specifically established for the QGS software package, we used gated MPS as a reference standard to evaluate the diagnostic performance of gated FDG PET and were able to identify Entropy as the best predictor of dyssynchrony with an optimized cut-off point of 63%.

CONCLUSION

Both gated MPS and gated FDG PET are promising and valuable tools for the assessment of LVMD. However, the agreement of both methods at the present time is limited and they cannot be used interchangeably without further modification. Establishing reference ranges and cut-off values is difficult due to the lack of an external gold standard. Further prospective research will be necessary as to which approach will prove more reliable and accurate in the long term, even though PET seems to have an advantage due to the better count statistics and superior spatial resolution.

LIMITATIONS

There are several limitations to our study, the reader should be aware of.

First and foremost, it is a retrospective study and as such the data will have to be validated in further prospective research and in larger patient cohorts.

Gated MPS was used as a reference standard for the evaluation of the diagnostic performance of FDG PET. We elected to proceed this way for the lack of a better external gold standard and since published QGS reference values were available only for gated MPS. Of course, this approach in itself is flawed, since gated FDG PET might prove to be the more accurate method. However, this way it was possible to conduct an analysis of gated FDG PET performance based on objective criteria for dyssynchrony instead of relying on visual assessment. Thus, we could deliver preliminary data to give more insight into which PET parameters might be especially useful for assessing dyssynchrony.

Finally, we elected to assign only those patients to the dyssynchrony cohort that simultaneously showed pathological values for BW, Phase SD, and Entropy (three-parameter criterion) or pathological results for at least two of those parameters (two-parameter criterion). Of course, it could be argued that less severe cases of LVMD might not result in as many parameters reaching pathological levels. But for the sake of clarity our approach seemed reasonable.

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Disclosures

The authors declare that they have no conflict of interest.

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